PET ^{18}F -flurpiridaz quantitative measurements of myocardial blood flow: Added value for diagnosis of coronary artery disease? Of course!

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Received Jan 13, 2020; accepted Jan 14, 2020
doi:10.1007/s12350-020-02043-1

See related article, pp. 2313–2329

INTRODUCTION

In the current issue of the *Journal*, Moody et al report the results of a retrospective analysis of ^{18}F -flurpiridaz (FPZ), PET quantitative measurements of myocardial blood flow (MBF) for diagnosis of coronary artery disease (CAD).¹ Patients ($n = 231$) were clinically stable and selected from a larger group enrolled in the flurpiridaz 301 trial ($n = 755$; NCT01347710). All participants were able to undergo either an exercise or vasodilator stress test for clinically indicated SPECT myocardial perfusion imaging (MPI). The sub-study was not pre-specified and required availability of dynamic PET data of sufficient technical quality to obtain quantitative PET MBF measurements. PET data processing and analysis was performed using Corridor4DMTM software (V 2017; INVIA Medical Imaging Solutions, Ann Arbor, MI). The gold standard comparator was quantitative, percent diameter, stenosis (QCA) as determined from invasive coronary angiography (ICA; 50% and 70% criteria considered). While ICA information was available on all patients, FFR data were not. The data analysis was exhaustive (8 figures and as many equally comprehensive tables) with similar supplemental data submitted as that in the body of the

paper. Accordingly, the editorial will focus only on key highlights as well as some limitations of the work.

HIGHLIGHTS

While the outcome of the study, namely improved diagnosis of obstructive epicardial CAD was predictable from results of earlier reports,^{2–4} the present investigation reflects a larger and more diverse patient population recruited from 81 participating centers, worldwide. The authors' data indicate stress MBF is a superior metric vs myocardial flow reserve (MFR) for CAD diagnosis defined at the 50% level (Figure 6A). At the 70% level, stress MBF appears marginally better vs MFR ($P = 0.08$) perhaps reflecting type II statistical error (alluded to by authors in study limitations). As would be expected, both stress MBF and MFR, each considered separately, enhanced CAD diagnosis (70% stenosis, Figure 7A, B) when compared to a base model of clinical variables alone.

However, in comparison to a model including clinical variables and total perfusion defect (TPD) (clinical + TPD), neither stress MBF nor MFR added additional diagnostic power (Figure 7A, B) and appear more or less equivalent after model adjustment for age and gender. The authors suggest (study limitations) inclusion in the full study data set of information from 32 normal patients used to define normal tracer retention, is self-referential and may have caused overestimation of the diagnostic performance of TPD, though they indicate the effect likely was small.

They also indicate both for stress MBF and MFR the "...importance of low stress MBF and MFR increased with larger and more severe defects (Figure 8)". While one would like to know if either (or

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J Nucl Cardiol 2021;28:2330–4.

1071-3581/\$34.00

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both) metrics alone are superior to TPD for CAD diagnosis as shown by others,^{3,5} there is no direct answer to the question from the data as presented. Nevertheless, Figure 8, which is more complex than meets the eye, provides some information in this regard. Thus, for stress MBF, the probability of CAD increases rapidly for MBF < 2 mL/min/g at all levels of stress % TPD (Figure 8A; 5% to 80% isolines). Or, stated another way, per Figure 8B, the probability of CAD at low levels of stress MBF (e.g., ≤ 1.0 mL/min/g) is quite high (especially 0.5 mL/min/g) and tends to plateau regardless of stress %TPD. Conversely, at moderate/high levels of stress MBF (≥ 1.8 mL/min/g), the probability of CAD is low and does not increase substantially with increase %TPD. At stress MBF of 2.5 mL/min/g, the probability of CAD appears negligible, regardless of stress %TPD (Figure 8B). Thus, a very strong case may be made for much greater reliance upon PET quantitative stress MBF measurement for CAD diagnosis including to the exclusion of objective quantitative %TPD data and certainly to subjective, visual interpretation of rest/stress retention images. In this regard, this results of the present study are confirmatory, as noted above, of prior work^{2–4} demonstrating superiority for CAD diagnosis of quantitative PET rest/stress MBF measurements in comparison with that of quantitative retention images.

LIMITATIONS

Authors Identified

The authors have identified many of the important limitations of the present study including its retrospective, single-center data set, and patient population not pre-specified for the current quantitative MBF analysis. Concern also was raised by the authors that women may have been underrepresented for purposes of regional CAD/MBF analysis. An anatomical rather than functional gold standard for defining CAD significance reflects another issue noted by the authors. Closely related is the fact that an absolute MBF gold standard was not available though they do address in great detail the general comparability of the FPZ MBF measurements, especially stress, with that of ⁸²Rb, ¹³N-ammonia, and ¹⁵O-water reported in the literature. Finally, concern was raised that the PET data acquisition itself may have been inadequate in some unspecified number of cases, which could have had an important impact on MBF determination.

