Experimental validation of a pulse wave propagation model for predicting hemodynamics after vascular access surgery

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ARTICLE INFO

Article history:
Accepted 14 March 2012

Keywords:
Vascular access
Patient-specific
Computational model
Pulse wave propagation model
In vitro experimental model
Validation

ABSTRACT

Hemodialysis patients require a vascular access that is, preferably, surgically created by connecting an artery and vein in the arm, i.e. an arteriovenous fistula (AVF). The site for AVF creation is chosen by the surgeon based on preoperative diagnostics, but AVFs are still compromised by flow-associated complications. Previously, it was shown that a computational 1D-model is able to describe pressure and flow after AVF surgery. However, predicted flows differed from measurements in 4/10 patients. Differences can be attributed to inaccuracies in Doppler measurements and input data, to neglecting physiological mechanisms or to an incomplete physical description of the pulse wave propagation after AVF surgery. The physical description can be checked by validating against an experimental setup consisting of silicone tubes mimicking the aorta and arm vasculature both before and after AVF surgery, which is the aim of the current study. In such an analysis, the output uncertainty resulting from measurement uncertainty in model input should be quantified. The computational model was fed by geometrical and mechanical properties collected from the setup. Pressure and flow waveforms were simulated and compared with experimental waveforms. The precision of the simulations was determined by performing a Monte Carlo study. It was concluded that the computational model was able to simulate mean pressures and flows accurately, whereas simulated waveforms were less attenuated than experimental ones, likely resulting from neglecting viscoelasticity. Furthermore, it was found that in the analysis output uncertainties, resulting from input uncertainties, cannot be neglected and should thus be considered.

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1. Introduction

Hemodialysis is a common treatment for end-stage renal disease (ESRD) patients (Lameire et al., 2005; Grassman et al., 2005). To facilitate hemodialysis, a well-functioning vascular access is needed. The vascular access should be able to provide a high blood flow and should be easily accessible for repeated cannulation over time (Allon and Robbin, 2002; Tordoir and Mickley, 2003). The preferred vascular access is an arteriovenous fistula (AVF) in the arm, which is a surgically created connection between an artery and vein (anastomosis), resulting in a significant flow increase (up to 30-fold) and vessel remodeling (Allon and Robbin, 2002; Tordoir and Mickley, 2003; Bakran et al., 2003; Tordoir et al., 2003; Access Work Group, 2006).

The AVF is usually created three months prior to initiation of hemodialysis either at wrist level (lower arm AVF) or at elbow level (upper arm AVF) (Dammers, 2003; Tordoir et al., 2004; Wijnen et al., 2005; Robbin et al., 2002). In the current clinical practice, the selection is based on the patient's medical history and the caliber of the involved vessels, i.e. when the caliber of the radial artery and the distal cephalic vein assessed by duplex ultrasound exceed 2 mm a lower arm AVF is created, otherwise an upper arm AVF. Despite the preoperative diagnostics, lower arm AVFs are hampered by non-maturation in up to 50% of all cases and upper arm AVFs by long-term complications like distal ischemia and/or cardiac failure in 20% of all cases (Allon and Robbin, 2002; Tordoir and Mickley, 2003; Bakran et al., 2003; Tordoir et al., 2003; Access Work Group, 2006; Tordoir et al.,

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http://dx.doi.org/10.1016/j.jbiomech.2012.03.028
To reduce the number of complications and optimize surgical decision-making, tools to optimize the location for an individual patient are of interest. Because a too low brachial flow directly after surgery is associated with non-maturation (Tordoir et al., 2003; Shemesh et al., 2007) and a postoperative flow larger than 30% of the cardiac output is associated with distal ischemia and cardiac failure (Dammers, 2003; Tordoir et al., 2004; Wijnen et al., 2005; Robbin et al., 2002), these tools should aim at providing, preoperatively, a quantitative patient-specific estimate for the immediate postoperative flow.

