Continuous infusion thermodilution for assessment of coronary flow: Theoretical background and in vitro validation

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1. Introduction

In the assessment of the coronary circulation intracoronary pressure and blood flow are the parameters characterizing the functional significance of disease. Intracoronary pressure is widely used to quantify the severity of an epicardial stenosis [1,2]. To assess the condition of the myocardial microvasculature, however, also quantification of absolute coronary and myocardial flow is needed [3,4].

Techniques for direct absolute coronary blood flow measurement are not available for common clinical practice in the catheterization laboratory. Therefore, indirect measures are used for the determination of coronary or myocardial blood flow, such as blood flow velocity or transit times [5,6]. During catheterization blood flow velocity measurements may be carried out using an ultrasound Doppler-crystal, mounted on a guide wire. Blood flow velocity is recorded and consequently absolute flow (flow rate) is estimated assuming a Poiseuille profile and integrating over the vessel’s cross-section. Relatively large errors up to 20% are made using this technique [7], whereas in a considerable number of patients (up to 35%) no reliable measurement can be obtained [8].

Another invasive method uses the injection of an indicator into the blood, and monitoring the transit time of this indicator in the blood flow. The conventional clinically applied indicator dilution method is thermodilution, where the indicator is a bolus of saline. The best-known application uses this technique to determine cardiac output [9]. For coronary flow measurements this technique is unsuitable. An amount of indicator might be lost into the aorta when injecting the saline briskly into the coronary ostium and only the mean transit time of the bolus can be used instead of the area under the curve. The mean transit time is inversely correlated to the coronary flow. However, no absolute flow rate can be measured unless the exact vascular volume is known [8,10,11]. Continuous infusion thermodilution was proposed by Ganz et al. [12] more than 30 years ago, for the measurement of blood flow in the coronary sinus. Theoretically, absolute coronary blood flow can be measured from the mixing temperature of a known infusion rate at known temperature, and the constant temperature of the blood. However, besides the fact that such coronary sinus measurements could not differentiate between blood flow from the different coronary sinus.
arteries and different myocardial territories, the variability was too high to be useful for clinical application and the methodology was soon abandoned [13,14]. Recently, we applied continuous infusion thermodilution in animal and patient studies to determine absolute coronary blood flow in a select coronary artery during cardiac catheterization [15].

In these studies, we found strong correlations between real coronary flow and the flow determined by the continuous infusion thermodilution method. The continuous infusion thermodilution technique slightly overestimated coronary flow determined by directly measured reference flow using a perivascular flow probe by 9 ± 21% over the entire physiological flow range of 50–250 ml/min in the animal experiments. Reproducibility was excellent (–2 ± 12%) [15]. In analyzing the data we hypothesized that complete mixing of the infusate and the blood comprised the main prerequisite for applicability of the continuous infusion method for measurement of absolute coronary blood flow. The design and characteristics of the infusion catheter appeared to be important.

In the current study we provide a more detailed theoretical background and take the method to the bench to investigate its fundamental characteristics more closely under well-controlled conditions in a physiologically representative model of the coronary circulation [3,16]. The model allows for measurement and control of all relevant parameters such as fluid temperature and coronary flow rate.

The aim of the present study is to investigate the boundary conditions for optimal mixing and accurate application of the method with respect to the design of the infusion catheter, different infusion rates, and the sites for measurement. Hereto, the flow rates derived by this method are compared with real flow, obtained with a perivascular ultrasonic flow probe.

2. Methodology

2.1. Theoretical background and measurement principle

Assuming that heat transport is convection dominated and heat exchange at the arterial wall can be neglected, it can be derived that after complete mixing with an continuously infused indicator fluid, blood flow (Qb) can be calculated from the temperatures of the blood (Tb), the infused indicator (Ti), and the mixture downstream from the infusion site (T), and the known infusion rate (Qi) by

\[ Q_b = \frac{\rho_b \cdot c_{p,b} \cdot (T - T_i)}{\rho_b \cdot c_{p,b} \cdot (T - T_i)} Q_i = \frac{\rho_b \cdot c_{p,b} \cdot (T - T_i)}{\rho_b \cdot c_{p,b} \cdot (T - T_i)} Q_i \]

where \( \rho_b \) and \( \rho_i \) are the densities of the blood and the indicator, respectively and \( c_{p,b} \) and \( c_{p,i} \) are the specific heats of the blood and the indicator, respectively. The derivation of this equation can be found in Appendix A.

