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

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

Methods and Results—In an open-chest pig model, CFR thermo was measured in the left anterior descending (LAD) artery and compared with CFR Doppler and CFR flow, measured with an external flow probe placed around the LAD. In 9 pigs, 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, CFR thermo correlated strongly with the reference standard CFR flow ($r=0.85$, $P<0.001$). CFR Doppler correlated less well with CFR flow ($r=0.72$, $P<0.001$). Bland-Altman analysis showed a closer agreement between CFR thermo and CFR flow.


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

Invasive assessment of coronary flow reserve (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 al1 and Pijls and colleagues2 proposed a novel coronary thermodilution technique for measuring CFR (CFR thermo). This method uses a pressure-temperature sensor-tipped guidewire, which is potentially advantageous compared with measuring CFR with a Doppler velocity wire (CFR Doppler), because the pressure-derived fractional flow reserve (FFR), an epicardial artery–specific index, can be measured simultaneously and help distinguish epicardial and microvascular pathology.

In an animal model, De Bruyne et al1 found a significant correlation between CFR thermo and CFR as measured from a Doppler velocity probe placed around the coronary artery ($r=0.76$, $P<0.001$). Pijls et al2 then compared CFR thermo to CFR 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, CFR Doppler may not be an appropriate reference standard.3,4 Which measurement, CFR thermo, or CFR Doppler correlates better with absolute flow-derived CFR (CFR flow) remains unclear. Therefore, the goal of the present study was to further validate CFR thermo by comparing it to both CFR Doppler and CFR 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, CFR thermo, CFR Doppler, and CFR flow were measured simultaneously, as described below. Measurements were made in the left anterior descending artery (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.

Animal Preparation

Yorkshire swine were premedicated with intramuscular ketamine (20 mg/kg), xylazine (2 mg/kg), and buprenorphine (0.005 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 by standard surgical technique, the pericardium was opened, and the proximal LAD was circumscribed by a combination of sharp and blunt dissection. An ultrasonic flow probe (Transonic Systems, Inc) was placed around the proximal LAD; a vascular occluder (Harvard Apparatus) was placed distal to the flow probe, ensuring that there were no branch vessels between the two. A bolus of 300 U/kg heparin was administered intravenously.

Epithelial stenoses were 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 selective injection into the LAD of 10^5 fluorescent microspheres (100 μm diameter; Interactive Medical Technologies).

**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_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 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 and then averaged. CFR_thermo was defined as the average resting mean transit time divided by the average hyperemic mean transit time. After an acceptable flow signal was obtained from the Doppler wire, which at times necessitated pulling the Doppler velocity wire more proximally, the resting average peak velocity was recorded. During peak hyperemia, the average peak velocity was again recorded, ensuring that the wire position had not moved. CFR_thermo was calculated by dividing the hyperemic by the resting average peak velocities.

Absolute flow (mL/min) at rest and during peak hyperemia was recorded from the external flow probe, which measures volume flow directly and independent of vessel diameter. CFR_flow was calculated from the ratio of hyperemic to resting coronary flow recorded from the flow probe. FFR was calculated during peak hyperemia by dividing the mean distal coronary pressure, recorded from the pressure wire, by the mean proximal coronary pressure, recorded from the guide catheter.

**Statistical Analysis**

Continuous values are presented as mean±SD. Simple regression analysis was used to calculate the correlation between CFR_thermo and CFR_flow and between CFR_Doppler and CFR_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_Doppler could not be measured in 1 case because an adequate hyperemic average peak velocity could not be recorded. CFR_flow could not be measured in a different case because of technical difficulties with the external flow probe during hyperemia. Mean CFR_flow was 2.0±0.96, mean CFR_thermo was 2.2±1.0, and mean CFR_Doppler was 2.0±0.90. Mean FFR was 0.97±0.03 in the setting of a normal epicardial artery, regardless of the status of the microcirculation. Mean FFR was 0.63±0.14 in the presence of an epicardial artery stenosis and 0.72±0.13 with an epicardial artery stenosis and a disrupted microcirculation. CFR_thermo correlated well with the reference standard, CFR_flow (r=0.85, y=0.34+0.94x, P<0.0001). CFR_Doppler also correlated with CFR_thermo, but not as strongly (r=0.72, y=0.61+0.62x, P<0.0001; Figures 1 and 2). There was a similar, less strong correlation between CFR_thermo and CFR_flow (r=0.74, y=0.54+0.66x, P<0.0001). Bland-Altman analysis demonstrated a closer agreement between CFR_thermo and CFR_flow than between CFR_Doppler and CFR_flow (Figures 1 and 2). Although FFR is an epicardial specific index, there was still a significant correlation between FFR and both CFR_thermo (r=0.46, y=0.66+0.08x, P<0.001) and CFR_flow (r=0.42, y=0.68+0.078x, P=0.001). FFR did not correlate significantly with CFR_Doppler (r=0.24, y=0.74+0.05x, P=0.07).

**Discussion**

In the present study, we found that CFR_thermo correlated better with the reference standard, CFR_flow, than did CFR_Doppler. Furthermore, the level of agreement between CFR_thermo and CFR_flow was closer than that between CFR_Doppler and CFR_flow. These data suggest that use of the coronary pressure wire to measure simultaneously FFR and CFR_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_Doppler and CFR_flow values, especially at higher levels of CFR; CFR_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...
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_{doppler} 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 \(^4\)–\(^10\) or the result of a percutaneous coronary intervention \(^11\)\(^,\)\(^12\) or in the determination of the culprit lesion in a patient with multivessel disease \(^13\); however, measuring both FFR and CFR simultaneously is complementary, because it allows one to distinguish better between epicardial and microvascular abnormalities. \(^14\) This ability to measure easily the 2 indices would be particularly applicable to patients with abnormalities in both areas of the coronary arterial system, such as diabetics, hypertensives, those with a previous myocardial infarction, and cardiac transplant recipients. \(^15\) To date, however, this has been hampered by the requirement for 2 coronary wires, a pressure wire and a Doppler velocity wire.

**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_{flow} served as the reference standard in this study and was measured in the proximal portion of the LAD, whereas CFR_{thermo} by definition was measured distally, and CFR_{doppler} 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_{thermo} 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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