

Myocardial Blood Flow and Myocardial Flow Reserve After Cardiac Transplantation: Mistakes in Diagnostic Value and Prognosis

TO THE EDITOR: I read with great interest the recent article by Miller et al. published in *The Journal of Nuclear Medicine* (1). Cardiac allograft vasculopathy (CAV) is a major cause of graft failure after cardiac transplantation. CAV is characterized by diffuse involvement of epicardial coronary arteries and the microvasculature. PET allows quantification of absolute myocardial blood flow (MBF) and myocardial flow reserve (MFR), which may be accurate markers of CAV severity. The authors aimed to compare the diagnostic and prognostic utility of stress MBF and MFR after cardiac transplantation. The diagnostic accuracy for significant CAV (grade 2/3) and prognostic accuracy of stress MBF and MFR, corrected and uncorrected for rate pressure product, were compared. They reported that higher MFR (adjusted hazard ratio, 0.30; $P < 0.001$), but not stress MBF (adjusted hazard ratio, 1.14; $P = 0.656$), was associated with reduced all-cause mortality. Preserved MFR (>2.0) identified relatively low-risk patients (annual mortality 4.7%) whereas the presence of left ventricular ejection fraction less than 45% and MFR less than 1.7 identified high-risk patients (annual mortality 51.6%).

Although this article has provided valuable information, there are some substantial points needing consideration to help the clarity of the method and ensure an accurate interpretation of the study. First, to evaluate diagnostic value, reliability (precision) as a different methodologic issue compared with validity (accuracy) should also be assessed. In this case, application of either weighted or Fleiss κ is suggested. Without assessing reliability (precision), we cannot talk about the diagnostic value of a test (2–9). Second, it should be noted that, due to the limitation of reported values for accuracy (e.g., sensitivity and specificity are generally used for public health purposes and limited in clinical practice; positive predictive value depends on the prevalence of the outcome), other validity estimates such as likelihood ratios should also be considered. These estimates are more appropriate for advice about accuracy of a diagnostic test for clinical purposes. Thus, reported estimates as in this study can be acceptable; however, when the rest of validity estimates are considered, our final decision can be changed (2–9).

Third, the receiver-operating-characteristic curve is usually used to assess diagnostic accuracy (discrimination) of a diagnostic model. However, for clinical purposes, reporting diagnostic added value of a test is crucially important. The reason is all validity estimates can be acceptable, but diagnostic added value may be negligible. Lastly, for prognosis, assessing internal and external validity is recommended. That is why we need 2 different cohort datasets (10,11). It would be reasonable to assess interaction between predictors before any judgment about prognosis.

In the light of the mentioned points, any conclusion in diagnostic value and prognosis needs to be supported by the methodologic and statistical issues mentioned above. Otherwise, misinterpretation cannot be avoided. So, there is not sufficient evidence to conclude

that quantitative PET analysis, and particularly MFR, has diagnostic and prognostic utility.

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Clarifying the Utility of Myocardial Blood Flow and Myocardial Flow Reserve After Cardiac Transplantation

REPLY: We would like to thank Dr. Sabour for taking an interest in our article, which highlights the potential diagnostic and prognostic utility of PET in patients after cardiac transplantation with known or suspected cardiac allograft vasculopathy (CAV) (1). As discussed by Dr. Sabour (2), there are additional test characteristics that need to be considered before routine implementation of a diagnostic test into clinical practice.

Several previous studies have established the precision and accuracy of PET myocardial blood flow (MBF) measurements (3–10). MBF

TABLE 1
Summary of Test Characteristics for Identifying CAV Grade 2 or 3

Cutoff	Sensitivity	Specificity	PPV	NPV	+LR	-LR
MFR < 2.0	71.4%	71.8%	29.4%	93.9%	2.53	0.40
MFR < 1.75	57.1%	77.7%	29.6%	91.7%	2.56	0.55
Stress MBF < 3.7	92.9%	22.4%	16.5%	95.0%	1.20	0.32
Stress MBF < 1.7	42.9%	95.3%	60.0%	91.0%	9.13	0.60
SSS > 1	64.3%	72.9%	28.1%	92.5%	2.37	0.49
SSS > 3	64.3%	92.9%	60.0%	94.1%	9.06	0.38
LVEF ≤ 45	42.9%	95.3%	60.0%	91.0%	9.13	0.60
MBF < 1.7 and SSS > 1 or LVEF ≤ 45	42.9%	97.7%	75.0%	91.2%	18.7	0.58
SSS ≥ 4, LVEF ≤ 45 or MFR < 1.75	71.4%	69.4%	27.8%	93.7%	2.3	0.41
LVEF ≤ 45% and MFR < 1.75*	35.7%	100.0%	100.0%	90.4%	> 99	0.64

PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; MFR = myocardial flow reserve; SSS = summed stress score; LVEF = left ventricular ejection fraction.

measurements demonstrate excellent repeatability across serial studies, with repeatability coefficients of 0.19 mL/min/g for rest MBF and 0.92 mL/min/g for stress MBF (5). Measurements obtained with different radiotracers demonstrate very close correlation ($r = 0.85$ to 0.92) (8,9). Additionally, the RUBY-10 study demonstrated excellent agreement between global and regional MBF measurements determined with 10 different software packages (3). As a result of this substantial body of evidence, guidelines recognize PET measurements of MBF and myocardial flow reserve as highly accurate and precise measurements (11).