In Eq. (1) \( Q_b \) is the blood flow during infusion of the indicator, usually saline, and is assumed not to be affected by the infusion. However, if aortic pressure is not increased by the infusion and the myocardial resistance remains constant, i.e. during maximal hyperemia in the in vivo situation, the total flow through the myocardium will not increase. Hence, \( Q_b \) is affected and part of the blood flow will be replaced by the infusion rate. In resting conditions myocardial resistance can vary and total flow through the myocardium might be increased during infusion (autoregulation). Therefore, only in the hyperemic situation when the vasodilatory capacity of the myocardium is exhausted, the measured flow during infusion is decreased by \( Q_b \) and the original blood flow before infusion can be found using

\[ Q_{b, orig} = \frac{\rho_b \cdot c_{p,b} \cdot (T_b - T_i)}{\rho_b \cdot c_{p,b} \cdot (T_b - T_i)} Q_i + Q_i \]

2.2. In vitro model and instrumental set-up

A full description of the physiologic representative experimental model we used is described elsewhere [3,16]. In short, the model consisted of a piston pump, a left ventricular chamber and two valves, representing the left ventricle of the heart, a systemic and a coronary circulation. The systemic circulation contained a polyurethane tube (with the dimensions and mechanical properties of the aorta), and a system of compliances and resistances, creating physiological aortic pressure and flow patterns. A polyurethane coronary artery branched off the aorta directly distal to the aortic valve and bifurcates in an epicardial branch and a sub-endocardial branch. The latter was led through the left ventricular chamber and collapsed during systole resulting in the typical physiological coronary flow signal. A perivascular ultrasound flow probe (4PSB, Transonic) was placed around the main branch of the coronary artery to measure true coronary flow. The arteriolar resistance was tuned to obtain hyperemic coronary flow of approximately 250 ml/min for all measurements. A coronary stenosis was created by a clamp directly distal to the flow probe, allowing for variation of coronary flow between 50 and 250 ml/min. The model was submerged in water which was kept at a constant temperature of 37.00 ± 0.05 °C by an external thermal bath and circulator (F34-HL, Julabo).

The instrumental set-up for the continuous infusion experiments is depicted in Fig. 1. Aortic pressure was measured directly distal to the aortic valve using a pressure transducer (P10EZ-1, Becton Dickinson) and bridge amplifier (Picas-CA2CF, Peekel Instruments). A guiding catheter was positioned near the ostium of the coronary artery. A sensor tipped guide wire (PressureWire-5, Radi Medical Systems) was advanced through the guiding catheter into the coronary artery to measure coronary pressure and temperature. The sensor of the guide wire is located 3 cm proximal to its tip. The infusion catheter was positioned in the coronary artery proximal to the site of the stenosis. The infusion catheter was connected by a Y-connector to the infusion pump (Angiomat 6000, Liebel-Flarsheim) and the guide wire was connected to the RADI Analyzer (Radi Medical Systems).

2.3. Measurement protocol

2.3.1. Infusion catheter and infusion rate

Two different over-the-wire infusion catheters were evaluated: the first one was a general model frequently used in the catheterization laboratory (model A), with three sideholes equally
Fig. 1. Physiologic representative model with magnification of the instrumental set-up. Left ventricle is denoted by LV. The infusion catheter and the sensor tipped guide wire are positioned in the coronary artery through the guiding catheter. Indicator is infused ($Q_i$) and temperatures are measured before ($T_b$) and during infusion ($T$). The guide is pulled back into the infusion catheter to obtain $T_i$. True coronary flow is measured by the ultrasound flow probe and coronary flow is adjusted by the clamp. Distributed over the distal 3 cm of the catheter, the second a specifically designed catheter (model B), in which four sideholes were laser-punched over a length of 0.5 cm, from 0.5 to 1.0 cm from the tip. The distal end of catheter B was tapered to minimize infusion through the end-hole. Geometrical properties of the catheters are detailed in Table 1. The most distal sidehole was positioned 5 mm from the tip of both catheters. Care was taken to locate the tip of the infusion catheter such that all sideholes were positioned inside the coronary artery, but close to the coronary ostium. Mixing is facilitated by non-fully developed entrance flow and secondary flows due to the curvature and irregular shape of the connection.

Measurements were carried out at two infusion rates: a low rate of 15 ml/min and a higher rate of 25 ml/min.

