Should patients hold proton pump inhibitors prior to ^{82}Rb Rubidium positron emission tomography myocardial perfusion imaging?

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Received Oct 7, 2019; accepted Oct 7, 2019
doi:10.1007/s12350-020-02072-w

See related article, pp. 1443–1451

In the recent years, there has been a clear shift toward increased utilization of cardiac positron emission tomography (PET) in myocardial perfusion imaging (MPI).^{1,2} This is seen in both the academic and private sectors. It is in part due to limited diagnostic accuracy of SPECT in the real world.³ Recent data suggested that SPECT performance outside clinical studies is limited by decreased specificity. PET MPI has been shown to have enhanced diagnostic accuracy in comparison to other imaging modalities.⁴ In the recent PACIFIC trial, cardiac PET had the highest accuracy and overall area under the curve when compared to other modalities using invasive hemodynamic assessment as the reference standard.⁵

On the other hand, PET is not free from artifacts. In the current era, most laboratories are utilizing hybrid systems which include PET and computed tomography (PET CT). In the systems, PET CT procedures may be prone to misregistration artifacts, a major reason for false positivity in PET MPI.² In addition, ^{82}Rb Rubidium is the most commonly utilized radiopharmaceutical in the current era.⁶ It is preferred in high volume centers as well as in sites that does not have a cyclotron onsite. ^{82}Rb Rubidium is produced from a ^{82}Sr Strontium/ ^{82}Rb Rubidium generator and is eluted every 10 minutes. ^{82}Rb Rubidium is an analog of potassium and requires active transport via

the sodium/potassium adenosine triphosphate transporter. In addition to cardiac uptake, there is significant uptake in the stomach, spleen and colon (Figure 1A, B). It is estimated that a small but non-negligible fraction of ^{82}Rb Rubidium PET MPI studies ($\sim 10\%$) suffer from high levels of tracer uptake in structures adjacent to the heart which may impact the interpretability of the MPI study.⁷ Identifying factors that increase the extracardiac uptake in the stomach, spleen and colon is very important to avoid having non-diagnostic studies.

In another shift in medicine, proton pump inhibitors (PPI) are frequently utilized for gastric symptoms. They are available over the counter and do not require a physician prescription. Many patients utilize these medications daily. However, there have been several reports in the recent years questioning the safety of their chronic use. The association between PPI use and infection, particularly *Clostridium difficile* and pneumonia, has been the subject of several studies.⁸ In addition, one study suggested that long-term PPI use increases the risk of dementia.⁸ On the other hand, observational studies suggested that PPIs are associated with an increased gastric cancer risk. These concerns have not been confirmed in randomized controlled trials.⁹ Many other less concerning side effects have been reported from PPI chronic use. However, the interaction between PPI use and MPI accuracy has not been evaluated before.

In this issue of the *Journal*, Alzahrani et al.¹⁰ performed an interesting prospective study evaluating the relationship between ^{82}Rb Rubidium gastric uptake and the use of PPIs. In 600 patients who underwent clinically indicated ^{82}Rb Rubidium PET MPI studies, the use of PPI use was prospectively ascertained (medication, dose, frequency and duration of use, and time of last dose). Absolute uptake values and gastric:hepatic ratios were compared in PPI and non-PPI users. The authors found that the gastric uptake of ^{82}Rb Rubidium was much greater

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J Nucl Cardiol 2020;27:1452–5.

1071-3581/\$34.00

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Figure 1. A representative case of a patient with significant subdiaphragmatic activity during **A** regadenoson ^{99}Tc SPECT imaging and **B** regadenoson ^{82}Rb PET MPI.

in patients actively using PPI. This was seen in the stress and rest scans, but the resting gastric:hepatic Rb-82 uptake ratio was 23% higher in PPI vs non-PPI users. Importantly, the gastric:hepatic ratios did not differ in patients with and without hiatus hernia. The differences in gastric uptake and gastric:hepatic ratios between PPI and no PPI patients were still significantly different in those without hiatus hernia.

This is a novel study based on a novel observation and the authors should be commended for the originality. It brings a new dimension to the performance of ^{82}Rb PET MPI and should be confirmed in larger studies. However, few important remarks should be taken into consideration while interpreting the current findings. This study utilized dipyridamole as the vasodilator agent. In the United States, regadenoson is the most used vasodilator agent and it is not clear if the same findings are expected in regadenoson vasodilation. In addition, the impact of this stomach uptake on myocardial blood flow and coronary flow reserve is not known and requires further investigation.

Future investigations should focus on the impact of PPI use and increased subdiaphragmatic uptake on the diagnostic accuracy of ^{82}Rb PET MPI. This could not be addressed in this study due to small sample size. The presence of an interaction with diagnostic accuracy and prognostic value would lead to new recommendations regarding the peri-procedural intake of PPIs.

