Catheter-Based Measurements of Absolute Coronary Blood Flow and Microvascular Resistance

Feasibility, Safety, and Reproducibility in Humans

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Background—The principle of continuous thermodilution can be used to calculate absolute coronary blood flow and microvascular resistance (R). The aim of the study is to explore the safety, feasibility, and reproducibility of coronary blood flow and R measurements as measured by continuous thermodilution in humans.

Methods and Results—Absolute coronary flow and R can be calculated by thermodilution by infusing saline at room temperature through a dedicated monorail catheter. The temperature of saline as it enters the vessel, the temperature of blood and saline mixed in the distal part of the vessel, and the distal coronary pressure were measured by a pressure/temperature sensor-tipped guidewire. The feasibility and safety of the method were tested in 135 patients who were referred for coronary angiography. No significant adverse events were observed; in 11 (8.1%) patients, bradycardia and concomitant atrioventricular block appeared transiently and were reversed immediately on interruption of the infusion. The reproducibility of measurements was tested in a subgroup of 80 patients (129 arteries). Duplicate measurements had a strong correlation both for coronary blood flow (ρ=0.841, P<0.001; intraclass correlation coefficient=0.89, P<0.001) and R (ρ=0.780, P<0.001; intraclass correlation coefficient=0.89, P<0.001). In Bland–Altman plots, there was no significant bias or asymmetry.

Conclusions—Absolute coronary blood flow (in L/min) and R (in mm Hg/L/min or Wood units) can be safely and reproducibly measured with continuous thermodilution. This approach constitutes a new opportunity for the study of the coronary microcirculation. **(*Circ Cardiovasc Interv*. 2018;11:e006194. DOI: 10.1161/CIRCINTERVENTIONS.117.006194.)**

Key Words: coronary angiography ■ fractional flow reserve ■ microvascular angina ■ microvessels ■ myocardial ■ reproducibility of results ■ temperature ■ thermodilution

Coronary microcirculatory dysfunction, believed to be common in patients with angina in whom the epicardial vessels are free from significant disease, carries an adverse prognosis.[1–3] In addition, the coronary microcirculation is also adversely affected by vasoconstriction and embolization of thrombotic material in the setting of acute coronary syndromes and percutaneous coronary intervention.[4,5] To date, few methods allow for the quantitative assessment of the microcirculation independent of the presence of epicardial stenoses.[6] The majority of techniques are based on imaging modalities, and therefore, they are not readily available in the cathlab as part of a comprehensive evaluation of the coronary arterial tree.[2]

The principle of continuous thermodilution can be used to calculate absolute coronary blood flow (Q).[7] The concomitant measurement of pressure in the distal part of the vessel allows the calculation of myocardial resistance. The recent development of a dedicated monorail infusion catheter has simplified the measurement of absolute Q and microvascular resistance (R) in the cathlab, opening a new window to the coronary microcirculation.[8] Although data on the in vitro validation of the method and the infusion catheter have been recently published, in vivo data are lacking.[8] The purpose of this study was to evaluate the safety of measuring absolute coronary flow and myocardial resistance with a novel infusion catheter in humans, as well as to explore the repeatability of these measurements.

Methods

Anonymized patient-level data will be made available by the corresponding author for reasonable requests. Consent was not obtained for data sharing, but the presented data are anonymized and risk of identification is minimal.

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WHAT IS KNOWN

- Absolute coronary blood flow and microvascular resistances can be measured by continuous thermodilution.
- Recent developments have markedly simplified the method.

WHAT THE STUDY ADDS

- Thermodilution-derived measurements of absolute coronary blood flow (in L/min) and microvascular resistances (in mm Hg/L/min) are safe and reproducible in humans.
- The method is simple, quantitative, operator independent, and thereby opens a new research window to explore microvascular function.

Study Population

Patients were selected on the basis of having an indication for coronary angiography either because of stable angina or acute coronary syndrome. In patients with acute coronary syndromes, measurements were performed after the intervention in the culprit lesion. The study protocol was approved by the institutional ethics committee, and all patients gave written informed consent.

Calculation of Absolute Q and R

Q (mL/min) can be calculated by continuous intracoronary infusion of saline, as previously described, according to the equation

$$Q = c_p\left[\frac{(T_b - T_i)}{(T_b - T)} - 1\right]Q_i + Q_i$$

where Q_i is the saline infusion rate in mL/min, T_b is the temperature of blood in the distal coronary before infusion of saline, T_i is the temperature of the infused saline when it exits the infusion catheter, and T is the temperature of the homogenous mixture of blood and saline in the distal part of the coronary artery during infusion.[9,10] The constant c_p relates to the difference between the specific temperature and density of blood and saline, and when saline is infused in blood, this is equal to 1.08.[11] In practice, the temperature of blood (Tb, ≈37°C) is taken as a reference, and the other temperatures are measured with respect to that value. Therefore, T_i and T stand for relative temperatures compared with T_b, and the equation is simplified as follows:

$$Q = 1.08\frac{T_i}{T}Q_i - 0.08Q_i$$

Because, in clinical practice, Q_i is chosen between 15 and 30 mL/min, the last part of the equation subtracts between 1.2 and 2.4 mL/min from the calculated Q and can, therefore, be neglected. Consequently, the equation is further simplified to $Q = 1.08\frac{T_i}{T}Q_i$

Absolute R is calculated in analogy to Ohm's law:

$$R = \frac{P_d}{Q}$$

where P_d is the distal coronary pressure and Q is the coronary blood flow. R can be expressed in dyn.s.cm^{-5}, mm Hg/L/min, or Wood units.

