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PAPER

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PAPER

Quantification of the temperature gradient through a catheter in continuous infusion thermodilution for coronary flow measurements

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Abstract

Objective: Quantifying the absolute coronary blood flow can be done using continuous infusion thermodilution requiring a dedicated infusion catheter. Up to now, there has been little insight into the effect of small variabilities in the physical parameters on the temperature gradient along this catheter. The key goal of this study is to develop and validate a computer model that predicts the temperature of the infusion fluid at the infusion site of the infusion catheter. A secondary goal is to gain insight into the influence of physical variations for the individual patient on the calculated blood flow rate. **Approach:** A numerical model of the temperature in the catheter was built using the convection–diffusion equation and validated using an *in vitro* setup. A sensitivity analysis was performed to investigate the influence of the catheter path inside the body and the temperature of the infusion fluid at different infusion rates. These results were compared to *in vivo* measurements of 94 patients. Finally, the variation in the computed blood flow rate is estimated considering an average patient, using small variations in the physical parameters. **Main results:** The computed temperature corresponded well with the *in vitro* measurements, since a maximal difference of 1.5% was observed. The length of the catheter path inside the body had the most influence on the temperature of the infusion fluid at the infusion site. Moreover, temperatures from the numerical model were similar to the results from *in vivo* measurements. By varying the length of the catheters with 0.04 m, the largest deviation in the calculated blood flow was 33.3 ml/min. **Significance:** Insight is gained into the influence of physical variations on the temperature of the infusion fluid at the infusion site of the catheter using thermodilution. The developed numerical model can possibly be used to reduce time in estimating the blood flow rate.

1. Introduction

Assessment of the microvascular condition of the heart muscle of a patient requires a reliable quantification of both the pressure gradient over the myocardial vascular bed and the absolute coronary blood flow rate (Aarnoudse *et al* 2007, Knaapen *et al* 2009). The pressure gradient is regularly measured and used to perform fractional flow reserve (FFR) measurements in the coronary arteries, which provides information about the myocardial perfusion distal to an epicardial lesion (de Bruyne *et al* 1996, Pijls *et al* 1996). In contrast, there is no standardized method for absolute blood flow quantification during catheterization in common clinical practice. Previous studies showed that the absolute blood flow can be safely and reproducibly measured using continuous infusion thermodilution (Pijls *et al* 2002, Aarnoudse *et al* 2007, Van 't Veer *et al* 2009, Xaplanteris *et al* 2018), as introduced by Ganz *et al* (Ganz *et al* 1971). While performing continuous infusion thermodilution, the temperature of a continuously infused fluid is measured at the infusion site of a dedicated infusion catheter and downstream where the infusion fluid and the blood have mixed. The blood flow rate is determined from the ratio between the temperature differences at the two sites (Van 't Veer *et al* 2009).

Figure 1. Schematic overview of the measurement set-up and model compartments: The contrast injector infuses the saline with an known flow rate Q_i through a high pressure tube into the infusion catheter (compartment 1). The infusion catheter is introduced through a guiding catheter which enters the vascular system by the femoral artery. A small part of the guiding catheter with the infusion catheter remains outside the body (compartment 2). The path of the catheters through the body is defined as compartment 3. The tip of the guiding catheter is positioned at the ostium of the coronary artery through which the infusion catheter and pressure-temperature guidewire enter the coronary artery (compartment 4). The pressure-temperature sensor is connected to a monitor next to the patient.

In clinical practice, the infusion catheter is inserted through a guiding catheter into the coronary artery by femoral or radial access (figure 1). Saline at room temperature is infused into the coronary artery with a constant flow rate using a contrast injector connected to the infusion catheter. Firstly, a pressure-temperature guide wire measures the blood temperature in the distal coronary artery as reference value. Secondly, saline is infused at a defined constant flow rate and the temperature of the mixture at steady-state is measured, approximately 5–6 cm from the distal tip of the infusion catheter (de Bruyne *et al* 2001, Van 't Veer *et al* 2009). Thirdly, the temperature sensor is pulled back and positioned inside the infusion catheter to measure the temperature of the saline when it enters the coronary artery. This third step is challenging. To obtain the temperature at the infusion location, the temperature sensor inside the infusion catheter needs to be positioned quite precisely at 2.5 mm distal to the sensor hole, a small open connection between the lumen of the temperature sensor wire and the lumen of the infusion fluid (Van 't Veer *et al* 2016). Besides, the

procedure could be shortened if the temperature at the infusion site of the infusion catheter is known prior to infusion.

Theoretically, the temperature of a moving fluid in a catheter is governed by the convection–diffusion equation (Patankar 1980). Although some research has been carried out on numerically modelling the temperature inside a catheter (Meckel *et al* 2015, Cattaneo *et al* 2015, González-Suárez and Berjano 2016), there are no existing results on gaining insight into the temperature in a catheter using partial differential equations for the purpose of continuous infusion thermodilution, as far as the authors know. A few studies reported the results from *in vitro* and *in vivo* continuous thermodilution measurements in which the infusion rate was varied (Dumas and Barozzi 1984, Aarnoudse *et al* 2007, Van ‘t Veer *et al* 2016, Xaplanteris *et al* 2018). However, these studies mainly focussed on the computed blood flow, while our interest is in the measured temperature at the infusion site of the infusion catheter.

The main interest of this study is assessing the effect of small variability in the physical parameters on the temperature of the infusion fluid at the infusion site. For this purpose, a key goal of this work is to develop and validate a computer model that predicts the temperature of the infusion fluid at the infusion site of the infusion catheter. A secondary goal is to gain insight into the influence of physical variations for the individual patient on the calculated blood flow rate.

2. Methods

The focus of this study was the development and verification of a numerical model to predict the fluid temperature at the infusion site of the infusion catheter for blood flow rate calculations. First, the numerical model will be explained. Thereafter, the method for model validation and a sensitivity analysis will be explained. Model validation will be performed using *in vitro* measurements. Finally, *in vivo* measurement data will be combined with the sensitivity analysis to investigate the agreement to the numerical results.

