JACC: CARDIOVASCULAR INTERVENTIONS VOL. 11, NO. 20, 2018

EDITORIAL COMMENT

The Challenges of Measuring Coronary Flow Reserve

Comparisons of Doppler and Thermodilution to $[^{15}O]H_2O$ PET Perfusion*

Morton J. Kern, MD,[a,b] Arnold H. Seto, MD, MPA[b,c]

In 1974, in seminal animal experiments with progressively applied arterial constrictions, Gould and Lipscomb (1) demonstrated that coronary stenoses reduced resting blood flow only when they were very severe, exceeding >85% diameter narrowed. By contrast, maximal hyperemic blood flow was affected by less severe stenoses, with reductions in hyperemic flow beginning with as little as a 50% narrowing (1). Given the individual flow variability, Gould and Lipscomb normalized the hyperemic flow to the resting flow in the same artery, naming the ratio *coronary flow reserve* (CFR). By characterizing the relationship between stenosis severity and CFR, Gould and Lipscomb established one of the foundational concepts of myocardial ischemia. From this animal experiment, clinicians extended the concept of CFR to visually estimated angiographic stenoses in humans, erroneously presuming that all angiographic stenoses with >50% diameter narrowing represented clinically significant lesions. Unfortunately, although true in the experimental animals, the relationship between stenosis and CFR demonstrably failed in patients because of the significant limitations of 2-dimensional angiography (e.g., foreshortening, calcifications, and branch overlap, especially for eccentric atherosclerotic lesions), and microvascular dysfunction. Recognizing the limitations of CFR, translesional pressure measurements such as fractional flow reserve (FFR) became a standard for physiological lesion assessment. Nonetheless, knowledge of the CFR remains critically important for a complete understanding of a patient's coronary circulation, especially the microcirculation, and the associated long-term clinical outcomes.

Over the years, CFR has been measured with multiple techniques, including radiolabeled microspheres (2), invasive and noninvasive coronary Doppler (3,4), thermodilution flow transit time recordings (5), magnetic resonance imaging (6), and recently, positron emission tomographic (PET)-measured perfusion using radiolabeled water, ammonia, or other diffusible blood flow tracers (7). All of these techniques have technical challenges; many are not widely available. The best PET tracers in particular require a nuclear cyclotron on site due to short half-lives. ^{15}Oxygen-labeled water most reliably quantifies blood flow because extraction of this highly diffusible tracer is complete and linearly related to the flow rate (8). At this time, $[^{15}O]H_2O$ PET perfusion imaging is considered the gold standard for quantification of myocardial perfusion and CFR.

SEE PAGE 2044

In this issue of *JACC: Cardiovascular Interventions*, Everaars et al. (9) directly compared invasive Doppler flow velocity reserve ($CFR_{Doppler}$) and thermodilution-derived coronary flow reserve (CFR_{thermo}) against $[^{15}O]H_2O$ PET CFR in 98 vessels from 40 consecutive patients. FFR, $CFR_{Doppler}$ and CFR_{thermo} were measured using pressure/flow sensor guidewires

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the [a]Department of Medicine, Veterans Administration Long Beach Health Care System, Long Beach, California; [b]Department of Medicine, University of California, Irvine, Irvine, California; and the [c]Department of Cardiology, Veterans Administration Long Beach Health Care System, Long Beach, California. Dr. Kern has been a consultant and speaker for Abbott/St. Jude Medical, Philips/Volcano, Acist Medical, Opsens, and Heartflow. Dr. Seto has received research funding from Philips/Volcano; and has been a speaker for ACIST Medical Systems, Boston Scientific, and Philips/Volcano.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2018.08.004

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 11, NO. 20, 2018
OCTOBER 22, 2018:2055–7

following coronary angiography. $[^{15}O]H_2O$ PET CFR was obtained within 2 weeks of the invasive study.