Measurement Protocol

A 6F arterial sheath was introduced in the femoral artery, and 2500 U of heparin were administered intravenously. The coronary artery to be interrogated was intubated with a guiding catheter, and 0.2 mg of nitroglycerin were administered intracoronarily. A guidewire equipped with a pressure and temperature sensor (PressureWire X, Abbott, IL) was passed through the guiding catheter, and a dedicated monorail catheter (RayFlow, Hexacath, Paris, France) was advanced over the guidewire. As previously described, the catheter allows the infusion of saline only through the outer 4 side holes, resulting in complete and optimal mixing with blood; the inner 2 side holes allow the measurement of temperature by the guidewire (Figures I and II in the Data Supplement).[8]

The tip of the infusion catheter was placed in the first centimeter of the coronary artery. The catheter was then connected to an infusion pump (Medrad Stellant; Medrad Inc, Warrendale, PA), and saline at room temperature infused at a prespecified flow rate (Q_i, usually 20 mL/min for the left anterior descending [LAD] and left circumflex artery [LCX] and 15 mL/min for the right coronary artery [RCA]). The infusion of saline in itself produces a hyperemic state similar to that produced by adenosine; therefore, the procedure is simplified because adenosine administration is not needed.[12] The temperature of the saline/blood mixture (T) is measured at the distality of the coronary artery after achieving a steady state; P_d is simultaneously measured in the distal part of the vessel. The temperature of the infused saline (T_i) is measured when the temperature sensor of the guidewire is pulled back into the infusion catheter. The measured temperatures and pressures of a thermodilution tracing, as well as the calculated Q and R, are presented in Figure 1.

During every step of the measurement protocol, the temperature is first set to zero (reference temperature comparable to 37°C in humans), and then infusion is started with the injector, and then the temperature in the distal coronary artery is decreased. After reaching a steady state, the temperature of the blood/saline mixture is recorded for ≈30 seconds. Thereafter, the sensor is pulled back into the infusion catheter to obtain Ti. After completion of the measurements, the guidewire, infusion, and guiding catheter are removed from the artery. For repeatability, a second set of measurements are obtained after reinstrumenting the artery.

All coronary pressure tracings and temperatures are wirelessly transmitted and analyzed by a dedicated console equipped with software that automatically calculates Q and R (Coroventis Coroflow, Uppsala, Sweden).

Resting Distal Coronary to Aortic Pressure Ratio (P_d/P_a) and Fractional Flow Reserve Measurements

The impact of the catheter on measured indices was assessed in a subgroup of vessels (n=25). Resting Pd/Pa and fractional flow reserve (FFR) values were measured with and without the catheter in the coronary artery and were compared pairwise. FFR measurements were performed by administering a bolus of intracoronary adenosine (200 μg for the LAD or the LCX and 100 μg for the RCA) as previously described.[13]

Statistical Analysis

Categorical values are presented as absolute counts and percentages; continuous variables are presented as mean±SD or median (25th–75th value) where appropriate. Normality was tested using the Shapiro–Wilk normality test. Measured temperatures and hemodynamic indices at baseline and during saline infusion were compared with the paired *t* test or the Wilcoxon-matched pairs signed-rank test where appropriate. Between-vessel measurements were compared with the Kruskall–Wallis rank test. Because measurements in the arteries of the same patient may be correlated, mixed (fixed and random) effects linear models with maximum likelihood and an independent covariance structure (Stata mixed command) were used. In these models, T, Ti, Q, R, and Pd/Pa during infusion were the dependent variables, coronary artery was the fixed factor variable, and the individual patient was the random component. The coefficient

of variation, that is, the ratio of the root mean squared error to the mean, was calculated for T, Ti, Q, R, and Pd/Pa during infusion. The repeatability of the 2 consequent measurements was assessed by calculating their intraclass correlation coefficients; a 2-way mixed single-measures model was used (intraclass correlation coefficients [3, 1]). In addition, Spearman ρ correlation coefficients were calculated, and the Bland–Altman plots of the difference of the 2 measurements plotted against their mean were examined. Analyses were performed with Stata 13 and GraphPad Prism 7. $P<0.05$ was considered statistically significant.

Results

Feasibility and Safety Data

The feasibility and safety of the method were tested in 135 patients who were referred for coronary angiography. Their baseline characteristics are presented in Table 1. Successful instrumentation of the coronary artery and acquisition of temperature tracings and calculation of Q and R were achieved in all patients. No significant adverse events were observed. In 11 (8.1%) patients, bradycardia and concommitant atrioventricular block appeared transiently during saline infusion at a rate of 20 mL/min in their RCA (6 patients), LCX (4 patients), and in a saphenous vein graft to the RCA (1 patient); the arrhythmia was resolved immediately on stopping the infusion. Three patients (2.2%) had premature ventricular beats during infusion in the LAD (1 patient), LCX (1 patient), and the RCA (1 patient). In 1 patient (0.7%), a drop in distal coronary pressure (Pd) was noted during infusion in the LAD artery; this was immediately restored after stopping the infusion. Three patients (2.2%) complained of chest discomfort during saline infusion in their LAD without accompanying electrocardiographic changes suggestive of ischemia; symptoms ceased when the infusion was interrupted.

The saline infusion induced a modest decrease in heart rate (69±1 at baseline versus 67±1 during infusion; $P=0.002$). The ratio of distal coronary pressure to proximal (aortic) pressure (Pd/Pa) was significantly affected by the saline infusion, with baseline Pd/Pa values being higher than the respective values during infusion (0.95 [0.91–0.98] versus 0.88 [0.79–0.93]; $P<0.0001$; Figure 2). The saline infusion induced an increase in blood pressure measured at the tip of the guiding catheter (Pa) from 86±20 mm Hg at rest to 91±18 mm Hg during infusion ($P=0.02$).