Previously, a pulse wave propagation model was developed that is able to simulate pressure and flow waveforms after upper and lower arm AVF surgery (Huberts et al., 2012). This computational model that is fed by patient-specific data was used to predict immediate postoperative mean flows in 10 ESRD patients. It was shown that the model selected the same AVF location as an experienced surgeon in 9 out of 10 patients. However, the postoperative flow measured by Doppler ultrasound was only adequately predicted in 6 out of 10 patients. Differences between model predictions and measurements might have several reasons. First, the accuracy of the measured flows, input data and boundary conditions might limit the correspondence between the simulated and measured flows. Second, the model neglects vascular adaptation and autoregulation of the peripheral bed which might result in differences between measured and predicted flows. A third reason might be that the physical description of the pulse wave propagation of the pressures and flows is incomplete. The way to determine if the physical description is complete, is by validating the pulse wave propagation model with an experimental setup which mimics the surgical AVF procedure and gives the possibility to determine a larger number and more accurate mechanical, geometrical and hemodynamic (pressure and flow waveforms) data than would be possible in an in vivo situation (Reymond et al., 2011; Matthys et al., 2007). In addition, vascular adaptation and regulation of the peripheral beds are excluded and do not influence the comparison of experimental and simulation results. Besides, an experimental setup can be used to validate the waveforms of the simulated pressures and flows which are needed when adaptation laws will be included in future work.

For arteries, in vivo and experimental validation studies for pulse wave propagation models (Reymond et al., 2011; Matthys et al., 2007; Reymond et al., 2009; Bessems et al., 2008; Swillens et al., 2008) have been performed previously. However, these studies mainly focused on the systemic arterial tree with arterial flows much smaller than the flow after AVF creation. No validation study is reported that validates a pulse wave propagation model simulating the extreme flow increase after AVF surgery. In addition, the hemodynamical complex anastomosis was not addressed earlier in a silicone tube network. Moreover, the propagation of measurement uncertainty in the model input to uncertainty in the model output (i.e. precision) was not analyzed previously. However, a quantitative estimate of the precision is required for a proper comparison between simulations and measurements. The output uncertainty can be assessed by using a method based on generalized chaos expansion (Xiu and Sherwin, 2007) or by means of Monte Carlo simulations (Robert and Casella, 2000). The advantage of the method of Xiu et al. is that less model runs are needed than for Monte Carlo simulations. However, the implementation is less straightforward since the model equations are made stochastic and the most suitable polynomials for expansion of the stochastic function need to be selected. As a result, Monte Carlo simulations are more intuitive and therefore used in this study.

The aim of this study is thus to validate the previously developed pulse wave propagation model for the prediction of pressure and flow before and after AVF creation. In this way, it is determined if the physical description of the pulse wave propagation is correctly captured by the model. The uncertainty in pressure and flow waveforms, resulting from uncertainties in the model input parameters, is accounted for by using Monte Carlo simulations.

The manuscript is outlined as follows. First, the experimental setup is described, followed by a brief description of the pulse wave propagation model. Next, how the model was adapted to the experimental conditions and how the model was validated with the experimental setup are discussed. In this context, the uncertainty analysis is described in detail.

2. Materials and methods

2.1. The experimental model

2.1.1. In vitro experimental setup

In this study, a pulse wave propagation model is validated that simulates the flow increase after AVF surgery. The experimental silicone tube model, mimicking the anatomy and physiology of the human vasculature in the arm, was built based on patient-specific data obtained in a previous study (Huberts et al., 2012). The arterial geometrical data, obtained from magnetic resonance (MR) and ultrasound (US) examinations, were used to generate a three-dimensional (3D) CAD-model which was used as a benchmark for manufacturing the 3D silicone tube model. For the construction of the silicone arterial model, Rapid Prototype models and dip-coating techniques were used (in-house techniques and knowledge). The venous silicone model, representing the venous outflow tract, was based on geometrical data obtained from US measurements of an ESRD patient and was constructed by painting silicone, layer by layer, on a steel rod (Van Canneyt et al., 2010b). This technique was chosen over dip-coating techniques as it was expected to result in lower wall thicknesses and thus lower stiffness. To mimic the AVF, the arterial and venous silicone models were connected by an anastomosis with an aperture of approximately 15 mm² and an in-plane angle of 30°. The resulting silicone network model consisted of the brachial, radial, ulnar and interosseous artery (arterial tract) and the cephalic, basilic, axillary and subclavian vein (venous tract).

