The Groningen hypothermic liver perfusion system for improved preservation in organ transplantation
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2005

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 3

Numerical Simulation of the Hepatic Circulation

Published in the International Journal of Artificial Organs 2004; 27: 222-30.

3.1 Introduction

Over the past decades liver transplantation has become a routine mode of therapy for patients suffering from end stage liver disease. To bridge the timespan between donor hepatectomy and transplantation, livers are nowadays routinely preserved by static cold storage (CS) which implies that the liver is flushed in situ with cold preservation solution and after hepatectomy the liver is stored in the same solution at 0-4°C. Using the CS technique allows a liver preservation time of approximately 12 hours\textsuperscript{1,2} which is relatively short and requires transplantation on a semi-emergency basis. Another method to store organs is hypothermic machine perfusion (HMP) which was first introduced by Belzer in the sixties for kidney preservation\textsuperscript{3,4}. The advantage of HMP over CS is the continuous wash-out of waste products and supply of nutrients and therefore it might offer a better preservation for the liver than CS\textsuperscript{5}. During HMP, the liver is continuously perfused with a cold preservation solution via the portal vein and/or the hepatic artery. To define an optimal setting for liver HMP several difficulties have to be considered. It has been observed that during HMP of kidneys with a cold preservation solution (0-4°C) vasoconstriction occurs and vascular compliance decreases. This could
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also play a role in liver HMP. Furthermore, by using a cold preservation solution, such as the University of Wisconsin (UW)-solution\textsuperscript{6}, viscosity increases compared to viscosity of blood at 37°C\textsuperscript{7,8}. Consequently, these features do not allow a definition of optimal perfusion pressure and flow by simply applying physiological values. Also, the optimal perfusion technique for the liver has not been determined yet, i.e. simple venous perfusion versus arterial perfusion or versus venous and arterial perfusion. Using hypothermic machine perfusion only via the portal vein has shown good survival rates after 72 hours HMP in the dog liver transplant model\textsuperscript{9}. Including a hepatic arterial perfusion, however, could be advantageous since now the biliary arterial tree is perfused as well, thus possibly preventing ischemic lesions in the bile ducts\textsuperscript{10}. In addition, contradictory results have been obtained regarding the benefits of pulsatile perfusion over continuous perfusion. Pienaar et al\textsuperscript{9} successfully preserved dog livers for 72 hours using hypothermic machine preservation via the portal vein using pulsatile perfusion. Yamamoto et al\textsuperscript{11} achieved comparable results using non-pulsatile perfusion of the portal vein. Also, hypothermic machine perfusion through the hepatic artery has been reported using either pulsatile perfusion\textsuperscript{12,13,14} or continuous perfusion\textsuperscript{15,16}. Since studies comparing both perfusion strategies do not exist, it is not clear whether a combination of arterial and portal perfusion characteristics is beneficial over portal perfusion alone.

The possibility to predict the effects of temperature, viscosity and perfusion characteristics on the (micro)circulation and thus define the setting of HMP would constitute an excellent tool in defining optimal characteristics for liver HMP. It furthermore could be helpful in better understanding microvascular changes due to injury.

Several methods, such as intra-vital microscopy\textsuperscript{17} and contrast-enhanced magnetic resonance imaging\textsuperscript{18} enable the visualisation of the superficial hepatic circulation and determination of peripheral and sinusoidal flow under various conditions. However, besides substantial costs, these procedures are time consuming and at the expense of many laboratory animals. Another approach in the attempt to approximate the optimal pressure and flow is numerical modelling. With numerical modelling quantitative data concerning the (micro)circulation, that can not be measured in vivo, are obtained by solving the equations of fluid dynamics of perfusion pressure and resulting flow.

As it is our goal to develop an appropriate hypothermic liver perfusion system, a numerical simulation model is desirable to better define the optimal
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3.2.1 Model

The liver is supplied with blood from both the portal vein and the hepatic artery. The portal vein, with a mean continuous blood pressure of 12 mmHg, supplies the liver with blood from the intestines, and contributes 2/3 of the perfusion of the liver. The hepatic artery, with a pulsatile blood pressure of 120/80 mmHg provides an additional blood supply to the liver sinusoids, vessel walls, as well as the biliary tree, and is an important factor in maintaining vessel structure and integrity of bile ducts\(^{10}\). Both afferent blood vessel systems join in the proximal sinusoids and the blood leaves the liver through the hepatic veins towards the inferior caval vein (Figure 3.1). The three distinguished vascular compartments (portal venous, hepatic arterial and hepatic venous) including their numerous branches can be seen as a cascade of generations of parallel blood vessels (Figure 3.1). With this approach the total hepatic vascular tree can be modelled as a series connection of 23 generations of blood vessels: seven generations for the portal venous system, eight for the arterial system, one representing the sinusoids and seven representing the hepatic vein.