Reproducibility

Duplicate measurements were made in 129 vessels in 80 patients; the baseline characteristics of this subgroup are presented in Table 2.

The range of temperatures measured in the distality of the coronary artery (T) was −0.08°C to −2.20°C below the reference temperature; for the temperatures of the infused saline (Ti), the range was −1.00°C to −6.05°C below the reference temperature. Based on these temperatures and the rates of saline infusion (Qi), the ranges of calculated absolute Q and R were 33 to 361 mL/min and 202 to 1691 mm Hg/L/min, respectively. Descriptive data for T, Ti, Q, R, and Pd/Pa during infusion on a per-vessel basis are presented in Table 3. The results of the mixed effects models are presented in Table I in the Data Supplement.

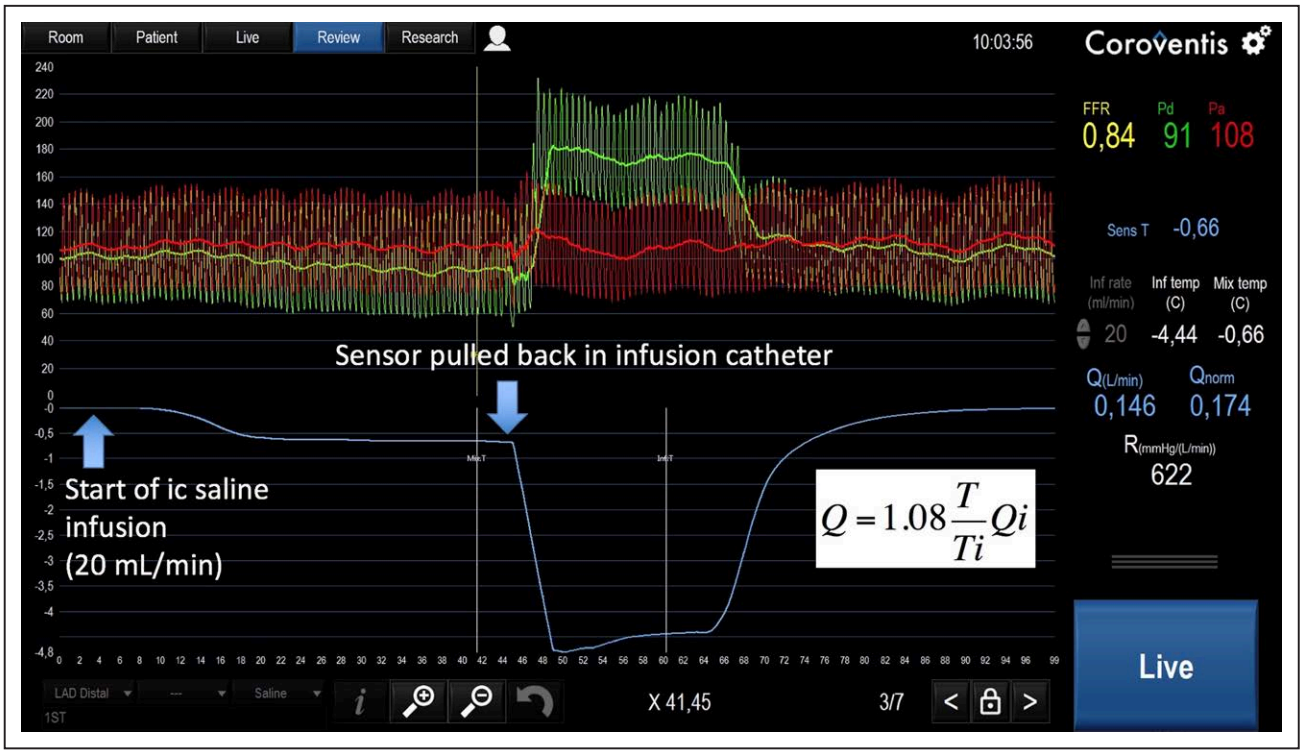

Figure 1. Thermodilution-derived absolute coronary blood flow and microvascular resistance measurement. Example of thermodilution-derived absolute microvascular resistance and coronary blood flow in a left anterior descending artery. The flow rate of the administered saline is 20 mL/min, and the calculated values of absolute coronary blood flow (Q) and microvascular resistance (R) are 0.146 L/min and 622 mm Hg/L/min, respectively. The theoretically achieved maximum blood flow in the absence of epicardial stenoses (Q_{norm}), that is, if fractional flow reserve (FFR) was equal to 1, is also displayed. Pa indicates aortic pressure; and Pd, distal coronary pressure.

Table 1. Baseline Characteristics of the Entire Cohort

No. of patients	135
No. of coronary arteries	203
Male/female, n (%)	102/33 (76%/24%)
Age, y	63 (56, 70)
LAD/LCX/ramus/RCA/SVG	102/43/2/55/1
Current smoking, n (%)	20 (15%)
Diabetes mellitus, n (%)	22 (16%)
Hypertension, n (%)	63 (47%)
Dyslipidemia, n (%)	72 (53%)
Stable angina, n (%)	112 (83%)
Acute coronary syndrome, n (%)	11 (8%)
Control angiogram after recent PCI, n (%)	12 (9%)

LAD indicates left anterior descending coronary artery; LCX, left circumflex coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; and SVG, saphenous venous graft.

The coefficients of variation for T, Ti, Q, R, and Pd/Pa during infusion were 18.4%, 9.4%, 19.7%, 19.7%, and 3.7%, respectively.

