Comparison of Coronary Thermodilution and Doppler Velocity for Assessing Coronary Flow Reserve

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Background—Thermodilution coronary flow reserve \( (\text{CFR}_{\text{thermo}}) \) is a new technique for invasively measuring coronary flow reserve \( (\text{CFR}) \) with a coronary pressure wire and is based on the ability of the pressure transducer to also measure temperature changes. Whether \( \text{CFR}_{\text{thermo}} \) correlates well enough with absolute flow-derived \( \text{CFR} \) \( (\text{CFR}_{\text{flow}}) \) to replace Doppler wire–derived \( \text{CFR} \) \( (\text{CFR}_{\text{Doppler}}) \) remains unclear.

Methods and Results—In an open-chest pig model, \( \text{CFR}_{\text{thermo}} \) was measured in the left anterior descending (LAD) artery and compared with \( \text{CFR}_{\text{Doppler}} \) and \( \text{CFR}_{\text{flow}} \), measured with an external flow probe placed around the LAD. In 9 pigs, \( \text{CFR} \) was measured simultaneously by all 3 means in the normal LAD and after creation of an epicardial LAD stenosis. To determine the added effect of microvascular disease, measurements of flow reserve were also performed after disruption of the coronary microcirculation with embolized microspheres. Intracoronary papaverine (20 mg) was used to induce hyperemia. In a total of 61 paired measurements, \( \text{CFR}_{\text{thermo}} \) correlated strongly with the reference standard \( \text{CFR}_{\text{flow}} \) \( (r=0.85, P<0.001) \). \( \text{CFR}_{\text{Doppler}} \) correlated less well with \( \text{CFR}_{\text{flow}} \) \( (r=0.72, P<0.001) \). Bland-Altman analysis showed a closer agreement between \( \text{CFR}_{\text{thermo}} \) and \( \text{CFR}_{\text{flow}} \).

Conclusion—\( \text{CFR}_{\text{thermo}} \) correlates better with \( \text{CFR}_{\text{flow}} \) than does \( \text{CFR}_{\text{Doppler}} \). (Circulation. 2003;108:2198-2200.)

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

Invasive assessment of coronary flow reserve \( (\text{CFR}) \) in the cardiac catheterization laboratory provides information about the functional status of both the epicardial coronary artery and the coronary microcirculation. Recently, De Bruyne et al.\(^1\) and Pijls and colleagues\(^2\) proposed a novel coronary thermodilution technique for measuring \( \text{CFR} \) \( (\text{CFR}_{\text{thermo}}) \). This method uses a pressure-temperature sensor-tipped guidewire, which is potentially advantageous compared with measuring \( \text{CFR} \) with a Doppler velocity wire \( (\text{CFR}_{\text{Doppler}}) \), because the pressure-derived fractional flow reserve \( (\text{FFR}) \), an epicardial artery–specific index, can be measured simultaneously and help distinguish epicardial and microvascular pathology.

In an animal model, De Bruyne et al.\(^1\) found a significant correlation between \( \text{CFR}_{\text{thermo}} \) and \( \text{CFR} \) as measured from a Doppler velocity probe placed around the coronary artery \( (r=0.76, P<0.001) \). Pijls et al.\(^2\) then compared \( \text{CFR}_{\text{thermo}} \) to \( \text{CFR}_{\text{Doppler}} \) in humans and again found a significant correlation \( (r=0.80, P<0.001) \). However, in the latter study, there were differences between the 2 techniques of more than 20% in one fourth of the cases. Moreover, because of its variability, \( \text{CFR}_{\text{Doppler}} \) may not be an appropriate reference standard.\(^3,4\)

Which measurement, \( \text{CFR}_{\text{thermo}} \) or \( \text{CFR}_{\text{Doppler}} \), correlates better with absolute flow-derived \( \text{CFR} \) \( (\text{CFR}_{\text{flow}}) \) remains unclear. Therefore, the goal of the present study was to further validate \( \text{CFR}_{\text{thermo}} \) by comparing it to both \( \text{CFR}_{\text{Doppler}} \) and \( \text{CFR}_{\text{flow}} \) in an animal model.