The Navier-Stokes equations describe the fluid dynamics (blood) in an elastic tube (blood vessel). De Pater et al\(^{19,20}\) translated the Navier-Stokes equations into four components of a \(\pi\)-filter (Figure 3.2). The four components \((R_s, L, C, R_p)\) represent the longitudinal steady flow resistance of the blood vessel, the inertia of the blood, the vessel compliance and the vessel wall visco-elasticity, respectively. For modelling purposes some assumptions were required\(^{19,20}\). The presence of laminar flow was assumed. Blood was considered to be incompressible and have a constant density and viscosity (Newtonian). Influences of tube diameter on apparent viscosity (Fahreus-Lindqvist effect) were neglected. Vessel wall material was assumed to be homogeneous, isotropic and to follow Hooke’s law (linear elastic). In addition, the thickness of the wall was considered to be much smaller than the inner radius of the vessel (thin-walled vessel). With these assumptions the components of the \(\pi\)-filter then become\(^{19,20}\):
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Figure 3.1: Schematic presentation of the hepatic vasculature.
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Figure 3.2: Analogue of a blood vessel represented as a \( \pi \)-filter, including \( R_s \) as the resistance to flow, \( L \) as the inertia of blood, \( C \) as the compliance and \( R_p \) as the visco-elasticity.

\[
R_s = \frac{8\eta l}{\pi r^4} \quad \text{[Ns]} \quad \text{(3.1)}
\]
\[
L = \frac{1.33\rho l}{\pi r^2} \quad \text{[Ns]} \quad \text{(3.2)}
\]
\[
C = \frac{l^2}{2\zeta^2 L} \quad \text{[m]} \quad \text{(3.3)}
\]
\[
R_p = 4 \times 10^{-6} \frac{C}{N} \quad \text{[Ns]} \quad \text{(3.4)}
\]

in which \( \eta \) is the dynamic viscosity of the blood [Pa\cdot s], \( l \) the length of the blood vessel [m], \( r \) the radius of the blood vessel [m], \( \rho \) the density of the blood [kg/m\(^{-3}\)] and \( c_p \) the pulse wave velocity [m/s]. As each generation of blood vessels in the hepatic vascular tree was represented by one \( \pi \)-filter, the total hepatic circulation could then be modelled as a series connection of \( \pi \)-filters. Consequently, the number of parallel vessels within each generation was taken into account by dividing the components of that particular \( \pi \)-filter (i.e. \( R_s \), \( L \), \( C \), \( R_p \)) by the number of parallel vessels\(^2\) (Figure 3.3).

To define the four components of each of the \( \pi \)-filters pertinent data concerning number of parallel branches, mean radius and length of the branch and density, viscosity and pulse wave velocity of blood is required. Data that deal with the number of generations, number of parallel vessels in each generation and the radii of the vessels are rare, but have been described for dog livers by Mall\(^2\). The length of the vessels in each generation was estimated from data of arteries, as summarized by Green\(^2\). The pulse wave velocities were estimated according to...
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Figure 3.3: Schematic representation of the electrical analogue of the hepatic circulation.