The average intraclass correlation coefficients for the first and second measurements of T, Ti, Q, R, and Pd/Pa during infusion were 0.92, 0.94, 0.91, 0.90, and 0.97 (P<0.001 for all), respectively. Similarly, the Spearman ρ correlation coefficients were 0.866, 0.905, 0.841, 0.780, and 0.93 (P<0.001 for all) for the repeated measurements of T, Ti, Q, R, and Pd/Pa during infusion (Figure 3).

The Bland–Altman plots of the difference between the 2 measurements plotted against their mean value are presented in Figure 4. The calculated biases for T, Ti, Q, R, and Pd/Pa during infusion were −0.01±0.09, 0.05±0.37, −3±36, 1±106, and 0.06±0.67, respectively; none of them differed significantly from zero (P>0.05 for all).

The presence of the catheter altered slightly the resting Pd/Pa values (0.96 [0.93–1.00] without RayFlow versus 0.95 [0.92–1.00] with the RayFlow catheter; P=0.004). During hyperemia, the presence of the catheter resulted in a small—albeit statistically significant—difference in FFR values (0.90 [0.87–0.96] without RayFlow versus 0.87 [0.84–0.94] with RayFlow; P=0.0004; Figure 5).

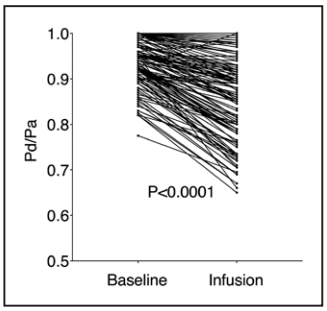

Figure 2. Distal coronary to aortic pressure ratios (Pd/Pa) at baseline and during infusion of saline with the RayFlow catheter. Continuous saline infusion induced a decline of Pd/Pa in almost all arteries, which reached a plateau within 10 s after the start of infusion.

Table 2. Baseline Characteristics and Measured Absolute Coronary Blood Flow and Resistances of Patients in Whom Duplicate Measurements Were Performed

No. of patients	80	No. of coronary arteries	129
Male/female, n (%)	60/20 (75%/25%)	LAD/LCX/ Ramus/RCA/SVG	64/30/2/32/1
Age, y	63±9	Pd, mm Hg	77±19
Current smoking, n (%)	16 (20%)	Q, mL/min	178±63
Diabetes mellitus, n (%)	14 (18%)	R, mm Hg/L/min	440 (367, 561)
Hypertension, n (%)	48 (60%)		
Dyslipidemia, n (%)	53 (66%)		
Stable angina, n (%)	55 (69%)		
Acute coronary syndrome, n (%)	11 (18%)		
Control angiogram after recent PCI, n (%)	12 (20%)		

The values of Pd, Q, and R are the average of the first and second measurements. In patients with acute coronary syndrome, measurements were performed after percutaneous coronary intervention of the culprit lesion. LAD indicates left anterior descending coronary artery; LCX, left circumflex coronary artery; PCI, percutaneous coronary intervention; Pd, distal coronary pressure; Q, absolute coronary blood flow; R, absolute microvascular resistance; RCA, right coronary artery; and SVG, saphenous venous graft.

Discussion

Summary of Findings

The present study reports the first data on the safety and repeatability of in vivo measurements of absolute coronary flow and R with a novel monorail infusion catheter using the

Table 3. Distribution of Measured Temperature, Absolute Coronary Blood Flow, and Microvascular Resistance per Vessel

	Left Anterior Descending Artery (n=64)	Left Circumflex Artery (n=30)	Right Coronary Artery (n=32)	*P* Value
T, °C	−0.48 (−0.59, −0.39)	−0.51 (−0.71, −0.37)	−0.43 (−0.51, −0.35)	0.09
Ti, °C	−4.2 (−4.4, −3.5)	−4.0 (−4.7, −3.6)	−3.5 (−4.3, −3.1)	0.07
Q, mL/min	189 (151, 232)	148 (120, 196)	166 (118, 210)	0.10
R, mm Hg/L/min	390 (347, 466)	519 (424, 584)	476 (391, 655)	<0.0001
Pd/Pa during infusion	0.80 (0.74, 0.85)	0.91 (0.85, 0.98)	0.91 (0.90, 0.95)	<0.0001

The presented values are the average of the duplicate measurements and are presented as median (25th–75th value). Values for ramus intermedius and venous grafts are not presented because of the limited number of measurements at such vessels (n=2 and n=1, respectively). For an optimal signal to noise ratio, T should be in the range 0.4°C–1.0°C and Ti 3°C–8°C below blood temperature. Pd/Pa indicates ratio of distal coronary to aortic pressure; Q, absolute coronary blood flow; R, absolute microvascular resistance; T, temperature of blood and saline mixture; and Ti, temperature of infused saline.