2.1. Numerical model

The blood flow rate (Q_b) can be determined from the ratio between the temperature differences at the infusion site of the infusion catheter and 5–6 cm distal from the infusion site, using

$$Q_b = \frac{\rho_i c_{p,i}}{\rho_b c_{p,b}} \frac{T_m - T_i}{T_b - T_m} Q_i. \quad (1)$$

Here, ρ_b and ρ_i are densities of the blood and indicator respectively, T_i is the temperature of the infused fluid at the site where the fluid enters the blood, T_b is the temperature of the blood, T_m is the temperature of the measured mixture and finally Q_i is the continuous infusion rate at steady-state (Van ‘t Veer *et al* 2009). This expression is obtained by considering a simplified form of the convection–diffusion equation. The goal of this work is to use the full, non-simplified, convection diffusion to take the temperature inside the catheter into account, in order to determine the temperature at the infusion site (T_i).

The temperature in the catheter was modelled using the convection–diffusion equation without source term (Patankar 1980):

$$\frac{\partial T}{\partial t} = \nabla \cdot (\alpha \nabla T) - \nabla \cdot (\vec{v} T). \quad (2)$$

Here, T is the temperature of the fluid at a specific location [$^{\circ}\text{C}$], t is time [s], α is diffusivity [m^2/s], $\vec{v}$ is the velocity field [m/s] and ∇T denotes the gradient of T . The diffusivity is defined by $\alpha = k / (c_p \rho)$, with k the thermal conductivity [$\text{W/m}\cdot\text{K}$], c_p the heat capacity of the material [J/K] and ρ the density [kg/m^3]. The thermal diffusivities of the materials used in this article are $1.46 \cdot 10^{-7} \text{ m}^2 \text{ s}^{-1}$ for water and saline at 25°C , $1.51 \cdot 10^{-7} \text{ m}^2 \text{ s}^{-1}$ for the catheter material and $1.35 \cdot 10^{-7} \text{ m}^2 \text{ s}^{-1}$ for blood. The steady-state solution is of primary interest, which is a simplification of equation (1) using $\frac{\partial T}{\partial t} = 0$.

The system under consideration consists of three catheters: a high pressure catheter, an infusion catheter and a guiding catheter. A contrast injector infuses the infusion fluid in the high pressure catheter, which is connected to the infusion catheter. The infusion fluid is infused in the blood at the infusion site of the infusion catheter. The guiding catheter surrounds the infusion catheter for optimal positioning inside the body.

Four compartments and accompanying lengths (L1 to L4) can be distinguished while the infusion fluid is in these catheters (as sketched in figure 2). The first and second compartment describe the catheters before entering the body, the third and fourth compartment describe the catheters inside the body. The first compartment consists of the high pressure tube and infusion catheter surrounded by air through which saline is infused by the contrast injector (figure 2, L1). The second compartment consists of the infusion catheter that enters the guiding catheter, which is surrounded by air (figure 2, L2). The third compartment consists of the infusion catheter surrounded by the guiding catheter in the patient's vascular system. In contrast to compartment 2, the guiding catheter is surrounded by flowing blood instead of air (figure 2, L3). The blood flow between the infusion and guiding catheter in the third compartment is assumed to be zero (i.e. the blood is stationary). The fourth and final compartment describes the infusion catheter exiting the guiding catheter into the coronary artery (figure 2, L4) and is therefore directly surrounded by flowing blood. The blood trapped between the guiding catheter and infusion catheter is assumed to be stationary, as the fluid is injected upstream and outside the guiding catheter.

The total length of the system, excluding the high pressure catheter, is 1400 mm. The exact length of this catheter is irrelevant for the current study, because the temperature of the infusion fluid when injected is assumed to be equal to the room temperature. There is a negligible temperature variation in the first compartment, since temperature variations originating from convection dominate those originating from diffusion. In all figures presented in this work, the length of the high pressure catheter is taken such that the length of the total system (i.e. all compartments combined) equals 1600 mm. This length is mainly chosen for aesthetic reasons, as it allows to easily visually compare the results.

2.1.1. Cylindrical coordinates and boundary conditions

The geometry of the catheter is described using cylindrical coordinates. These coordinates are denoted using (x, θ, r) , where x denotes length, θ denotes angle and r denotes radius. The problem is symmetric in radial direction and flow is assumed to exist in axial direction only. Hence the flow field, denoted by $\vec{v}$, is independent of the angle θ . Moreover, the flow field is independent of x (details are discussed later). Thus $\vec{v}(x, \theta, r) = v(r) \vec{e}_x$, where $v(r)$ is a scalar function denoting the magnitude of the flow and $\vec{e}_x$ denotes the unit vector in axial direction (i.e. $\vec{e}_x = (1, 0, 0)$, using the aforementioned cylindrical coordinates). With a similar reasoning, it is assumed that $\alpha = \alpha(r)$, i.e. the diffusivity only depends on r . It is therefore convenient to model only half of the cylindrical tube, from the centre to the edge of the tube, and neglect the angle θ from the nomenclature, so $T = T(x, r)$. Notice that $\nabla \cdot (v(r) \vec{e}_x) = \frac{\partial}{\partial x} v(r) = 0$, meaning that the flow field is incompressible. Based on these considerations, equation (2) is reformulated as follows:

$$\frac{\partial T}{\partial t} = \nabla \cdot (\alpha(r) \nabla T) - v(r) \frac{\partial}{\partial x} T, \quad (3)$$

with $\nabla T = \frac{\partial T}{\partial r} \vec{e}_r + \frac{\partial T}{\partial x} \vec{e}_x$. Here, $\vec{e}_x$ and $\vec{e}_r$ are unit vectors in axial and radial direction respectively.

