Gastric wall uptake and attenuation artifact in 99m-Tc sestamibi SPECT: Hold the proton pump inhibitors!

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Myocardial perfusion imaging (MPI) is an important modality in the management of patients with known or suspected coronary artery disease (CAD); it plays a key role in the detection and quantification of ischemic burden, assessment of residual viability, risk stratification and prognostication of patients, and evaluation of the effectiveness of therapy. However, MPI faces many challenges that often limit its diagnostic accuracy.[1] These include: (1) factors related to suboptimal patient preparation and pre-imaging issues (fasting state, withholding beta-blockers and other cardiac medications, caffeine intake prior to pharmacological stress testing, infiltration of the intravenous line and contamination); (2) technical factors (motion and gating artifacts, inadequate quality control and machine calibration); (3) heart related issues (left bundle branch block, hypertrophic cardiomyopathy, balanced ischemia); and (4) patient related factors (attenuation artifacts and subdiaphragmatic activity).[1]

Prominent activity is often present in subdiaphragmatic organs adjacent to the heart: in the liver and bowels as a result of hepatobiliary excretion of 99m-Tc radiopharmaceutical; and in the stomach due to reflux of the tracer into the gastric lumen from the duodenum or due to uptake of free 99mTc-pertechnetate by the gastric mucosa. Either way, increased activity in subdiaphragmatic organs can result in apparent increased activity in the adjacent inferior wall as a result of scatter and volume averaging (masking a true defect), or counterintuitively, an apparent decreased activity in the adjacent myocardium when performing the reconstruction algorithm with filtered backprojection (causing a false defect).[1,2]

There are several ways to minimize the prominent subdiaphragmatic activity. Prone imaging helps displace subdiaphragmatic organs away from the heart[3,4]; while CT-attenuation correctio [3] and post-processing with masking can correct the artifact. Yet, neither may not be enough to fully overcome this pitfall. In addition, while drinking water may help clear activity from the stomach,[5] a study showed that unlike stomach cavity activity, stomach wall activity cannot be prevented by the ingestion of even half a liter of water before imaging.[6] The addition of low-level exercise in patients undergoing pharmacologic stressing can reduce adjacent subdiaphragmatic activity by increasing skeletal muscle blood flow.[7] One of the most important approaches, however, is to wait an adequate amount of time between injection of the radiopharmaceutical and imaging to allow subdiaphragmatic activity to clear. However, time is a luxury that patients and nuclear laboratories often do not have.

Another factor associated with increased subdiaphragmatic activity is large stomach volume. In a recent study of 200 patients undergoing stress 82-Rubidium Positron Emission Tomography (PET), Rasmussen et al showed that a large stomach volume correlated with significant subdiaphragmatic activity and was associated with more severe MPI interference, particularly among those with smaller body mass index.[8]

Alzahrani et al took the analysis further and showed that is not only the stomach volume that impacts subdiaphragmatic radiotracer uptake, but also proton pump inhibitor (PPI) intake.[9] In this prospective study that

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enrolled 600 patients, the authors found that the gastric wall uptake (GWU) of 82-Rb was greater in patients actively using PPI, in both stress and rest scans, and independently of the presence of a hiatal hernia.

The impact of PPI on GWU in MPI was previously described with single photon emission computed tomography (SPECT) imaging. Indeed, Goel et al evaluated 121 patients (91 women) undergoing single-day rest/stress 99m-Tc-sestamibi SPECT (26 taking PPIs, 14 H2-receptor antagonists and 81 neither).[6] GWU was strongly associated with prolonged use of PPIs (Chi square = 51.9, $P < .0001$) but not with H2-receptor antagonists. They concluded that PPI therapy significantly increase stomach wall activity, potentially resulting in Compton scatter or ramp filter artifacts affecting the inferior wall of the left ventricle.