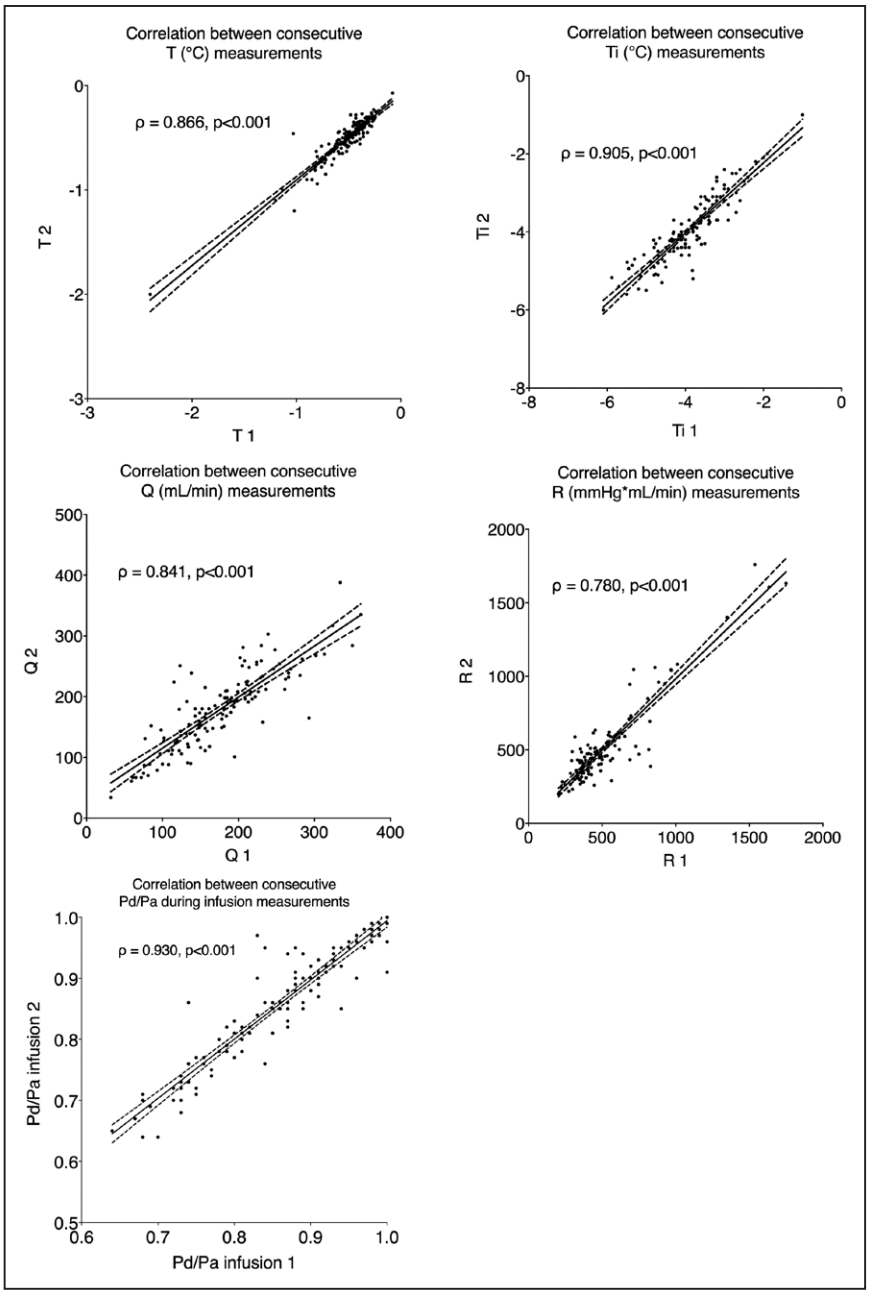

Figure 3. Scatter plots and correlations of first and second measurements for temperature of blood and saline mixture (T), temperature of infused saline (Ti), absolute coronary blood flow (Q), absolute microvascular resistance (R), and ratio of distal coronary to aortic pressure (Pd/Pa) during infusion. The pairs of values were obtained before and after reinstrumenting the artery.

principle of continuous thermodilution and calculated on line using specialized novel software.

The feasibility of the method was described 10 years ago, but the technique has been hampered by the absence of an appropriate monorail infusion catheter, the need for additional intravenous adenosine, and the absence of suitable software.[9] Now, all 3 issues have been solved: the RayFlow catheter allows the appropriate infusion of saline, there is no need for additional adenosine because the saline infusion induces hyperemia, and dedicated software for calculating Q and R online has been developed. Therefore, the procedure has become easy, taking ≈5 minutes including the 60 seconds of infusion of saline at room temperature, once the guide catheter, the pressure/temperature wire, the RayFlow catheter, and the pump with saline are all set.

The safety was confirmed by the absence of any significant complications. When saline was infused, we observed bradycardia in 8.1% of measurements mainly in the RCA and the LCX, never in the LAD. We did not observe any total atrioventricular block nor significant drop in systemic pressure. Three patients (2.2%) spontaneously mentioned some chest discomfort during the infusion. The description of symptoms was similar to complaints often mentioned during adenosine infusion albeit less pronounced, suggesting that the experience is related to the induction of hyperemia. Recently, in a comparable group of patients, it was shown that even prolonged infusion (>2 minutes) of saline at room temperature in the proximal LAD did not induce any changes in indices of systolic or diastolic function.[12]

Test–retest repeatability was investigated in 80 patients. It is important to note that these duplicated measurements were obtained after removing the wire from the artery and pulling back the guide catheter into the aorta and reinstrumenting the