This network model was built in a mock loop (van’t Veer et al., 2009; Beulen et al., 2011) including a silicone aorta and subclavian artery constructed by Hemolab B.V. (Eindhoven, The Netherlands) (Fig. 1, top). The arterial and venous...
silicone network was placed in a water tank to allow for ultrasound measurements. The complete circulation circuit was filled with water and the water was pumped through the mock loop by a step pump (Parker Hannifin GmbH; Offenburg, Germany) that was regulated by a normalized modified sinus-squared ISO5840 function (Fig. 2) in LabView (National Instruments Inc., version 7.1, Austin, TX, USA). This resulted in a pump flow rate of approximately 5 l/min which is comparable to a physiological cardiac output (Guyton and Hall, 1996). The fluid entered the proximal aorta via a flexible valve (Hemolab B.V) and could thereafter flow in two directions: to the distal aorta which was closed by a windkessel and to the subclavian artery which was the inflow artery of the silicone network model. This silicone network model had three outflows in the arterial part (at radial, ulnar and interosseous artery) and one in the venous part (at the subclavian vein). For mimicking the preoperative situation, the venous outflow was closed with a clamp, whereas for the postoperative situation the clamp was released to mimic the presence of a lower arm AVF. The lower arm AVF was chosen because it involves the largest arterial and venous network and thus the most complex topology was studied.

Details on the measurement techniques can be found in Appendix A.

2.2. The mathematical model

The pulse wave propagation model used here was previously developed by Huberts et al. (2012), and will only be described in short. The computational domain for the simulations consisted of a truncated part of the aorta, the subclavian, brachial, radial, ulnar and interosseous arteries, the anastomosis, the cephalic, median cubital, basilic, axillary and subclavian veins, and, in addition, all connecting tubes (Fig. 1, bottom). The vessels were divided into segments. In each segment the local relation between pressure and flow is described. For the scope of modeling, the effect of vascular access creation on blood pressure and flow distribution, segments are needed that represent arteries, veins and the anastomosis. All arterial and venous segments were modeled with a lumped parameter model derived from local mass and momentum equations (see Appendix B). The anastomosis segment was modeled with a nonlinear resistance based on two semi-empirical loss coefficients, $K_v$ and $K_d$, that describe the loss from the

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### Table 1

All input data for the wave propagation model that are derived from measurements on the experimental setup. The mean pressure, mean flow and time constant are only given for the edges that are closed by a windkessel segment. In brackets the estimated measurement uncertainty is given in percentages. The vessels that are changed simultaneously during the uncertainty analysis are grouped in one cell.

