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

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ABSTRACT

Direct volumetric assessment of coronary flow during cardiac catheterization has not been available so far. In the current study continuous infusion thermodilution, a method based on continuous infusion of saline into a selective coronary artery is evaluated. Theoretically, volumetric flow can be calculated from the known infusion rate (Q_i), the temperatures of the blood (T_b), the saline (T_i), and the mixture downstream to the infusion site (T). We aimed to validate and optimize the measurement method in an in vitro model of the coronary circulation. Full mixing of infusate and blood was found to be the main prerequisite for accurate determination of the coronary flow. To achieve full mixing the influence of catheter design, infusion rate, and location of temperature measurement were assessed.

We found that continuous infusion thermodilution slightly overestimated coronary flow determined by directly measured reference flow by $7 \pm 8\%$, over the entire physiological flow range of 50–250 ml/min. These results were found using a specially designed infusion catheter (infusion mainly through distally located sideholes), a high enough infusion rate (25 ml/min), and measurement of the mixing temperature between 5 and 8 cm distal from the tip of the infusion catheter.

Absolute coronary flow rate can be measured reliably by the continuous infusion method when full mixing is present, under the conditions mentioned above.

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

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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 $9 \pm 21\%$ over the entire physiological flow range of 50–250 ml/min in the animal experiments. Reproducibility was excellent ($-2 \pm 12\%$) [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 (Q_b) can be calculated from the temperatures of the blood (T_b), the infused indicator (T_i), and the mixture downstream from the infusion site (T), and the known infusion rate (Q_i) by

$$Q_b = \frac{\rho_i c_{p,i}(T - T_i)}{\rho_b c_{p,b}(T_b - T)} Q_i = \frac{\rho_i c_{p,i}}{\rho_b c_{p,b}} \left[\frac{T_b - T_i}{T_b - T} - 1\right] Q_i \quad (1)$$

where ρ_b and ρ_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_i and the original blood flow before infusion can be found using

$$Q_{b,orig} = \frac{\rho_i c_{p,i}}{\rho_b c_{p,b}} \left[\frac{T_b - T_i}{T_b - T} - 1\right] Q_i + Q_i \quad (2)$$

In the remainder of this article Q_{th} will be used instead of $Q_{b,orig}$.

In the current in vitro study water is used both as the flow medium (instead of blood) and for the infusate (instead of saline) resulting in a value for the specific heat density-fraction of 1.002. The water used for the infusate was at room temperature.

As mentioned, the principal condition for this technique requires for the infusate and the flow medium to be fully mixed. A non-homogeneous mixture might lead to a fluctuating mixing temperature measured distal from the site of infusion corresponding to an over- or underestimation of the coronary flow rate. The design of the infusion catheter influences the mixing process.

Secondly the mixing temperature is assumed to be only determined by the two inflow fluids, flow medium and infusate, and is not influenced by heat transfer between the mixed fluid and the wall. Theoretically, the fluid will be heated gradually with increasing distance from the infusion site.

Third, in the calculation of blood flow from fluid temperatures an assumption for the possible change in myocardial resistance should be made: hence the influence of the infusion to total myocardial flow should be determined. These boundary conditions are studied in the in vitro experiments.

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 $37.00 \pm 0.05\,^{\circ}C$ 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 an 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