<table>
<thead>
<tr>
<th>Vessels</th>
<th>Number</th>
<th>Radius $r$ [10^{-3} \text{ m}]</th>
<th>Length $l$ [10^{-3} \text{ m}]</th>
<th>Pulse wave velocity $c_p$ [10^{-3} \text{ m/s}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal vein</td>
<td>1</td>
<td>4.5</td>
<td>50</td>
<td>3000</td>
</tr>
<tr>
<td>1^{st} order branches</td>
<td>6</td>
<td>2.5</td>
<td>100</td>
<td>3600</td>
</tr>
<tr>
<td>2^{nd} order branches</td>
<td>70</td>
<td>0.85</td>
<td>40</td>
<td>4200</td>
</tr>
<tr>
<td>3^{rd} order branches</td>
<td>700</td>
<td>0.4</td>
<td>14</td>
<td>4800</td>
</tr>
<tr>
<td>4^{th} order branches</td>
<td>8000</td>
<td>0.2</td>
<td>1</td>
<td>5400</td>
</tr>
<tr>
<td>5^{th} order branches</td>
<td>800000</td>
<td>0.075</td>
<td>1.5</td>
<td>6000</td>
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<td>960000</td>
<td>0.025</td>
<td>2</td>
<td>6600</td>
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<tr>
<td>Sinusoids</td>
<td>1850000000</td>
<td>0.004</td>
<td>0.5</td>
<td>7000</td>
</tr>
<tr>
<td>6^{th} order branches</td>
<td>480000</td>
<td>0.045</td>
<td>2</td>
<td>6600</td>
</tr>
<tr>
<td>5^{th} order branches</td>
<td>80000</td>
<td>0.085</td>
<td>1.5</td>
<td>6000</td>
</tr>
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<td>1</td>
<td>5400</td>
</tr>
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<td>3^{rd} order branches</td>
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<td>0.5</td>
<td>14</td>
<td>4800</td>
</tr>
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<td>2^{nd} order branches</td>
<td>70</td>
<td>1</td>
<td>40</td>
<td>4200</td>
</tr>
<tr>
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<td>7</td>
<td>2.5</td>
<td>100</td>
<td>3600</td>
</tr>
<tr>
<td>Hepatic vein</td>
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<td>5.5</td>
<td>50</td>
<td>3000</td>
</tr>
<tr>
<td>Hepatic artery</td>
<td>1</td>
<td>1.375</td>
<td>50</td>
<td>5000</td>
</tr>
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<td>1^{st} order branches</td>
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<td>0.59</td>
<td>150</td>
<td>5250</td>
</tr>
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<td>2^{nd} order branches</td>
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<td>0.4</td>
<td>100</td>
<td>5500</td>
</tr>
<tr>
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<td>0.15</td>
<td>40</td>
<td>5750</td>
</tr>
<tr>
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<td>14</td>
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<td>6250</td>
</tr>
<tr>
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<td>0.01</td>
<td>1.5</td>
<td>6500</td>
</tr>
<tr>
<td>7^{th} order branches</td>
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<td>0.005</td>
<td>2</td>
<td>6750</td>
</tr>
<tr>
<td>Sinusoids</td>
<td>1850000000</td>
<td>0.004</td>
<td>0.5</td>
<td>7000</td>
</tr>
</tbody>
</table>

Table 3.1: Geometric data for the vascular tree of the dog liver.
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data summarized by Millnor\textsuperscript{23}. Values are listed in Table 3.1. Blood density is 1050 kg/m\textsuperscript{3} and viscosity 3.5·10\textsuperscript{-3} Pa·s\textsuperscript{23}.

<table>
<thead>
<tr>
<th>Standard hemodynamic units</th>
<th>Electrical analogue units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance</td>
<td>10\textsuperscript{5} (\frac{Ns}{m^2})</td>
</tr>
<tr>
<td>Time</td>
<td>1 s</td>
</tr>
<tr>
<td>Pressure</td>
<td>1 mmHg</td>
</tr>
<tr>
<td>Flow</td>
<td>10\textsuperscript{-6} (m^3/s)</td>
</tr>
<tr>
<td>Inertia</td>
<td>10\textsuperscript{5} (\frac{Nsm^2}{m^5})</td>
</tr>
<tr>
<td>Compliance</td>
<td>10\textsuperscript{-15} (\frac{Nm^5}{N})</td>
</tr>
</tbody>
</table>

Table 3.2: Conversion of standard hemodynamic units to electrical analogue units

3.2.2 Simulation

For simulation purposes, the network of \(\pi\)-filters has been implemented in Orcad Pspice 9.2 (Cadence Design Systems Inc, San Jose CA, USA). For Pspice an electrical analogue is required so a conversion of fluid dynamical units to electrical units was performed\textsuperscript{20} (Table 3.2). A 40 ms transient simulation is performed discarding the initial equilibration time. The maximum step size was 6.67·10\textsuperscript{-6} s, the accuracy of voltages was 1 mV, the accuracy of currents 1 pA and the minimum conductance for any branch was 1·10\textsuperscript{-12} ohm\textsuperscript{-1}.

