Coronary Thermodilution to Assess Flow Reserve
Experimental Validation

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Background—Fractional flow reserve (FFR) and coronary flow reserve (CFR) are indices of coronary stenosis severity that provide the clinician with complementary information on the contribution of epicardial arteries and microcirculation to total resistance to myocardial blood flow. At present, FFR and CFR can only be obtained by 2 separate guidewires. The present study tested the validity of the thermodilution principle in assessing CFR with one pressure-temperature sensor-tipped guidewire.

Methods and Results—In an in vitro model, absolute flow was compared with the inverse mean transit time (1/Tmn) of a thermodilution curve obtained after a bolus injection of 3 mL of saline at room temperature. A very close correlation (r=0.95) was found between absolute flow and 1/Tmn when the sensor was placed 6 cm from the injection site. In 6 chronically instrumented dogs (60 stenoses; FFR from 0.19 to 0.98), a significant linear relation was found between flow velocity and 1/Tmn. A significant correlation was found between CFR Doppler, which was calculated from the ratio of hyperemic to resting flow velocities, and CFR thermo, which was calculated from the ratio of resting to hyperemic Tmn (r=0.76; SEE=0.24; P<0.001).

Conclusion—The present findings demonstrate the validity of the thermodilution principle to assess CFR. Because the pressure-temperature sensor was mounted in a commercially available angioplasty guidewire, this technique permits simultaneous measurements of CFR and FFR. (Circulation. 2001;104:2003-2006.)

Key Words: thermodilution ■ blood flow ■ microcirculation ■ coronary disease

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Coronary flow reserve (CFR) and fractional flow reserve (FFR) are 2 indices of stenosis severity that can be obtained during catheterization. FFR is derived from pressure measurement and specifically accounts for the contribution of the epicardial artery to total coronary resistance. CFR, as derived from Doppler flow velocities, accounts for both the epicardial and the microvascular resistances. FFR and CFR, therefore, provide the clinician with complementary information.

Currently, these indices are not obtained simultaneously because two separate wires, one pressure monitoring wire and one Doppler flow velocity wire, must be used. Actually, the sensor of the pressure-monitoring guidewire is also highly sensitive to changes in temperature. Thus, while measuring coronary pressure, it is possible to obtain a coronary thermodilution curve by injecting a bolus of saline at a temperature lower than that of blood.

We hypothesized that, from coronary thermodilution curves obtained at rest and during hyperemia, it is possible to calculate CFR. Accordingly, in the present study, we compared thermodilution-derived indices to absolute blood flow measurements in an in vitro model and to Doppler velocity–derived indices in an animal model.

Methods

Pressure/Temperature Sensor
A regular angioplasty pressure-monitoring guidewire (PressureWire 3, Radi Medical Systems) was used. The shaft of the wire, on which the temperature-dependant electrical resistance is monitored, acts as a proximal thermistor, which allows for the detection of the start of the injection. A microsensor is mounted 3 cm from the tip and enables simultaneous high-fidelity pressure and temperature measurements. Pressure and temperature are sampled at a frequency of 500 Hz. The wire is connected to a dedicated interface (RADI Analyzer, Radi Medical Systems) with modified software for online analysis of the thermodilution curves.

Principle and Indices
According to the indicator dilution theory,

\[ F = \frac{V}{T_{mn}} \]

(1)

where F indicates flow; V, vascular volume between the injection site and the measuring site of the indicator; and Tmn, the mean transit...
time of the indicator to travel from the injection site to the distal sensor. $T_{mn}$ is calculated as follows.

$$T_{mn} = \frac{\int_{0}^{\infty} t \cdot c(t) dt}{\int_{0}^{\infty} c(t) dt}$$

where $c(t)$ is the distal dilution curve.

$T_{mn}$ is independent of the amount and absolute temperature of the indicator. The injection of saline into the coronary tree is recorded by the proximal thermistor.