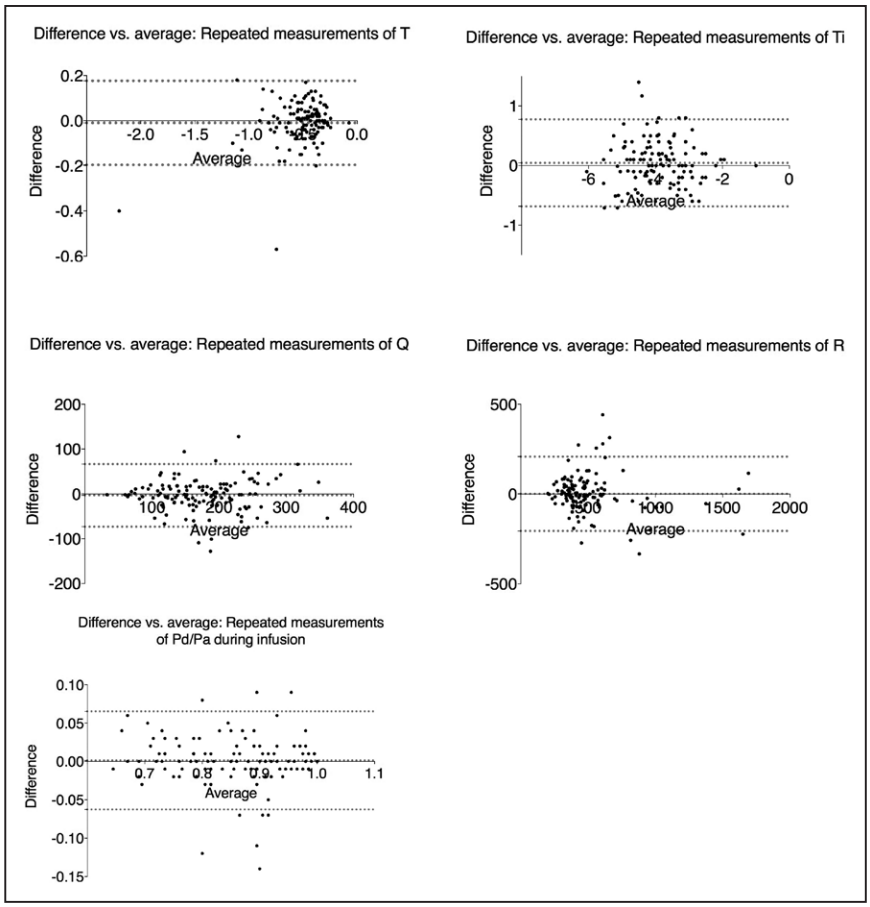

Figure 4. Bland–Altman plots of difference vs average values for repeated measurements of temperature of blood and saline mixture (T), temperature of infused saline (Ti), absolute coronary blood flow (Q), absolute microvascular resistance (R), and ratio of distal coronary to aortic pressure (Pd/Pa) during infusion. The pairs of values were obtained before and after reinstrumenting the artery.

artery again. This was intended to mimic as much as possible 2 separate measurements, and this approach is strikingly different from performing 2 measurements a couple of seconds apart during the same registration.[14,15] Measurements of Q and R have been shown to be reproducible and reliable as demonstrated by the intraclass correlation coefficients, correlation coefficients, and Bland–Altman analyses. The present test–retest repeatability data are in line with the previously reported in vitro validation results of the RayFlow catheter.[8] Some intraindividual variability can, however, not be disregarded. The latter relates to some possible biological variability but also to technical factors, such as the exact positions of the sensor and the infusion catheter. Yet, the variability was found to be a bit greater than that of other metrics obtained simultaneously, such as mean systemic pressure and heart rate, distal coronary pressure, or FFR measured twice with a time interval of 1 or 2 minutes (Table II in the Data Supplement). None the less, the variability of flow and R is in the same range or smaller than the variability of many other metrics frequently used for clinical decision making, such as fasting blood sugar levels, C-reactive protein, and cholesterol.[16–18]

Assessment of the Microcirculation

Among the noninvasive methods proposed to assess the microcirculation, positron emission tomography remains the standard of reference for quantifying myocardial blood flow as it can be expressed in mL/min per gram of tissue mass. However, the actual coronary driving pressure, often lower than central aortic pressure in patients with atherosclerosis, remains unknown and makes reliance on positron emission tomography–derived resistance measurements hazardous. Robust outcome data have emphasized the importance of assessing the microcirculation.[19–23] Fearon et al introduced the

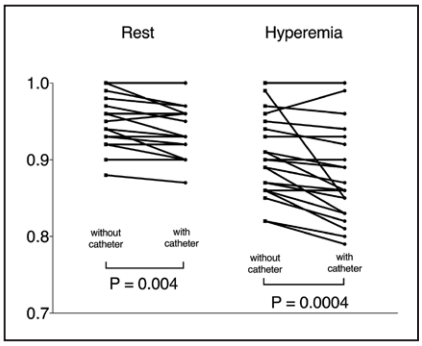

Figure 5. Ratio of distal coronary to aortic pressure (Pd/Pa) at rest and hyperemia with and without the RayFlow catheter. Pairwise comparisons of Pd/Pa at rest and during hyperemia, that is, fractional flow reserve (FFR), with and without the presence of the RayFlow catheter in the coronary artery (n=25). FFR was measured by administering a bolus of intracoronary adenosine (200 μg for the left anterior descending and left circumflex artery or 100 μg for the right coronary artery). The presence of the RayFlow catheter induced a decline in hyperemic Pd/Pa (FFR) from 0.90 (0.87–0.96) to 0.87 (0.84–0.94). Although statistically significant, the absolute decline is small and reflects the effect of the RayFlow catheter in the first millimeters of the epicardial artery.

concept of index of microcirculatory resistance that is based on the simultaneous recording of distal coronary pressure and bolus thermodilution-derived mean transit time. Compared with coronary flow reserve, an index that characterizes both the macro and microcirculation, index of microcirculatory resistance is more reproducible and is not dependent on resting values and therefore less dependent on hemodynamic changes.[24,25] The coronary microvascular resistance index has also been proposed as a metric of microcirculatory function.[26] Both flow velocity and pressure measurements during maximal hyperemia are required for its calculation, thus precluding its widespread use.[27,28]

