Could ^{82}Rb-PET be the next best thing in evaluation of myocardial salvage?

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Success of revascularization of an infarct-related artery (IRA) currently relies on a combination of clinical, laboratory, electrocardiographic, and echocardiographic markers. Despite integrated use of these myriad tests, they do not always accurately represent the actual amount of salvaged myocardium. In an effort to more objectively quantify success of reperfusion strategies, imaging of both the initial myocardial area at risk (AAR) and the final infarct size (FIS) are now being explored as surrogates for successful reperfusion. In addition, the difference between AAR and FIS gives the amount of salvaged myocardium. The ratio of the difference over initial AAR represents the myocardial salvage index (MSI), which has the advantage of allowing for comparisons among infarcts of variable size.

Traditionally, quantification of AAR, FIS, and MSI was done with 99m-Tc sestamibi single-photon emission computed tomography (SPECT). Calculation of AAR by SPECT is done by injecting 99m-Tc right before revascularization and then obtaining images a few hours later. Estimation of FIS has to be done on a separate occasion, at least 120 hours after infarction, and ideally weeks-months following revascularization.[1] FIS measured by SPECT correlates with histopathological assessment and more importantly has been shown to be of prognostic value.[2,3] Based on AAR and FIS, MSI calculation by SPECT has been validated as a means for comparing different therapeutic strategies. Despite its advantages, SPECT comes with pitfalls and caveats that should be taken into consideration. Firstly, it does not allow for quantification of AAR and FIS (and thus MSI) based on just a single study, rather performing two separate studies is necessary as described above. This also means that 24-hours availability of the tracer and nuclear lab is necessary to administer the tracer and obtain the first (AAR-focused) study later. SPECT-related radiation exposure is another considerable risk. Importantly, it is not possible to differentiate old from acute infarcts, when trying to assess FIS, which might lead to false results. The presence of multivessel disease might also complicate interpretation of findings and make measurements of AAR and FIS unreliable. Moreover, the presence and extent of collaterals might result in falsely decreased AAR (which is measured pre-revascularization) and regression of those collaterals might also affect size of FIS on future SPECT studies. Cardiac magnetic resonance (CMR) and more recently positron emission tomography (PET) have also been used to more efficiently measure AAR, FIS, and MSI.

In the study published in this issue of the Journal of Nuclear Cardiology by Ghotbi et al., the researchers compared the efficacy of ^{82}Rb-PET to SPECT and CMR in patients without a prior history of myocardial infarction or coronary artery bypass surgery who underwent primary percutaneous coronary intervention (pPCI).[4] A total of eleven patients underwent AAR quantification by all three modalities, and FIS was assessed in ten patients. SPECT was used as the gold standard for quantification of AAR and CMR for FIS. The study showed that ^{82}Rb-PET, CMR, and SPECT correlated well, however, the limits of agreement were wide both for quantification of AAR and FIS. In addition, PET underestimated AAR by 7% compared to

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SPECT (a statistically significant value). A perfusion deficit cut-off of 50% of maximal counts was used to estimate AAR by ^{82}Rb-PET; however, the investigators found a lower cut-off of 35% to be better [sensitivity of 85%, specificity of 94%, accuracy 91%, area under the ROC curve 0.92 (CI 0.87-0.97, $P < 0.001$)]. They concluded that ^{82}Rb-PET can be used to quantify FIS and MSI shortly after pPCI and on follow-up in patients with STEMI and larger infarcts; however, they do note that results among the three modalities were highly variable, which prohibits direct translation and comparison of findings among the three (PET, SPECT, and CMR).[4]

Prior studies have already examined the efficacy of CMR in quantifying AAR, FIS, and MSI.[5–17] A number of different CMR techniques can be used for image processing (T2-weighted, pre-contrast T1-weighted, early and late gadolinium enhancement), thus facilitating acquisition of a wide range of data on cardiac anatomy, regional and global function, and blood flow. The main difference between CMR and SPECT is that with CMR, acquisition of images for estimation of AAR is retrospectively done after reperfusion, as opposed to SPECT where the radiotracer is injected right before revascularization.