2.3.2. Temperature registration during guide wire pullback

To investigate the mixing behaviour of the infusedate with the heated water in the model, the influence of warming of the mixture via the vessel wall, and the optimal location for measurement of the infusate temperature $T_i$, a pullback protocol was carried out. The local temperature during infusion was measured by step-wise manual pullback of the guide wire, from a sensor position 10 cm distal to the tip of the infusion catheter to 4 cm inside the infusion catheter at intervals of 1 cm. Pullback temperature curves were made for both catheters at coronary flow rates of 50 and 250 ml/min.

2.3.3. Flow measurement at fixed position

Coronary flow was derived by continuous infusion thermodilution ($Q_{th}$) using Eq. (2) and was correlated to the real flow measured by the ultrasound flow probe. The coronary flow rate was varied from 50 to 250 ml/min in steps of 50 ml/min. From the pullback curves the optimal sensor positions for measurement of mixing temperature $T$ and infusate temperature $T_i$ were derived. Aortic pressure, temperature, and coronary pressure and flow were monitored. The sensor was positioned distal to the tip of the infusion catheter at the location determined by the guide wire pullback experiment. Infusion was started at a rate of $Q_i$ and the time-averaged mixing temperature $T$ was determined, subsequently the guide wire was pulled back into the infusion catheter for the determination of $T_i$. Consequently mean coronary flow was calculated. Simple linear regression was performed to test whether the data points differed from the line of identity. Data were analyzed using Bland–Altman plots [17,18].

3. Results

3.1. Temperature registration during guide wire pullback

All temperature registrations during the pullback curves show variations in temperature between 3 and 10 cm from the catheter tip for both infusion catheters and infusion rates (Fig. 2), for both catheters. The instationary variations in temperature between 0 and 3 cm from the tip were larger than further downstream. To evaluate the course of the temperature difference as a function of the distance, all temperatures were normalized to the mean temperature between 3 and 10 cm (Fig. 3). The shape of the curves was

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Model A</th>
<th>Model B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of sideholes</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Sideholes distributed over</td>
<td>30 mm</td>
<td>5 mm</td>
</tr>
<tr>
<td>Outer $\phi$</td>
<td>1 mm</td>
<td>1.17 mm</td>
</tr>
<tr>
<td>Inner $\phi$</td>
<td>0.53 mm</td>
<td>0.97 mm</td>
</tr>
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</table>
Fig. 3. Detail of Fig. 2 outside the catheter. Temperature difference ($T_b - T$) is normalized to the mean temperature difference over 3–10 cm, distal to the infusion site for both catheters (model A (top) and model B (bottom)). Open symbols denote coronary flow of 250 ml/min, filled symbols 50 ml/min, infusion rates: (○) 25 ml/min and (□) 15 ml/min.

Fig. 4. Example of pressure, flow, and temperature signals. Simultaneous aortic (red) and coronary (green) blood pressures in mmHg are shown in the top panel. Due to the pulsatile nature of the coronary blood flow (middle panel) variations in the temperature were observed due to the pulsatile nature of the coronary blood flow. Strictly speaking, due to these variations in the mixing temperature are observed due to the pulsatile nature of the coronary blood flow. Hence, the mixing temperature was unsteady (model A) or decreasing (model B) towards the tip.

The mixing is influenced by the infusion catheter design, position of the temperature sensor, and infusion flow rate. The effects of variation in these parameters on the determination of the coronary flow were investigated. From the guide wire pullback a position 5 to 6 cm distal to the tip of the infusion catheter appeared to be a proper distance to obtain the relevant mixing temperature $T$. However, a varying temperature with the distance to the tip of the infusion catheter was found, which indicates incomplete mixing. The pattern of the variations was similar for both infusion catheters and both flow rates used. The first few centimetres distal to the tip may be defined as mixing chamber, from 5 to 8 cm the temperature was similar for both catheters and infusion rates and the distance could be divided into three characteristic zones, (a) <5 cm: the temperature was unsteady (model A) or decreasing (model B) towards the tip, (b) 5–8 cm: a steady or decreasing temperature was present with increasing distance distal from the tip, (c) >8 cm: a gradual rise in temperature was seen with both catheters.