Methods

Protocol

The study protocol was approved by Stanford’s Institutional Animal Care and Use Committee. In an open-chest porcine model, \( \text{CFR}_{\text{thermo}} \), \( \text{CFR}_{\text{Doppler}} \), and \( \text{CFR}_{\text{flow}} \) were measured simultaneously, as described below. Measurements were made in the left anterior descending artery \( (\text{LAD}) \) at baseline and after induction of an epicardial stenosis. The microcirculation was then disrupted with embolized microspheres, and measurements were repeated with a normal epicardial artery and after creation of an epicardial artery stenosis.\(^5\)

Animal Preparation

Yorkshire swine were premedicated with intramuscular ketamine \( (20 \text{ mg/kg}) \), xylazine \( (2 \text{ mg/kg}) \), and buprenorphine \( (0.005 \text{ mg/kg}) \). Anesthesia was maintained with 2% isoflurane, and supplemental oxygen was given via endotracheal intubation. An arterial sheath was surgically placed in the right carotid artery. Angiography of the LAD was performed with a 6F catheter. A lateral thoracotomy was performed.
Coronary Pressure and Flow Measurements

A coronary pressure wire (Radi Medical Systems) and Doppler velocity wire (Jomed Inc) were advanced into the distal LAD. CFR\textsubscript{thermo} was measured with the pressure wire and modified software (Radi Medical Systems). The software allows the pressure sensor, which is located 3 cm from the tip of the standard coronary pressure wire, to also act as a distal temperature sensor, whereas the shaft of the wire acts as a proximal temperature sensor; thus, the transit time of an injectant can be calculated. Approximately 3 mL of room-temperature saline was injected rapidly by hand into the left coronary artery 3 times. The resting mean transit time was recorded each time and then averaged. Intracoronary papaverine (20 mg) was given, and 3 more injections of 3 mL of room temperature saline were quickly performed. The hyperemic mean transit time was recorded each time an epicardial artery was created with the vascular occluder so that the distal coronary pressure was 90% of the proximal coronary pressure at rest. The microcirculation was disrupted by subject injection into the LAD of 10\(^5\) fluorescent microspheres (100 \(\mu\)m diameter; Interactive Medical Technologies).\(^{2,5}\)

Statistical Analysis

Continuous values are presented as mean \pm SD. Simple regression analysis was used to calculate the correlation between CFR\textsubscript{thermo} and CFR\textsubscript{flow} and between CFR\textsubscript{Doppler} and CFR\textsubscript{flow}. Bland-Altman analysis was performed to further determine the agreement between the measurement methods. A probability value <0.05 was considered statistically significant. Statistical calculations were performed with StatView software (SAS Institute Inc) and MedCalc software.

Results

In 9 pigs, a total of 61 measurements were made: 19 in the setting of a normal epicardial artery and microcirculation, 16 with an epicardial artery stenosis, 15 with a disrupted microcirculation, and 11 with both an epicardial artery stenosis and an abnormal microcirculation. CFR\textsubscript{Doppler} could not be measured in 1 case because an adequate hyperemic average peak velocity could not be recorded. CFR\textsubscript{flow} could not be measured in a different case because of technical difficulties with the external flow probe during hyperemia. Mean CFR\textsubscript{flow} was 2.0 \pm 0.96, mean CFR\textsubscript{thermo} was 2.2 \pm 1.0, and mean CFR\textsubscript{Doppler} was 2.0 \pm 0.90. Mean FFR was 0.97 \pm 0.03 in the setting of a normal epicardial artery, regardless of the status of the microcirculation. Mean FFR was 0.63 \pm 0.14 in the presence of an epicardial artery stenosis and 0.72 \pm 0.13 with an epicardial artery stenosis and a disrupted microcirculation.