$CFR_{Doppler}$ correlated modestly with CFR_{thermo} ($r = 0.59$; $p < 0.001$) and better than CFR_{thermo} with CFR_{PET} ($r = 0.82$ and 0.55, respectively; both $p < 0.001$). CFR_{thermo} overestimated CFR_{PET} at high values. The relationship between CFR_{thermo} and CFR_{PET} deteriorated when only vessels with FFR >0.80 were included, whereas the relationship between $CFR_{Doppler}$ and CFR_{PET} remained constant. The quality of Doppler flow signals was worse than those of thermodilution, but Doppler flow velocity measurements showed lower intraobserver variability. Overall, this study, from a center of expertise in coronary Doppler and PET, suggests that $CFR_{Doppler}$ is better correlated with the PET gold standard than CFR_{thermo}, but is harder to measure accurately.

DIFFERENCES BETWEEN DOPPLER VELOCITY AND THERMODILUTION FLOW

Prior comparisons of $CFR_{Doppler}$ and CFR_{thermo} in both experimental animal (10) and human (11) studies suggested near equivalency. Fifteen years later, with the availability of PET as a CFR standard, Everaars et al. (9) now demonstrate superior agreement of $CFR_{Doppler}$ over CFR_{thermo} with regard to CFR_{PET}. Given that each technique uses a different method for measuring blood flow, perfect agreement amongst the different methods should not be expected. Moreover, CFR sounds easier to measure than it really is. CFR is not routinely acquired during clinical catheterization procedures due to multiple technical challenges that are worth reviewing in detail.

Intracoronary Doppler ultrasound measures red cell velocities assuming a parabolic laminar flow profile. Velocity is displayed as a spectral waveform and quantitated by the average peak (instantaneous) velocity (APV) value. Coronary flow velocity reserve (CFVR), $APV_{hyperemia}/APV_{rest}$ is not always identical to other CFR measurements calculated by volumetric ratios. For CFVR, volumetric flow can be calculated as the product vessel cross-sectional area (CSA) $\times$ APV/2. The CSA at the interrogation site is presumed to remain constant over the measurement, thus CFVR may more closely approximate CFR by volume. Unfortunately, hyperemic flow-mediated vasodilation and changes in CSA are rarely incorporated, a factor contributing to the variance between $CFR_{Doppler}$ and other CFR measures. Lastly, accurate signal acquisition is challenging as the Doppler ultrasound beam must be maintained in a stable position within the narrow flow field, and acute sensor angulation relative to the flow vector will reduce the measured velocity.

In contrast to Doppler velocity flow, thermodilution coronary flow is measured by the mean transit time of the room temperature saline indicator as detected by the temperature change from the sensor on the coronary guidewire. Flow is calculated as 1/mean transit time ($1/T_{mn}$), with signals from several small saline bolus injections through the guide catheter averaged. CFR_{thermo} is calculated as [hyperemic $1/T_{mn}$]/[resting $1/T_{mn}$]. The $1/T_{mn}$ is affected by quality of the injections, sensor wire position, adequate guide seating without damping, and the coronary flow rate. The technique of manual bolus injection accounts for some variance. The thermodilution method becomes less accurate at high flow rates.

To their credit, Everaars et al. (9) accepted only good-quality signals. Acceptable Doppler signals were those with clearly identifiable systolic and diastolic phases with early diastolic peak flow having a gradual decline. Good-quality thermodilution curves were those with a unimodal shape without distortion. Low-quality tracings for both techniques were excluded. Intraobserver variability of flow signals was higher with $1/T_{mn}$ at rest and at hyperemia ($11.5 \pm 7\%$ and $14.6 \pm 9\%$, respectively; $p < 0.016$) than APV ($4.8 \pm 3\%$ and $5.3 \pm 4\%$, respectively; p = ns). Variability of $CFR_{Doppler}$ and CFR_{thermo} was $6.6 \pm 5\%$ and $18.8 \pm 11\%$, respectively.