**Calculation of Thermodilution CFR**

Thermodilution CFR (CFR thermo) is calculated as follows. CFR is defined as the ratio of hyperemic divided by resting coronary flow ($F$).

$$\text{CFR} = \frac{F_{\text{at hyperemia}}}{F_{\text{at rest}}}$$

Flow is the ratio of the volume ($V$) divided by $T_{mn}$. Thus, CFR can be expressed as follows.

$$\text{CFR} = \frac{\frac{V}{T_{mn}}}{\frac{V}{T_{mn}}} \text{ at hyperemia}$$

Assuming the epicardial volume ($V$) remains unchanged, CFR can be calculated as follows.

$$\text{CFR} = \frac{T_{mn \text{ at rest}}}{T_{mn \text{ at hyperemia}}}$$

**In Vitro Model**

The in vitro model consisted of 4-mm inner diameter tubes mimicking the left coronary system. The “left main stem” was connected by a Y-connector to a pump providing pulsatile flow of saline at $37^\circ\text{C}$. Through the other port of the Y-connector, a 6F guiding catheter was inserted. Through this guiding catheter, a PressureWire 3 was advanced into the distal part of the “left anterior descending coronary artery” (LAD). The distance between the guiding catheter and the distal sensor varied from 3 to 12 cm. The distal extremity of the LAD and the “left circumflex” was left open to enable the measurement of volumetric flow. The flow through the LAD varied from 30 to 250 mL/min. To obtain a thermodilution curve, 3 mL of saline at room temperature was briskly injected by hand through the guiding catheter. For each value of absolute flow and for each distance between the injection site (guiding catheter) and the measuring site (distal sensor), 3 thermodilution curves were obtained.

**Animal Model**

Four weeks after surgical instrumentation with a 20-MHz Doppler flow probe and a hydraulic occluder around the left circumflex, 6 mongrel dogs underwent catheterization under general anesthesia. Through a 6F left Amplatz guiding catheter, which was introduced under fluoroscopic guidance through a puncture of the right femoral artery, a PressureWire 3 was positioned distal to both the occluder and flow probe. ECG, coronary flow velocity signals, arterial and coronary pressure, and temperature signals were continuously digitized (Notocord; Figure 1). In each dog, incremental volumes (1 to 6 mL) of saline were injected as a bolus to determine which produced an optimal thermodilution curve without disturbing flow velocities. In all dogs, an optimal thermodilution curve could be obtained with 3 mL, and no influence on baseline flow was observed for volumes >5 mL. Therefore, 3 mL of saline was used to perform the measurements. In each dog, an average of 10 degrees of stenosis was induced. For each degree of stenosis, a set of 3 measurements was obtained at rest and during maximal hyperemia (induced by the intracoronary administration of 20 mg of papaverine). In 4 animals (8 stenoses), 10 ECG-triggered injections and 10 hand injections of saline were compared at rest and at hyperemia.

**Statistics**

The data are presented as mean±SD. Variability between measurements and linear regression analysis were used when appropriate.

**Results**

**In Vitro Model**

A total of 126 measurements was performed. The time needed to inject the 3 mL bolus of saline was $0.46\pm0.16$ s.
The absolute flow values varied from 30 to 247 mL/min. Overall, there was a significant correlation between the absolute flow values and \( T_{mn} \) \( (r = -0.75; P < 0.001) \). The correlation between absolute flow values was markedly closer when the sensor was located \( \pm 6 \) cm from the injection point (Figure 2). In addition, the variability between the 3 measurements of \( T_{mn} \) was significantly larger when the distance between the injection site and the measuring site was \( \leq 5 \) cm than when this distance was \( \geq 6 \) cm (Figure 2).