At the inflow side of the cylinder, Dirichlet boundary conditions are used: $T|_{x=0} = T_{\text{inflow}}$. This boundary condition models the inflow from the injector. At the outflow side ($x = L$), Neumann boundary conditions are implemented: $\frac{\partial T}{\partial x}|_{x=L} = 0$. This boundary condition models a well-developed temperature gradient. The temperature of the surrounding environment is either equal to room temperature, which is assumed to be 22.0°C , or blood at 37.0°C . The interaction between the catheter and the surrounding environment is modelled using a Robin boundary condition, so $\frac{\partial T}{\partial x}|_{r=R} = -\frac{h}{\kappa} (T - T_{\text{surr}})$. Here, h and κ are the thermal

conductivity and the heat transfer coefficient, respectively. Contrary to the coefficients of the convection–diffusion equations, the exact values of h and κ are unknown *a priori* and difficult to determine, since they depend on the geometry and other specific properties of the system. In all figures presented in this article, $h = 1000 \text{ W}/(\text{m}^2 \cdot \text{K})$ and $\kappa = 0.02 \text{ W}/(\text{m} \cdot \text{K})$ are used, describing a large thermal conductivity due to the blood flow (resulting into a constant heat supply) and a small heat transfer coefficient due to the insulating properties of the plastics used for catheters, respectively (Barozzi and Dumas 1991, Kreith *et al* 2011). Since these values are estimates, the influence of these coefficients is studied in more detail by means of a sensitivity analysis. Finally, due to symmetry, the boundary condition at the centre of the tube (lower boundary) is $\frac{\partial T}{\partial r}|_{r=0} = 0$.

2.1.2. Numerical discretisation

Equation (3) is discretised using standard finite difference schemes for spatial discretisation (Mattheij *et al* 2005). For this purpose, a numerical model is implemented in MATLAB (version R2019b) that obtains the temperature in the cylinder for given parameters α , $\vec{v}$, T_{inflow} and T_{surr} . The exact details of the discretisation are discussed in more detail in the appendix.

The focus is solely on the steady state solution, having $\frac{\partial T}{\partial t} = 0$. To confirm that the steady state is reached over the course of the conducted experiments, transient simulations have been performed using implicit time integration. Since this is slightly out of scope of this study, the details are not considered in the main text, but discussed in the appendix.

Combining the spatial discretisation and the boundary conditions leads to a linear equation of the form $A\vec{T} = \vec{b}$, with A the spatial discretisation including the Neumann and a part of the Robin boundary conditions, $\vec{T}$ the vector containing temperature values at each grid point and $\vec{b}$ the vector containing the Dirichlet and the second part of the Robin boundary conditions. The matrix A is a sparse matrix and the linear system is solved using a fully pivoted LU decomposition in MATLAB (Golub and Van Loan 1996, Saad 2003).

2.1.3. Poiseuille flow

The incompressible flow in the cylindrical tube is laminar and the velocity profile in the infusion catheter can therefore be represented by a Poiseuille flow. To this end, let $r_1 < r_2$ be the two radii of the pressure-temperature guide wire and the infusion catheter respectively and assume v is the velocity of a fluid in an annular section with inner radius r_1 and outer radius r_2 . Then v has approximately a parabolic profile in radial direction and scales as follows:

$$v(r) \propto \begin{cases} (r_1^2 - r^2) + (r_2^2 - r_1^2) \frac{\log\left(\frac{r}{r_1}\right)}{\log\left(\frac{r_2}{r_1}\right)} & \text{if } r_1 < r < r_2, \\ 0 & \text{otherwise.} \end{cases} \quad (4)$$

The scaling constant is determined by enforcing that the flow averaged over the annular section is equal to the imposed flow rate, or in other words:

$$2\pi \int_{r_1}^{r_2} v(r) r dr = Q_i. \quad (5)$$

The mean temperature $T(r)$ in an annular section of the catheter is computed similarly. All reported temperatures are computed at $x = L$ (i.e. at outflow), described by the temperature averaged over the annular section:

$$\bar{T} = \frac{1}{\pi(r_2^2 - r_1^2)} \int_0^{2\pi} \int_{r_1}^{r_2} T(r) r dr d\theta = \frac{2}{r_2^2 - r_1^2} \int_{r_1}^{r_2} T(r) r dr. \quad (6)$$

Here, r_1 and r_2 are the two radii as described previously, $T(r)$ denotes the temperature at outflow and $\bar{T}$ denotes the average temperature over the annular section of the temperature wire. Therefore, the computed average temperature is comparable to the measured temperature using the temperature wire.

The integral of equation (6) is computed from the obtained temperature field straightforwardly using a Trapezoidal rule (Butcher 2008).

2.2. Model validation

The numerical model was validated by comparing the results with measurement data from an *in vitro* setup under similar conditions. The *in vitro* setup mimics the set-up in the human body, as described in figure 1, where the human body is replaced by a temperature-controlled warm water tank ($37 \pm 0.05 \text{ }^\circ\text{C}$). Water at room temperature ($22 \text{ }^\circ\text{C}$) was injected by the contrast injector (Rempress, Medicor International, Belgium)

into a high-pressure tube (MeritMedical, U.S.A.). This catheter was connected to the 2 Fr infusion catheter (RayFlow®, Hexacath, Paris, France, total length 1400 mm, outer diameter 0.67 mm for the length of 1150 mm and outer diameter 0.84 mm for the distal length of 250 mm, wall 0.10 mm) (Van 't Veer *et al* 2016). The infusion catheter was inserted in a 6 Fr guiding catheter (Launcher, Medtronic, Inc. U.S.A., length 1000 mm, outer diameter 2.08 mm, wall 0.14 mm) and both catheters entered the warm water tank. The length of the guiding catheter inside the warm water tank was 0.95 m. The water at room temperature was infused through the infusion catheter into the warm water tank. The temperature of the infusion fluid [$^{\circ}\text{C}$] was measured at the infusion site of the infusion catheter (T_i) by the pressure-temperature guide wire (PressureWire X, Abbott, MN, diameter 0.014 inch; 0.36 mm).