The accuracy of the method could be determined, provided the regression line did not differ from the line of identity. In Fig. 5a–c the absolute flow rate is progressively underestimated with increasing flow rate. This indicates that the accuracy of the measurement is strongly related to the absolute value of the coronary flow. In these cases the regression lines differed from the line of identity. A general estimation for the accuracy can therefore not be given. For catheter B in combination with a high infusion rate the regression line did not differ significantly from the line of identity ($p = 0.17$). Therefore it can be stated that only a slight overestimation of $7 \pm 8\%$ of true coronary flow is found with catheter B in combination with a high infusion rate. This corresponds to a mean absolute difference between calculated and direct measured flow over the entire range of $7 \pm 4\%$.

4. Discussion

An in vitro model was used to investigate the most critical boundary condition for clinical application of continuous infusion flow measurement: the mixing of the flow medium and infusate. The mixing is influenced by the infusion catheter design, position of the temperature sensor, and infusion flow rate. The effects of variation in these parameters on the determination of the coronary flow were investigated. From the guide wire pullback a position 5 to 6 cm distal to the tip of the infusion catheter appeared to be a proper distance to obtain the relevant mixing temperature $T$. However, a varying temperature with the distance to the tip of the infusion catheter was found, which indicates incomplete mixing. The pattern of the variations was similar for both infusion catheters and both flow rates used. The first few centimetres distal to the tip may be defined as mixing chamber, from 5 to 8 cm the temperature was
Fig. 5. Comparison of the calculated flow $Q_{th}$ to the direct measured flow $Q_{meas}$ for the two catheters A and B and for infusion rates of 15 ml/min and 25 ml/min. On the right-hand side the relative differences between the techniques are plotted against the average of the two techniques.

relatively stable, and after 8 cm the temperature difference between the mixture and inflow blood decreased. The latter effect may be due to heat loss through the wall. However, no clear reason for the characteristic 8 cm for this effect to occur is available. An alternative explanation for the varying temperature over the range from 3 to 10 cm may be found in the presence of a swirl of the cold infusate in the vessel. In that case the reliability of the method is negatively influenced, because no guarantee for complete mixing can
be given then. It is less likely that this effect occurs in a coronary artery, because of the large variety in curvature of the vessels and the motion of the coronary arteries due to the beating of the heart. In this respect the presence of side branches needs attention when performing continuous infusion experiments in vivo. The results for determination of coronary flow are not influenced by side branches provided that mixing is complete before a side branch is reached. However, if mixing is not complete, loss of infusate negatively influences the accuracy of the technique and true coronary flow will be overestimated. In our in vivo experiments [15] we found that the mixing area was indeed smaller due to the favourable conditions for mixing as mentioned. Mixing was found to be adequate at a distance of 3 cm distal to the infusion site. Such a distance without side branches can be obtained in almost any coronary artery.

The infusate temperature \( T \) is determined inside the infusion catheter during the procedure. For catheter A small variations in \( T \) were observed, whereas for catheter B variations were larger. However, the variations in \( T \) did not significantly influence the calculations, because of the limited relative importance of a small absolute variation in \( T \) to the ratio of \( T \) and \( T_c \). Therefore, 1 cm within both catheters was found to be an adequate location to obtain \( T \).

The mixing became worse with increasing coronary flow rates reflected in lower (more negative) mixing temperatures of \( T \). Consequently, these lower values translate into lower calculated coronary flow values. This observation may be explained by the decreasing ratio of infusion flow velocity and coronary flow velocity. The presence of sideholes, and their size and position, determine the inflow velocity and direction of the infusate. The sideholes positioned closely together in combination with a tapered endhole are factors which we expected to enhance mixing due to the “spraying” effect during infusion. The measurement with catheter B was the most accurate over the entire range for the high infusion rate of 25 ml/min (Fig. 5), confirming our hypothesis. The influence of the infusion velocity on the flow might have been damped out between the sideholes of catheter A, which were relatively large apart. Moreover, infusate infused through the open endhole, in the direction of the main coronary flow, would not have facilitated mixing, also explaining the inferior results of catheter A.

