Quantitative ^{82}Rb dynamic pet perfusion analysis with kinetic modeling for myocardial viability: Can we get away with just ^{82}Rb perfusion kinetics?

Karthik Ananthasubramaniam, MD, FACC, FASE, FASNC, FSCCT, FRCP,[a] and Parthiban Arumugam, MBBS, FRCP[b]

[a] Heart and Vascular Institute, Henry Ford Hospital, Detroit, MI
[b] Nuclear Medicine Centre, Manchester Royal Infirmary, Manchester, UK

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INTRODUCTION AND CLINICAL PERSPECTIVE

Multiple non-randomized studies and meta-analysis of patients with impaired left ventricular function and multivessel coronary artery disease (CAD) have suggested that in the presence of ischemic viable myocardium (hibernating myocardium) as detected by myocardial viability testing, subsequent revascularization is associated with better outcomes compared to medical therapy, despite higher surgical risk and long-term mortality rates.[1–3] Although the role of viability testing and its impact on patient outcomes has been brought into question recently by the STICH trial,[4] most clinicians continue to believe that there exists a role for myocardial viability testing in selected patients for helping in management decisions.

Numerous established techniques for detection of myocardial viability exist: cell membrane integrity evaluation with SPECT isotopes such as TL-201 and Tc-99m, contractile reserve assessment with dobutamine employing echocardiography or magnetic resonance, cellular metabolic integrity assessment with positron emission tomography (PET) using perfusionsuch as N-13 ammonia or 82-Rubidium (^{82}Rb) and metabolic imaging using ^{18}F- fluorodeoxyglucose (^{18}F-FDG), and finally scar assessment using magnetic resonance imaging.[5] Positron emission tomography (PET) imaging with a combination of perfusion and metabolic radiotracers is a widely accepted and robust non-invasive modality for assessing myocardial viability and detecting hibernating myocardium in patients with coronary artery disease.[3,4] PET identification of viable and ischemic (hibernating) myocardium as demonstrated by the ''flow-metabolism mismatch'' has been shown to be predictive of outcomes after coronary revascularization.[5,6] Numerous studies have shown that there is increased risk of cardiac events in patients with hibernating myocardium who are not revascularized in a timely manner.[7–9]

REVISITING ^{82}RB KINETICS FOR DETERMINING MYOCARDIAL VIABILITY

PET viability imaging requires a combination of perfusion (typically using cyclotron produced N-13 ammonia or generator produced ^{82}Rb) and metabolic information provided ^{18}F -FDG. FDG is cyclotron produced and hence limited to centers in reasonable proximity to a cyclotron (t1/2 of FDG = 110 min). Furthermore, imaging with FDG adds additional cost, poses interpretation difficulties due to unpredictable uptake in diabetics[8] and abnormal patterns in patients with left bundle branch block,[9] and finally increases overall patient imaging time.

Hence, the feasibility of identifying hibernating myocardium with perfusion agents alone would present an attractive alternative, particularly to centers without access to a cyclotron. ^{82}Rb is a positron emitting isotope

Reprint requests: Karthik Ananthasubramaniam MD, FACC, FASE, FASNC, FSCCT, FRCP, Heart and Vascular Institute, Henry Ford Hospital, K14, 2799 West Grand Blvd, Detroit, MI 48202; *kananth1@hfhs.org*
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with a short half-life (t½ = 76 second) which is widely used as a PET perfusion radiotracer and easily available by elution via a Strontium-Rb generator system obviating the need for a cyclotron. The basis of ^{82}Rb as a cellular marker of viability can be best understood by comparing it to cellular potassium kinetics. The extraction and retention of ^{82}Rb are very similar to potassium. When cell membrane integrity is compromised potassium leaks out of cells. The extent of potassium leak has also been directly correlated with creatinine phosphokinase levels, thus reflective of myocardial necrosis. ^{82}Rb, similar to potassium, enters myocardial cells from the bloodstream. If the cell membrane is intact, it is retained, but if the cell is necrotic or membrane integrity is compromised due to irreversible injury, uptake is severely reduced and/or it washes out of the tissue. However, perfusion analysis alone may not be a reliable marker of myocardial viability as shown in prior study of Go et al.[10] They studied 145 patients who underwent ^{82}Rb/^{18}F -FDG PET for viability assessment and tested if varying levels of perfusion alone with ^{82}Rb was sufficient to differentiate hibernating from scarred myocardium. They concluded that relative decreased perfusion in irreversible defects alone did not enable the distinction of scarred and hibernating myocardium ($P = 0.61$). But in their study, the value of clearance kinetics was not assessed in differentiating hibernating myocardium form scar.