In the numerical model, the temperature sensor was modelled throughout the catheter (figure 2), which is a simplification compared to the actual situation. This simplification was made to avoid non-linear equations describing the complex fluid flow around a temperature sensor that actually enters the infusion catheter in the final 250 mm. To compensate for the temperature sensor, the omnipresent temperature sensor was therefore modelled with diameter 0.064 mm and the infusion catheter is modelled with outer diameter 0.698 mm.

The T_i was measured using infusion rates (Q_i) of 0, 10, 15, 20, and 25 ml min $^{-1}$. In addition, the end of the infusion catheter was positioned at −20, 30, and 80 mm relative from the tip of the guiding catheter (see figure 2, L4). Thus, at −20 mm, the infusion catheter is located inside the guiding catheter. The results of the numerical model and the *in vitro* measurements were compared by calculating the relative difference between the computed and measured temperatures. Temperature difference between the measured or computed fluid will be presented relative to the body temperature (37 $^{\circ}\text{C}$).

2.3. Sensitivity analysis

Using the model, a sensitivity analysis was performed to assess the influence of various physical parameters on the computed T_i . The parameters used for the analysis were specifically selected based on their frequent occurrence in clinical practice. Moreover, the influence of the unknown convective parameter of the Robin boundary condition is also considered in the analysis. The analysis was performed by considering a range of physically possible values of these parameters and determining the minimal, average and maximal temperature within this interval of possible values. The computed temperature values from the model were consequently compared to temperature values obtained from *in vivo* T_i measurements. The following parameters were considered (with the range of possible values in parentheses): Q_i fixed at 15, 20 or 25 ml min $^{-1}$, as used in the *in vivo* measurements, length of the guiding catheter inside the body (0.75 ± 0.15 m; L3 in figure 2), length between the infusion site of the infusion and guiding catheter (0.025 ± 0.025 m; L4 in figure 2), the temperature of the infusion fluid (room temperature) in the contrast injector ($21.5^{\circ}\text{C} \pm 1.5^{\circ}\text{C}$) and the convective parameter of the Robin boundary condition ($\frac{h}{\kappa} = 5 \cdot 10^4 \pm 10\% \text{ m}^{-1}$). Other parameters, i.e. catheter size, are equal to the conditions used to obtain the *in vivo* dataset.

To assess the effect of physical variations as observed in clinical practice, a second sensitivity analysis is conducted. Here, a smaller range is selected for the parameters, representing possible measurement errors within an average patient. The obtained results from the model are expressed as variation in the blood flow, which is the usual quantity reported in thermodilution. For this purpose, equation (1) is written as follows (Aarnoudse *et al* 2007):

$$Q_b = 1.08 \left(\frac{T_i}{T} \right) Q_i, \quad (7)$$

with T and T_i the deviation from the blood temperature T_b . The measured temperature T of the saline infusion fluid is obtained from the *in vivo* measurements. Small variations in the physical parameters are used to determine T_i , based on results obtained from the model. The guiding catheter is positioned 0.73–0.77 m inside the body of the patient (figure 2, L3) and the temperature of the infusion fluid is equal to the room temperature, 21.5 $^{\circ}\text{C}$. The length of the infusion catheter outside the guiding catheter at the infusion site (figure 2, L4) varies from 0.01 to 0.05 m. Infusion flow rates of 15, 20 and 25 ml min $^{-1}$ are used.

2.3.1. In vivo measurements

In vivo measurements from continuous infusion thermodilution with saline were used in addition to the sensitivity analysis to further compare the results from the model with results obtained in clinical practice. These measurements were conducted as follows. Temperature measurements were performed in the right coronary artery (RCA), left anterior descending artery (LAD) and/or left circumflex artery (Cx) in 94 patients during the period of 1 January 2016 until 1 July 2019 in the Catharina Hospital Eindhoven. Data was anonymized and only Q_i , T and T_i in the three main coronary arteries were known. The temperature was

Table 1. *In vivo* measurements of the temperature at the infusion site (T_i) and distal from the infusion site in the coronary artery (T) at different infusion velocities.

Infusion velocity [mL/min]	#	T_i within model range [%]	Mean T_i [°C]	Std. dev. T_i [°C]	Mean T [°C]	Std. dev. T [°C]
15	80	98,8	3,52	0,77	0,49	0,34
20	238	89,1	4,44	0,67	0,51	0,19
25	43	67,4	5,00	0,66	0,56	0,13

Table 2. Calculated blood flow rates (Q_b) at varying flow rates (Q_i), length of guiding catheter inside body of 0.73 m and 0.77 m (figures 2, L3), and (a) length of 0.01 m and 0.05 m of the infusion catheter outside the guiding catheter at the infusion site (figure 2, L4).

Infusion velocity [mL/min]	T <i>In vivo</i> [°C]	T_i model [°C]		Q_b [mL/min]		Q_b [mL/min]
		L3 = 0.73 m L4 = 0.01 m	L3 = 0.77 m L4 = 0.05 m	L3 = 0.73 m L4 = 0.01 m	L3 = 0.77 m L4 = 0.05 m	
15	0,49	3,96	3,26	130,9	107,9	23,1
20	0,51	5,71	4,99	241,7	211,3	30,4
25	0,56	7,11	6,42	342,7	309,4	33,3

expressed as the difference between the blood temperature and the measured temperature. The length of the catheter path within the patient's body and the temperature of the infusion fluid in the contrast injector were unknown, because these parameters are not recorded for clinical care. Therefore, the length of the guiding catheter within the patient's body was assumed to be 0.60–0.90 m and the length between the infusion site of the infusion and guiding catheter was assumed to be 0.00–0.05 m. The temperature of the infusion fluid was assumed to be room temperature (20 °C–23 °C) as chosen in the sensitivity analysis. Prior to the clinical data retrieval, ethical clearance was obtained for this study from the local medical ethical committee of the Catharina Hospital Eindhoven (nWMO-2019.078).