<table>
<thead>
<tr>
<th>Edge name</th>
<th>Edge number</th>
<th>Length (mm)</th>
<th>Diameter (mm)</th>
<th>Distensibility (Pa$^{-1}$)</th>
<th>Mean flow (ml/min)</th>
<th>Mean pressure (mmHg)</th>
<th>Time constant (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigid connecting element</td>
<td>1</td>
<td>50 (5%)</td>
<td>28.9 (10%)</td>
<td>28.9 (10%)</td>
<td>$10^{-7}$ (-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal aorta</td>
<td>2</td>
<td>150 (5%)</td>
<td>28.9 (10%)</td>
<td>28.9 (10%)</td>
<td>$2.1 \times 10^{-5}$ (15%)</td>
<td>4650 (10%)</td>
<td>98 (10%)</td>
</tr>
<tr>
<td>Distal aorta</td>
<td>3</td>
<td>310 (5%)</td>
<td>28.9 (10%)</td>
<td>28.9 (10%)</td>
<td>$2.1 \times 10^{-5}$ (15%)</td>
<td>4375 (10%)</td>
<td>90 (10%)</td>
</tr>
<tr>
<td>Subclavian artery</td>
<td>4</td>
<td>100 (5%)</td>
<td>8.0 (10%)</td>
<td>8.0 (10%)</td>
<td>$7.7 \times 10^{-6}$ (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigid (tapered) connecting tube</td>
<td>5</td>
<td>60 (5%)</td>
<td>8.0 (10%)</td>
<td>10 (10%)</td>
<td>$10^{-7}$ (-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliant connecting tube</td>
<td>6</td>
<td>130 (5%)</td>
<td>10 (10%)</td>
<td>10 (10%)</td>
<td>$1.1 \times 10^{-6}$ (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigid connecting tube</td>
<td>7</td>
<td>80 (5%)</td>
<td>10 (10%)</td>
<td>10 (10%)</td>
<td>$10^{-7}$ (-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliant (tapered) connecting</td>
<td>8</td>
<td>20 (5%)</td>
<td>10 (10%)</td>
<td>6.0 (10%)</td>
<td>$1.1 \times 10^{-6}$ (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigid connecting tube</td>
<td>9</td>
<td>55 (5%)</td>
<td>6.0 (10%)</td>
<td>6.0 (10%)</td>
<td>$10^{-7}$ (-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial artery</td>
<td>10</td>
<td>215 (5%)</td>
<td>6.0 (10%)</td>
<td>4.5 (10%)</td>
<td>$1.7 \times 10^{-5}$ (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal ulnar artery</td>
<td>11</td>
<td>67 (5%)</td>
<td>3.6 (10%)</td>
<td>3.6 (10%)</td>
<td>$1.1 \times 10^{-6}$ (15%)</td>
<td>46 (10%)</td>
<td>96 (10%)</td>
</tr>
<tr>
<td>Distal ulnar artery</td>
<td>12</td>
<td>173 (5%)</td>
<td>2.7 (10%)</td>
<td>1.9 (10%)</td>
<td>$1.7 \times 10^{-5}$ (15%)</td>
<td>42 (10%)</td>
<td>88 (10%)</td>
</tr>
<tr>
<td>Interosseous artery</td>
<td>13</td>
<td>110 (5%)</td>
<td>1.3 (10%)</td>
<td>1.3 (10%)</td>
<td>$1.1 \times 10^{-5}$ (15%)</td>
<td>5 (10%)</td>
<td>98 (10%)</td>
</tr>
<tr>
<td>Radial artery</td>
<td>14</td>
<td>240 (5%)</td>
<td>3.4 (10%)</td>
<td>3.2 (10%)</td>
<td>$1.5 \times 10^{-5}$ (15%)</td>
<td>50 (10%)</td>
<td>96 (10%)</td>
</tr>
<tr>
<td>Cephalic vein lower arm</td>
<td>15</td>
<td>210 (5%)</td>
<td>2.9 (10%)</td>
<td>3.0 (10%)</td>
<td>$1.4 \times 10^{-5}$ (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalic vein upper arm</td>
<td>16</td>
<td>180 (5%)</td>
<td>4.3 (10%)</td>
<td>4.3 (10%)</td>
<td>$2.4 \times 10^{-5}$ (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subclavian vein</td>
<td>17</td>
<td>32 (5%)</td>
<td>5.6 (10%)</td>
<td>5.6 (10%)</td>
<td>$8.4 \times 10^{-6}$ (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median cubital vein</td>
<td>18</td>
<td>30 (5%)</td>
<td>4.5 (10%)</td>
<td>4.5 (10%)</td>
<td>$8.4 \times 10^{-6}$ (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basilic vein</td>
<td>19</td>
<td>180 (5%)</td>
<td>4.5 (10%)</td>
<td>4.6 (10%)</td>
<td>$8.4 \times 10^{-6}$ (15%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Assumed value for the rigid tubes.
* Estimated from static volume compliance measurements.
proximal artery to, respectively, the proximal vein and the distal artery and have been defined by Gardel (1957a,b).

Parts of the cardiovascular system, for which no detailed information on pressure and flow was required, were truncated and terminated with three-element windkessel models (Westerhof, 1971). Assembling all lumped segments resulted in a system of differential equations that describes the pulse wave propagation of the pressure and flow waveforms. This system was solved by numerical integration applying the trapezium rule for implicit time integration. On the first node, a measured (aortic) flow was prescribed, whereas the venous outflow was closed with a fixed intravenous pressure.

The pressure and flow waveforms simulated by the pulse wave propagation model were validated with experimentally derived pressure and flow waveforms. The input parameters of the pulse wave propagation model were thus adapted to the experimental setup. For this, geometrical (vessel length, vessel diameters) and mechanical characteristics of the vessels (vascular compliance) were used. Furthermore, information on anastomosis configuration (location, angle), windkessel parameters, fluid properties (density and dynamic viscosity), intravenous pressure and an input (aortic) flow waveform were required.