Furthermore, the effect of PPI on GWU of 99m-Tc is independent of the type of radiopharmaceutical or camera. Indeed, in a former paper, the impact of chronic use of PPI (more than 2 weeks) on stomach wall activity was evaluated in 127 patients (43% on PPI) that underwent pharmacological SPECT MPI using 99m-Tc-tetrofosmin and were imaged using cadmium-zinc-telluride camera. Patients on PPIs were more likely to have clinically relevant stomach wall uptake (score 2 to 3) as compared to patients not using PPIs (22% vs 7%, $P = .017$), and irrespective of gastric symptoms.[10]

Therefore, it is important to elicit a history of prolonged PPI use, anticipate the possibility of increased stomach wall activity, which can confound the image quality and diagnostic interpretation. Withholding PPI prior stress MPI seems therefore a reasonable approach. In a prospective study, Sing et al[11] evaluated 156 patients undergoing same day stress/rest 99m-Tc sestamibi SPECT (control group, $n = 48$; PPI group, $n = 47$; H2-receptor antagonist group, $n = 19$; and intervention group with PPI discontinued for 3 days, $n = 42$). Clinically relevant GWU was seen in 36% of PPI group patients as compared to 8 to 10% in the remaining 3 groups. Therefore, stopping PPI for 3 days or substituting it with H2-receptor antagonists were associated with significant reduction in clinically relevant GWU.[11]

The study by Sing et al however, evaluated the post stress images only rather than having the research method based on a before and after design. In this current prospective trial of 351 patients scheduled for 2 day rest/stress 99mTc sestamibi SPECT, Norouzi et al aimed to evaluate the impact of gastroprotective medications on GWU and the means to overcome the limitations.[12] The authors randomized patients with history of taking PPI to: Group A (discontinued PPI, no replacement); Group B (replace PPI with H2-receptor antagonist); and Group C (continue PPI). The remaining patients already on H2-receptor antagonists (Group D) or neither (Group E, control) were also included. The PPI used were omeprazole and lansoprazole (oral) and pantoprazole (intravenous) as these were the only available ones. Patients on PPI has significantly higher GWU compared to the remaining groups (intravenous even greater than oral PPI), with a clear association between duration of oral PPI intake and GWU, but not with intravenous PPI. Furthermore, stopping PPI was associated with significant decrease in GWU to an equal degree whether the discontinuation period was 3 to 5 days or 5 to 7 days. Replacing PPI with H2 receptor antagonist was associated with some GWU (greater than control, but significantly less than PPI intake). Moreover, there was a significant difference in GWU of the patients who underwent exercise stress ($n = 64$) versus vasodilator stress ($n = 276$) across all groups, with lower incidence of GWU in the exercise group (P value = .003). Finally, there was no significant association on multivariate analysis with gender and diabetes.[12]

SO WHAT DO WE KNOW FOR NOW AND WHAT CAN WE CONCLUDE FOR THE CURRENT AND PRIOR STUDIES?

1. It seems there is clearly an association between PPI and increased GWU, that correlates with duration of PPI intake. While prior study showed that 2 weeks of PPI increased GWU by 36%,[11] the current study by Norouzi et al evaluated patients with long term use of PPI with a mean duration of 514 days.[12]
2. Discontinuing PPI prior to stress MPI for 3 to 5 days is as good as 5 to 7 days and results in significant decrease in GWU.[12]
3. Substituting PPI with H2 receptor antagonists prior to the stress MPI is an acceptable alternative.[11,12]
4. Drinking up to 500 mL of water after completion of the stress test does not reduce the GWU.[6]
5. PPI increases GWU whether using 99m-TC sestamibi, 99m-Tc tetrofosmin, or 82-Rb, gamma camera or cadmium-zinc-telluride SPECT camera or PET imaging.
6. Gender and history of diabetes do not impact GWU by PPI.[12]
7. PPI associated increase in GWU was seen in pharmacological stress MPI (adenosine [11] and dipyridamole [6,9,12]) and is significantly reduced with exercise stress testing.[6,11,12]

WHAT IS STILL MISSING OR REMAINS UNCLEAR?