**Animal Experiments**

In 60 stenoses, a total of 360 paired flow velocity measurements and thermodilution curves were obtained. Overall, FFR was 0.63 ± 0.16 (range, 0.19 to 0.98) and CFR\(_{Doppler}\) was 1.63 ± 0.61 (range, 0.73 to 3.40). The variability of \( T_{mn} \) within each set of 3 measurements was 14 ± 14% (range, 0.9% to 98%). The injection time of the bolus of saline was 0.50 ± 0.08 s (range, 0.30 to 0.82 s). In each dog, there was a significant linear inverse relationship between Doppler flow velocities and the values of \( T_{mn} \) (correlation coefficients from -0.73 to -0.83). The \( T_{mn} \) values obtained by ECG-triggered and hand injection of saline were similar (1.27 ± 0.75 s versus 1.31 ± 0.52 s at rest and 0.77 ± 0.25 s versus 0.84 ± 0.28 s at hyperemia; for both, \( P = \text{NS} \)), and the variability of \( T_{mn} \) values obtained after hand injections and after ECG-triggered injections was similar (11 ± 2.6% versus 13 ± 5.8%, respectively; \( P = \text{NS} \)).

There was a significant relationship between CFR\(_{Doppler}\) and CFR\(_{thermo}\) \( (\text{CFR}_{thermo} = 0.78 \times \text{CFR}_{Doppler} + 0.445; r = 0.76; P < 0.001; \text{Figure 3}) \).
Therefore, CFR\textsubscript{thermo} (and CFR\textsubscript{Doppler}) should be obtained after the administration of nitrates to offset flow-mediated epicardial dilation. (2) The indicator itself should not influence coronary flow. In animals, this was never the case if the bolus of saline was <5 mL. In addition, the present data suggest that ECG-triggered injection was not superior to hand injection. This should, however, be controlled in patients with marked bradycardia because an injection taking place exclusively in diastole or in systole could give rise to strikingly different thermodilution curves. Therefore, we advocate performing these measurements in triplicate and averaging the values of \( T_{mn} \). (3) The indicator should be adequately mixed with blood before reaching the sensor. This probably explains why the variability between \( T_{mn} \) measurements was larger and the correlation between \( T_{mn} \) and absolute flow values was weaker when the sensor was placed <6 cm from the injection site. In humans, this distance between the guiding catheter and sensor can easily be reached in the LAD or in a dominant right coronary artery. However, some caution should be applied when the measurements are performed in a nondominant left circumflex artery.

**Conclusions**

Provided some simple precautions are taken, it is possible to measure pressure-derived FFR and thermodilution-derived CFR simultaneously with one angioplasty guidewire. This should provide better insight into the separate contribution of epicardial arteries and microvasculature to myocardial hypo-perfusion for clinical decision-making in patients with coronary atherosclerosis.

**References**

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In the article “Abnormal Epicardial Coronary Resistance in Patients With Diffuse Atherosclerosis but ‘Normal’ Coronary Angiography,” by De Bruyne et al that appeared in the October 23, 2001, issue of the journal (Circulation. 2001;104:2003–2006), an error occurred in the affiliations footnote. The authors’ affiliations should have read as follows:

“From the Cardiovascular Center Aalst, (B.D.B., G.R.H.), Aalst, Belgium; the Cardiology Department, Catharina Hospital, and the Department of Biomedical Engineering, Eindhoven University of Technology (N.H.J.P.), Eindhoven, the Netherlands; Radi Medical Systems (L.S., M.W.), Uppsala, Sweden; and the University of Louvain (G.R.H.), Brussels, Belgium.”

In the article by Cooper and Epstein, “Use of Intracardiac Echocardiography to Guide Ablation of Atrial Fibrillation,” which appeared in the December 18/25, 2001, issue of Circulation (Circulation. 2001;104:3010–3013), an error appeared in the legend to Figure 2. Figure 2 and its corrected legend appear below.

Figure 2. A phased array catheter is used to image the left inferior pulmonary vein after ablation lesions were placed at its ostium. Color Doppler and pulse-wave Doppler demonstrate an elevation in the velocity of the blood flow in the pulmonary vein after the application of radiofrequency energy, thereby indicating pulmonary vein stenosis. Reprinted with permission from Acuson Corporation.