### 2.3. Experimental validation: experiment versus pulse wave propagation model

Simulations with the pulse wave propagation model were performed for both the pre- and postoperative configuration. To examine the propagation of input uncertainty to the output, Monte Carlo simulations were performed. Varying all input parameters independently within their uncertainty domain might result in non-physiological combinations of input parameters and thus non-physiological output (e.g. a small artery continuing in a larger artery). Therefore, the input parameters of adjacent vessels were changed simultaneously (Table 1). This resulted in 44 independent input parameters for the preoperative configuration and 58 parameters for the postoperative configuration. Input samples were generated by Latin Hypercube sampling, i.e. for each input variable, its previously defined uncertainty domain is divided into equiprobable intervals and within each interval a value is randomly selected. Consequently, an input value is used only once for each interval and a full coverage of the parameter input space is obtained (McKay et al., 1979). One sample is thus a point in the input parameter space. The total number of samples generated was 5000 times the total number of input parameters in analogy with Huberts et al. (submitted for publication).

For the preoperative configuration, the simulated pressure waveforms in the aorta, the proximal and distal brachial artery, the proximal and distal radial artery and the proximal ulnar artery were compared to the measured pressure waveforms (Fig. 1, bottom). This was extended by the distal and proximal cephalic vein, and the basilic vein for the postoperative configuration. The flow waveforms were compared at proximal aorta and subclavian artery. For comparisons, the median of the simulated pressure and flow waveforms of all Monte Carlo simulations was used as well as a confidence interval, formed by the 25th and 75th percentile interval.

### 3. Results

#### 3.1. Preoperative results

Table 2 shows that the simulated mean flows correspond to the measured mean flows in the aorta, subclavian artery, the radial artery and the ulnar artery. The shapes of the simulated aorta and subclavian artery flow waveforms correspond to the measured flow waveforms, though the simulated subclavian artery flow appears less attenuated (Fig. 3). For all arteries, simulated and measured mean pressures are similar (Table 2). The shapes of the simulated pressure waveforms (Fig. 3) correspond to the measured pressure waveforms, although the simulated pressures are less attenuated resulting in a more pronounced second peak, which is clearer in distal pressure waveforms. For the aortic pressure waveform, a phase difference of approximately 50 ms is observed. Presumably, the timing of the measured aortic pressure waveform is inaccurate as the systolic pressure peak arrives before the flow peak.

#### 3.2. Postoperative results

During the analysis of the postoperative results, it was observed that, in first instance, the resistance in the distal cephalic vein was not properly determined. After excising the distal cephalic vein from the setup, a non-smooth vessel lumen that was twisted over the full length was found resulting in a large pressure drop of 24 mmHg from the distal cephalic vein to the proximal cephalic vein (Table 3). This pressure drop was approximately 10 times larger than the expected pressure drop as calculated from Poiseuille’s law. As this additional pressure drop was not captured by the model, all Monte Carlo simulations were performed once more with a 10-fold increased resistance in the distal cephalic vein with an uncertainty of ±10%. Since vessel abnormalities could also be present in human vasculature and the resulting additional pressure drop has significant effect, the results of both analyses, with and without the extra resistance, are given in Table 3.

When considering the additional resistance of the distal cephalic vein, the simulated mean flow of the subclavian artery and the distal cephalic vein in Table 3 now corresponds to the measured mean flow. Besides a better agreement between measured and simulated flows, this is also the case for pressures. In Table 3, it can be observed that the previous observed underestimation of the measured mean arterial flows and pressures are reduced, while measurements and simulations now coincide. This especially holds for the distal cephalic vein pressure. As in the preoperative simulations, the simulated arterial pressure waveforms (Fig. 4) are less attenuated than the experimentally measured ones. In addition, a similar phase difference in the aorta is observed. The shape of the measured and simulated venous pressure waveforms (Fig. 5) is similar, although the differences are larger than for the arterial site, i.e. a phase difference of approximately 50 ms in the proximal cephalic and basilic vein.

