EDITORIAL COMMENT

Does a Shortened Hyperemia With Regadenoson Stress Pose a Concern for Quantitative Rb-82 PET Imaging?

Optimization of Regadenoson PET Imaging*

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Although regadenoson has nearly replaced other vasodilator stressors for single-photon emission computed tomography perfusion imaging, the benefits of regadenoson stress for positron emission tomography (PET) perfusion are less clearly established, particularly in the estimation of absolute stress flow with dynamic PET imaging. In the estimation of absolute flow with dynamic PET, the timing of radiotracer administration needs to be carefully matched to the time and duration of coronary hyperemia. In this issue of iJACC, Johnson and Gould (1) suggest the regadenoson stress Rb-82 may underestimate flow that can be achieved with dipyridamole stress, and this underestimation is critically dependent on the timing of Rb-82 administration relative to the administration of regadenoson.

The authors performed a prospective study comparing the peak hyperemia achieved with dipyridamole stress Rb-82 PET imaging with that of the bolus administration of regadenoson using different time delays between regadenoson vasodilator stress and radiotracer infusion. Their data suggest that the optimal timing for Rb-82 may be between 90 and 120 s after administration of regadenoson stress, which represents a delay greater than that recommended in the package insert for stress perfusion imaging.

COMPARISON WITH PRIOR STUDIES

In a group of control subjects without history of ischemic heart disease or evidence of significant coronary stenosis on coronary angiography, Lieu et al. (2) compared the effects of the bolus intravenous administration of regadenoson (10 to 500 µg) with that of intracoronary adenosine (18 µg) on coronary flow. They demonstrated a significant variability with regard to peak coronary flow velocity as assessed with an intracoronary Doppler-tipped guidewire following administration of regadenoson ranging from 0.5 to 2.3 min. Regadenoson was also shown to increase peak coronary flow in a dose-dependent manner. These investigators did appropriately withhold all other drugs that could have potentially affected coronary flow, and still produced the observed variability in response to regadenoson stress. These important observations with regard to the variability of the coronary flow response must be taken into consideration when applying regadenoson stress in conjunction with quantitative dynamic Rb-82 PET imaging. How this variability in stress-induced flow might impact the diagnostic accuracy and clinical decision making following regadenoson stress and rest Rb-82 PET imaging is still not fully defined.

Goudarzi et al. (3) performed a retrospective analysis of regadenoson and dipyridamole stress/rest dynamic PET Rb-82 PET perfusion imaging studies in matched populations (not the same patients) in evaluation of absolute blood flow and flow reserve, and demonstrated no difference in mean stress flows in 104 patients without perfusion defects or known history of coronary artery disease. Cullom et al. (4) performed a direct comparison of regadenoson and dipyridamole pharmacological stress in combination with Rb-82 PET perfusion imaging, demonstrating visually equivalent perfusion defects in a small

*Editorials published in JACC: Cardiovascular Imaging reflect the views of the authors and do not necessarily represent the views of JACC: Cardiovascular Imaging or the American College of Cardiology.

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number of patients, although did not evaluate absolute flow. These investigators administered 400 µg of regadenoson over 10 s according to the package insert followed by a 5-ml flush, with initiation of the Rb-82 infusion (25 s) immediately after the flush, similar to the group in the current study (1) that received Rb-82 with the shortest delay.

Previous pre-clinical and clinical studies have demonstrated that coronary flow reserve is affected by heart rate, arterial pressure, loading conditions, contractile state, anemia and associated changes in blood viscosity, presence of hypertrophy, and previous myocardial injury (5). Sudden changes in heart rate can result in significant reductions in maximum coronary flow reserve (5). Heart rate is the major factor affecting the diastolic duration, and the diastolic filling time is an important determinant of coronary perfusion pressure and flow. Although differences in the changes in heart and arterial pressure were assessed in the study by Johnson and Gould (1), these indexes were evaluated at relatively sparse time points considering the variability in the hemodynamic response and the critical time for myocardial extraction of Rb-82 relevant to the estimation of absolute coronary flow. In the current study, they did observe significant difference in the heart rate between dipyridamole stress in the various regimens for administration of regadenoson relative to the infusion of Rb-82.

LIMITATIONS OF THE CURRENT STUDY

The authors have not addressed the issue of duration of administration of regadenoson versus the timing of a 10-s bolus of regadenoson in relation to Rb-82 administration. Anecdotal observations we initially made in pre-clinical studies, and later, in our clinical evaluation of methods for optimal regadenoson administration in conjunction with perfusion imaging, have demonstrated that the duration over which regadenoson is administrated may be just as important as the timing between a 10-s bolus administration of regadenoson and radiotracer delivery. Administering regadenoson over 30 s resulted in less dramatic acute changes in heart rate and blood pressure, and a more uniform hyperemic response, and clinically fewer side effects. We performed a pre-clinical study directly evaluating the effects of regadenoson administration over 30 s on global hemodynamic, coronary flow, regional myocardial flow assessed by microspheres, and radiotracer uptake (6). This study demonstrated that regadenoson administered over 30 s produced on average a stable peak hyperemic response from 1 to 3 min following completion of the regadenoson infusion, and similar to the hyperemic response achieved with continuous infusion of adenosine over 4.5 min.

Could the finding of the current study be specific for the imaging protocol and methodology applied? In performing 2-dimensional PET imaging these investigators adjusted the delivery dose of Rb-82 depending on the age of the Rb-82 generator. However, other sites performing quantitative dynamic Rb-82 3-dimensional (3D) PET imaging always administer a lower standard dose of Rb-82 that can be delivered over the entire 6-week life of the Rb-82 generator. Using this 3D imaging approach, the age of the generator affects the duration over which the Rb-82 dose is administrated, as well as the initiation of the delivery. Therefore, their findings may be somewhat unique to 2-dimensional Rb-82 PET imaging and their specific method of flow quantification. Further studies would be required to evaluate the optimal timing and method of regadenoson administration in conjunction with 3D dynamic Rb-82 PET imaging for estimating maximal coronary hyperemia.

The more transient coronary hyperemia induced by regadenoson might also potentially confound the application of quantitative Rb-82 PET in patients with depressed left ventricular function, because in these patients there is a significantly slower right ventricle to left ventricle transit time. This delay in transit time could affect circulating arterial blood levels of Rb-82 at the time of peak hyperemia, thereby influencing myocardial extraction of Rb-82. Further clinical studies would be needed to evaluate the influence of this additional confounding variable.

CONCLUSIONS

In summary, Johnson et al. (1) have definitively demonstrated that the current recommendations for administration of regadenoson in conjunction with dynamic Rb-82 PET imaging for evaluation of quantitative flow require modification, as they suggest, with the critical need to adjust the timing between regadenoson stress and radiotracer administration and imaging. Their observations probably also have implications for other types of PET perfusion imaging with or without determination of absolute flow. However, further studies may be required to better define the truly optimal approach for regadenoson PET perfusion imaging depending on the radiotracers, clinical conditions, and instrumentation applied.

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KEY WORDS absolute flow, dipyridamole, positron emission tomography, regadenoson