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

/H11005

0.84 CFR_

Doppl

/H11001

0.17; r/H11005

0.80; P/H11021

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.\(^\text{9}\) 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 \(\mu\)g 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 1 to 2 cm distal to the tip of the wire, acting as a second thermistor.

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 \(\mu\)g/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.\(^{15}\) 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,\(^{16–18}\) flow (\(F\)) equals \(V/T_{mn}\), where \(V\) represents the vascular volume between injection site of the indicator (ie, the tip of the wire) and the coronary ostium, \(T_{mn}\) is the mean transit time, and \(R\) is the resistance of the vascular bed.

FFR was calculated by the ratio \(P_d/P_a\) at maximum hyperemia. CFR\(_{\text{doppl}}\) was calculated by the ratio of APV at hyperemia and at baseline, according to regular clinical practice.

Figures

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 (\(T_{mn}\)) 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), coronary pressure (\(P_d\), by the Flowire), 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

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

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 semi-logarithmic 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 \( <20\% \). \( CFR_{\text{thermo}} \) 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±SD. Variability between 3 measurements was defined as

\[
\text{Var}(a_1,a_2,a_3) = \max_{1,2,3} | a_i - \overline{a} |
\]

Variability at baseline and hyperemia was compared by the Wilcoxon signed-rank test. \( CFR_{\text{thermo}} \) was compared with \( CFR_{\text{Doppl}} \) 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 patients. FFR could be successfully measured in all arteries, \( CFR_{\text{Doppl}} \) in 94 arteries, and \( CFR_{\text{thermo}} \) 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, \( CFR_{\text{Doppl}} \), and \( CFR_{\text{thermo}} \) were performed successfully in 33 of them. Therefore, complete data with respect to \( CFR_{\text{thermo}} \), \( CFR_{\text{Doppl}} \), 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±2.3 minutes.

**Patient Characteristics and Angiographic and Hemodynamic Data**

<table>
<thead>
<tr>
<th>No. patients</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. arteries</td>
<td>119</td>
</tr>
<tr>
<td>Male/female</td>
<td>41/9</td>
</tr>
<tr>
<td>Age, y</td>
<td>55±8</td>
</tr>
<tr>
<td>Reference vessels (n=41)</td>
<td></td>
</tr>
<tr>
<td>LAD/LCX/RCA:</td>
<td>19/8/14</td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>2.87±0.52</td>
</tr>
<tr>
<td>FFR</td>
<td>0.87±0.08</td>
</tr>
<tr>
<td>CFR_{\text{Doppl}}</td>
<td>2.64±0.59</td>
</tr>
<tr>
<td>CFR_{\text{thermo}}</td>
<td>2.90±1.11</td>
</tr>
<tr>
<td>Target vessels (n=45)</td>
<td></td>
</tr>
<tr>
<td>LAD/LCX/RCA:</td>
<td>18/5/22</td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>3.01±0.22</td>
</tr>
<tr>
<td>% Stenosis</td>
<td>68±13</td>
</tr>
<tr>
<td>mld</td>
<td>0.95±0.17</td>
</tr>
<tr>
<td>FFR</td>
<td>0.53±0.16</td>
</tr>
<tr>
<td>CFR_{\text{Doppl}}</td>
<td>1.47±0.52</td>
</tr>
<tr>
<td>CFR_{\text{thermo}}</td>
<td>1.49±0.51</td>
</tr>
<tr>
<td>Vessels with FFR&lt;0.75: n=33 (subsequently dilated)</td>
<td></td>
</tr>
<tr>
<td>Target vessels after PCI (n=33)</td>
<td></td>
</tr>
<tr>
<td>LAD/LCX/RCA:</td>
<td>14/3/16</td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>3.06±0.14</td>
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<tr>
<td>% Stenosis</td>
<td>11±5</td>
</tr>
<tr>
<td>mld</td>
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</tr>
<tr>
<td>FFR</td>
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</tr>
<tr>
<td>CFR_{\text{Doppl}}</td>
<td>2.40±0.44</td>
</tr>
<tr>
<td>CFR_{\text{thermo}}</td>
<td>2.45±0.67</td>
</tr>
</tbody>
</table>

Values are number or mean±SD.

