The “fixed” SPECT MPI defect: Where are we and where should we be going?

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This brief review focuses on reasons why myocardial perfusion imaging (MPI) SPECT defects may appear “fixed” (rest vs stress). A combination of technical and physiology factors are responsible in most cases and are discussed. Perhaps the major reason defects will appear fixed is that there is no absolute quantitative measurement of myocardial blood flow (MBF, rest and stress) with which to assess the magnitude and potential direction of change in the defect vs reference zone with stress. Cardiac PET MPI provides absolute measurements of MBF required to understand the clinical significance of the SPECT “fixed” defect and are highlighted. Emphasis is given to use of the actual MBF measurements though indexing stress MBF to that of truly normal subjects (RFR or FFR_{PET}) will prove useful in recognition of multi-vessel CAD. The availability of 18F flurpiridaz for clinical use is likely to encourage more widespread adoption of cardiac PET MPI for evaluation of patients with known or suspected CAD.

CLINICAL QUESTIONS

1. Why is the defect fixed?

One way to think of the problem is to recall the methods used for normalization of the SPECT image display. ASNC guidelines indicate that “series” normalization is preferred while “frame” normalization is optional.^{1,2} Briefly, series normalization finds the “hottest” pixel in the entire series (e.g. stress data set, HLong, VLong, Short axis) and scales all others to that one. The rest images are handled in the same way. The problems with the approach include vulnerability to a single unrepresentative or artifactual hot spot which then causes the entire slice display to be suboptimal.² A fixed defect with series normalization simply displays the approximate ratio in activity between best and worst perfused zones. Since rest and stress

images sets are normalized identically, so long as the ratio between best and worst perfused is approximately preserved the defect must appear “fixed”, with a number of caveats recognized. The problem lies with the fact that there are no absolute measurements of tracer concentration to guide the physician. Series normalization guarantees that, tracer content in the best perfused region of the heart at stress must look the same as the best perfused region at rest (generally the same) and so contrast between the normal and abnormal regions is maintained (i.e. fixed) even though the MBF ratio may not.

Further, the fact that the 2 most commonly used SPECT MPI tracers (MIBI and Tetrofosmin) are known to markedly underestimate vasodilator or exercise stress MBF (due to fall off of tracer extraction with increasing flow (Figure 1)) also contributes to making the defect appear fixed since the reference area does not get “full credit” for any increase in stress MBF which may occur (Figure 1).

Frame normalization finds the hottest pixel in each frame of the series and normalizes the image accordingly.^{1,2} Each frame is optimized

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Figure 1. Cartoon of relative myocardial tracer uptake (ordinate, arbitrary units) vs myocardial blood flow (MBF, mL/min/g). Uptake of ^{15}O -water, which is freely diffusible, matches MBF over the full range of MBF. ^{18}F -flurpiridaz is very similar. Other tracers exhibit plateau to greater (MIBI, tetrofosmin) or lesser (^{13}N -ammonia) extent with increasing MBF. PET tracer kinetic models typically incorporate a term for tracer roll off as applicable. The SPECT tracers have no such option available at present.

for viewing but also suffers from the fact that it stands alone. Accordingly, the “best perfused” region in one frame may not be the same in another and so the interpretation across the entire image stack in all 3 views is complicated by separate normalization for each frame. Again, so long as the approximate activity in the worst perfused region is relatively constant compared to best, the defect will appear “fixed” even though one has no indication of the absolute tracer concentration in the region and hence its change (or not) with stress.

Thus, both for technical and physiological reasons the defect at rest, which reflects a myocardial segment with reduced flow and limited ability to increase with stress, appears “fixed” primarily because the reference zone in essence does not get full credit for an increase in MBF with stress. Both the drop-off of tracer uptake and retention with increasing MBF and the system for display of the images, will work in concert to render the rest defect apparently fixed with stress. It has been recognized for many years that such defects do not necessarily reflect infarcted myocardium since less severe rest defects which remain fixed with stress may reflect myocardial hibernation.³⁻⁸ Finally, it should be noted work with modern CZT detector technology has raised the possibility that true quantitative measurements of absolute MBF may be attainable in the future⁹ though not ready for routine clinical use at present.

2. Is the sequence of imaging important? Stress/rest vs. rest/stress

The sequence of imaging, empirically, has been found not to matter in the vast majority of cases. Further, a stress only protocol is employed by many laboratories to reduce patient radiation dose if the images are normal.^{1,2} In other cases the rest/stress sequence facilitates patient throughput and is the preferred protocol used in many labs. Two day protocols have been advocated by some when imaging very obese patients.^{1,2} The two day protocol permits maximal tracer dose with each exam and so is thought useful in clarifying whether the defect is truly fixed or not.