### Table 2

<table>
<thead>
<tr>
<th>Vascular location</th>
<th>Mean pressure (mmHg)</th>
<th>Mean flow (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal aorta</td>
<td>95</td>
<td>93 (88,99)</td>
</tr>
<tr>
<td>Subclavian artery</td>
<td>98</td>
<td>93 (88,99)</td>
</tr>
<tr>
<td>Proximal brachial artery</td>
<td>98</td>
<td>93 (88,99)</td>
</tr>
<tr>
<td>Distal brachial artery</td>
<td>98</td>
<td>93 (87,99)</td>
</tr>
<tr>
<td>Proximal radial artery</td>
<td>98</td>
<td>93 (87,99)</td>
</tr>
<tr>
<td>Distal radial artery</td>
<td>98</td>
<td>92 (86,99)</td>
</tr>
</tbody>
</table>

[a] Measured value without uncertainty interval.
[b] Median value with 25th and 75th percentiles.
In this study, we aimed to experimentally validate a previously developed pulse wave propagation model for the prediction of pressure and flow before and after AVF creation, thus to analyze the physical description of the pulse wave propagation model. Experimental setups have previously been used to validate pulse wave propagation models, but not in the situation after AVF creation.

**Fig. 3.** The preoperative pressure and flow waveforms on several arterial locations.

**Table 3**
Measured postoperative mean pressures and flows and their simulated values.

<table>
<thead>
<tr>
<th>Vascular location</th>
<th>Mean pressure [mmHg]</th>
<th>Mean flow [ml/min]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Measured</td>
<td>Simulated</td>
</tr>
<tr>
<td>Proximal aorta</td>
<td>90</td>
<td>83 (79,88)</td>
</tr>
<tr>
<td>Subclavian artery</td>
<td>378</td>
<td>508 (422,594)</td>
</tr>
<tr>
<td>Proximal brachial artery</td>
<td>90</td>
<td>83 (78,87)</td>
</tr>
<tr>
<td>Distal brachial artery</td>
<td>90</td>
<td>81 (76,87)</td>
</tr>
<tr>
<td>Proximal ulnar artery</td>
<td>88</td>
<td>81 (76,87)</td>
</tr>
<tr>
<td>Proximal radial artery</td>
<td>86</td>
<td>80 (75,86)</td>
</tr>
<tr>
<td>Distal radial artery</td>
<td>84</td>
<td>76 (71,82)</td>
</tr>
<tr>
<td>Distal cephalic vein</td>
<td>31</td>
<td>8.3 (7.5,9.2)</td>
</tr>
<tr>
<td>Proximal cephalic vein</td>
<td>7.0</td>
<td>6.0 (5.8,6.2)</td>
</tr>
<tr>
<td>Basilic vein</td>
<td>6.0</td>
<td>6.0 (5.8,6.2)</td>
</tr>
<tr>
<td>Subclavian vein</td>
<td>5.7d</td>
<td>5.7d</td>
</tr>
</tbody>
</table>

- Measured value without uncertainty interval.
- Median value with 25th and 75th percentiles.
- Flow split percentages through proximal cephalic and basilic vein unknown.
- Prescribed intravenous pressure.

4. Discussion

In this study, we aimed to experimentally validate a previously developed pulse wave propagation model for the prediction of pressure and flow before and after AVF creation, thus to analyze the physical description of the pulse wave propagation model. Experimental setups have previously been used to validate pulse wave propagation models, but not in the situation after AVF creation.
surgery when flows are significantly increased compared to normal and the anastomosis is included. Bessems et al. (2008) have validated their pulse wave propagation model with both a straight and tapered viscoelastic silicone tube. Swillens et al. (2008) used a silicone setup to validate their pulse wave propagation model in an aneurysm case study. An experimental setup that included a more detailed representation of the arterial tree and thus also physiological wave reflections resulting from bifurcations was used by Matthys et al. (2007). Next to these experimental validations, Reymond et al. performed, recently, an in vivo validation of a patient-specific pulse wave propagation model of the systemic arterial tree (Reymond et al., 2009, 2011). However, although geometry, flow and pressure measurements were all performed on one individual patient, it was impossible to measure all input parameters patient-specifically. Thereby, pressure and flow measurements are only possible on a limited number of positions over the systemic tree (Matthys et al., 2007; Reymond et al., 2009, 2011). In addition, clinical measurements are usually hampered by large measurement uncertainties, which were not considered in any of the studies.

