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 ($1/T_{mn}$) 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 $1/T_{mn}$ when the sensor was placed $\geq 6$ 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 $1/T_{mn}$. 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 $T_{mn}$ ($r=0.76$; 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

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 thermostor, 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,

$$F = \frac{V}{T_{mn}}$$

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

$$
T_{mn} = \frac{\int_0^t t \cdot c(t) \, dt}{\int_0^t c(t) \, dt}
$$

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 ($F$).

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

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

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

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

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

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°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±0.16 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 $\geq 6$ 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 $0.63 \pm 0.16$ (range, 0.19 to 0.98) and $CFR_{doppler}$ was $1.63 \pm 0.61$ (range, 0.73 to 3.40). The variability of $T_{mn}$ within each set of 3 measurements was $14 \pm 14\%$ (range, 0.9% to 98%). The injection time of the bolus of saline was $0.50 \pm 0.08$ 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 ($1.27 \pm 0.75$ s versus $1.31 \pm 0.52$ s at rest and $0.77 \pm 0.25$ s versus $0.84 \pm 0.28$ s at hyperemia; for both, $P = NS$), and the variability of $T_{mn}$ values obtained after hand injections and after ECG-triggered injections was similar ($11 \pm 2.6\%$ versus $13 \pm 5.8\%$, respectively; $P = NS$).

There was a significant relationship between $CFR_{doppler}$ and $CFR_{thermo}$ ($CFR_{thermo} = 0.78 \times CFR_{doppler} + 0.445$; $r = 0.76; P < 0.001$; Figure 3).

**Discussion**

The present study indicates that the thermodilution theory can be extended to the measurement of CFR. The data show that the mean transit time ($T_{mn}$) of a 3 mL, hand-injected bolus of saline at room temperature closely correlates with absolute flow (in vitro) or flow velocities (in animals). $CFR_{thermo}$ can therefore be calculated from the ratio of resting to hyperemic $T_{mn}$. Because both the in vitro and the animal model were set up to mimic clinical conditions as much as possible and because the thermistor used in this experiment is the same as the pressure sensor of a commercially available pressure-monitoring angioplasty guidewire, it is possible, for the first time, to measure CFR and FFR simultaneously. Both indices provide the clinician with complementary and useful information for clinical decision-making.

In contrast to the approach of the thermodilution principle commonly used when measuring cardiac output with a Swan-Ganz catheter, the present approach does not necessitate the knowledge of exact volume nor of exact temperature. Calculating $T_{mn}$ requires the precise timing of the start of the injection (proximal sensor) and the measurement of the changes over time in coronary blood temperature (distal sensor).

Nevertheless, according to the general indicator dilution theory, several prerequisites should be fulfilled. (1) The epicardial volume (between injecting and measuring sites) is assumed to remain unchanged at rest and at hyperemia. This implies that the sensor should not be displaced between resting and hyperemic measurements. In addition, in case of epicardial vasodilation during hyperemia, absolute CFR (ie, the ratio of hyperemic to resting absolute blood flow) would be underestimated by the ratio of resting to hyperemic $T_{mn}$.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Plots of the relation between the values of absolute flow (mL/min) and $1/T_{mn}$ (s$^{-1}$), according to the distance between the injection and the measuring site (in vitro model).

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Correlation between $CFR_{doppler}$ and $CFR_{thermo}$ in dogs.
Therefore, CFR thermo (and CFR 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 Tmnu. (3) The indicator should be adequately mixed with blood before reaching the sensor. This probably explains why the variability between Tmnu measurements was larger and the correlation between Tmnu 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 hypoperfusion for clinical decision-making in patients with coronary atherosclerosis.

References

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.