In contrast to Everaars et al. (9), earlier studies suggested a closer agreement between $CFR_{Doppler}$ and CFR_{thermo} (10,11). The authors (9) postulate that the discrepancy between these studies is due, in part, to technical differences (e.g., intravenous vs. intracoronary adenosine, accurate wire position relative to side branches, and so on). Everaars et al. (9) note that when examined in normal or minimally narrowed vessels with FFR >0.80, the higher flow rates produced an even great disparity between CFR_{thermo} with CFR_{PET}. Lastly, patient selection may have contributed to variance of CFR measurements, as only a minority of patients had Doppler recordings of sufficient quality for comparison in the earlier studies. Advocates for the thermodilution technique would undoubtedly disagree (10,11).

WHICH TECHNIQUE TO CHOOSE?

Everaars et al. (9) remind us that both current invasive CFR techniques have different strengths and weaknesses. The variance of measurements and only modest correlations to CFR_{PET} reinforce a longstanding need for improved techniques, technology, and equipment to measure flow. Without effective tools to measure flow, large multicenter studies that would make CFR a routine cath lab practice will not be performed. Having used both techniques, we appreciate the technical challenges and errors of each. At the present time, the conflicting comparative CFR data suggest that the best technique to use is still the one with which the operator and lab have the most expertise.

ADDRESS FOR CORRESPONDENCE: Dr. Morton J. Kern, Department of Medicine, Veterans Administration Long Beach Health Care System, 5901 East 7th Street, Long Beach, California 90822. E-mail: mortonkern2007@gmail.com.

REFERENCES

1. Gould KL, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. Am J Cardiol 1974;34:48–55.

2. Tadamura E, Tamaki N, Yonekura Y, et al. Assessment of coronary vasodilator reserve by N-13 ammonia PET using the microsphere method and Patlak plot analysis. Ann Nucl Med 1995;9:109–18.

3. Kern MJ, Donohue TJ, Aguirre FV, et al. Assessment of angiographically intermediate coronary artery stenosis using the Doppler FloWire. Am J Cardiol 1993;71:26D–33D.

4. Florenciano-Sánchez R, de la Morena-Valenzuela G, Villegas-García M, et al. Noninvasive assessment of coronary flow velocity reserve in left anterior descending artery adds diagnostic value to both clinical variables and dobutamine echocardiography: a study based on clinical practice. Eur J Echocardiogr 2005;6:251–9.

5. Barbato E, Aarnoudse W, Aengevaeren WR, et al., Week 25 study group. Validation of coronary flow reserve measurements by thermodilution in clinical practice. Eur Heart J 2004;25:219–23.

6. Brown LAE, Onciul SC, Broadbent DA, et al. Fully automated, inline quantification of myocardial blood flow with cardiovascular magnetic resonance: repeatability of measurements in healthy subjects. J Cardiovasc Magn Reson 2018;20:48.

7. Danad I, Uusitalo V, Kero T, et al. Quantitative assessment of myocardial perfusion in the detection of significant coronary artery disease: cutoff values and diagnostic accuracy of quantitative [(15)O]H2O PET imaging. J Am Coll Cardiol 2014;64:1464–75.

8. Bergmann SR, Fox KA, Rand AL, et al. Quantification of regional myocardial blood flow in vivo with H215O. Circulation 1984;70:724–33.

9. Everaars H, de Waard GA, Driessen RS, et al. Doppler flow velocity and thermodilution to assess coronary flow reserve: a head-to-head comparison with $[^{15}O]H_2O$ PET. J Am Coll Cardiol Intv 2018;11:2044–54.

10. Fearon WF, Farouque O, Balsam LB, et al. Comparison of coronary thermodilution and Doppler velocity for assessing coronary flow reserve. Circulation 2003;108:2198–200.

11. Pijls NHJ, De Bruyne B, Smith L, et al. Coronary thermodilution to assess flow reserve: validation in humans. Circulation 2002;105:2482–6.

KEY WORDS coronary flow reserve, coronary hemodynamics, PET perfusion