In contrast to these studies, in this work the uncertainty of the model input was taken into account, yielding an estimation of the precision on the pressure and flow waveforms. The 25th-to-75th percentile interval captured a decrease or increase ranging, dependent on location, from 2% to 14% of the median value for the mean pressures, while for the mean flow uncertainties larger uncertainties were observed. Preoperatively, the uncertainties of the mean flows in the subclavian artery, the radial artery and the ulnar artery were respectively 60%, 20% and 30%, while postoperatively the uncertainties of flows in these vessels were about 17%, 20% and 25%. The uncertainty in mean flow in the distal cephalic vein was approximately 13%. Considering precision is thus essential in validation studies. The large uncertainties in mean flows can be explained by the fact that the flow waveform oscillates around 0 which means that a small deviation in the waveform will result in a significant change in mean flow. Clinically, an uncertainty of approximately 20% in the mean flow in the subclavian/brachial artery is acceptable because the surgeon aims at an inflow of 400–500 ml/min while 300 ml/min is sufficient for proper hemodialysis treatment.

For adequate postoperative simulations, it was needed to incorporate the additional pressure drops resulting from structures such as twisting or kinking in the computational model. For this, a clear picture of the vascular topology is required. Clinically, this can be obtained by using MR or ultrasound.

The experimental setup constructed for this study allowed for model validation, since we were able to mimic flow enhancement after AVF creation and since all measured pressure and flow waveforms were comparable to physiological ones (Strandness

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**Fig. 4.** The postoperative pressure and flow waveforms on several arterial locations for simulations with additional resistance.
and Sumner, 1975; Nichols and O'Rourke, 1998). The mean pressures and flows, both arterial and venous, simulated by the pulse wave propagation model, were adequately predicted and the overall shape of the pressure and flow waveforms was similar. However, the simulated waveforms were less attenuated than the measured ones, indicating that introduction of viscoelasticity might improve the computational model's capability to describe the physical phenomena. Previous studies (Reymond et al., 2009; Matthys et al., 2007; Swillens et al., 2008) already showed that a pulse wave propagation model is able to simulate pressure and flow waveforms in elastic arteries and that the introduction of viscoelasticity improves the simulations (Alastruey et al., 2011; Reymond et al., 2011; Bessems et al., 2008; Raghu et al., 2011; Steele et al., 2011). Since viscoelasticity is observed in human arteries (Learoyd and Taylor, 1966; Imura et al., 1990), including viscoelasticity in the model for patient-specific modeling, is required when the waveforms are of interest.

However, even after incorporating viscoelasticity into the pulse wave propagation model, which results in a better description of the physical phenomena, clinical implementation might still be challenging. The reason for this is that the model needs to be adapted to patient-specific conditions which require patient-specific model input parameters. Clinically, it is difficult to determine these parameters accurately due to limitations in measurement modalities or because the burden on the patient should be minimized. Fortunately, a sensitivity analysis can be applied to the model to determine which model input parameters are most important to assessed. Consequently, the number of required patient-specific measurements can significantly be reduced (Huberts et al., submitted for publication).

Another challenge is including vascular adaptation (e.g. flow-mediated dilatation, maturation) and regulation (e.g. autoregulation of the peripheral bed) in the model. These physiological mechanisms should be especially introduced when the (long-term) adaptation of a vascular access is of interest. The current model is only aiming at predicting mean flows directly after surgery.

5. Conclusion

The pulse wave propagation model was successfully validated with an experimental setup, mimicking pressure and flow changes following an AVF creation. Mean pressures and flows were adequately predicted and the overall shape of the pressure and flow waveforms was similar for the experiment and measurement. However, the experimental waveforms were more attenuated most likely resulting from neglecting viscoelasticity in the model. Furthermore, it was found that the uncertainties in model input parameters significantly influenced the output and should thus be taken into consideration in the analysis.

Conflict of interest statement

All the authors have been involved in the design of the study and the interpretation of the data and they concur with its content. There are no conflicts of interest between the authors of this paper and other external researchers or organisations that could have inappropriately influenced this work.

Acknowledgments

The authors acknowledge the Maastricht University Medical Center Profileringsfonds, the Belgian Fund for Research Flanders (FWO-Vlaanderen) and the European Commission Seventh framework programme (ARCH ICT-224390) for their funding. Furthermore, we acknowledge N. Bijnens, PhD, and M.C.M. Rutten, PhD, from Eindhoven University of Technology for their support during the experiments and C. de Jonge, BSc, from Philips Research Laboratories Eindhoven, for his help with developing the computational framework used for the Monte Carlo simulations. Finally, we also acknowledge J. Deviche from Ghent University for his support during the creation of the experimental model and K. Van...
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