Assessment of FIS by CMR with late gadolinium enhancement (LGE) has long been tested and validated and is now considered the gold standard for assessment of FIS.[12,18–20] Determination of AAR by CMR has been somewhat more challenging, however. It is assessed in one of two ways: (a) detecting myocardial edema (which is proportional to the AAR) by T2-weighted technique or (b) measuring endocardial surface length or area (ESL or ESA—taken as a surrogate for size of the acute perfusion abnormality) by contrast CMR.[13,20] Its advantages are its ability to measure both AAR and FIS in one single study, its superiority to SPECT when it comes to spatial and temporal resolutions, and avoiding use of radioactivity. Furthermore, CMR allows for determination of regional wall motion of both the left and right ventricles and homogeneous myocardial tissue signal, thus obtaining accurate assessment of both anterior and inferior infarcts (since images are not affected by tissue attenuation as much as SPECT). Finally, T2-weighted CMR enables differentiation between old and acute infarcts, a distinct advantage over SPECT.

Out of all CMR processing techniques, T2-weighted CMR has been the one most extensively studied in quantification of myocardial salvage. Carlsson et al. in their 2009 study of 16 patients showed that T2-weighted short tau inversion recovery (STIR) CMR correlated well with SPECT in assessing AAR ($r^2 = 0.70$, $P < 0.001$), and was able to accurately quantify FIS and myocardial salvage.[7] In 2013, Hadamitzky et al. studied 207 patients with pPCI and showed that CMR with T2-weighted turbo spin-echo sequences and late enhancement imaging correlated well with SPECT in quantifying AAR and FIS, respectively (r for AAR 0.80, r for scar size 0.87, r for myocardial salvaged area 0.66, all $P < 0.0001$).[14] Measuring ESL (or ESA) has been proposed as another way of determining AAR and has been shown to correlate well with both T2-weighted CMR {{Wright J et al. 2009}} and angiographic markers of AAR.[13] T1-weighted CMR has also been used, however, additional validation is required before being widely utilized.[15,16] Currently, there is no agreement on which CMR technique is best for determining AAR. Most sources recommend using a combination of different techniques: pre-contrast T1- and T2-weighted protocols as well as early and late gadolinium enhancements. The most optimal timing for obtaining a CMR study—for quantification of both AAR and FIS—is about 1-2 weeks following infarction.[10]

Despite its many advantages, CMR does have certain drawbacks. Firstly, not all scanners are able to safely image, or acquire diagnostic quality images, on patients with pacemakers/defibrillators. Secondly, gadolinium-based contrast agents are contraindicated in patients with advanced renal disease due to the risk of nephrogenic systemic fibrosis. Quantification of AAR and FIS may sometimes be challenging with infarcts complicated by intramyocardial hemorrhage and/or microvascular obstruction. Finally, even though CMR quantitative estimates of AAR, FIS, and myocardial salvage have been shown to correlate well with SPECT,[7,11,14,15] Bøtker et al. reported that their data showed a consistent overestimation of CMR-based AAR compared to SPECT, which would preclude interchangeable use of CMR and SPECT quantitative reperfusion markers.[1]

PET is the newest of the modalities to have been studied in assessment of myocardial salvage. Compared to SPECT, PET has significant advantages, namely less radiation, higher sensitivity (higher count rates), improved spatial resolution, and its inherent ability to quantify myocardial blood flow. Most current PET cameras are hybrid PET-CT cameras that not only provide faster and more reliable attenuation correction, thus resulting in improved image quality, but also allow for anatomical evaluation of coronary arteries and calcium scoring. Similar to CMR, only one study is required to quantify both AAR and FIS, but, contrary to CMR, PET is not contraindicated in patients with renal dysfunction or those with implanted devices (pacemakers, defibrillators). PET tracers currently approved for use in myocardial perfusion imaging include ^{82}Rb and $^{13}NH_3$. PET can also assess metabolic activity of the myocardium using free fatty acid tracers and ^{18}F-FDG.

In the current study by Ghotbi et al., ^{82}Rb PET was used to quantitate myocardial salvage.[4] Prior studies have used integrative ^{18}FDG PET-MRI as a quantitative tool in assessing reperfusion in patients following STEMI.[21,22] Bulluck et al. in 2015 performed hybrid ^{18}FDG PET-MRI in 21 patients at a median of 5 days after STEMI and at a 12-months follow-up visit.[21] They found that AAR measured by ^{18}FDG-PET correlated well and demonstrated good agreement with T2-mapped AAR (37.2% ± 11.6% vs. 36.3% ± 12.2%; $P = 0.10$, $R = 0.98$, bias 0.9% ± 4.4%).[21] After 12 months, FIS—measured by decreased FDG uptake—correlated well with LGE-determined FIS (R 0.98) despite a small bias of 2.0% ± 5.6%. In addition, their findings suggested that an FDG uptake of at least 45% on initial hybrid studies was associated with myocardial viability (by CMR assessment) at 12 months.[21] Finally, FDG uptake on the initial scan could determine recovery of regional wall motion just as well as the extent of transmurality of LGE.[21] In 2016, Nensa et al. prospectively examined the efficacy of hybrid ^{18}FDG PET-MRI in 25 patients following reperfusion of STEMI by comparing the FDG-determined AAR and FIS to the ones measured with LGE CMR based on the ESL method.[22] They found that AAR by FDG correlated moderately well with AAR according to ESL (Spearman $P = 0.44$, $P < 0.026$) and that, in all but two patients, AAR determined by ^{18}FDG-PET was larger than the one by ESL (31% ± 11% vs. 17% ± 13%; paired t test, $P < 0.0001$).[22]

