

EDITORIAL COMMENT

Serial PET Measurements of Myocardial Blood Flow for Prognosis Assessment in Heart Transplant Patients

The Forest and the Trees*

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In this issue of *JACC*, Feher et al. (1) report the use of serial positron emission tomography (PET) rubidium-82 myocardial perfusion imaging (MPI) for follow-up and risk stratification of heart transplant (HT) recipients. Although clinical guidelines recommend invasive coronary angiography (Class I) with intravascular ultrasound (Class IIa) at 1, 3, and 5 years post-HT and less frequently thereafter for detection of coronary artery vasculopathy (CAV) (2), alternatives are required, especially for patients with impaired renal function, a common occurrence (3), and for less costly noninvasive long-term surveillance. Single-photon emission computed tomography (SPECT) MPI, dobutamine stress echocardiography, cardiac magnetic resonance, and computed tomography angiography all have been used, and their relative merits have been comprehensively reviewed (3,4).

The sensitivity of dobutamine stress echocardiography for CAV detection recently has been questioned (4). SPECT MPI provides only relative information concerning myocardial blood flow (MBF) distribution and is ill-suited for detection of diffuse CAV disease. Cardiac magnetic resonance and computed tomography angiography are optimal in patients with a reduced heart rate, which is more difficult to achieve with beta-blocker administration in the denervated HT, and, more importantly, require contrast agents that are relatively, or possibly absolutely, contraindicated in patients with renal insufficiency (3,4). Accordingly, a better way is required for detection,

follow-up, and prognostication of CAV in HT recipients.

Feher et al. (1) suggest an excellent alternative. They obtained rest and dipyridamole stress scans at baseline (mean 7 years post-HT) and ~2 years later, with a median follow-up of 8.6 years. The primary endpoint was all-cause mortality. Absolute values of rest and stress MBF, each normalized to rate pressure product (RPP), were used to compute coronary flow reserve (CFR). Dichotomized CFR (low ≤ 1.5 vs. high > 1.5) was used to predict all-cause mortality.

Low baseline CFR was independently associated with a 2.8-fold increase in all-cause mortality. A 3.6-fold increase all-cause mortality risk per 0.9 decrease in CFR from first to second PET also was noted (95% confidence interval [CI]: 1.49 to 8.74; $p = 0.005$). Figures 2A and 2B in the article by Feher et al. (1) demonstrate the importance of decreased stress MBF, from first to second PET, in CFR decline (rest MBF unchanged). Further, 18 patients reclassified from high to low CFR, from first to second PET, had all-cause mortality similar to that of patients with CFR that remained low. Patients reclassified from low to high CFR ($n = 7$), all the result of increased stress MBF, had survival similar to patients with CFR that remained high.

Initial stress MBF was a univariate predictor of mortality and borderline in multivariate analysis (95% CI: 0.20 to 1.16; $p = 0.10$). However, a decline in stress MBF (from first to second PET) was predictive of mortality (5.1-fold increase risk per 0.9 decrease; 95% CI: 1.68 to 15.28; $p = 0.004$) (Online Figures 4A and 4B in the article by Feher et al. [1]) and was comparable to that of the change in CFR from first to second PET (3.6-fold). Accordingly, Feher et al. (1) indicated: "...temporal decrease in peak hyperemic MBF might be responsible for the predictive value of the CFR reduction."

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The study is important because it demonstrates the utility of quantitative PET measurements of MBF for assessment of CAV and associated prognosis in HT recipients (the Forest). The information will become increasingly helpful as more efficacious CAV therapies become available (4). Accordingly, it is worth considering in more detail (the trees) how the measurements may be best used.

Clinical context must be considered given the propensity for the incidence of complications, especially CAV, to increase with time post-HT (3-6). Thus, acute rejection, the number of prior rejection episodes, and previously documented CAV would be expected to influence absolute values of rest or stress (vasodilator) MBF, or both (3,4,7), and hence CFR (1,7). Moreover, the incremental value of stress MBF in estimating prognosis in HT recipients recently has been reported by other investigators (8,9). Accordingly, it behooves the clinician to understand the absolute values of each (10).

A cross-sectional HT recipient study further illustrates these points (11). Patients studied within the first year post-HT had reduced myocardial flow reserve (MFR) versus patients 13 to 34 months post-operatively (2.27 ± 1.23 vs. 3.66 ± 1.82 , respectively; $p < 0.05$). Reduced MFR was entirely the result of increased rest MBF in ≤ 1 year (1.86 ± 1.01) versus 13 to 34 months (1.17 ± 0.73) ($p < 0.02$). Adenosine stress MBF did not differ between them (3.44 ± 0.09 vs. 3.40 ± 0.69 , respectively; $p =$ not significant). A third group studied ≥ 37 months after HT had significantly reduced stress MBF (2.54 ± 1.25 [$p < 0.05$] vs. others) associated with reduced MFR (2.53 ± 0.56), a finding that did not differ from the ≤ 1 -year group (2.27 ± 1.23). Thus, whereas MFR in patients studied early (≤ 1 year) versus late (≥ 37 months) likely reflected very different pathophysiology (often non-CAV-related factors early vs. CAV-related factors late [3,4]), both shared indistinguishable and thus potentially misleading MFR unless one considered the rest and stress components of the ratio.

A word about normalizing rest and vasodilator stress MBF to RPP in a group of HT recipients: Although Feher et al. (1) report that uncorrected MBF data would not have changed study conclusions, from a physiological view the transform is concerning. RPP

provides only a rough measure of myocardial oxygen consumption (MVO_2) in the intact heart because it fails to account for myocardial contractility. Reported values of R^2 in non-HT patients range from nil (12,13) to 0.61 (14) to 0.67 (15) and as little as 0.08 in HT patients for RPP adjusted PET MFR versus invasive CFR (9). In the transplanted heart, the extent of parasympathetic and sympathetic reinnervation varies both from patient to patient and as functions of time and region (16). Sympathetic reinnervation when it occurs favors the anterior wall of the LV to variable extent (16) and so may contribute to additional heterogeneity in the MBF/RPP relationship. Indeed, in HT patients studied mean 24 months post-HT, basal heart rate and mean arterial pressure was increased compared with controls. Nevertheless, at any given level of directly measured MVO_2 , rest coronary sinus blood flow was increased versus controls (17), an observation indicating in HT patients that a simple linear transform to "correct" MBF to RPP fails to account for a more fundamental alteration in the regulation of MBF with respect to prevailing MVO_2 . Indeed, in the study (and their Online figure 1C) by Feher et al. (1), the correlation between global MBF and RPP arguably was nil ($R^2 = 0.016$; $<2\%$ of the variation of MBF attributable to RPP), borderline $p = 0.04$ notwithstanding. Accordingly, it would be best to use uncorrected PET MBF to assist with clinical assessment of HT recipients.

In conclusion, the study by Feher et al. (1) demonstrates the added value of serial, quantitative PET measurements of MBF for assessment of all-cause mortality risk in HT recipients. It appears likely, as these investigators note, that such information will prove useful in considering treatment options as more efficacious options become available. Optimal use of MBF data will require careful attention not only to clinical context but also to the rest and stress values, rather than reliance on their ratio alone, which may be misleading.

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