3. Would the same thing be present if PET-MPI was used?

The answer to this question depends in part on which tracer is used and when the imaging occurs. The commonly employed tracers (^{82}Rb , ^{13}N -ammonia, ^{15}O -water) each have tracer kinetic models with which permit quantitative measurements of absolute MBF. Thus, the ratio of stress MBF (MBFs) to rest MBF (MBFr) will increase if MBFs of the normal zone (NZ) increases with stress while MBFs of the abnormal zone (IZ) either increases less than that of the NZ, decreases (e.g. coronary steal) or remains unchanged.^{5,10} Accordingly, the ratio NZ:IZ at rest may or may not change with the stress tracer injection assuming actual MBF measurements are used and a truly normal reference zone is present to begin with.^{5,10,11}

Detection of 3VD is relatively straightforward using the actual MBFs for each vascular territory. The absolute responses may be employed or indexed to that of a truly normal region represented by MBFs of healthy normal volunteers.¹⁰⁻¹² The metric obtained is FFR_{pet} since it theoretically is much the same as invasive FFR.^{12,13} Recall, FFR compares the measured pressure drop across a stenosis (Pd/Pa) to the assumed actual value in the absence of the stenosis, which would be unity if the entire distal vasculature is free of disease.¹⁴ Hence it is a measure of relative flow reserve (RFR) and avoids many of the pitfalls of CFR (absolute flow reserve) which is quite sensitive to confounding by changes in the level of MBFrest.^{15,16}

Myocardial retention images do not necessarily reflect the same thing as the parametric, images of quantitative MBF.¹⁷ For example, ^{82}Rb has been reported to wash out of myocardium faster from the IZ vs NZ.¹⁸ Thus, if imaging has been timed appropriately, a defect on delayed images would be expected and may be larger in size than an earlier one.¹⁸ The rapid wash in/out of ^{15}O -water generally makes it unsuitable for tracer retention imaging though some have reported success using advanced

Table 1. Hypothetical myocardial blood flow (MBF, mL/min/g) in Normal (NZ) and abnormal (IZ) zones

	NZ	IZj	IZk
REST	1.00	.50	.75
STRESS	4.00	1.50	3.00
FFRpet (RFR)	4.0/4.5 = .89	1.5/4.5 = .33	3.0/4.5 = .66
MFR	4.0/1.0 = 4.0X	1.5/.5 = 3.0X	3.00/.75 = 4.0X

techniques.^{16,19}

Further, ¹³N-ammonia images obtained at 20-30 min post injection often exhibit tracer retention, particularly after normalization to region with best retention which fail to accurately reflect K1 values normalized in identical fashion.²⁰ The images therefore may not satisfactorily reflect the actual distribution of MBFs or MBFr and hence the ratio of the two. While ammonia is converted to glutamine (glutamine synthase reaction), trapping is not complete and some is washed out of the myocardium. Moreover, the arterial input function is a major determinant of K1/MBF and typically is recorded over the initial few minutes following tracer injection,²¹ a time well before completion of the delayed tracer retention images. In general, a large arterial input function will require a lesser quantity of myocardial tracer activity to satisfy modeling conditions for a given level of MBF and vice versa.²¹ Thus, all else being equal, for the same true value of MBF (MBFt) an arterial input function too large will underestimate MBFt and one too small will overestimate MBFt.²¹ Given the complexity involved, perhaps it should come as no surprise that tracer retention maps for ¹³N-ammonia may not accurately reflect the true distribution of MBF.

4. Finally, and most importantly, what would the MBF be in the IZ at rest and stress and under what circumstances would the MBF measurements help in explain the findings?

Please see answers to # 1-3 above. Further, the answer, as noted previously, is to employ the actual MBF values, MBFr and MBFs for an accurate assessment of distribution of MBF under each condition.^{5,17,20} It has been recognized for some time that very dense rest defects most often correspond to regions of prior infarct.^{3,7,22,23} As defects are less and less intense the probability of viable, hibernating myocardium increases.²³ Under such circumstances MBFr in the IZ will approach that in the NZ at rest. The defect will be apparent on viewing the standard 17 segment model of MBF's.

With stress, the NZ would be expected to increase more than that of the IZ given a truly normal NZ and so the NZ:IZ ratio increases. Again, reference to the map of absolute flows (rest and stress) with indexing the stress MBFs plot to absolute values of healthy normal volunteers permits defining a third map of relative flow reserve (AKA, FFRpet^{12,13}) which will be essential to detection of multi-vessel CAD (Table 1).

The above illustrates the 3 main coronary vascular territories. The best perfused at rest, NZ has MBF greater than that of the other 2, designated IZj and IZk. In response to stress (e.g. adenosine) MBF increases in each zone. However, since stress MBF in healthy volunteers is taken as 4.5 mL/min/g, each territory is reduced relative to it, especially IZj and IZk which have FFRpet .33 and .66, respectively. The RFR ratios, (.33 and .66) indicate high risk by FFR standard²⁴ even though MFR is 3.0X and 4.0X, respectively. The NZ has FFRpet which would be considered "non-obstructive" by FFR standard and in this case concordant with MFR (4X).

SUMMARY/CONCLUSIONS

Clinical cardiology runs on numbers; arterial blood pressure, lipid status, left and right heart pressures and flows, FFR, iFR, valve areas and gradients, regurgitant volumes, LVEF, to name only a few. All have established metrics to guide clinical decision making. It is unfortunate, therefore, that utilization of a powerful and accurate imaging modality (cardiac PET) for assessment of patients with known or suspected CAD has been so limited in its incorporation into modern cardiology practice. A specialized field already exists (i.e. nuclear cardiology) which should be able to facilitate more widespread use of absolute MBF as a reliable, helpful metric for objective assessment of the coronary circulation, particularly the ability to increase MBF in response to stress (both absolute and relative to true normal response).^{5,10,16,17,19} The availability of 18F

flurpiridaz²⁵⁻²⁷ should go a long way to advancing PET quantitative measurements of MBF into the clinical mainstream and provide more meaningful assessment of what a “fixed” defect does or does not reflect.

Disclosures

None.

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