Coronary Thermodilution to Assess Flow Reserve Validation in Humans

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Background—Guide wire–based simultaneous measurement of fractional flow reserve (FFR) and coronary flow reserve (CFR) is important to understand microvascular disease of the heart. The aim of this study was to investigate the feasibility of simultaneous measurement of FFR and CFR by one pressure-temperature sensor-tipped guide wire with the use of coronary thermodilution and to compare CFR by thermodilution (CFR thermo) with simultaneously measured Doppler CFR (CFR Doppl).

Methods and Results—In 103 coronary arteries in 50 patients, a pressure-temperature sensor-tipped 0.014-inch floppy guide wire and a 0.014-inch Doppler guide wire were introduced. Both normal vessels and a wide range of stenotic vessels were included. With 3 mL of saline at room temperature used as an indicator, by hand-injection, thermodilution curves in the coronary artery were obtained in triplicate, both at baseline and at intravenous adenosine-induced maximum hyperemia. After adequate curve-fitting, CFR thermo was calculated from the ratio of inverse mean transit times and compared with CFR Doppl calculated by velocities at hyperemia and baseline. Adequate sets of thermodilution curves and corresponding CFR thermo could be obtained in 87% of the arteries versus 91% for Doppler CFR and 100% for FFR. CFR thermo correlated fairly well to CFR Doppl (CFR thermo = 0.84 CFR Doppl + 0.17; r = 0.80; P < 0.001), although individual differences of >20% between both indexes were seen in a quarter of all arteries.

Conclusions—This study shows the feasibility of simultaneous measurement of FFR (by coronary pressure) and CFR (by coronary thermodilution) in humans by one single guide wire in a practical and straightforward way and will facilitate assessment of microvascular disease. (Circulation. 2002;105:2482-2486.)

Key Words: blood flow ● stenosis ● arteries ● microcirculation ● coronary artery disease

Guide wire–based measurement of fractional flow reserve (FFR) and coronary flow reserve (CFR) has become increasingly important to understand the physiological significance of coronary artery disease.1–9

Fractional flow reserve, calculated from coronary pressure measurement, is an accurate and specific index of epicardial stenosis severity.3,5,8,9 It can be simply determined by a pressure wire and enables decision-making with respect to the need for an intervention and evaluation of PTCA or coronary stenting.8–12 However, it does not account for increased microvascular resistance.

Coronary flow reserve, on the other hand, mostly measured so far by the Doppler wire, investigates both epicardial and microvascular disease but does not allow discrimination between these entities.2,6,13 Therefore, simultaneous measurement of CFR and FFR should give the clinician better insight in the respective contribution of the epicardial vessel and microvasculature to total resistance to myocardial blood flow.2,6,13–15

Up to now, two different sensor-tipped guide wires are necessary to measure CFR and FFR, making such a procedure expensive and time-consuming. It would be an advantage to measure both indexes at the same time by using one single guide wire.

Recently, we validated experimentally a novel technology by using coronary thermodilution to assess CFR in conjunction with pressure-derived FFR by one single guide wire.15

The aim of this study was to investigate the feasibility of such simultaneous measurement of FFR and CFR in humans by one pressure-temperature sensor-tipped guide wire and to compare CFR measurement by thermodilution with Doppler CFR measurement.

Methods

Pressure-Temperature Guide Wire

In this study, a commercially available 0.014-inch floppy pressure guide wire (PressureWire-3, Radi Medical Systems) was used with...
modified software. This wire has a microsensor at a location 3 cm from the floppy tip, which enables simultaneous recording of high-fidelity coronary pressure measurement as well as temperature measurement at the location of that sensor, with an accuracy of 0.02°C. The shaft of this wire, acting as an additional electric resistance, can be used as a second thermistor, providing the input signal at the coronary ostium of any fluid injection with a temperature different from blood (Figure 1). All signals can be displayed on the regular catheter laboratory recording system or at a suitable interface (Radi-Analyzer, Radi Medical Systems), enabling on-line analysis as described below. Pressure and temperature are sampled with a frequency of 500 Hz.

