

EDITORIAL VIEWPOINT

# Positron-Emission Tomography Quantitative Measurements of Myocardial Blood Flow

## Just the Facts...\*

Henry Gewirtz, MD,<sup>a</sup> Ami E. Iskandrian, MD,<sup>b</sup> Charity Morgan, PhD,<sup>c</sup> Heinrich R. Schelbert, MD, PhD<sup>d</sup>



Although positron-emission tomography (PET) quantitative measurements of myocardial blood flow (MBF) are widely available, full integration into clinical practice has been slow. Unfamiliarity with how best to use these measurements may play a role. A guide follows to facilitate adoption for clinical care.

### INDICATIONS FOR QUANTITATIVE PET MEASUREMENTS OF MBF

Most PET quantitative MBF exams are performed for evaluation of known or suspected coronary artery disease (CAD) (1). Another common indication is evaluation of the microcirculation, particularly in patients with atypical chest pain syndromes (2,3). Diffuse conduit vessel disease also may be present in the setting of CAD and will contribute to the total physiological burden as will endothelial dysfunction at both conduit and microvascular levels (3-6). Teasing apart these entities may not be possible because all are typically present in the setting of coronary atherosclerosis (4,5).

### GLOBAL AND REGIONAL QUANTITATIVE MEASUREMENTS OF STRESS MBF

PET measurements of MBF with vasodilator stress are pivotal (7-9). The measurement must be referenced to normal values, preferably for a given lab, alternatively from the published data. Ultimately, methodology should be standardized such that absolute values are comparable across labs.

Absolute values of stress MBF are best considered for each of the 3 major coronary vessels. The precise distribution of segments with submaximal MBF will be very helpful in localizing a stenosis (proximal, mid, and distal) and whether major side branches are compromised. The more segments of a given vascular territory distinctly below the normal limit (e.g., at least ~25% less), the greater the likelihood focal stenosis is present (10). In contrast, when multiple vascular territories are diffusely below normal, particularly in base to apex pattern (11), the more likely it is that one is dealing with some combination of small vessel and coronary microvascular disease (CMD). Mixed patterns with focal stenosis in 1 or more territories and diffuse disease in others is common (5).

### GLOBAL AND REGIONAL MEASUREMENTS OF CORONARY FLOW RESERVE

The ratio of stress/rest MBF is absolute flow reserve, widely known as coronary flow reserve (CFR). A more physiologic approach indexes regional stress MBF to an external normal standard to obtain relative flow reserve (RFR or FFR<sub>PET</sub>) (12,13). Although there are numerous reports of prognostic information from global CFR (14-16), physiologically regional RFR appears preferable (17,18). This is so because it is independent of the level of resting MBF, a parameter that

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

From the <sup>a</sup>Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; <sup>b</sup>Cardiovascular Diseases, Department of Medicine, University of Alabama at Birmingham School of Medicine, Birmingham, Alabama; <sup>c</sup>Department of Biostatistics, University of Alabama at Birmingham School of Public Health, Birmingham, Alabama; and <sup>d</sup>Nuclear Medicine, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, California. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

with small changes may swing CFR to very different ends of the major adverse cardiac event (MACE) spectrum. Thus, given stress MBF 1.5 ml/min/g, distinctly less than normal (9,10,13,19-21), resting MBF of 1 ml/min/g associates with CFR of 1.5 (high risk [10,15]), whereas resting MBF of 0.5 ml/min/g associates with CFR of 3.0 (low risk [10,15]). Stress MBF remains less than normal ( $\geq 2.2$  ml/min/g) (20) with either CFR value but would be physiologically indexed by RFR (FFR<sub>pet</sub>) at  $\leq 0.68$ , high risk by invasive fractional flow reserve (FFR) and regional RFR standards (4,17,18).