The value of ^{82}Rb kinetics in distinguishing necrotic from viable myocardium has been elegantly demonstrated in an animal studies by Goldstein[11] who measured regional myocardial-time activity curves after experimental coronary occlusion followed by reperfusion in dogs. They demonstrated that time activity curves could be used to determine the patency of an infarct-related artery and assessment of residual viability after reperfusion in acute myocardial infarction. Failure to increase extraction at low flow was indicative of an early indicator of cell death, with lack of accumulation of ^{82}Rb suggestive of membrane damage after loss of viability.

The clinical applicability of ^{82}Rb kinetics in differentiating scar from normal tissue has been evaluated in limited fashion by few prior studies briefly discussed below.[12,13] These studies were small and mainly based on the analysis of early and late static images due to the technical limitations of the PET scanners of that time. These studies used mono-exponential least square fit model to non-decay corrected regional time activity curves. Based on these curves, percentage maximal uptake of ^{82}Rb, its tissue half-life, and % of maximal FDG Patlak slope were derived. The analysis was affected by noisy data from the late static images and did not fully account for the tracer kinetics, for example, redistribution/recirculation.

Gould et al.[12] studied patients with evolving myocardial infarction with ^{82}Rb/^{18}F -FDG and used two static PET images to investigate ^{82}Rb washout as an indicator of cell membrane integrity and myocardial viability. Infarct size with ^{82}Rb correlated closely with location on FDG images suggesting that loss of cell membrane integrity paralleled loss of intracellular glucose metabolism. However, it is known that evolving myocardial or recent myocardial infarction are situations where myocardial perfusion and metabolism patterns are dynamic and FDG has been shown to be variable to the point of being uninterpretable during evolving MI or early after MI.

Vom Dahl et al.[13] used ^{82}Rb dynamic PET imaging and studied 27 patients with angiographically proven coronary disease who underwent ^{82}Rb/^{18}F-FDG imaging. The myocardial regions were categorized as normal, ischemic viable, and as scar tissue. Functional polar maps were used for further analysis and estimation of ^{82}R kinetics and demonstrated a significant and close relationship between cell membrane integrity as assessed by ^{82}Rb clearance and myocardial glucose utilization. They noted that the kinetics of ^{82}Rb in regions containing viable but infarcted tissue may be best characterized by using the *distribution volume*. For in vivo imaging, the distribution volume (V_D) is a measure of the accumulation or concentration of tracer in tissue compared to that in plasma and is independent of perfusion. In this case, larger values of V_D would correspond to active accumulation of the tracer, and vice versa. Measurement of V_D, however, requires full mathematical modeling of the ^{82}Rb kinetics to derive the k1 and k2 influx and efflux rates from dynamically acquired PET data. With the advances in PET/CT camera technology, this has now been achieved by Moody et al. in their current publication.

In this current study, Moody et al.[14] explore the utility of ^{82}Rb in myocardial perfusion assessment in comparison to ^{82}Rb/^{18}F- FDG PET specifically focusing on kinetics of ^{82}Rb as a potential alternative to combined perfusion/metabolic assessment for viability. They retrospectively studied 120 patients referred for viability imaging compared to normal volunteers ($n = 37$). All patients had dynamic 3D PET data which were evaluated using a 1-compartmental model to define ^{82}Rb uptake (k1) and washout (k2) and finally the equilibrium fraction (KP = k1/k2). 3D ^{18}F-FDG PET data were acquired using hyperinsulinemic euglycemic clamp. Their analysis concluded that regional ^{82}Rb and KP differed significantly between scarred and hibernating segments as defined and identified by established ^{82}Rb-