3. Results

3.1. Numerical model and validation

Figure 3 shows an illustration of the temperature decay along the infusion catheter for different lengths of the path of the catheter inside the body and inside the coronary artery (L3 and L4 from figure 2). As expected, the T_i is higher with 1) increased length of compartment 3 of the catheter (L3), 2) increased distance between the infusion site of the infusion and guiding catheter (L4) and 3) lower infusion rates.

Validation results of the *in vitro* measurements (dots) and the numerical model (solid lines) are shown in figure 4. The largest temperature difference was measured at an infusion rate of 25 ml min⁻¹, with the infusion catheter positioned inside the guiding catheter (−20 mm). The biggest relative errors between the numerical model and *in vitro* measurements were observed at high infusion rates. The maximal relative difference of T_i at values for Q_i of 0, 10, 15, 20, 25 ml min⁻¹ was 0.3%, 1.0%, 1.0%, 1.2%, −1.5% respectively.

3.2. Sensitivity analysis

The results from the sensitivity analysis are shown in figure 5. Effect of varying values for the length of path of the catheter inside the body (figure 5, panel A), the distance between the tip of the guiding catheter and the infusion site (figure 5, panel B), the temperature of the infusion fluid/room temperature (figure 5, panel C) and the convective parameter of the Robin boundary conditions (figure 5, panel D) are shown. The length of the path of the catheter inside the body has the most influence on the T_i . At higher flow rates the computed T_i is more sensitive to small variations in the input parameters. The T_i for *in vivo* measurements was lower with higher infusion rates, which is in accordance with the numerical model and *in vitro* measurements (table 1 and figure 4). The results obtained with the numerical model by varying input parameters overlap largely with the *in vivo* results (see figure 6 and table 1).

Finally, the variation in blood flow rate is determined for an average patient with the length of the infusion catheter outside the guiding catheter at infusion site (figure 2, L4) of 0.01 and 0.05 m and the length of the guiding catheter inside the body of 0.73 and 0.77 m (see table 2). The absolute difference in calculated blood flow rate between both lengths at an infusion flow rate of 15, 20 and 25 ml min⁻¹ is respectively 23.1, 30.4 and 33.3 ml min⁻¹.

Figure 3. Temperature gradient through the model: Temperature gradient over all catheters at steady state, with guiding catheter inside the body for 0.9 m (figure 2, L_3), the infusion site of the infusion catheter outside the guiding catheter (figure 2, L_4) for 30 mm and a flow of 15 ml min^{-1} (subfigure A). All other subfigures are equal to subfigure (A), except for a single parameter: Subfigure (B) length L_3 is 0.6 m, (C) length L_4 is 0.01 m, (D) length L_4 is 0.08 m, (E) flow Q_i is 20 ml min^{-1} , (F) flow Q_i is 25 ml min^{-1} .

4. Discussion

In this study the temperature decay of the infusion fluid in an infusion catheter was modelled using a discretised convection–diffusion equation. The temperatures computed with the model agreed well with the temperatures obtained from the *in vitro* and *in vivo* measurements.

Being able to estimate the temperature of the infused fluid when it enters the coronary artery (T_i) without the need to retract the pressure-temperature wire would significantly simplify the coronary blood

flow rate measurement and reduce the risk of these measurements, especially in cases where it is undesirable from a clinical point of view to pull back the guide wire from the coronary artery. The sensitivity analysis demonstrated that the infused flow rate and the length of the catheter inside the body have major impact on the T_i . Since small variations in these parameters could yield large deviations in T_i , it is not straightforward to assume a specific T_i for each infusion rate under consideration.

A few studies reported the results from continuous thermodilution measurements in which the infusion rate was varied from 10 to 25 ml min⁻¹ (Van 't Veer *et al* 2016, Xaplanteris *et al* 2018). These *in vivo* studies mainly report the calculated blood flow, whereas there is less information provided about the measured temperature values. For instance, Xaplanteris *et al* reported values for T_i ranging from 1.00 to 6.05 °C below the blood temperature at an infusion rate 20 ml min⁻¹, with median values of 4.2 °C for the left anterior descending artery, 4.0 °C for the left circumflex artery and 3.5 °C for the right coronary artery (Xaplanteris *et al* 2018). The variability in these measured temperatures is presumably attributed to, among others, variability in the positions of the sensor and infusion catheter. This is in accordance with our study (figure 6), where many of the clinical temperature measurements fell within the interval of possible values for T_i when taking clinical ranges of different influencing parameters into account. These parameters are not recorded in clinical practice, but could be measured in future measurements to assess whether these would enable the model to estimate the T_i more accurately.

The system of differential equations used in this study contains several simplifications which have not been thoroughly assessed both in this work and in literature. For instance, a Poiseuille flow has been used to model the flow in the catheter, which neglects all effects of complex flows in the tube-shaped infusion catheter. Ideally, the flow in the catheter is based on the Navier–Stokes equations, combined with the convection–diffusion equation as used in this work, which yield a complete three dimensional description of both the temperature values and the velocity field within the infusion catheter. However, it is far from trivial to numerically approximate solutions of a system of the obtained non-linear partial differential equations. Nonetheless, doing so would add much more flexibility to the description of the system. For example, this would allow to model the temperature sensor in a more realistic way.

The system of differential equations considered in this work has several tuneable parameters, e.g. the thermal diffusivity and the convective parameter of the Robin boundary condition. As demonstrated by the sensitivity analysis, these parameters affect the accuracy of the obtained temperature estimates. The convective parameter as used in the Robin boundary condition is particularly difficult to estimate correctly, since it depends on the exact geometry of the system under consideration. It was out of the scope of this study to determine the exact value that should be used in this boundary condition, but improving the overall accuracy of the coefficients in the model used would make the model more reliable (Consiglieri *et al* 2003, Dos Santos *et al* 2008).

