CMR quantitative measurements of myocardial blood flow: Not ready for routine clinical application

Henry Gewirtz, MD[a]

[a] Cardiac Unit, Department of Medicine (Cardiology Division), Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Editorial (Invited):

In this issue of the *Journal*, Kero et al. report results of quantitative measurements of myocardial blood flow (MBF) obtained with 3 T, PET/MR (CMR; with Gd-DOTA) compared with simultaneously acquired ^{15}O-water-quantitative MBF.[1] The study was performed in a small (n = 12) group of subjects with known or suspected CAD. CMR MBF [global, regional and myocardial perfusion reserve) was compared to PET measurements, which were considered the gold standard. The authors note that prior studies comparing CMR MBF with PET measurements typically were done on separate instruments at separate times[2] and thus susceptible to physiological variation, which was nullified in the current study by simultaneous data acquisitions with the hybrid PET/MR scanner. What was to all intents and purposes an identical study, save with ^{13}N-ammonia as the PET tracer, and larger sample size (n = 29), has been previously reported.[3] The CMR pulse sequences employed as well as other specifics (e.g. native T1 signal and hematocrit corrections, signal deconvolution algorithms) have varied between studies in efforts to optimize transformation of CMR signal into true blood and tissue Gd concentrations required for purposes of tracer kinetic modeling. Thus, CMR estimates of MBF are heavily dependent on the accuracy of these transforms and as noted by others may produce very different estimate of MBF depending on which one is chosen.[3] Further, as noted by the authors of the present study,[1] CMR methodology typically permits sampling of only 4 LV slices in contrast with PET which samples the entire LV. Accordingly, the issue of image registration as well as incomplete LV sampling may further confound efforts to compared CMR and PET estimates of absolute MBF, both global and regional. That said, a particular strength of the present study is the nullification of physiological variation as a source of differences between methods and so offers a more straightforward comparison of the CMR methodology with that of the ^{15}O-water PET gold standard.

Given that CMR methodology will affect the comparison of MBF measurements with that of PET, what can be learned from results of the present study? As noted above small sample size limits any conclusion(s) drawn. Absence of invasive or CCTA anatomical, and more importantly, invasive, coronary physiological data also is another limitation since such information could shed light on the issue of when the measurements are most likely to agree and when they may diverge with respect to an independent physiological gold standard (e.g. FFR,[4] IFR,[5] IMR[6]). The authors data indicate CMR and PET differences are most pronounced at MBF levels $\geq \sim 1.8$ mL·min^{-1}·g^{-1} (Figures 3A, 4A); an observation which has important implications both for use of the CMR stress MBF measurement for assessment of hemodynamic severity of focal (Ref. # 1, 48-51) and diffuse CAD,[7] as well as MFR (see below).

Indeed, the data of the present study are best understood with reference to Figures 3A, B; 4A, B and 6A, B, which, respectively, demonstrate correlations and Bland–Altman (BA) plots for global (Figure 3) and regional (Figure 4) rest and stress MBF taken together and global MFR (Figure 6). It should be noted dynamic data for both CMR and PET were fit to a one tissue

Reprint requests: Henry Gewirtz, MD, Cardiac Unit, Department of Medicine (Cardiology Division), Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114; *hgewirtz@partners.org*

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compartment model with standard corrections applied for PET ^{15}O-water (Ref. #36). CMR data, however, were fit to a model which incorporated an empirically derived permeability surface area product (PS) based on Renkin-Crone model[8] to correct K1[9] but did not use the complete extraction fraction (EF) since MBF values obtained ''…correlated poorly with PET MBF at high values.'' The EF of Gd-DOTA rolls off markedly beginning at MBF $\sim$ 1.25 mL·min^{-1}·g^{-1} (Figure 2A). Although the correlations for global ($R^2 = 0.74$) and regional ($R^2 = 0.56$) MBF both are at least moderate, the data exhibit considerable scatter around the regression line at higher flow. The BA plots and the authors' own analysis bear this out in recognizing the ''wide limits of agreement'' between CMR and PET rest and stress MBF measurements. The limits of agreement (95%) for global MBF ranged from $-$ 1.24 to + 1.25 and for regional values $-$ 2.17 to + 2.17. Noteworthy, too, is the fact that CMR global rest MBF failed to correlate with PET (Figure 5A) though stress (global, Figure 5C) did ($R^2 = 0.48$). Thus, there was no correlation between MFR determined by CMR and PET (Figures 6A, B). Similar data concerning poor agreement between 3T PET/CMR and PET ^{13}N-ammonia determined global MFR has been reported by others.[3] In that study, systematically higher CMR rest MBF (vs PET) resulted in consistently lower MFR,[3] whereas in the present study, the differences were random in nature (Figures 6A, B). In light of these findings, it is clear currently employed PET-based stress MBF as well as MFR (commonly referred to as coronary flow reserve CFR, even though strictly speaking it is not) cut points both for diagnosis and prognosis in a variety of cardiovascular disease states[7,10] do not necessarily apply to CMR based measurements of these parameters.