Study Population and Catheterization Protocol
Fifty patients were studied (103 coronary arteries), referred for physiological assessment of at least one coronary stenosis. The institutional review boards of both hospitals approved the study, and informed consent was obtained from all patients before the study. Cardiac catheterization was performed as usual; 10,000 U of heparin was administered, a 7F guiding catheter was advanced into the coronary ostium, and 300 μg of nitroglycerin was administered, after which reference images were made.

The sensor-tipped guide wire was calibrated for the pressure recording as usual and advanced to the tip of the guiding catheter to check equality of pressure signals. The temperature signal was then calibrated at that location, which means that the temperature at the coronary ostium was taken as reference temperature for further measurements. Next, the wire was introduced into the coronary artery and advanced across the stenosis in the case of a stenotic artery or to the distal third part of the artery in the case of a nonstenotic artery and advanced across the stenosis in the case of a stenotic artery or to the distal third part of the artery in the case of a nonstenotic vessel. Thereafter, a 0.014-inch Doppler wire (Flowire, Endosonics Inc) was also introduced through the guiding catheter into the same vessel. Thereafter, a 0.014-inch Doppler wire (Flowire, Endosonics Inc) was also introduced through the guiding catheter into the same vessel.

Measurement of FFR and CFR
For all arteries, simultaneous measurements were performed of mean aortic pressure (P_a), by the guiding catheter, mean distal coronary pressure (P_d, by the PressureWire), and average peak velocity (APV, by the Flowire), both at baseline and at steady-state maximum coronary hyperemia induced by intravenous administration of 140 μg/kg per minute adenosine or by intracoronary administration of 15 to 20 mg papaverine.

Thermodilution Procedure
Thermodilution curves in the coronary artery were obtained by short manual injections of 3 mL of saline at room temperature in a similar way as in the animal study. It was checked carefully at the monitor that blood flow velocity was not influenced by the injection itself. As already described, the rapid injection was recorded by the input signal at the ostium of the coronary artery (Figure 2) derived from the temperature of the shaft of the wire. Measurements were performed 3 times at baseline and 3 times at hyperemia, after which curve analysis was performed as described below. Care was taken not to advance or pull back the wire during such series of measurements. An example of a registration of P_a, P_d flow velocity, and temperature is presented in Figure 3.

Analysis of Coronary Thermodilution Curves
According to theory, flow (F) equals V/Tmn, where V represents the vascular volume between injection site of the indicator (ie, the tip of the floppy tip) and injection site of saline (Figure 2).

Figure 1. Schematic representation of pressure-temperature wire used in the study (PressureWire-3, Radi Medical Systems). Distal coronary pressure and coronary temperature are measured by the sensor located 3 cm from the tip of the wire. Injection of saline at the tip of the guiding catheter is registered by the temperature change of the shaft of the wire, acting as a second thermistor.

Figure 2. Calculation of mean transit time (Tmn) from thermodilution curve (sensor) and injection signal (shaft). Inj indicates injection of saline; t=0 is defined as halfway injection.

Figure 3. Example of registration (from top to bottom) of ECG, aortic pressure (P_a, measured by the guiding catheter), distal coronary pressure (P_d), and coronary temperature (both measured by the pressure wire) and flow velocity (measured by the Doppler wire). Injection of 3 mL of saline and t=0 are indicated by arrows. Note that coronary blood flow is not influenced by injection of indicator.
of the guiding catheter) and location of the sensor, and where $T_{mn}$ is the mean transit time and calculated by

$$T_{mn} = \frac{\int_{0}^{\infty} C(t) \, dt}{n}$$

where $C(t)$ is the thermodilution curve registered by the distal thermistor and $t=0$ is defined as the time halfway the injection, indicated by the temperature change at the ostium of the catheter as described above (Figure 2).