The discretisation used in this work is based on finite differences, which is a straightforward and well-understood approach to discretise systems of differential equations. However, using finite volume or even finite elements methods might yield in a more stable and accurate discrete system. Such an extension allows to model non-straight and more realistically shaped catheters (Mattheij *et al* 2005, van Kan *et al* 2005).

Various alternative methods exist to model the temperature field in a cylinder. An example is to model temperature decay using Fick's law, equipped with the Biot and Fourier number. Fick's law does not require solving a partial differential equation, but it is not evident whether it can be rightfully applied to the model

under consideration. We believe that the assumptions made in our model are justified to describe the general influences on the temperature gradient along the catheter length, but a careful assessment of the assumptions made in this work is necessary before generalizing the model to other geometries.

Even for an optimal model, uncertainties in the physical system limit its applicability. The catheter is not a straight cylinder and it is unlikely that the temperature sensor is exactly positioned in the centre of the catheter. Moreover, it is unlikely that the temperature of the blood is exactly 37 °C, the value which was used in the Robin boundary conditions. These assumptions do not limit the accuracy of using a model-based approach, as demonstrated in this study, but do require care when drawing conclusions based on results obtained from the model.

The sensitivity analysis performed in this study is based on propagating intervals of physical realistic values of the parameters through the model. The accuracy of the sensitivity analysis can be improved by enhancing this approach using probability theory, i.e. by using a statistical framework. Then the obtained temperature predictions would be fully uncertain, describing the uncertainty of the model output to a larger degree than as done in this study. However, these probability distributions are not known.

5. Conclusion

In this study it was shown that a numerical model can be used to predict the temperature of infusion fluid in a catheter at an infusion site when the influencing parameters are known. Based on the sensitivity analysis, it can be concluded that these temperature values are highly dependent on the catheter path within the body and the flow rate of the infused fluid. Quantifying these influencing parameters might improve the accuracy of a model-based temperature estimation.

Appendix—Discretisation of the convection–diffusion equation

Convection–diffusion equation

The convection–diffusion equation is expressed as

$$\frac{\partial T}{\partial t} = \nabla \cdot (\alpha \nabla T) - \nabla \cdot (\vec{v} T) + R, \quad (\text{A1})$$

with the variable of interest T , the diffusivity α , the velocity $\vec{v}$, the gradient ∇T and the source term R . The first term of the right hand side describes the diffusion and the second term the convection in the flow. In this work, cylindrical coordinates are used to describe the temperature in the catheter (see main article). Recall that the following assumptions have been used to simplify this equation:

1. There are no sources or sinks in the catheter, hence $R = 0$.
2. The flow is symmetric in θ , i.e. $\frac{\partial T}{\partial \theta} = 0$ and T is a scalar function of x and r only.
3. There is only flow in axial direction that is independent of x , i.e. $\vec{v} = v(r) \vec{e}_x$, where $v(r)$ is a scalar function denoting the flow magnitude.
4. The diffusivity only depends on r , i.e. $\alpha = \alpha(r)$.

Based on these assumptions, the convection–diffusion can be denoted coordinate-wise as follows:

$$\frac{\partial T}{\partial t} = \frac{1}{r} \frac{\partial}{\partial r} \left(\alpha(r) \left(r \frac{\partial T}{\partial r} \right) \right) + \alpha(r) \frac{\partial^2 T}{\partial x^2} - v(r) \frac{\partial T}{\partial x}. \quad (\text{A2})$$

Recall that the velocity profile $v(r)$ is expressed using a Poiseuille flow.

Discretisation in MATLAB

The goal is to obtain an approximate solution of the partial differential equation from Equation (A2). For this, standard finite difference schemes are used. These schemes ultimately rewrite (A2) into

$$\frac{\partial \vec{T}}{\partial t} = A \vec{T} - \vec{b}. \quad (\text{A3})$$

Here, $\vec{T}$ denotes a vector containing a finite number of temperature locations in the domain. These locations form a rectangular grid in the (x, r) -plane. Time integration is used to discretise the temporal derivative in (A3). Separating the treatment of spatial and temporal derivatives in this way is usually called

Figure A1. Temperature at the infusion site of the infusion catheter over time [s].

the ‘Method of Lines’. In particular, if the interest is solely in the steady state solution, a linear equation of the form $A\vec{T} = \vec{b}$ is obtained.

Firstly, the domain is discretised by introducing $T_{i,j} = T(x_i, r_j)$, for $0 \leq i \leq N_x$ and $0 \leq j \leq N_r$. Here $x_i = i\Delta x$, with $\Delta x = L/N_x$, such that $x_0 = 0$ and $x_{N_x} = L$. Similarly, $r_j = j\Delta r$ with $\Delta r = R/N_r$. The distance between two consecutive discrete grid points used for all simulations is 2.5 mm in axial direction (x) and $2.0 \mu\text{m}$ in radial direction (r), which form a balance between accuracy and speed of the reached solution (as determined using a grid-convergence study).

Consequently, the main idea is to replace the derivative with a linear expression, which can consequently be used to write the partial differential equation from (A2) as a linear equation as described by (A3). These expressions are obtained by repeatedly applying one of the following (somewhat equivalent) approximations for the derivative in x at (x_i, r_j) :

$$\frac{\partial T}{\partial x} = \lim_{h \rightarrow 0} \frac{T(x+h, r) - T(x, r)}{h} \approx \frac{T_{i+1,j} - T_{i,j}}{\Delta x}.$$

$$\frac{\partial T}{\partial x} = \lim_{h \rightarrow 0} \frac{T(x + \frac{1}{2}h, r) - T(x - \frac{1}{2}h, r)}{h} \approx \frac{T_{i+\frac{1}{2},j} - T_{i-\frac{1}{2},j}}{\Delta x}.$$

$$\frac{\partial T}{\partial x} = \lim_{h \rightarrow 0} \frac{T(x, r) - T(x-h, r)}{h} \approx \frac{T_{i,j} - T_{i-1,j}}{\Delta x}.$$

The discretisation of these derivatives in axial and radial coordinates is treated separately. Each component of the convection–diffusion equation from (A2) is discretised separately, see equations (A4), (A5) and (A6).