A word about statistical bias in BA plots is in order here. In brief, the mean of differences for each measurement of methods being compared (i.e., CMR vs PET) is equal to bias while ± 1.96 * SD of the mean defines the limits of agreement, also known as 95% coefficient of reproducibility.[11,12] The authors note bias for CMR vs PET global and regional MBF measurements is ''negligible'' (i.e. near or equal to zero). However, it is readily apparent CMR may provide an unbiased estimate of PET MBF either because relatively large negative and positive differences cancel and so the average approaches zero, the case in the present study or because the one provides almost identical measurements as the other and so individual differences are near or at zero, hence the mean of difference also approaches zero, certainly not the case in the study under consideration. Accordingly, as the authors correctly note it is the limits of agreement which matter. Characterization of bias as ''negligible'', while mathematically correct, is uninformative without calling attention to the associated limits of agreement (quite wide), as the authors, to their credit, do. Thus, ''negligible'' bias in the present study should not be construed as supportive of CMR vs PET measurements of MBF.

Since PET/MR scanners are limited in availability, it is worth considering what results may be obtained with current standalone 1.5 T MR and PET/CT instruments. In a recent study of 21 patients, with known or suspected CAD, rest and stress (adenosine) MBF measurements were made on the same day; once with the 1.5 T MR instrument (Gd-DOTA contrast) and then again with the PET/CT scanner (^{13}N-ammonia, reference method).[2] The correlation between global MBF by CMR and PET was strong ($R^2 = 0.85$, with slope = 0.94 and intercept = 0.14). Bias was small $\sim -$ 0.1 and 95% CR $\sim \pm$ 0.8. However, there was greater scatter at global MBF $\geq$ 2 mL·min^{-1}·g^{-1}. Regional CMR MBF demonstrated even wider scatter. Thus, $R^2 = 0.69$, with small bias ($\sim -$ 0.1) but larger CR ($\sim \pm$ 1.1) and many MBF $\geq$ 2 at or beyond the 95% CR limits. Finally, CMR MFR on a global and regional basis correlated only modestly with PET ($R^2 = 0.48$ and 0.32, respectively). Thus, while the overall results of the study indicate closer agreement between CMR and PET measurements of MBF on both global and regional basis than that of current report, both demonstrate (1) closer agreement for global in comparison with that of regional MBF measurements (2) considerably greater divergence of CMR vs PET regional stress MBF at levels $\geq$ 2 mL·min^{-1}·g^{-1} and (3) weakest correlations between CMR and PET assessment of both global and regional MFR (nil in the present study and 0.48 and 0.32, respectively, in that of the other[2]).

Earlier work in which CMR estimates of endocardial (endo) and epicardial (epi) MBF was compared to that of fluorescent microspheres understandably has been more encouraging and demonstrated what is possible in human studies as well.[13] Thus, pixel wise (32 μL/voxel resolution) CMR images (2-3 slices, 7-mm thick) were obtained which permitted detailed transmural resolution of MBF distribution. After correction for misregistration, CMR MBF correlated quite closely with that of microspheres for transmural, epi and endo layers (all $R^2 = 0.94$) with little bias ($\sim$ 0 to $-$ 0.1) though CR was more substantial ($\sim \pm$1.0 mL·min^{-1}·g^{-1} for transmural and endo but ($\sim \pm$ 1.5 for epi with bias $\sim -$ 0.12).[13]

There were, however, important disparities between CMR and microspheres measurements of endo and epi MBF at baseline and with adenosine induced hyperemia.[13] Thus, per Table 1,[13] ''remote'' CMR rest endo/epi was 0.99 ± 0.19 vs expected > 1[14–16] and observed

PET MBF ratio 1.16 ± 0.17.[13] However, with local hyperemia (ado) CMR endo/epi ratio was essentially unchanged (1.05 ± 0.15) compared with baseline, whereas microspheres demonstrated expected greater epi vs endo dilator capacity such that the ratio inverted (0.88 ± 0.14).[13] Both layers it should be noted exhibiting substantial increases in MBF in comparison with that of the unstimulated remote region. Nonetheless, CMR examples provided of patients with known IHD (n = 5) demonstrated excellent correlations with invasive coronary angiography. Expected stress-induced transmural gradients in endo epi MBF were demonstrated as well as transmural MBF deficits relative to baseline. Comparison with an external gold standard (possibly CCTA) was not available. Nevertheless, the methodology clearly holds promise particularly if quantitative MBF data are employed.

Indeed, current practice guidelines consider CMR a class I/II indication for evaluation of stable IHD in patients unable to exercise.[17,18] Validation studies typically have been against invasive coronary angiography (anatomical stenosis generally at 50% diameter reduction cut point[19]) though at least one study used FFR at 0.75 cut point.[20] CMR images were evaluated qualitatively or semi-quantitatively for comparison of stress vs rest defect(s) and presence or absence of scar (late Gd enhancement).[21,22] Qualitative assessment of rest, stress endo/epi contrast distribution also has been reported to enhance CAD detection particularly with multi-vessel CAD.[20,21] Quantitative MBF data, however, generally has not been employed for clinical use. This is unfortunate since the practice considerably degrades the capabilities of the methodology and subjects it to many of the limitations of SPECT MPI in terms of relative imaging comparisons. Though much higher spatial resolution and technically superior images are available with CMR, they are proportionately more difficult and time consuming to obtain and analyze; a problem, along with other administrative and financial issues which together have worked to preclude high capacity, high throughput clinical service in comparison with that of PET, which the current study and others[23] recognizes as the gold standard for quantitative MBF determination in patients.

In conclusion, the data obtained in the current small study[1] suggest CMR methods for quantitative MBF measurements require considerably more development before their full potential is realized and they can offer accurate, reproducible data suitable for high throughput, routine, clinical use. Until then, quantitative PET measurements of MBF will remain the gold standard for clinical practice.

Disclosures

None.

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