Ghotbi et al. are the first to examine the performance of ^{82}Rb-PET in quantifying AAR, FIS, and MSI and add more data on our so far limited knowledge with respect to PET in the evaluation of reperfusion strategies.[4] Despite its innovative concept, the study does have certain limitations that should be kept in mind when interpreting the results. Firstly, AAR measured by ^{82}Rb-PET was found to be significantly underestimated compared to SPECT (considered as the gold standard) and CMR (28.1% ± 16.1% vs. 35.2% ± 16.6% and 34.7% ± 11.3%, $P = 0.02$ and $P = 0.04$, mean AAR for PET, SPECT and CMR, respectively). Estimation of FIS was not statistically different among the three modalities (11.9% ± 14.6% vs. 12.3% ± 15.4% and 13.7% ± 10.4%, mean FIS for PET, SPECT and CMR respectively, $P = 0.72$), however, the limits of agreement were wide [−11.4% to 13.8% (SPECT vs. PET), −20.1% to 19.9% (SPECT vs. CMR), and −16.9% to 14.3% (CMR vs. PET)]. With regards to MSI, similar to FIS, even though no statistically significant difference was noted among the three techniques ($P = 0.78$), correlations were weak and not significant between CMR and the other two. These discrepancies could in part be due to the small study size, since AAR was measured in only 11 patients and FIS in only ten. The significantly smaller AAR seen with PET could be explained by use of inappropriate cut-off for PET-estimated AAR. This could be related to differences in performance of the tracers used (99 m-Tc vs. ^{82}Rb) and processing of image acquisitions between SPECT and ^{82}Rb-PET. An AAR cut-off of 35% vs. 50% (which was actually used in the study) was found to have better accuracy (91%) with an area under the curve of 0.92 (CI 0.87-0.97, $P < 0.001$). Finally, it should be noted that no patients with STEMIs of their circumflex artery were included. It would have been interesting to examine how PET would do with depicting lateral and infero-lateral AARs and FSIs, areas which have been traditionally difficult to image with SPECT.

Myocardial PET imaging in theory has multiple advantages, given it can provide a comprehensive anatomical and functional evaluation in one single study. In the case of post-STEMI patients, this means that they could be used not only to assess the extent of AAR, FIS, and MSI, but also to quantify myocardial blood flow and coronary reserve, thus identifying non-infarct-related problematic areas as well. Studies examining the efficacy of ^{18}FDG-PET (as part of hybrid PET-MRI protocols) and now this one looking at ^{82}Rb-PET do show promise; however, their small size precludes any definitive conclusions to be drawn with respect to the accuracy and reliability of PET. Moving forward, a lot of work and larger studies need to be done to evaluate different aspects of myocardial PET scans. To name a few:

(a) What are the optimal AAR, FIS, and MSI cut-offs?
(b) Which is the best technique, 18-F FDG vs. ^{82}Rb-PET vs. a different one ($^{13}NH_3$ or ^{18}F-flurpiridaz). It may be that ^{18}F-FDG might be more accurate in AAR and FIS quantifications. Studies directly comparing the two, and also comparing them against SPECT and CMR, could answer this question.
(c) Our understanding of ^{18}F-FDG metabolism is not complete. We lack understanding of the mechanism underlying reduced FDG uptake in reversibly injured myocardium, and we do not have a gold standard for accurately measuring the decrease in FDG uptake.
(d) Inclusion of more women (previous studies only included 8%, 9%, and 24% women) and assessment of certain high-risk groups with PET, such as diabetics and patients with chronic kidney disease.
(e) Comparison of the cost-effectiveness of the three modalities (PET vs. SPECT vs. CMR), which should be weighed against their overall diagnostic and prognostic value.

In an era of constant advancements in reperfusion strategies and percutaneous interventions of lesions of

an ever increasing complexity, optimal utilization of imaging techniques remains a challenge. Myocardial PET imaging techniques have potential, but it still needs to prove itself in real-life clinical practice.

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