FDG perfusion-metabolic patterns. As compared to ^{82}Rb-FDG analysis, segmental ^{82}Rb KP had a c-index, sensitivity, and specificity of 0.809, 76%, and 84%, respectively, for distinguishing hibernating and scarred segments. Segmental k1 performed similarly but had lower specificity than KP of 75% which was statistically significant ($P < 0.001$). In contrast to prior studies where washout rate (k2) was not much of focus, these authors found that k2 also provided comparable sensitivity to KP for detecting hibernating versus scarred tissue albeit with lower specificity. An interesting observation is that the % uptake of ^{82}Rb by itself was pretty well correlated to KP and provided the highest sensitivity for distinguishing scarred versus hibernating myocardium at segmental level but had low specificity and positive predictive value. Concordance of ^{82}Rb kinetics with ^{82}Rb-FDG data was 85% and when the discordant data were analyzed, 3 factors were identified potentially contributing to this: Reduced whole body insulin sensitivity, recent myocardial infarction < 15 days ,and higher resting heart rate. The concordance of KP improved from 85 to 96% when these patients were excluded. They concluded that ^{82}Rb kinetics (mainly KP and k2) could help distinguish scarred and hibernating myocardium.

Moody et al. have used the standard one-tissue compartmental model for ^{82}Rb to estimate segmental values of K1 and k2. This is an important consideration as the method should therefore be potentially translatable to clinical practice, as most vendors' software uses a single-compartmental model or its equivalent providing comparable blood flow quantitation.[15] As the authors have demonstrated in their supplemental material, the derivation of V_D is straightforward if one assumes equilibrium. Therefore, the authors were able to present a segmental map of V_D (or partition coefficient, KP as it is termed in their publication), with a value of unity representing no active accumulation of the tracer and value higher than 1 representing the degree of active involvement. To translate into a metric for viability, the authors used traditional data-mining techniques, namely, a k-fold cross-verification algorithm, to ascertain the thresholds for identifying segments as containing normal, hibernating, and scar tissue using the combined ^{82}Rb -FDG analysis as a gold standard.

As noted by the authors, the analysis and interpretation of FDG viability images can be subject to variations in normalization methods. In fact, any method which relies on normalization for interpretation is subject to the same pitfalls of the choice of reference voxel, or voxels, and loss of quantitative information. Just as how quantification of myocardial blood flow has provided incremental and useful information over and above relative perfusion images, by using kinetic analysis to derive estimates of K1, k2, and KP, the authors provide a potentially more robust methodology of viability interpretation. The current study has numerous strengths including acquisition of dynamic ^{82}Rb 3D datasets, I-tissue compartmental modeling with quantification of k1, k2, and KP, tight glucose control with hyperinsulinemic euglycemic clamp, and data cross correlation in datasets with avoidance of patient variability errors with kinetic models used and evaluation of early-late datasets. Furthermore, the authors analyzed whole body glucose disposal and evaluated reasons for discrepancy identifying important factors outlined above.

The study by Moody et al. has many limitations of any retrospective analysis. Patients were retrospectively identified but were representative of patients with stable chronic ischemic left ventricular dysfunction. As with other myocardial tracers, retention of ^{82}Rb enables visualization of myocardium and is based on cellular integrity. However, metabolic changes which could affect uptake and retention of (such as acute ischemia, stunning, hyperkalemia, altered ph, hypoxia) were not specifically evaluated in the study. Information regarding functional outcomes of patients following revascularization is also not available from the current study and thus data on impact of using kinetics analysis are obviously not feasible such as wall motion recovery data after revascularization. To our knowledge, there is only one follow-up study by Yoshida et al. from Gould's original study patients looking at outcomes of patients after revascularization based on ^{82}Rb kinetics for viability using static PET imaging.[16]

Although small areas of scar were included in this study, the limited spatial resolution of PET does not permit adequate differentiation of small scars admixed with viable myocardium effectively.

As thought provoking and interesting that the concept of just using perfusion-based kinetic modeling to assess viability as shown by Moody et al., it is primarily hypothesis generating given revascularization and outcomes. FDG metabolic information should continue to play a major role in viability assessment of patients with coronary disease and left ventricular dysfunction in conjunction with perfusion. However, having the ^{82}Rb kinetics data may help in sorting out either questionable abnormalities or difficult to interpret FDG data (poor diabetes control, recent MI, etc.). As such, this novel concept now requires prospective studies to validate the methodology using clinical endpoints as the gold standard, namely, functional recovery of the jeopardized segments following percutaneous or surgical revascularization and impact on outcomes.

Disclosure

Dr. Ananthasubramaniam receives research grants and is on advisory panel for Astellas Pharma Inc. Parthiban Arumugam has nothing to disclose.

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