Discretisation in axial coordinates

In axial direction, the discretisation is relatively straightforward. The diffusive part is discretised as follows:

$$\alpha(r) \frac{\partial^2}{\partial x^2} T \approx \alpha(r_j) \frac{\partial}{\partial x} \frac{T(x_{i+\frac{1}{2}}, r_j) - T(x_{i-\frac{1}{2}}, r_j)}{\Delta x} \approx \alpha(r_j) \frac{T_{i+1,j} - 2T_{i,j} + T_{i-1,j}}{\Delta x^2}. \quad (\text{A4})$$

Using this expression, the equation $\partial^2 T / \partial x^2 = 0$ can be transformed into a linear equation in $T_{i+1,j}$, $T_{i,j}$ and $T_{i-1,j}$. This approximation is commonly known as the central-difference scheme. An upwind scheme is used for the convective part:

$$v(r) \frac{\partial}{\partial x} T \approx v(r_j) \frac{T_{i+1,j} - T_{i,j}}{\Delta x}. \quad (\text{A5})$$

Discretisation in radial coordinates

Discretisation in radial direction is less straightforward due to the radial coordinates and the dependence of α on r . Nonetheless, discretising the radial component of $\nabla \cdot (\alpha \nabla T)$ still consists of iteratively applying the approximations mentioned above. In this article, the following central-difference scheme is used (at (x_i, r_j)):

$$\begin{aligned} \frac{1}{r} \frac{\partial}{\partial r} \left(\alpha(r) \left(r \frac{\partial}{\partial r} T \right) \right) &\approx \frac{1}{r} \frac{\partial}{\partial r} \left(\alpha(r_j) r_j \frac{T_{i,j+\frac{1}{2}} - T_{i,j-\frac{1}{2}}}{\Delta r} \right) \\ &\approx \frac{1}{r_j} \frac{\alpha(r_{j+\frac{1}{2}}) r_{j+\frac{1}{2}} (T_{i,j+1} - T_{i,j}) - \alpha(r_{j-\frac{1}{2}}) r_{j-\frac{1}{2}} (T_{i,j} - T_{i,j-1})}{\Delta r^2} \\ &= \frac{1}{r_j} \frac{\alpha(r_{j+\frac{1}{2}}) r_{j+\frac{1}{2}} T_{i,j+1} - \left(\alpha(r_{j+\frac{1}{2}}) r_{j+\frac{1}{2}} - \alpha(r_{j-\frac{1}{2}}) r_{j-\frac{1}{2}} \right) T_{i,j} + \alpha(r_{j-\frac{1}{2}}) r_{j-\frac{1}{2}} T_{i,j-1}}{\Delta r^2}. \end{aligned} \quad (\text{A6})$$

Again, a linear expression in $T_{i,j+1}$, $T_{i,j}$ and $T_{i,j-1}$ is obtained. The diffusivity at $r_{j+\frac{1}{2}}$ is computed using a harmonic mean of $\alpha(r_j)$ and $\alpha(r_{j+1})$, as is common in the convection–diffusion equation.

Boundary conditions

The boundary condition on the outflow side (right side, $\frac{\partial T}{\partial x} = 0$) and at $r = 0$ is a Neumann boundary condition. This boundary condition is implemented by using a so-called ghost node outside the domain. For instance, consider the boundary condition $\frac{\partial T}{\partial x} = 0$. In this case, the ghost node is $T_{N_x+1,j}$, which is resolved using the Neumann boundary condition:

$$0 = \frac{\partial T}{\partial x} \approx \frac{T_{N_x+1,j} - T_{N_x,j}}{\Delta x}.$$

This expression yields $T_{N_x+1,j} = T_{N_x,j}$, which can consequently be used in (A4) to reobtain a linear equation in $T_{i,j}$ and $T_{i-1,j}$.

On the left of each compartment, the temperature is explicitly stated, which are Dirichlet boundary conditions. Incorporating these boundary conditions is relatively straightforward. For example, consider $T|_{x=0} = T_{\text{inflow}}$. Hence $T_{i,j} = T_{\text{inflow}}$ for any $i < 1$. Using this expression in the scheme above results (again) in a linear expression. For instance, consider the discretisation of $\frac{\partial T}{\partial x} = 0$. Then

$$0 = \frac{\partial T}{\partial x} \approx \frac{T_{i+1,j} - T_{i,j}}{\Delta x} = \frac{T_{\text{inflow}} - T_{i,j}}{\Delta x} \rightarrow T_{i,j} = T_{\text{inflow}}. \quad (\text{A7})$$

Hence this boundary condition yields a non-zero right-hand side $\vec{b}$.

The Robin boundary condition is implemented as a combination of the two. By means of a ghost node, the nodes outside of the domain are replaced in the discretisation, as done in the treatment of Neumann boundary conditions. Then all constant values that are independent from the temperature are moved to the right hand side of the equation, as done in the treatment of Dirichlet boundary conditions.

Temporal discretisation

Even though the interest is mainly in the steady-state condition (i.e. $\frac{\partial \vec{T}}{\partial t} = 0$), time integration is implemented to assess the time until steady state is reached. This time can be used to assess whether the *in vivo* and *in vitro* measurements have been conducted using a fully developed flow. For this purpose, time is discretised in time steps $n\Delta t$ (with $n = 0, 1, 2, \dots$). Then an implicit Euler time integrator is used (Butcher 2008):

$$\vec{T}_{t+1} = \vec{T}_t + \Delta t (A \vec{T}_{t+1} - \vec{b}). \quad (\text{A8})$$

Here, $\vec{T}_t$ denotes the vector of temperature values at time step t . This time integrator requires an initial condition $\vec{T}_0$. In this study, $\vec{T}_0 \equiv 37^\circ\text{C}$, modelling a catheter without fluid flow.