Moreover, because bicycle exercise at 150 W  $\times$  10 min ( $\sim 9$  metabolic equivalents [METs]) requires an MBF of 2 to 3 ml/min/g and exercise to 70% of maximal  $\times 10$  min ( $\sim 10$  to 13 METs) requires 3.5 to 4.1 ml/min/g (22), it is possible to approximate vasodilator stress MBF to that of exercise. The METs involved ( $\sim 9$  to 13) are levels which indicate excellent clinical prognosis (23). The resting measurement is required for diagnosis of coronary steal (regional stress MBF less than that of resting), associated with a high MACE risk (10). Global (and regional) resting MBF may be elevated either early post heart transplantation (24) or in cases of acute rejection (25). The CFR ratio in such cases is less useful than knowing its individual components because stress MBF may be in the normal range whereas resting MBF carries the relevant information (26).

The regional stress MBF measurements either alone or indexed to a normal vasodilator response, taken together, contain the most helpful information concerning the overall vasodilator status of the coronary circulation (17,18,26). It is recognized if coronary anatomy is not previously known that either invasive or coronary computed tomography angiography will be required to distinguish severe multivessel epicardial CAD from diffuse, severe small vessel and CMD. Global CFR may be abnormal in both conditions unless rest MBF is relatively reduced even more than stress in which case, as noted previously, CFR is “normal” and therefore misleading. In contrast, RFR would be reduced and hence informative although etiology remains undefined without anatomic data.

**REGIONAL STRESS MBF, RFR, AND CFR.** Indexing the value of stress MBF to that of a true normal response, rather than “best” response in a given patient (27), avoids the problem posed by triple-vessel CAD with absence of a truly normal segment and may contain prognostic information over and above that in stress MBF alone (17,18,28). Further, the role of quantitative stress MBF measurements

indexed to a true normal response may be very helpful in evaluation of both coronary endothelial and microvasculature function. Whether it will prove more useful than global CFR (29) is uncertain. It appears, however, that a large fraction of previously diagnosed CMD as defined by global CFR is, in fact, attributable to diffuse epicardial conduit and small vessel disease (17). Relatively preserved epicardial small conduit vessel and microvascular dilator capacity vis-a-vis the endocardium may result in absolute decline in stress endocardial MBF, and total flow, as blood is preferentially shunted to the epicardium (17,30).

When RFR is used in conjunction with regional CFR, a recent retrospective analysis of a large clinical database indicates that these parameters have been successful in predicting outcomes with coronary revascularization (18). Prospective, randomized clinical trials will be required to test the ability of RFR either alone or in conjunction with regional CFR to guide interventional therapy. Similar considerations apply to use of RFR in comparison with global CFR for outcome prediction in various CAD risk factor groups (e.g., hypertension, diabetes, and chronic kidney disease) (29).

#### GLOBAL CFR VERSUS STRESS MBF FOR PROGNOSIS.

Global CFR was a stronger indicator of prognosis than stress MBF in 2 retrospective studies, although the reason was uncertain (15,31). In 1 study, the authors noted that “...reduction of CFR was due primarily to progressive reduction in peak stress MBF...” but suggested that CFR may “... reduce systematic errors in measurement,” hence providing a better indicator of coronary vasodilator capacity (15). The other study, also retrospective, again asserted superior prognostic power of global CFR reflected the fact that “measurement errors cancel” when the division is made (15,31).

Other explanations should be considered. First, statistical principles indicate division of 2 measurements, each with known error (e.g.,  $\pm 10\%$  to  $20\%$  for PET MBF [32]), does not cancel the errors but rather increases the error of the ratio relative to that of each of its components (33). Further, dispersion of aggregate global CFR data is less than that of global stress MBF (31) (identical values of CFR may reflect various combinations of rest and stress MBF). So, what appears to mitigate the “measurement error” is not the case-by-case division per se but rather its reduction of variation of the aggregate data. Finally, global stress MBF may average away important regional low flow disparities which also may decrease its prognostic power.

## CONCLUSIONS: THE FACTS

Quantitative PET measurements of MBF have considerable potential to improve clinical decision-making in a wide variety of cardiac diseases, particularly when the facts are brought to bear in an informed, comprehensive fashion. Important facts include: 1) coronary stenosis pressure flow relations including pressure losses along a diffusely diseased but apparently “nonobstructive” coronary artery; 2) transmural as well as inter-regional coronary steal; 3) the relationship between PET RFR and invasive FFR; both are independent of rest MBF; 4) potential value

of PET regional RFR for management of patients with known or suspected CAD, including CMD; 5) importance, in clinical decision making of considering both numerator and denominator of CFR; and 6) utility of global CFR in clinical prognostication notwithstanding important limitations as a metric of vasodilator capacity of the coronary circulation.

