Striving to improve ^{82}Rubidium PET MPI accuracy

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The ability to make quantitative measurements of MBF with positron-emission tomography (PET) allows to detect an impairment of vasodilatory capacity expressed by myocardial flow reserve (MFR) also in LV regions that are not subtended by a significantly obstructed artery in patients with angina and suspected CAD.[1–3] In the past decade, studies with PET have provided evidence that risk factors such as hypercholesterolemia, hypertension, diabetes mellitus, and smoking, in the absence of symptoms, translate into measurable damage to the coronary microcirculation involving the entire left ventricle.[2]

The generator-produced ^{82}Rb is a very convenient tracer for measurement of MBF, because it does not require an on-site cyclotron and has a very short t1/2. Nowadays, improved scanner performance, iterative data reconstruction, and commercially available analysis software have enabled routine quantification of absolute myocardial blood flow (MBF) and MFR with good reproducibility among centers provided that dynamic time binning protocols and kinetic modeling are the same.[4–6] MPI with ^{82}Rb purports a high prognostic value which nowadays is well documented,[6–10] it would appear that MFR is a more robust parameter and less prone to methodological bias both in patients with overt CAD[11] and in non-obstructive lesions.[12] In the absence of epicardial lesions, impaired MFR is a hallmark of microvascular disease, undetectable at invasive or CT angiography, such as coronary allograft vasculopathy in heart transplant[3,13] and heart failure with preserved ejection fraction.[14,15]

The ''conditio sine qua non'' for a superior diagnostic performance is the accuracy and reproducibility of absolute measurements, this entails avoiding any artifact or source of error such as movement or high activity from adjacent organs.

Some limitations[6], on spatial resolution imposed by the long positron range of ^{82}Rb, can be corrected by gated acquisition and post-processing of the images; however, the detrimental effect on spatial resolution derived from high signal from adjacent organs has not yet been rectified. ^{82}Rb is a potassium analog which enters the myocardium both by passive diffusion and active transport, via the ATP-dependent sodium-potassium cotransporter; a similar active uptake is present in the stomach via the gastric proton pump.

In this issue of the *Journal of Nuclear Cardiology*, Rasmussen et al[16] report their findings on the prevalence of severe interference caused almost exclusively by the stomach on the radiotracer ^{82}Rb uptake in the LV wall and its inverse association with BMI. They computed the stomach volume by means of delineation of the walls in CT slices and subsequent interpolation to a 3D contour. The degree of interference was derived with the method described by Orton et al[17] a validated algorithm detecting extracardiac interference with 97% sensitivity, 82% specificity, and a very low failure rate in ^{82}Rb PET MPI. The interference severity was classified into four severity groups according to the maximum relative uptake of the region of the overlapping myocardium and stomach. Interference was classified on the base of both relative intensity and angular coverage of SA slices.

Nearly half of the population (31% to 46%) did not show any interference, and a small subset 3% to 5% of cases were classified as severe interference. Interference levels were significantly lower during stress MPI compared to rest MPI. On the one hand, a higher BMI was significantly associated with less severe levels of interference both at rest and stress. On the other hand, more

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severe levels of interference were present with larger stomach volumes after 2 hours fasting at rest but not during stress.

Albeit commendable for making an effort to shed light on a potentially important limitation to reproducible quantification of MBF with ^{82}Rb, this paper missed the opportunity to provide a glimpse on what could be the weight of the interference of the stomach activity on absolute segmental measurements and in final clinical judgement.

Global MBF at rest and stress and MFR reported are comparable independently of the presence of interference. An additional confounding factor was the heterogeneity of the etiology of the heart disease in this cohort, for instance, irreversible myocardial ischemia was diagnosed in 30% of men and 11% of women while reversible ischemia was 43% and 16%, respectively.

Severe interference is, in a relatively small fraction of the population, a problem that is unpredictable and might require repeat imaging. Hence, the weight of the stomach wall activity spill over on the adjacent LV wall segments MBF measurements is of substantial importance similarly to the spillover from the LV and RV blood pools,[18] unfortunately in this paper it was not calculated.

This study highlights the important finding that a small BMI has a higher level of interference and this can be particularly important in women. Women have a smaller BMI and a higher prevalence of non-obstructive CAD and microvascular dysfunction associated with significant cardiovascular morbidity and mortality.[19] Symptomatic women with intermediate- to high-risk for ischemic heart disease are characterized by higher prevalence of risk factors obesity, diabetes mellitus, and hypertension which eventually might evolve into HFpEF.[15] Fully quantitative MBF and MFR, as measured by PET, improve risk reclassification of intermediate-risk patients and provide a better understanding of the function of the entire coronary circulation which can guide systemic therapies and be the gatekeeper to inappropriate revascularization. The proximity of a stomach with high activity to the LV wall, may cast doubts on the accuracy of perfusion measurements in the adjacent myocardial wall and can create artifactual perfusion abnormalities whose degree has still to be precisely defined.

In the past years, a number of maneuvers have been tested to reduce interference from subdiaphragmatic organs with Tc-99m sestamibi MPI spanning from ingesting milk to soda water to displace the bowel. Rasmussen and Coll. suggest that sufficient fasting immediately prior to imminent ^{82}Rb PET scan may be effective to reduce interference from radiotracer activity in the stomach and consequently improve interpretation of MPI results with a more accurate assessment of resting MBF. A validated protocol with a well-characterized fasting time would be very convenient; however, only 2 hours of fasting protocol was applied in this study so we do not know if a more prolonged fasting period could reduce the level of interference from the stomach. Another option could be to inhibit the gastric proton pump, but this possibility remains hypothetical as data in the current literature are scarce and the treatment of patients was not reported in the paper by Rasmussen and colleagues.

At this point in time what could be the way forward to pre-empt the problem of stomach interference in ^{82}Rb MPI? First of all to assess the actual clinical relevance of extracardiac interference in absolute terms.

Then the straightforward solution would be to test the impact of longer fasting periods both in patients with small BMI and a large stomach. This latter is more challenging as the volume of the stomach is detected only at the time of low-dose CT scan. The most elegant solution would be to automatically screen images with the algorithm proposed by Orton and colleagues for the detection of images requiring correction and to implement simultaneous compensation for partial-volume and spillover effects.[20] Still a long way to go, but one step further from where we used to be.

Disclosure

The author has no relationships relevant to the contents of this paper to disclose.

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