It is not evident that the time integrator as described by equation (A8) is numerically stable, which means that the temperature does not increase unphysically over time. This particular integrator is stable if $|1/(1 - \Delta t \lambda)| \leq 1$, where λ the largest absolute eigenvalue of A . This is the case since all eigenvalues of the matrix A have negative real part.

The temperature at the infusion site of the infusion catheter has reached a stable value after 4 s from the start of infusion at different infusion velocities. This result holds for all parameter values considered in this study (see figure A1 for an example).

Summary

All these expressions and boundary conditions yield linear expressions of the form $a_{i-1,j}T_{i-1,j} + a_{i,j-1}T_{i,j-1} + a_{i,j}T_{i,j} + a_{i+1,j}T_{i+1,j} + a_{i,j+1}T_{i,j+1} = b_{i,j}$. Here, $a_{i,j}$ is known for all i and j and follow from the discretised partial differential equation and the Neumann boundary conditions. The values of $b_{i,j}$ follow from the Dirichlet boundary conditions. If all $a_{i,j}$ are gathered in a matrix and $b_{i,j}$ are stored in a vector, a linear equality $A\vec{T} = \vec{b}$ is obtained, which can be solved using various well-known linear algebra toolboxes.

References

- Aarnoudse W et al 2007 Direct volumetric blood flow measurement in coronary arteries by thermodilution *J. Am. Coll. Cardiol.* **50** 2294–340
- Barozzi G S and Dumas A 1991 Convective heat transfer coefficients in the circulation *J. Biomech. Eng.* **113** 308–13
- Butcher J 2008 *Numerical Methods for Ordinary Differential Equations* Second Edition (New York: Wiley)
- Cattaneo G, Schumacher M, Wolfertz J, Jost T and Meckel S 2015 Combined selective cerebral hypothermia and mechanical artery recanalization in acute ischemic stroke: in vitro study of cooling performance *Am. J. Neuroradiol.* **36** 2114–20
- Consiglieri L, Dos Santos I and Haemmerich D 2003 Theoretical analysis of the heat convection coefficient in large vessels and the significance for thermal ablative therapies *Phys. Med. Biol.* **48** 4125–34
- de Bruyne B, Bartunek J, Sys S, Pijls N, Heyndrickx G and Wijns W 1996 Simultaneous coronary pressure and flow velocity measurements in human: feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve *Circulation* **94** 1824–49
- de Bruyne B, Pijls N, Smith L, Wievegg M and Heyndrickx G 2001 Coronary thermodilution to assess flow reserve: experimental validation *Circulation* **104** 2003–6
- Dos Santos I, Haemmerich D, da Silva Pinheiro C and Ferreira da Rocha A 2008 Effect of variable heat transfer coefficient on tissue temperature next to a large vessel during radiofrequency tumor ablation *Biomed. Eng. Online* **7**
- Dumas A and Barozzi G S 1984 Laminar heat transfer to blood flowing in a circular duct *Int. J. Heat Mass Transf.* **27** 391–8
- Ganz W, Tamura K, Marcus H, Donoso R, Yoshida S and Swan H 1971 Measurement of coronary sinus blood flow by continuous thermodilution in man *Circulation* **44** 181–95
- Golub G and Van Loan C 1996 *Matrix Computations* Third edition (Baltimore, MD: The John Hopkins University Press)
- González-Suárez A and Berjano E 2016 Comparative analysis of different methods of modeling the thermal effect of circulating blood flow during RF cardiac ablation *IEEE Trans. Biomed. Eng.* **63** 250–9
- Knaapen P et al 2009 Coronary microvascular resistance: methods for its quantification *Basic Res. Cardiol.* **104** 485–98
- Kreith F, Manglik R M and Bohn M S 2011 *Principles of Heat Transfer* (Stanford, CA: Cengage Learning)
- Mattheij R, Rienstra S and Ten Thije Boonkkamp J 2005 *Partial Differential Equations: Modeling, Analysis, Computation* (Philadelphia, PA: Society for Industrial and Applied Mathematics)
- Meckel S, Cattaneo G and Guber A 2015 Mathematical, numerical and in-vitro investigation of cooling performance of an intra-carotid catheter for selective brain hypothermia *Curr. Directions Biomed. Eng.* **1** 390–4
- Patankar S 1980 *Numerical Heat Transfer and Fluid Flow* (New York: Hemisphere Publishing Corporation)
- Pijls N, de Bruyne B, Peels K, van der Voort P, Bonnier H, Bartunek J and Koolen J 1996 Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses *New Engl. J. Med.* **334** 1703–8
- Pijls N, de Bruyne B, Smith L, Aarnoudse W, Barbato E, Bartunek J, Bech G and van de Bosse F 2002 Coronary thermodilution to assess flow reserve: validation in humans *Circulation* **105** 2482–6
- Saad Y 2003 *Iterative Methods for Sparse Linear Systems* Second edition (Philadelphia, PA: Society for Industrial and Applied Mathematics)
- Van 't Veer M, Adedj J, Wijnbergen I, Tóth G, Rutten M, Barbato E, van Nunen L, Pijls N and de Bruyne B 2016 Novel monorail infusion catheter for volumetric coronary blood flow measurement in humans: in vitro validation *EuroIntervention* **12** 701–7
- Van 't Veer M, Geven M, Rutten M, van der Horst A, Aarnoudse W, Pijls N and van de Vosse F 2009 Continuous infusion thermodilution for assessment of coronary flow: theoretical background and in vitro validation *Med. Eng. Phys.* **31** 688–94
- van Kan J, Segal G and Vermolen F 2005 *Numerical Methods in Scientific Computing* (New York: Academic)
- Xaplanteris P et al 2018 Catheter-based measurements of absolute coronary blood flow and microvascular resistance: feasibility, safety, and reproducibility in humans *Circ. Cardiovasc. Interv.* **11** e006194