1. The mechanism of action remains debatable. On one hand, Goel et al proposed that PPI inhibit

Table 1. Important medications that may be continued or need to be withheld prior to stress myocardial perfusion imaging

Medications	Exercise stress testing	Vasodilator stress testing
Beta blockers	Stress test ordered to diagnose CAD or new ischemia: Withhold Stress test ordered to assess perfusion on optimal medical therapy: continue	Safe to continue-No impact on perfusion or diagnostic accuracy[17]
Calcium channel blockers, nitrates, ranolazine	Stress test ordered to diagnose CAD or new ischemia: Withhold Stress test ordered to assess perfusion on optimal medical therapy: continue	May continue (no solid data on impact on diagnostic accuracy)
Caffeine	Continue (unless there is a chance of converting to vasodilator stress testing)	Withhold for at least 12 h
Oral dypiridamole	Continue (unless there is a chance of converting to dypiridamole stress test)	Withhold if dypiridamole is the vasodilator used in the nuclear lab
H2-receptor antagonist	Continue	May continue but better to withhold
Proton Pump Inhibitor	Preferably withhold for 3–5 days, particularly if there is a chance of converting to vasodilator stress testing	Withhold for 3–5 days and/or replace with H2-receptor antagonist

luminal secretion of MIBI via the H+/K+ ATP-ase leading to more retention in the abundant gastric parietal mitochondria.[6] On the other hand, Rose et al proposed that hypergastrinemia caused by prolong PPI intake, acts as a cell growth factor resulting in increased perfusion and gastric wall uptake of MIBI.[13] In the case of 82-Rb, the mechanism is not well defined

2. The effect of intravenous PPI and duration needed to withhold it prior to MPI remain to be explored.
3. More data are needed to explore whether there is a class and dose effects of PPI.
4. There are no studies exploring the effect of PPI on GWU in patients undergoing regadenoson stress MPI.[14] This is the most commonly used vasodilator in the United States. It is also worth exploring the GWU with PPI in patients undergoing hybrid stress testing, particularly those having rescue dose of regadenoson during exercise testing.[15]
5. The GWU of 13 N-ammonia and interaction with PPI have not been studied.
6. Given the recent evidence that aspirin may potentially be a factor decreasing GWU in patients on PPI,[13] it would have been great to have a subgroup getting aspirin plus PPI to compare to other groups.
7. Given that grade 3 uptakes potentially cause non-interpretable scans and occur in up to than 10% of cases, clinical data are needed to assess the impact of PPI intake during MPI on the diagnostic accuracy of stress SPECT and PET, on myocardial blood flow and reserve quantification, whether it results in further downstream testing and affects outcomes. Indeed, Qutbi M clearly showed the clinical impact of withholding omeprazole for 2 weeks on the diagnostic interpretation of the MPI in an illustrative image.[16]
8. While diabetes per say was not a predictor of increased GWU on multivariate analysis in the study by Norouzi et al [12] it is not clear whether any of these patients had diabetes induced gastroparesis. Indeed, it is interesting to evaluate whether gastroparesis can further enhance GWU. Conversely, the impact of pernicious anemia, sleeve and gastric bypass on GWU can also shed more light on the matter.
9. It seems we lack a randomized controlled blinded study to assess the impact of PPI on the diagnostic accuracy of stress MPI, subsequent clinical decisions and outcomes.

WHERE DO WE DO NOW?

Given the evidence at hand, it is quite reasonable to recommend withholding PPI for at least 3 to 5 days prior to stress MPI, whether 82Rb-PET or MPI SPECT, particularly if performed with vasodilator pharmacological agents (dipyridamole or adenosine). While there are

no data with regadenoson, it is prudent to follow the same recommendation until more data are made available. While the GWU is significantly reduced with exercise stress testing, many patients would require rescue dose of regadenoson or converted to a vasodilator if they fail to reach target heart rate. As such, in order not to reschedule the patient, it is also fair to suggest withholding PPI for at least 3 to 5 days in this cohort. For patients with significant reflux symptoms or dyspepsia, substitution with H2-receptor antagonist prior to the stress test is an acceptable alternative. The following table summarizes key instructions/suggestions that may be provided to patients pertaining to taking or withholding certain medications prior to stress MPI (Table 1).

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