Important Conceptual Issue (Briefly Alluded to in the Text)

An important conceptual issue, which the authors allude to briefly should be addressed in more detail. They appear to accept the notion that MFR is an independent physiological parameter, which contains clinical information regarding the dilator capacity of the coronary circulation over and above that of stress MBF. While there are empirical data, for example, which appear to support this view with respect to prognostication,^{6–8} they are not as clear cut as frequently portrayed, including in the present report.¹ Unfortunately, it bears repeating, MFR is stress divided by rest MBF. Thus, the authors themselves recognize the susceptibility of MFR to the level of rest MBF.¹ They indicate rest MBF may be increased by increased rate pressure product, as well as “decreased myocardial efficiency or autonomic dysfunction (45,46)”.¹ The converse, of course, also is true (i.e., reduced rest MBF relative to stress makes the ratio higher). Accordingly, if one wished to know something about the maximal dilator capacity of the coronary circulation one would seek to maintain rest MBF constant and assess the myocardial flow response to a primary coronary vasodilator stimulus (e.g., adenosine “stress”).⁹ Considering the case in which stress MBF response was judged impaired, one could not know without additional, typically anatomical information, if the cause was discrete conduit vessel stenosis, more distal small conduit vessel disease,^{10,11} true microvascular disease, all 3, or various combinations. The MFR ratio in all scenarios will be abnormal and so no more informative than stress MBF alone.

If the rest MBF is permitted to “float” as is commonly the case in individual clinical exams and in retrospective analyses of clinical data sets,^{1,6,7,12} the MFR ratio becomes more difficult to interpret and potentially very misleading without knowledge of its component parts.¹³ Summary data from Table 2 of the present study are illustrative. Though stress MBF on average is clearly abnormal in the “2 or 3 VD” group (1.46 ± 0.39 mL/min/g), MFR is not (i.e., 2.21 ± 0.75 ; greater than the frequently used cut-point (2.0) for most clinical studies, including the present¹). The reason MFR appears maintained (i.e., > 2.0) is that rest MBF in this group, (0.69 ± 0.16 mL/min/g) is even lower relative to stress MBF. Thus, reference to MFR alone (2.21), as if some independent metric, leads to the erroneous conclusion that coronary vasodilatory capacity is “normal” in this subset, false negative for both epicardial and microvascular disease, when nothing could be further from the truth, given maximal MBF of 1.46 mL/min/g and known coronary anatomy (i.e., “2 or

3 VD'', Table 2). Contrariwise, with stress MBF at least moderately reduced, as the authors note, consistent with "2 or 3 VD'', one commonly observes associated distal diffuse small vessel and true microvascular disease.^{10,14} Parsing the loci of various resistance to flow is difficult in this setting. Invasive measurements of coronary flow (thermodilution) or flow velocity (doppler ultrasound) and pressures (proximal, distal, occlusive, and pull back) are required to help parse the components.^{10,15–18} Knowledge of size of the distal perfusion bed and status of the collateral circulation also must be accounted for.

So, while the MFR metric may be "fooled" in a variety of ways, stress MBF is what it is. If one requires a reference standard then comparison to a truly normal vasodilator response provides relative flow reserve (RFR also known as FFR-PET^{19,20}) and likely is the more stable and hence informative metric. Prospective randomized clinical trials are certainly warranted to test this hypothesis as well as defining the true prognostic power of MFR.

In clinical practice, one either has the quantitative PET data first, in which case measurement of stress MBF, as in the present study, is likely to be most informative not only for purposes of CAD diagnosis but also prognosis, since it is really ischemic potential that is being assessed especially if global measurements are under consideration. In an earlier study of CAD prognosis, it was noted MFR declined across tertiles because of a progressive decline in stress MBF, while rest MBF remained constant.⁶ Accordingly, the signal was in stress MBF and not MFR.

An important PET MBF study with ¹⁵O-water demonstrated this very point.²¹ In multi-variable analysis, which held CFR (i.e., MFR) constant, the association of hyperemic MBF (global and regional) with CAD prognosis was found to be a significant ($P = 0.04$) predictor of MACE (death or myocardial infarction) over follow-up median 6.9 (5.0 to 7.9) years. In contrast, the reverse procedure with the same data set failed to identify MFR as a significant predictor, once the effect of stress MBF was accounted for. Cut-points identified for global and regional stress MBF were < 2.65 and < 2.10 mL/min/g, respectively, after adjustment for clinical parameters and holding MFR at optimal level (< 2.88 and < 2.07 , global and regional, respectively).

Interestingly, other, retrospective reports using different cut-points and data analysis found that global CFR (MFR) was a better predictor of MACE than stress MBF.^{8,22} The reason(s) for differences is unclear though patient populations and experimental design, data analysis, especially patient grouping, MBF and MFR cut-points, and MACE end-points certainly must be considered. Ultimately, only data from a prospective, carefully

designed randomized clinical trial hopefully will provide an answer.