3.2.3 Boundary conditions

Since the geometric data and material properties which are used to model the liver were based on values found in 10-15 kg dogs, the boundary conditions and subsequent loading of the model were based on dog values as well\textsuperscript{24}. The hepatic arterial pressure was found to be pulsatile 120/100 mmHg, with a pulse frequency of 120 BPM (=2 Hz). According to Table 3.2, the pressure results in an AC voltage with a mean of 55 V, amplitude of 5 V and a frequency of 2000 Hz as the input signal of the arterial circuit. The pressure in the portal venous branch has been found to be a continuous 10 mmHg, which results in an input signal of 5 V DC. At the caval venous side, the pressure is decreased to 2 mmHg while the outflow is approximately 390 ml/min. These values were needed to create an end resistance to the circuit of 410 \(\Omega\), to simulate the peripheral afterload.

Next, the model was validated by comparing the flows that result from the model with flow values that have been found in literature\textsuperscript{24}.
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3.3 Results

Using the above described boundary conditions, the simulation resulted in a pressure at the inlet of the hepatic artery of 120/100 mmHg and decreased to 5 mmHg at the level of the sinusoids (Figure 3.4). The largest arterial pressure drop occurred between generation 7 and 8, just before the sinusoids. Throughout the arterial tree the pulsatile character of the pressure gradually diminished and disappeared in the sinusoids (Figure 3.5). The pressure drop from the portal vein to the sinusoids was 5 mmHg and from the sinusoids to the hepatic veins 2.3 mmHg (Figure 3.4). No pulse was present in the venous pressure profiles (Figure 3.5).

![Figure 3.4: The pressure profile in hepatic artery, portal vein and hepatic vein as a function of the branching generation.](image)

Simulating a pulsatile hepatic arterial pressure input of 120/100 mmHg resulted in a calculated mean flow at the inlet of 7.1 ml/min (Figure 3.6). This flow was highly pulsatile in the first three generations but the pulse decreased rapidly towards the sinusoids. There was even a substantial back flow in the first two generations (Figure 3.7). In the portal vein, a continuous pressure of 10 mmHg created a flow of 525.3 ml/min (Figure 3.6). Subsequently, the collective flow in the hepatic vein was the sum of arterial and portal flow, 532.4 ml/min (Figure 3.6). In both venous systems a small pulse was visible (figure 3.7).

The velocity profile could be found by dividing the flow profile by the cross-sectional area of the vessels (Figure 3.8). The mean velocity was highest in the portal vein (0.13 m/s) and decreased towards the sinusoids where the velocity was very small (1.26·10^{-6} m/s). In the hepatic venous vessels the velocity increased
3.3. Results

Figure 3.5: Pressure pulse shape in each branch of the hepatic artery (top), portal vein (middle) and hepatic vein (bottom) as a function of time.

Figure 3.6: The flow profile in hepatic artery, portal vein and hepatic vein as a function of the branching generation.
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Figure 3.7: Flow pulse shape in each branch of the hepatic artery (top), portal vein (middle) and hepatic vein (bottom) as a function of time.

again towards the hepatic vein to a value of 0.09 m/s. The velocity profile in the hepatic artery was similar to the portal venous profile.

3.4 Discussion

This study demonstrates the feasibility of analyzing hemodynamics in the hepatic (micro)vascular system utilizing a numerical simulation model. The validity of the electrical analogue we have developed is judged by the ability of the model to describe physiological pressure and flow characteristics. For this purpose, we made a qualitative comparison of the hepatic circulatory system and the total circulatory system. In the total circulatory system, the pressure profile changes with the vessel radius. The profile is pulsatile in the aorta and large arteries, but pulsatile behavior decreases with a decrease in arterial diameter. Especially, in the arterioles blood pressure decreases rapidly and the pulse diminishes entirely. The pressure subsequently decreases gradually in capillaries and veins until it reaches a minimal level in the caval vein\textsuperscript{25}.

As a consequence of the changing pressure profile and the changing vessel radius, mean blood flow velocity throughout the circulatory system is not constant. In the aorta the velocity is the highest; it gradually decreases until it reaches its lowest velocity in the capillaries, after which the velocity increases again\textsuperscript{25}.
3.4. Discussion

When the results of our simulation model of the hepatic circulation are reviewed qualitatively (Figures 3.3-3.7) the changing pressure and velocity profiles are in accordance with the profiles of the circulatory system. Maximal pressure and velocity occur at the beginning of the hepatic artery and portal vein, where the vessel radius is large. Pressure then drops in the narrowing arteries, and rapidly decreases in the arterioles while pulses disappear, a behavior comparable with the circulatory system. When veins then widen, pressure gradually drops to a minimal level while velocity increases again after reaching a minimal level in the sinusoids. We can thus conclude that our simulation model qualitatively describes the pressure and flow profiles throughout the liver satisfactorily.