Continuous Thermodilution

The present method relies on a simple basic principle. Three parameters should be known: the infusion rate of saline (in mL/min), the temperature of the saline when it enters the coronary tree (in degrees), and the temperature of the blood when saline and blood have been mixed in the distal part of the artery (in degrees). This rule of three allows the calculation of absolute Q. The calculated flow is hyperemic flow because it has been shown that the infusion of saline at room temperature through the RayFlow catheter reliably uniformly induces maximal hyperemia. This average proximal arterial flow in mL/min does not assess or account for specific stenosis or separate focal from diffuse coronary artery disease as does FFR. This implies that resting coronary flow, and therefore, coronary flow reserve, cannot be calculated by continuous thermodilution. Because the pressure in the distal coronary artery (ie, at the entrance of the microcirculation) is known, minimum (hyperemic) R can be calculated by dividing the pressure by the flow, expressed in mm Hg/L/min or Wood units. In addition, because FFR is known, the software also computes instantaneously the hyperemic flow that would have been present in case of strictly normal epicardial conductance. This allows the distinction between microvascular and epicardial resistance in case of diffuse atherosclerosis.[29] Even though statistically significant, the influence of the presence of the ultrathin infusion catheter on measured FFR was minimal and added little to the epicardial resistance. In addition, the FFR value without the presence of the RayFlow catheter can be calculated on the basis of the present as well as previously published data.[8]

A major advantage of this method is that—in contrast to Doppler or index of microcirculatory resistance—it is completely operator independent. The saline infusion can be continued until a true steady state is achieved (typically within 10–15 seconds), and during the entire measurement sequence, the operator does not touch the patient nor any catheter.

Limitations

The safety of the method was tested in too small number of patients and should be extended by further experience. In addition, we are still lacking data to demonstrate the innocuity of infusion of saline through small side holes. In the present study, we systematically ended the measurement with an high-quality angiogram at large magnification to ensure the absence of damage to the vessel wall. However, the angiogram might be too crude to be completely reassuring, and optical coherence tomography would have given more detailed information about the endothelial surface. Animal studies are being conducted to exclude endothelial damage because of prolonged infusion of saline at high flow rate. With high infusion rates—far above what is needed for a good measurement—damage to the vessel wall might occur as described recently in a case report where 120 mL/min instead of 20 mL/min was accidently infused.[30] Thus, it is advocated not to exceed 20 mL/min; in our experience, we have never seen any damage to the vessel wall in humans using this flow rate.

Besides being invasive and necessitating the need for additional material, the thermodilution-derived coronary flow approach has the limitation of not knowing the volume of myocardial mass that is perfused. Although neither convenient nor practical, the association of thermodilution with computed tomography or magnetic resonance imaging might provide some approximation of the myocardial mass. Therefore, substantial work is still required to determine what the normal coronary flow and resistance values are, in order to then be able to compare these values in different territories and different patients.

Conclusions

Despite some limitations, the present data confirm the feasibility, safety, and reproducibility of thermodilution-derived hyperemic coronary flow (expressed in L/min) and of coronary R measurements (expressed in mm Hg/L/min or Wood units) that can be performed simply and easily. If further confirmed and validated, this approach should allow a more quantitative and operator-independent quantification of the microvasculature and help in assessing treatment of microvascular dysfunction.

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Disclosures

Dr De Bruyne reports that his institution gets consultancy fees on his behalf for St Jude Medical, Opsens, and Boston Scientific. Dr Barbato reports that his institution gets consultancy fees on his behalf for St Jude Medical and Boston Scientific. Dr Pijls is consultant for St Jude Medical. The other authors report no conflicts.

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Catheter-Based Measurements of Absolute Coronary Blood Flow and Microvascular Resistance: Feasibility, Safety, and Reproducibility in Humans

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SUPPLEMENTAL MATERIAL

To the paper entitled:

Catheter-based measurements of absolute coronary blood flow and microvascular resistance: feasibility, safety and reproducibility in humans

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Supplemental table 1

Linear mixed effects regression models

Dependent variable:	Odds ratio	P value
T, ^{o}C		
Left anterior descending artery	-.16678 to .02428	0.144
Left circumflex artery	-.20085 to .02389	0.123

Dependent variable:	Odds ratio	P value
Ti, ^{o}C		
Left anterior descending artery	-.60194 to -.06924	0.014
Left circumflex artery	-.62856 to .00419	0.053

Dependent variable:	Odds ratio	P value
Q, mL/min		
Left anterior descending artery	-3.03920 to 44.31512	0.088
Left circumflex artery	-32.96534 to 23.34053	0.738

Dependent variable:	Odds ratio	P value
R, mmHg/L/min		
Left anterior descending artery	-247.4134 to -63.42376	0.001
Left circumflex artery	-170.2342 to 47.95417	0.272

Dependent variable:	Odds ratio	P value
Pd/Pa during infusion		

Left anterior descending artery	-0.14390 to -0.09153	<0.0001
Left circumflex artery	-0.03202 to 0.03023	0.955

T: temperature of blood and saline mixture; Ti: temperature of infused saline; Q: absolute coronary blood flow; R: absolute microvascular resistance.

In the models above, the coronary artery in which the measurements were made was used as an independent predictor (fixed effects) with three levels (left anterior descending artery/ left circumflex artery/ right artery). The right coronary artery was used as the reference group, to which the two other arteries were compared. Individual patients were used as the random component of the model.