**ADDRESS FOR CORRESPONDENCE:** Dr. Gewirtz, Cardiac Unit, Massachusetts General Hospital, Boston, Massachusetts 02114. E-mail: [gewirtz.henry@mgh.harvard.edu](mailto:gewirtz.henry@mgh.harvard.edu).

## REFERENCES

- Gewirtz H, Dilsizian V. Integration of quantitative positron emission tomography absolute myocardial blood flow measurements in the clinical management of coronary artery disease. *Circulation* 2016;133:2180-96.
- Marinescu MA, Loffler AI, Ouellette M, Smith L, Kramer CM, Bourque JM. Coronary microvascular dysfunction, microvascular angina, and treatment strategies. *J Am Coll Cardiol Img* 2015;8:210-20.
- Schindler TH, Schelbert HR, Quercioli A, Dilsizian V. Cardiac PET imaging for the detection and monitoring of coronary artery disease and microvascular health. *J Am Coll Cardiol Img* 2010;3:623-40.
- Gould KL, Johnson NP. Physiologic severity of diffuse coronary artery disease: hidden high risk. *Circulation* 2015;131:4-6.
- De Bruyne B, Hersbach F, Pijls NH, et al. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but “normal” coronary angiography. *Circulation* 2001;104:2401-6.
- Huggins GS, Pasternak RC, Alpert NM, Fischman AJ, Gewirtz H. Effects of short-term treatment of hyperlipidemia on coronary vasodilator function and myocardial perfusion in regions having substantial impairment of baseline dilator reserve [see comments]. *Circulation* 1998;98:1291-6.
- Gewirtz H. PET measurement of adenosine stimulated absolute myocardial blood flow for physiological assessment of the coronary circulation. *J Nucl Cardiol* 2012;19:347-54.
- Johnson NP, Gould KL. Integrating noninvasive absolute flow, coronary flow reserve, and ischemic thresholds into a comprehensive map of physiological severity. *J Am Coll Cardiol Img* 2012;5:430-40.
- Kajander SA, Joutsiniemi E, Saraste M, et al. Clinical value of absolute quantification of myocardial perfusion with 15O-water in coronary artery disease. *Circ Cardiovasc Imaging* 2011;4:678-84.
- Johnson NP, Gould KL. Physiological basis for angina and ST-segment change PET-verified thresholds of quantitative stress myocardial perfusion and coronary flow reserve. *J Am Coll Cardiol Img* 2011;4:990-8.
- Gould KL, Nakagawa Y, Nakagawa K, et al. Frequency and clinical implications of fluid dynamically significant diffuse coronary artery disease manifest as graded, longitudinal, base-to-apex myocardial perfusion abnormalities by noninvasive positron emission tomography. *Circulation* 2000;101:1931-9.
- Johnson NP, Gould KL. Fractional flow reserve returns to its origins: quantitative cardiac positron emission tomography. *Circ Cardiovasc Imaging* 2016;9: pii:e005435.
- Stuijzand WJ, Uusitalo V, Kero T, et al. Relative flow reserve derived from quantitative perfusion imaging may not outperform stress myocardial blood flow for identification of hemodynamically significant coronary artery disease. *Circ Cardiovasc Imaging* 2015;8: pii:e002400.
- Dorbala S, Di Carli MF, Beanlands RS, et al. Prognostic value of stress myocardial perfusion positron emission tomography: results from a multicenter observational registry. *J Am Coll Cardiol* 2012;61:176-84.
- Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation* 2011;124:2215-24.
- Taqeti VR, Hachamovitch R, Murthy VL, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation* 2015;131:19-27.
- Gould KL, Johnson NP. Coronary physiology beyond coronary flow reserve in microvascular angina: JACC state-of-the-art review. *J Am Coll Cardiol* 2018;72:2642-62.
- Gould KL, Johnson NP, Roby A, et al. Regional artery specific thresholds of quantitative myocardial perfusion by PET associated with reduced MI and death after revascularization in stable CAD. *J Nucl Med* 2019;60:410-7.
- Hajjiri MM, Leavitt MB, Zheng H, Spooner AE, Fischman AJ, Gewirtz H. Comparison of positron emission tomography measurement of adenosine-stimulated absolute myocardial blood flow versus relative myocardial tracer content for physiological assessment of coronary artery stenosis severity and location. *J Am Coll Cardiol Img* 2009;2:751-8.
- Joutsiniemi E, Saraste A, Pietila M, et al. Absolute flow or myocardial flow reserve for the detection of significant coronary artery disease? *Eur Heart J Cardiovasc Imaging* 2014;15:659-65.
- Sdringola S, Johnson NP, Kirkeeide RL, Cid E, Gould KL. Impact of unexpected factors on quantitative myocardial perfusion and coronary flow reserve in young, asymptomatic volunteers. *J Am Coll Cardiol Img* 2011;4:402-12.
- Laaksonen MS, Kalliokoski KK, Luotolahti M, et al. Myocardial perfusion during exercise in endurance-trained and untrained humans. *Am J Physiol Regul Integr Comp Physiol* 2007;293:R837-43.
- Bourque JM, Charlton GT, Holland BH, Belyea CM, Watson DD, Beller GA. Prognosis in patients achieving  $\geq 10$  METS on exercise stress testing: was SPECT imaging useful? *J Nucl Cardiol* 2011;18:230-7.
- Kushwaha SS, Narula J, Narula N, et al. Pattern of changes over time in myocardial blood flow and microvascular dilator capacity in patients with normally functioning cardiac allografts. *Am J Cardiol* 1998;82:1377-81.
- Schelbert HR, Stevenson LW. Toward an improved understanding and management of human heart transplant recipients. *J Am Coll Cardiol* 1992;19:107-9.
- Gewirtz H. Serial PET Measurements of myocardial blood flow for prognosis assessment in heart transplant patients: the forest and the trees. *J Am Coll Cardiol Img* 2018 Oct 17 [E-pub ahead of print].
- Lee JM, Kim CH, Koo BK, et al. Integrated myocardial perfusion imaging diagnostics improve detection of functionally significant coronary artery stenosis by 13N-ammonia positron emission tomography. *Circ Cardiovasc Imaging* 2016;9:1-11.
- Bravo PE, Bergmark BA, Vita T, et al. Diagnostic and prognostic value of myocardial blood flow quantification as non-invasive indicator of cardiac allograft vasculopathy. *Eur Heart J* 2018;39:316-23.