CFR\textsubscript{thermo} correlated well with the reference standard, CFR\textsubscript{flow} (r=0.85, y=0.34+0.94\(x\), P<0.0001). CFR\textsubscript{Doppler} also correlated with CFR\textsubscript{flow} but not as strongly (r=0.72, y=0.61+0.62\(x\), P<0.0001; Figures 1 and 2). There was a similar, less strong correlation between CFR\textsubscript{thermo} and CFR\textsubscript{Doppler} (r=0.74, y=0.54+0.66\(x\), P<0.0001). Bland-Altman analysis demonstrated a closer agreement between CFR\textsubscript{thermo} and CFR\textsubscript{flow} than between CFR\textsubscript{Doppler} and CFR\textsubscript{flow} (Figures 1 and 2). Although FFR is an epicardial specific index, there was still a significant correlation between FFR and both CFR\textsubscript{thermo} (r=0.46, y=0.66+0.08\(x\), P<0.001) and CFR\textsubscript{flow} (r=0.42, y=0.68+0.078\(x\), P=0.001). FFR did not correlate significantly with CFR\textsubscript{Doppler} (r=0.24, y=0.74+0.05\(x\), P=0.07).

Discussion

In the present study, we found that CFR\textsubscript{thermo} correlated better with the reference standard, CFR\textsubscript{flow}, than did CFR\textsubscript{Doppler}. Furthermore, the level of agreement between CFR\textsubscript{thermo} and CFR\textsubscript{flow} was closer than that between CFR\textsubscript{Doppler} and CFR\textsubscript{flow}. These data suggest that use of the coronary pressure wire to measure simultaneously FFR and CFR\textsubscript{thermo} provides reliable information about the status of both the epicardial artery and the microcirculation.

In particular, there was a greater degree of scatter between the CFR\textsubscript{Doppler} and CFR\textsubscript{flow} values, especially at higher levels of CFR; CFR\textsubscript{Doppler} tended to underestimate the true CFR. There may be both conceptual and technical reasons to explain this underestimation. For example, accurate measurement of CFR

Figure 1. a, Linear regression and b, corresponding Bland-Altman plots comparing CFR\textsubscript{thermo} with CFR\textsubscript{flow}.
with the Doppler wire assumes the same (parabolic) flow profile exists at all flow rates; in fact, the flow profile may be different at high and low flow rates, and thus the peak velocity recorded by Doppler may not correlate precisely with the actual flow. In addition, early work validating CFR<sub>Doppler</sub> found that technical issues, such as vessel tortuosity, could limit the accuracy of this technique, presumably by not allowing the Doppler sensor to remain in the middle of the vessel. The significance of this technical issue may be greater at higher flow rates.

CFR remains a useful measurement in the cardiac catheterization laboratory because it interrogates the functional status of the entire coronary arterial system, including both the epicardial artery and the microcirculation, whereas FFR is epicardial artery specific. Determination of FFR alone can be helpful when evaluating an intermediate coronary lesion<sup>8</sup>–<sup>10</sup> or the result of a percutaneous coronary intervention<sup>11,12</sup> or in the determination of the culprit lesion in a patient with multivessel disease<sup>13</sup>; however, measuring both FFR and CFR simultaneously is complementary, because it allows one to distinguish better between epicardial and microvascular abnormalities.<sup>14</sup> This ability to measure easily the 2 indices with the Doppler wire assumes the same (parabolic) flow profile exists at all flow rates; in fact, the flow profile may be different at high and low flow rates, and thus the peak velocity recorded by Doppler may not correlate precisely with the actual flow. In addition, early work validating CFR<sub>Doppler</sub> found that technical issues, such as vessel tortuosity, could limit the accuracy of this technique, presumably by not allowing the Doppler sensor to remain in the middle of the vessel. The significance of this technical issue may be greater at higher flow rates.

Study Limitations

This study is limited by the fact that it was performed in an animal model. However, an invasive “gold standard” for CFR is not readily available in patients. CFR<sub>thermo</sub> served as the reference standard in this study and was measured in the proximal portion of the LAD, whereas CFR<sub>Doppler</sub>, by definition was measured distally, and CFR<sub>Doppler</sub> most commonly was measured distally. The position of measurement could have affected the results, although one would expect CFR to be uniform along the length of the LAD. Despite the findings in the present study, CFR<sub>thermo</sub> is subject to the same limitations of CFR in general; in particular, CFR is affected by baseline conditions, hemodynamic perturbations, and interindividual variability.

Conclusions

Thermodilution-derived CFR appears to correlate better with absolute flow-derived CFR than does Doppler velocity-derived CFR.

References

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