Dr. Sabour also accurately points out that no single measure of a diagnostic test accurately reflects all aspects of its clinical performance. Table 1 contains additional measures of diagnostic accuracy. Stress MBF < 3.7 has the highest negative predictive value (95.0%), whereas the combination of left ventricular ejection fraction < 45% and myocardial flow reserve < 1.75 had 100.0% positive predictive value. Notably, the prevalence of CAV varies with time after cardiac transplantation, which will also influence test characteristics (12). The median time after transplantation was 12.5 y in our cohort, so the results are most applicable to screening patients late after transplantation.

Lastly, we would like to clarify that in our study we tested previously established thresholds for PET measurements in transplantation patients in a population distinct from previous similar studies. Therefore, our results demonstrate generalizability of the diagnostic accuracy of PET across patient populations as well as providing valuable external validation of the prognostic utility. Our article contributes to a robust body of literature outlining the potential superiority of PET for CAV surveillance (13), and cardiac transplantation programs should strongly consider its implementation.

DISCLOSURE

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Reversibility of ^{68}Ga -FAPI-2 Trapping Might Prove an Asset for PET Quantitative Imaging

TO THE EDITOR: In a recent paper, Giesel et al. analyzed the tissue biodistribution and preliminary dosimetry of 2 quinoline-based PET tracers that act as fibroblast activation protein (FAP) inhibitors, namely, ^{68}Ga -FAPI-2 and ^{68}Ga -FAPI-4 (1). The authors reported a fast clearance via the kidneys, a low tracer uptake in normal organs, equal tumor-to-background contrast ratios at 1 h after injection, and an almost equal uptake in comparison with ^{18}F -FDG. However, from 1 to 3 h after injection, in contrast to ^{68}Ga -FAPI-4, which displayed a prolonged tumor retention (25% washout), ^{68}Ga -FAPI-2 tumor uptake decreased by 75%, thus reflecting release of the tracer from the malignant tissue. This difference explains why a companion paper by Kratochwil et al. used ^{68}Ga -FAPI-4 for identifying the most promising indications for future application (2).

We suggest that ^{68}Ga -FAPI-2 trapping reversibility, evidenced by a decrease in tumor uptake observed at late imaging, might prove an asset for PET quantitative imaging. Figure 2, by Giesel et al., shows ^{68}Ga -FAPI-2 and ^{68}Ga -FAPI-4 maximal SUV (SUV_{max}) at 10, 60, and 180 min after injection in 2 patients with metastasized breast cancer, respectively (1). Because the 2 tracers have rapid clearance from blood, we assume their input function (IF) has become negligible at 60, and, a fortiori, at 180 min after injection. Thus, a previously published method designed for ^{18}F -FDG may be adapted to ^{68}Ga -FAPI-2 and ^{68}Ga -FAPI-4 for assessing their release rate k_B (in min^{-1} ; Eq. 3 in Laffon et al. (3)). For the sake of clarity, let us assume an IF monoexponential decay with decay-corrected time constant α and initial amplitude $A_P(t = 0)$ (in min^{-1} and $\text{kBq}\cdot\text{mL}^{-1}$, respectively). The decay-corrected tissue activity concentration related to trapped tracer (in kBq/mL), which is proportional to SUV_{max} , can be approximated from 60 to 180 min after injection, by:

$$A_T(t) \approx K_i \times A_P(t = 0) \times \exp(-k_B \times t) / (\alpha - k_B), \quad \text{Eq. 1}$$

where K_i is the uptake rate constant of the tracer (in $\text{mL}\cdot\text{min}^{-1}\cdot\text{mL}^{-1}$). Fitting the outer extreme metastasis data (extracted with the Web-

PlotDigitizer software) at 60 and 180 min after injection in Figure 2 with a monoexponentially decaying function leads to the following range for k_B : 0.01435–0.01439 and 0.00129–0.00212 min^{-1} for ^{68}Ga -FAPI-2 and ^{68}Ga -FAPI-4, respectively. For comparison, k_B for ^{18}F -FDG trapping in the normal human liver has been estimated to be 0.00650 min^{-1} on average (4). It is noteworthy that, because only 2 time points were analyzed and only 1 patient per tracer was examined in Figure 2 by Giesel et al., the assessment of k_B measurement uncertainty is out of the scope of the current paper (1). Therefore, additionally to SUV, we suggest that one could take advantage of the significant ^{68}Ga -FAPI-2 trapping reversibility to better characterize tumors by means of calculating k_B . Furthermore, the above-proposed fitting of k_B might be easily performed at the voxel level, thus allowing parametric imaging of tracer release. Finally, let us note that a multiexponentially decaying IF does not alter the current line of argument.

To conclude, ^{68}Ga -FAPI PET/CT is a promising new diagnostic method for imaging various cancers that overexpress FAP (1). We suggest that the choice between ^{68}Ga -FAPI-2 and ^{68}Ga -FAPI-4 should not be only based on the criterion of reversible versus irreversible (or nearly) trapping of the tracer, even if the latter is an indubitable advantage for a theranostic purpose. Indeed, one could also take advantage of the significant trapping reversibility of ^{68}Ga -FAPI-2 to better characterize malignant tissues. Furthermore, we suggest that performing both uptake and release quantitation of ^{68}Ga -FAPI-2 trapping might be an innovative tool for assessing the response to treatment.

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