Supplemental table 2

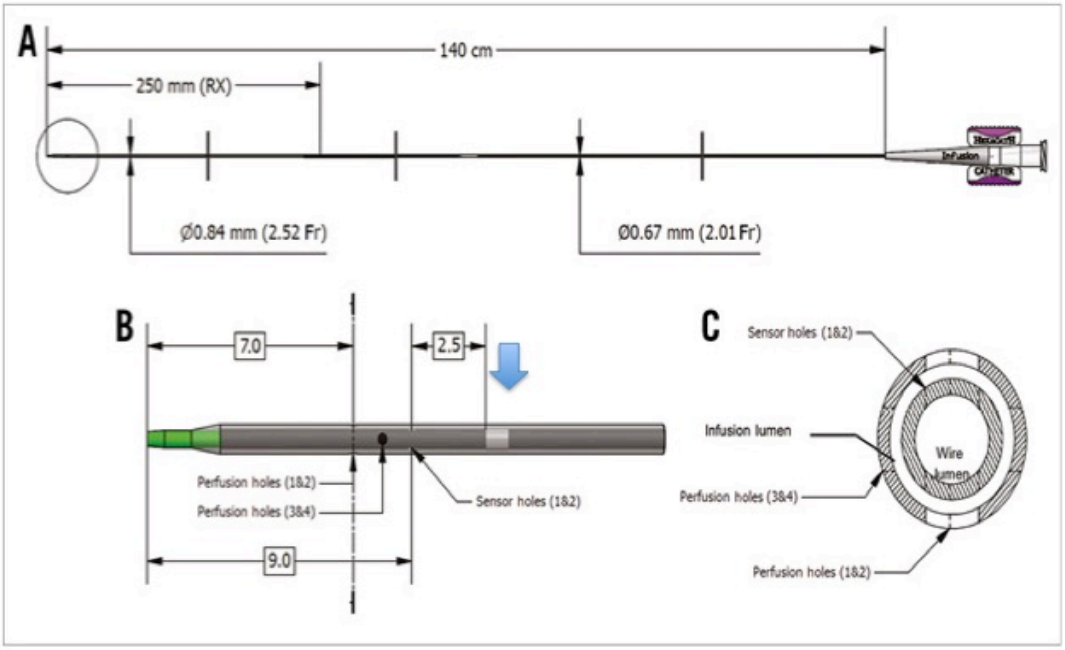
	Spearman's ρ correlation coefficient	Intraclass correlation coefficient	Coefficient of variation
T, °C	0.866 *	0.92 *	18.4%
Ti, °C	0.905 *	0.94 *	9.4%
Q, mL/min	0.841 *	0.91 *	19.7%
R, mmHg/L/min	0.780 *	0.90 *	19.7%
Heart rate, beats/min	0.912 *	0.94 *	9.9%
Pd/Pa	0.930 *	0.97 *	3.7%
Pd, mmHg	0.929 *	0.97 *	8.5%
Pa, mmHg	0.899 *	0.97 *	7.3%

Repeatability indices for duplicate measurements of T, Ti, Q, R, heart rate, Pd/Pa, Pd and Pa during saline infusion with the RayFlow catheter.

T: temperature of blood and saline mixture; Ti: temperature of infused saline; Q: absolute myocardial flow; R: absolute microvascular resistance; Pd/Pa: ratio of distal coronary to aortic pressure; Pd: distal coronary pressure; Pa: aortic pressure

* denotes $P<0.001$

Supplemental figure 1



RayFlow infusion catheter. A) Schematic drawing and dimensions of the design of the infusion catheter. B) Close-up of the tip (indicated in the circle in A), highlighting the four infusion holes and the two sensor holes. The blue arrow indicates the radiopaque marker of the catheter. C) The cross-section of the catheter tip at the most distal infusion holes (1 & 2), as indicated by the dashed line in B. The lumen for the guidewire and for the infusion as indicated.

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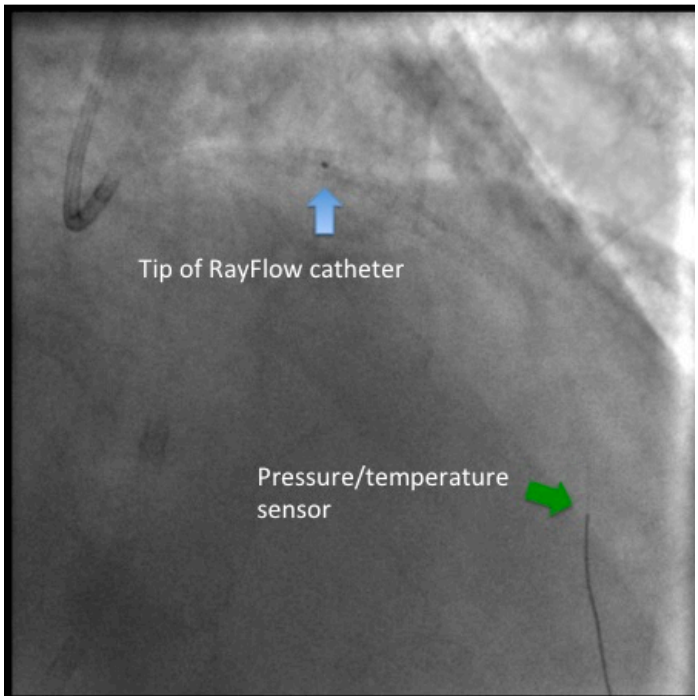
van ’t Veer *et al*. Novel monorail infusion catheter for volumetric coronary blood flow measurement in humans: in vitro validation EuroIntervention 2016 Aug 20;12(6):701-7. doi: 10.4244/EIJV12I6A114.

Supplemental figure 2



A guidewire equipped with a pressure/temperature sensor is advanced through a guiding catheter to the distality of the artery. Subsequently, the monorail RayFlow catheter is loaded on the wire and is advanced to the ostium of the coronary artery in which flow and resistances will be measured. The proximal part (hub) of the RayFlow catheter is connected to a pump that infuses saline at a constant flow rate. The temperature and pressure recordings from the sensor are transmitted wirelessly to a dedicated computer equipped with software (CoroFlow, Coroventis, Uppsala, Sweden) that allows for online calculation of absolute coronary blood flow and resistance.

The blue arrow indicates the position of the tip of the RayFlow catheter at the ostium of the vessel (here a left anterior descending artery) and the green arrow indicates the temperature/pressure sensor of the guidewire at the distal part of the artery.