To test the quality of the thermodilution curves objectively, after a semilogarithmic transformation of the acquired data, the second part of the curve was fitted to the best linear fit. Measurements of $T_{mn}$ were only accepted if the mean square error (MSE) of the fitted curve was $\leq 0.05$; if the time for analysis of the thermodilution curve equaled at least one heart cycle; and if the variability between the 3 values obtained for $T_{mn}$ from the 3 measurements was $< 20\%$. CFR$_{thermo}$ was then calculated as the average $T_{mn}$ at baseline divided by average $T_{mn}$ at hyperemia. According to general indicator dilution theory, $T_{mn}$ is independent of the amount of indicator as long as the indicator does not physically influence blood flow, 16-18 Importantly, the injection of saline as described here did not influence coronary blood flow itself, as could be checked by the Doppler signal (Figure 3). The criterion of at least one heart cycle was taken to avoid influence of systolic-diastolic differences in blood flow and the necessity of triggered saline injection.

**Statistical Analysis**

All data are presented as mean $\pm$SD. Variability between 3 measurements was defined as

$$\text{Var}(a_1,a_2,a_3) = \max_{1,2,3} \left| \frac{a_i - \bar{a}}{\bar{a}} \right|$$

Variability at baseline and hyperemia was compared by the Wilcoxon signed-rank test.

CFR$_{thermo}$ was compared with CFR$_{Doppl}$ by linear regression analysis.

**Results**

**Baseline Characteristics and Procedural Outcome**

One hundred three arteries were studied in 50 patients.

Baseline and angiographic characteristics of the patients are presented in the Table. The studies were uneventful in all arteries. FFR could be successfully measured in all arteries, CFR$_{thermo}$ in 94 arteries, and CFR$_{Doppl}$ in 92 arteries. Both adequate Doppler and thermo registrations were obtained in 86 arteries. In 36 stenoses, FFR was $\leq 0.75$, and all these vessels were subsequently dilated and/or stented, after which similar measurements of FFR, CFR$_{Doppl}$, and CFR$_{thermo}$ were performed successfully in 33 of them. Therefore, complete data with respect to CFR$_{thermo}$, CFR$_{Doppl}$, and FFR were available from 119 arteries.

**Feasibility and Variability of Thermodilution Curves**

The average time needed to perform a complete set of 3 baseline and 3 hyperemic thermodilution curves was $6.4 \pm 2.3$ minutes.

**Comparison of CFR$_{thermo}$ With CFR$_{Doppl}$**

A fair correlation was found between CFR$_{thermo}$ and CFR$_{Doppl}$ as presented in Figure 4A:

$$\text{CFR}_{thermo} = 0.84 \times \text{CFR}_{Doppl} + 0.17 \quad (r=0.80; \ P<0.0001).$$

The average absolute difference between both indexes was
Discussion

In a number of patients with coronary artery disease, not only epicardial coronary stenosis is present, but the microvasculature may be involved. Although in such cases FFR still reliably indicates the functional severity of the epicardial stenosis (given that particular state of the microvasculature) and therefore indicates if and to what extent a patient may benefit from mechanical revascularization (PTCA or CABG) of the respective epicardial stenosis, for correctly estimating the contribution of microvascular disease to inducible ischemia, the combination of FFR and CFR will clarify whether it is the residual epicardial stenosis or the damaged microvasculature that is responsible for low flow, with implications for the decision to dilate or to treat the patient medically.9 Also, in the subacute or chronic phase after previous myocardial infarction, combination of FFR and CFR will clarify whether it is the residual epicardial stenosis or the damaged microvasculature that is responsible for low flow, with implications for the decision to dilate or to treat the patient medically.9

Therefore, methodology to assess FFR and CFR simultaneously by one single guide wire is important and feasible, as demonstrated in this study. CFR, determined by the thermodilution method, showed a fair correlation to Doppler CFR measurement.

According to thermodilution theory, flow equals vascular volume between injection site and measuring site (V), divided by mean transit time.10 In our study, 300 μg of nitroglycerin was administered at the start of the procedure to offset changes in epicardial vascular volume by flow-mediated vasodilatation during hyperemia. Therefore, the vascular volume of the coronary arterial segment can be assumed to remain constant, flow is proportional to inverse Tmn, and CFR can be assessed by the ratio of Tmn at baseline and hyperemia.10 As a matter of fact, it is required that the wire is not moved forward or backward between baseline and hyperemic measurements. In contrary to that part of thermodilution theory used for cardiac output measurement, the approach used in this study is independent of the amount of indicator,10,11 which was unknown in this study because of heating up of the saline in the guiding catheter and loss of indicator in the aortic root and in side branches.