29. Taqueti VR, Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC state-of-the-art review. *J Am Coll Cardiol* 2018;72:2625-41.
30. Gewirtz H, Gross SL, Williams DO, Most AS. Contrasting effects of nifedipine and adenosine on regional flow distribution and metabolism distal to a severe coronary arterial stenosis: observations in sedated, closed-chest domestic swine. *Circulation* 1984;69:1048-57.
31. Gupta A, Taqueti VR, van de Hoef TP, et al. Integrated noninvasive physiological assessment of coronary circulatory function and impact on cardiovascular mortality in patients with stable coronary artery disease. *Circulation* 2017;136:2325-36.
32. Kitkungvan D, Johnson NP, Roby AE, Patel MB, Kirkeeide R, Gould KL. Routine clinical quantitative rest stress myocardial perfusion for managing coronary artery disease: clinical relevance of test-retest variability. *J Am Coll Cardiol Img* 2017;10:565-77.
33. Lindberg V. Uncertainties and Error Propagation; Part I of a Manual on Uncertainties, Graphing, and the Vernier Caliper. 2000. Available at: <http://www.geollsuedu/jlorenzo/geophysics/uncertainties/Uncertaintiespart2html>. Accessed November 19, 2018.

---

**KEY WORDS** coronary artery disease, coronary microvascular disease, myocardial blood flow and flow reserve, positron-emission tomography, prognosis, relative flow reserve