A quantitative validation of the simulation model can be obtained by comparison of the resulting calculated flow values with values that are measured in vivo. Richardson and Withrington\textsuperscript{24} reviewed 27 experiments measuring hepatic arterial, portal venous and hepatic venous pressure and flow values in anaesthetised dogs. They presented control flow values in the hepatic artery, portal vein and hepatic vein of 50 ml/min/100gr liver, 80 ml/min/100gr liver and 130 ml/min/100gr liver, respectively. For a 10-15 kg dog with a liver of approximately 200 gr, control flow values are 150 ml/min, 240 ml/min and 390 ml/min, respectively. Hepatic arterial flow, as calculated by the simulation model, is 7.1 ml/min, while it should be 150 ml/min at a pulsatile pressure of 120/100 mmHg, according to the control values. The resulting flow in the portal vein is calculated to be 525.3 ml/min, and should

![Figure 3.8: The velocity profile throughout the liver.](image-url)
3. Hepatic Simulation

be 240 ml/min. Consequently, the hepatic venous flow is incorrect as well: 532.4 ml/min instead of the intended 390 ml/min. Reasons for this discrepancy between the simulation model and previously published control values are difficult to unravel. The principle of modelling fluid dynamics in elastic tubes (i.e. blood vessel) by the electrical analogue as it is depicted in Figure 3.1 has been used by a number of authors. Therefore it is unlikely that the inaccuracy of the simulation model originates from the model itself. The assumptions made to define the model appear to be valid as well. Calculation of Reynolds numbers shows laminar flow conditions. Shear rates ($\gamma$), calculated by:

$$\gamma = \frac{4 \cdot Q}{\pi \cdot R^3} \quad [s^{-1}]$$

did not drop below 50 s$^{-1}$, the shear rate below which a Newtonian approach of hemodynamics is not valid anymore. Furthermore, the assumption of thin-walled vessels obeying Hooke’s law is valid, but for 5th order vessels and smaller the thin wall assumption becomes less apparent, yet this is of minor importance in explaining the inaccuracy of the model.

A much more difficult topic in the simulation model is the input of data that concern number, length and diameter of the blood vessels. This data was obtained from a study by Mall in the early 1900’s analyzing the structural unit of the liver, and is the only available data to our knowledge as regards a numerical description of liver anatomy. Mall based his data on a combination of measurements on corrosion specimen of dog liver vascular casts and estimations. Although Mall did not fully describe his method, we assume that for the casting technique he used a low-pressure perfusion. As a result, the diameters of the hepatic arterial vascular bed could be much smaller than in physiologic circumstances, when a high pulsatile pressure dilates these vessels. This effect is assumed to be less in the venous vascular beds, because physiological pressures are lower in these networks. To investigate this hypothesis, the simulation model was re-defined, now using altered diameters while all the other input parameters and boundary conditions were left unchanged. As a result, it could be shown that increasing the diameters of the hepatic arterial bed by 113% is required to realize the level of arterial flow control values. In addition, a decrease in diameter with 15% of the venous vascular bed is required to match venous flow control values. As a consequence of this re-definition of input parameters, internal relations between generations are not optimally defined anymore. While in- and output values of pressure and flow are physiological correct, values in e.g. 3rd generation vessels have no longer physiological meaning because
the vessel diameter is now arbitrary. The original strength of the numerical simulation model and the possibility to predict influences of changing perfusion pressures on the internal (micro)circulation, is reduced and the model can only be used as a 'black box'. Current techniques such as magnetic resonance imaging and computer tomography will significantly enhance detailed descriptions of vascular dimensions of the hepatic circulation in the near future. However, since their resolution is still not precise enough, improvement of our model is not feasible yet.

Nevertheless, this simulation model remains perfectly suitable for use in a black box approach. It can be reliably used in transport process studies in liver perfusion, e.g. to study the effect of temperature on flow and pressure in hypothermic liver perfusion or the effect of certain diseases on microvascular changes in the liver.

In our project, we have benefited from the data and the calculations. These results obtained by the numerical simulation model were mandatory to allow an assessment of the settings of the prototype for a hypothermic machine perfusion system in liver preservation with subsequent transplantation and our effort to maintain optimal donor organ viability.

3.5 References


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