The paper adds to the prior observation where 200 subjects underwent a clinical ^{82}Rb myocardial perfusion rest/stress PET.¹¹ A large stomach volume was correlated with significant subdiaphragmatic activity and severe MPI interference. The authors suggested that fasting prior to ^{82}Rb PET MPI may be important to reduce this subdiaphragmatic radiotracer activity. This analysis takes this observation further and suggest that it is not only the stomach volume that impacts subdiaphragmatic radiotracer uptake, but also PPI intake. Whether there is a relation between PPI intake and stomach volume requires further evaluation that should take into account PPI dosage, PPI type and duration of use. At this stage, it is not clear if this a class effect or is encountered more often in patients using a specific PPI. Similarly, different patient subgroups should be investigated including those with gastroesophageal reflux or those with diabetes mellitus induced gastroparesis.

How should the above findings impact clinical practice? The authors recommend withholding PPI more than 36 hours prior to ^{82}Rb PET MPI. Theoretically, this may reduce the potential spillover from gastric uptake. This is a reasonable approach that should be investigated further in a study that includes a good representation of patients with diabetes and

gastroesophageal reflux. Similarly, whether this should be extrapolated to SPECT imaging or Ammonia PET is unclear. In SPECT imaging, partial volume averaging could be more determinantal to the image quality as shown in the images above (Figure 1A) and the benefits of holding PPIs prior to SPECT imaging may be more pronounced.

In summary, this novel analysis opens the door to a new recommendation for the patients' preparation prior to performing vasodilator ^{82}Rb PET MPI. While further studies are needed prior to routine adoption, it may reasonable to start holding PPI prior ^{82}Rb PET MPI and maybe some SPECT studies while waiting for further guidance from future studies and professional societies recommendations.

Disclosures

Mouaz H. Al-Mallah has no relations to disclose.

References

1. Al Badarin F, Aljizeeri A, Almasoudi F, Al-Mallah MH. Assessment of myocardial blood flow and coronary flow reserve with positron emission tomography in ischemic heart disease: Current state and future directions. *Heart Fail Rev* 2017;22:441-53.
2. Al-Mallah MH, Sitek A, Moore SC, Di Carli M, Dorbala S. Assessment of myocardial perfusion and function with PET and PET/CT. *J Nucl Cardiol* 2010;17:498-513.
3. Chinnaiyan KM, Peyser P, Goraya T, Ananthasubramaniam K, Gallagher M, Depetris A, Boura JA, Kazerooni E, Poopat C, Al-Mallah M, Saba S, Patel S, Girard S, Song T, Share D, Raff G. Impact of a continuous quality improvement initiative on appropriate use of coronary computed tomography angiography. Results from a multicenter, statewide registry, the Advanced Cardiovascular Imaging Consortium. *J Am Coll Cardiol* 2012;60:1185-91.
4. Mc Ardle BA, Dowsley TF, deKemp RA, Wells GA, Beanlands RS. Does Rubidium-82 PET have superior accuracy to SPECT perfusion imaging for the diagnosis of obstructive coronary disease?: A systematic review and meta-analysis. *J Am Coll Cardiol* 2012;60:1828-37.
5. Danad I, Raijmakers PG, Driessen RS, Leipsic J, Raju R, Naoum C, Knuuti J, Mäki M, Underwood RS, Min JK, Elmore K, Stuijfsand WJ, van Royen N, Tulevski II, Somsen AG, Huisman MC, van Lingen AA, Heymans MW, van de Ven PM, van Kuijk C, Lammertsma AA, van Rossum AC, Knaapen P. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol* 2017;2:1100-7.
6. Dilsizian V, Bacharach SL, Beanlands RS, Bergmann SR, Delbeke D, Dorbala S, Gropler RJ, Knuuti J, Schelbert HR, Travin MI. ASNC imaging guidelines/SNMMI procedure standard for positron emission tomography (PET) nuclear cardiology procedures. *J Nuclear Cardiol* 2016;23:1187-226.
7. Orton EJ, Al Harbi I, Klein R, Beanlands RSB, deKemp RA, Glenn Wells R. Detection and severity classification of extracardiac interference in ^{82}Rb PET myocardial perfusion imaging. *Med Phys* 2014;41:102501.

8. Jaynes M, Kumar AB. The risks of long-term use of proton pump inhibitors: A critical review. *Ther Adv Drug Saf* 2018;10:2042098618809927.
9. Cheung KS, Leung WK. Long-term use of proton-pump inhibitors and risk of gastric cancer: A review of the current evidence. *Ther Adv Gastroenterol* 2019;12:1756284819834511.
10. Alzahrani AH, Arasaratnam P, Massalha S, Alenazy A, Lee A, Clarkin O, deKemp RA, Hossain A, Beanlands RS, Ruddy TD, Chow BJW. Effect of proton pump inhibitors on Rubidium-82 gastric uptake using positron emission tomography myocardial perfusion imaging. *J Nuclear Cardiol*. 2019. <https://doi.org/10.1007/s12350-019-01954-y>.
11. Rasmussen T, Kjær A, Hasbak P. Stomach interference in 82Rb-PET myocardial perfusion imaging. *J Nuclear Cardiol* 2018;26:1934-42.

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