The variability of \( T_{mn} \) within a set of 3 measurements was 10.5±8.2\% for the baseline measurements and 8.0±6.4\% at hyperemia (\( P<0.05 \)).

The duration of injection of the indicator was 0.49±0.10 seconds and ranged between 0.4 and 0.6 seconds in 94\% of the curves.

Adequate thermodilution curves were obtained in 733 of 846 studies, corresponding with 87\% of all curves. The main reason for not obtaining adequate curves was an interval too short for adequate curve fitting (\(<1\) cycle), mostly accompanied by a variability of \( >20\% \) in 104 curves.

This latter problem mainly occurred in normal coronary arteries at hyperemia when the course of the artery was short and the sensor could not be placed sufficiently distally. This observation is in accordance with in vitro observations on the relation between curve quality and distance between injection site and measuring site as published by De Bruyne et al\(^{15}\) recently.

**Comparison of CFR_{\text{thermo}} With CFR_{\text{Doppl}}**

A fair correlation was found between \( CFR_{\text{thermo}} \) and \( CFR_{\text{Doppl}} \) as presented in Figure 4A:

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

The average absolute difference between both indexes was...
Bland-Altman plot.

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 CFRdyndy 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

According to thermodilution theory, flow equals vascular volume between injection site and measuring site (V), divided by mean transit time. 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. 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, 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).

We did not use automatic and ECG-triggered injection of the indicator but manual injection. Therefore, the curve fit should be obtained from data from at least one complete heart cycle. As a consequence, we could not obtain reliable data in some arteries with very high flow, especially not if the sensor could not be introduced far enough to the distal coronary artery.

Theoretically, ECG-triggered injections could solve this problem but would make the procedure more complex, whereas in the experimental study triggered injections were not better than manual injections. For reasons of safety and simplicity, we chose saline at room temperature to be taken from the reservoir on the table. Because of the extreme sensitivity of the sensor, 3 mL of saline at room temperature was sufficient to obtain adequate curves in the majority of the studies.

The relation between CFRthermo and CFRdyndy was fair but not excellent, with an absolute difference of 17±14% between both values. It should be noted, however, that Doppler does not provide a true gold standard for CFR in humans and has an intrinsic variability of at least 15% to 20%. The use of PET could have yielded a better gold standard for CFR, but in that case, simultaneous acquisition of CFRthermo would not have been possible.

**Advantages and Limitations of CFRthermo**

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 CFRdyndy 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

Figure 4. A, Relation between CFR measured by Doppler (CFRdoppler, horizontal axis) and coronary flow reserve determined by thermodilution (CFRthermo, vertical axis); B, corresponding Bland-Altman plot.

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 pressure and flow measurement is mandatory. Theoretically both parameters together should yield necessary information to discriminate between increased epicardial or microvascular resistance and their respective contribution to myocardial hypoperfusion. Especially in patients with diffuse epicardial disease or a mild or moderate stenosis but without significant pressure drop along the epicardial artery, a low CFR in addition to nonischemic FFR confirms the involvement of the microvasculature and the need for aggressive medical treatment. 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.

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.

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.

The relation between CFRthermo and CFRdyndy was fair but not excellent, with an absolute difference of 17±14% between both values. It should be noted, however, that Doppler does not provide a true gold standard for CFR in humans and has an intrinsic variability of at least 15% to 20%. The use of PET could have yielded a better gold standard for CFR, but in that case, simultaneous acquisition of CFRthermo would not have been possible.
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, intracoronary 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 coronary 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.20 In the present validation study, such a correction was not necessary because CFRthermo and CFRdoppler were both measured 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 blood 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.7,44 Further studies are mandatory to develop suitable algorithms 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 simultaneous 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 assessment of microvascular disease.

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References

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