Calculation of Tmn requires temperature measurement in the distal coronary artery as well as registration of the injection signal for definition of t=0, obtained in this study by using the shaft of the wire as a second thermistor (Figure 2).

Doppler CFR measurement (NS) and a success rate of 100% for thermodilution CFR measurement (No significant differences between CFR measured by Doppler and CFR by thermodilution) were 17±14% (range, 0% to 51%). In 26% of all studies, the difference between both parameters was >20%. The corresponding Bland-Altman diagram is shown in Figure 4B.

Advantages and Limitations of CFR thermodilution

The method of simultaneous measurement of FFR and CFR as described in this study is safe because only small amounts of saline are administered. It can be rapidly performed and is not associated with any extra costs compared with the present physiological measurement of FFR alone, and there is no need for extra hardware.

However, there are some limitations. First, the success rate was 87%, compared with a success rate of 91% for successful Doppler CFR measurement (NS) and a success rate of 100% for FFR measurement.

Second, the differences between CFRthermo and CFRdoppler were in the range of 20%.

Third, CFR by thermodilution may be overestimated in the case of large sidebranches, especially if such a sidebranch originates closely proximal to the stenosis and the sensor is...
located shortly distal of the stenosis. This limitation is not very 
prominent for proximal stenoses but may lead to overestimation of 
CFR by thermodilution in the case of stenoses in the mid or 
distal part of a coronary artery.

Another limitation compared with Doppler is that steady-state 
hyperemia should be present during at least 30 seconds to 
perform the manipulations necessary to obtain the hyperemic 
thermodilution curve. Therefore, unlike for Doppler CFR, intra-
coronary adenosine cannot be used and intravenous adenosine 
or intracoronary papaverine are mandatory. Although this is a 
limitation on one hand, the use of intravenous adenosine or 
intracoronary papaverine has the advantage of being more 
accurate to determine FFR and offers the possibility to analyze 
sequential and diffuse abnormalities along the complete coro-

nary artery during a so-called pressure pull-back curve, once 
FFR and CFR have been determined.6,9,20

Next, intravenous adenosine is accompanied by a decrease of 
blood pressure of ≈10% to 15%, and therefore CFR may be 
underestimated by 10% to 15% if not corrected for these 
pressure changes. Such a correction can be made as described 
earlier.19 In the present validation study, such a correction was 
not necessary because CFRflow and CFRDoppler were both mea-
sured with intravenous adenosine or intracoronary papaverine 
simultaneously and therefore were affected in the same way by 
hemodynamic variations.

Careful attention should be given to the position of the guiding 
catheter. On one hand, it needs to be sufficiently engaged in the 
coronary artery to guarantee adequate delivery of the indicator into 
the vessel; on the other hand, easy backflow into the aortic root is 
necessary to avoid mechanical influence of the injection on baseline 
flow, resulting in underestimation of CFR.

Finally, as a matter of fact and in contrast to FFR, correct 
interpretation of CFR may be difficult, and CFR determined by 
thermodilution has the same limitations inherent to the concept 
of CFR in general, like the aforementioned dependency on heart 
rate, blood pressure, age, interindividual variability between 
persons, and its dependency on true baseline flow, which is often 
hard to achieve in the catheterization laboratory.2,4

Only qualitative assessment of microvascular disease by 
combination of pressure and flow data has been described so 
far.7,14 Further studies are mandatory to develop suitable algo-
rithms for true quantitative description of the microvasculature. 
Such studies may be facilitated by having available the present 
methodology.

Recently, interest has been raised in temperature changes in the 
coronary wall to identify unstable plaques.21,22 Although potentially 
important, we did not address this issue in the present study.

In conclusion, despite several conceptual limitations and 
issues to be solved, this study shows the feasibility of simulta-
neous measurement of FFR (by coronary pressure) and CFR (by 
coronary thermodilution) by a single guide wire in humans in a 
practical and straightforward way and will facilitate the assess-
ment of microvascular disease.

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