The argument that dividing stress by rest MBF to obtain MFR results in a signal with less noise than stress MBF alone is correct only in so far as systemic bias is present in both measures. Not removed is random statistical noise, day to day, month to month intra- and inter-patient variation ($\sim 20\%$ ²³) as well as other factors of which input function determination is a key as noted by the authors of the present study and others.²⁴ Indeed, division increases relative error of the metric (<http://www.geol.lsu.edu/jlorenzo/geophysics/uncertainXes/UncertainXespart2.html>). Moreover, Bland Altman plots of the differences between PET MBF ⁸²Rb measurements and a gold standard such as ¹⁵O-water in vivo²⁵ or ¹⁵O-water and radiolabeled microspheres ex vivo²⁶ indicate bias ~ 0.14 mL/min/g ($P = \text{ns}$ vs zero) in the former study²⁵ and similar bias in the latter.²⁶ Both, however, had considerably wider 95% coefficient of reproducibility relative to bias. Unsurprisingly, greater in the human study (± 1.14 mL/min/g)²⁵ vs the porcine (± 0.75 mL/min/g).²⁶

Thus, as with the present investigation and others,^{12,21} it is becoming increasingly clear it is the physiological parameter which matters most. It is very unlikely a level of stress requiring MBF 3.0 mL/min/g (think ~ 10 to 15 METs²⁷) will be met, without ischemia, by maximal MBF < 2 mL/min/g (Figure 8B) simply because rest MBF is 0.50 with stress MBF 1.50 and MFR = 3.0. Indeed, speaking of FPZ, it is worth restating myocardial mitochondria require a certain level of oxygen flux to fuel the electron transport chain (ETC) and generate ATP aerobically. Metabolic evidence of ischemia results when myocardial oxygen demand exceeds supply (i.e., MBF), also very well-known, but worth repeating in this context.

Further, the ability of the myocardium to survive in face of impairment of MBF is limited. While adaptive mechanisms certainly exist to maintain myocardial viability,^{28–31} for the most part they are inadequate to permit normal contractile function.^{32,33} Thus, it is generally accepted that repetitive bouts of myocardial ischemia result in a state of chronic stunning (MBF $>$ contractile function) which merges over time with chronic hibernation^{32–35} (matched low flow and low function) which in turn may progress to cell death and scar if it persists long enough.^{32,33} Clinically, the end result is ischemic cardiomyopathy characterized by left ventricular dilatation, reduced ejection fraction (HFrEF), and propensity to sudden cardiac death often due to ventricular arrhythmias (VT/VF)^{31,36} and also bradyarrhythmia including asystole.³⁶ The fact that coronary revascularization, when feasible, improves left ventricular function and survival speaks volumes about the root

cause of the problem, which is impairment of MBF and not correction of a ratio which often floats with the level of rest MBF. Just consider, if CABG in the example above permitted rest MBF of 1.50 and stress MBF to 2.75, then MFR would be only 1.83; not only less than pre-op (MFR = 3.0) but less than 2 as well, indicative of moderate/high ischemic risk (Figure 8; current study); a conclusion which appears unlikely given the absolute level of stress MBF attainable (2.75 mL/min/g).

SUMMARY

Despite certain limitations noted above and others recognized, to their credit, by the authors themselves (Study Limitations), the data in the present study provide strong evidence in support of incorporating PET quantitative measurements of MBF into clinical practice. Knowledge of the level of stress MBF either alone, or preferably indexed to normal values obtained in a given lab will provide RFR^{18–20} a robust, physiological measure of the dilator capacity of the coronary circulation (or vascular distribution) under consideration. The RFR metric, as noted by others,^{19,20} is directly comparable to FFR which indexes MBF distal to a coronary stenosis under conditions of maximal vasodilation to that (1) in the absence of a stenosis and (2) in the presence of a truly normal distal circulation.^{9,19} Conceptually, it appears the most appropriate PET metric to compare with FFR data.

MFR (Global and regional), as the authors note, was a less reliable indicators of the presence or absence of obstructive CAD at 50% anatomical level and likely at 70% as well ($P = 0.08$, Figure 6B). Unfortunately, RFR (FFR-PET) and FFR data were not available for diagnostic evaluation.

The role of MBF and MFR (global or regional) in CAD prognostication was beyond the scope of the present study. However, to the extent that it has demonstrated stress MBF to be a more robust predictor of CAD than MFR particularly at the 50% stenosis level, the results are consistent with outcome data of at least 2 prior studies^{6,21} and suggest reasons (e.g., technical, methodological, and population selection) for potential outcome differences with others, which found MFR superior.^{7,8,22} The reader should keep in mind in the setting of CAD, outcomes (e.g., CV death or MI) in the vast majority of patients ultimately are indicative of MBF inadequate to meet a given level of myocardial oxygen demand (i.e., ischemia/infarction). The ratio, which actually counts, myocardial oxygen supply/demand, appears to be variable both within and between patients, and will determine not only when/how angina occurs but type 2 MI and probably Types 1 and 3 as well. Thus, careful attention to what can be measured,

both rest and stress MBF, in particular stress as shown in the present study, is likely to be most informative in clinical decision making. Their ratio, MFR, less so.

Disclosure

None.

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