However, when the position of the tip of the infusion catheter B was only slightly advanced into the coronary artery by 3 cm, mixing was immediately worse and the flow was underestimated (data not shown). Thus, the occurrence of secondary flows or flow disturbances, resulting from the inflow which is not fully developed in the irregularly shaped modelled coronary ostium, is of great importance for the mixing to take place. Proper mixing is the main determinant for the technique to be useful. The smooth nature of the coronary artery in the in vitro model limit formation of complex flow patterns which consequently complicates mixing. The complex geometry of the blood vessel in combination with the beating of the heart will enhance proper mixing in the in vivo situation and hence more accurate flow calculations may be obtained. On the other hand, water is used as a medium in our in vitro set-up, while the flow was not scaled, so the relatively high Reynolds number could indicate an increased probability for flow instabilities to occur, enhancing the mixing process. The difference in viscosity between water and blood may additionally affect the mixing process. Also the heat transfer to the wall may be different between the water in the model tube and the blood in the vessel. However, when the sensor position is chosen close to the end of the mixing zone, no significant influence is expected.

It might be argued that iced saline could be used for this technique instead of saline at room temperature. However, iced saline at the same infusion rates as in these experiments would induce severe cooling of the myocardium resulting in conduction disorders. From pilot experiments we found that the mixing temperature \( T \) should not decrease three degrees below blood temperature.

Therefore the infusion rate should be chosen such that \( T \) is around one to three degrees below blood temperature. Using iced saline, this would result in unfavourable low infusion rates which, as we have shown in this study, negatively influence adequate mixing and therefore the accuracy of the technique.

5. Conclusion

Absolute coronary flow rate can be directly measured reliably over the entire physiologic range of 50–250 ml/min by the continuous infusion method, under the condition that a suitable infusion catheter is used at a high infusion rate of 25 ml/min and positioned in an area with a complex flow pattern as presently in a coronary artery. The measurement location should be chosen appropriately, slightly distal to the mixing zone.

5.1. Clinical implications

Because clinically applicable catheters and infusion equipment were used, the optimization of the methodology and catheter design performed in this study can be directly used in the catheterization laboratory. Optimal mixing between the saline and the blood was indicated to be the main prerequisite for successful measurement of coronary flow. The nature of coronary flow in vivo is expected to be even more favourable towards optimal mixing than the in vitro flow, due to the complex geometry and the beating of the heart. Therefore, this study contributes to the feasibility of continuous infusion flow measurement in selective coronary arteries, providing the first methodology to perform such absolute flow measurement.

Acknowledgements

This study was supported by the Dutch Technology Foundation (STW) project EPG.5454, and by RADI Medical Systems, Uppsala, Sweden. The authors would like to thank Boston Scientific, Natick (MA), USA, and Occam International, Eindhoven, The Netherlands, for the design and production of the infusion catheters.

Appendix A The temperature distribution in the vessel during infusion can be described using the heat equation, expressing the conservation of energy within the system. The general form is given by

\[
\rho c_p \left[ \frac{\partial T}{\partial t} + (\mathbf{u} \cdot \nabla) T \right] = k \nabla^2 T \tag{A.1}
\]

where \( \rho \) is density, \( c_p \) is specific heat, \( T \) is temperature, \( t \) is time, \( \mathbf{u} \) is velocity, and \( k \) is thermal conductivity. The first term on the left-hand side of Eq. (A.1) describes the local temperature variations in time. In the continuous infusion experiments the heat transfer due to mixing is assumed to be stationary, hence \( \partial T / \partial t = 0 \). The diffusion of heat is assumed to be small compared to convective heat transfer due to the fluid flow: \((\mathbf{u} \cdot \nabla) T \gg k \nabla^2 T \). Now the simplified heat equation becomes

\[
\rho c_p \left( \mathbf{u} \cdot \nabla \right) T = 0 \tag{A.2}
\]

In this general form, only one fluid is considered. In the measurement situation cold fluid (subscript i) is added to the blood (subscript b):

\[
\rho_b c_{p,b} \left( \mathbf{u}_b \cdot \nabla \right) T + \rho_i c_{p,i} \left( \mathbf{u}_i \cdot \nabla \right) T = 0 \tag{A.3}
\]

When optimal mixing is assumed, integration over the vessel cross-section (to achieve volumetric flow \( Q \)) and in the direction of the flow (to derive temperature differences from temperature gradients) is allowed and gives

\[
\rho_b c_{p,b} Q_b (T_b - T) + \rho_i c_{p,i} Q_i (T_i - T) = 0 \tag{A.4}
\]
and after rearranging:

\[ Q_b = \frac{\rho b c_p, i}{\rho b c_p, b} \left[ \frac{T_b - T_i}{T_b - T_f} - 1 \right] Q_i \] (A.5)

Conflict of interest statement

None.

References


