Regadenoson myocardial perfusion imaging predicts prognosis in patients with either left bundle branch block or a ventricular paced rhythm

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Received Jul 13, 2019; accepted Jul 15, 2019

doi:10.1007/s12350-019-01828-3

See related article, pp. 967–977

Iskander, Doukky, and colleagues of the John H. Stroger, Jr. Hospital of Cook County and Rush University Medical Center provided us with another well-performed prognostic study of regadenoson MPI.¹ They convincingly found that patients with either a baseline left bundle branch block (LBBB) or a ventricular-paced rhythm (V-paced) can be risk stratified by the perfusion results of MPI into high and low-risk groups. Risk increased with increasing Summed Stress (SSS) and Summed Difference Scores (SDS).

This result is consistent with previous prognostic studies which found vasodilator stress MPI to risk stratify LBBB and V-paced patients using the first and second-generation vasodilators, dipyridamole and adenosine. Gil et al, for example, followed 69 LBBB patients who presented with typical or atypical angina or new onset LBBB whose dipyridamole MPI was normal over a mean of 33 months.² Only 2 required revascularization and none had experienced MI or cardiac death during follow-up. Wagdy et al. risk stratified 245 LBBB patients into low and high-risk groups who had undergone dipyridamole or adenosine MPI.³ Low-risk patients had a mortality consistent with the general age-matched U.S. population.

Ventricular pacing, which mimics LBBB with both delaying conduction of the left ventricle, was evaluated by Lapeyre et al. in 91 V-paced patients following dipyridamole or adenosine MPI over 5 years.⁴ Cardiac annual mortality was 1.4% in low-risk group vs 6% in the high-risk group.

Regadenoson, however, induces a greater increase in heart rate (HR) than adenosine or dipyridamole. For example, in the ADVANCE 1 MPI trial, Iskandrian et al. observed a mean increase in HR of 25 bpm with regadenoson vs 20 bpm with adenosine.⁵ Might this greater increase in HR induce defects in the LAD territory in patients with LBBB or V-paced rhythm, as is not infrequently observed with the HR increases observed with exercise and dobutamine?^{6–9}

This was examined by one of us and colleagues in a study of 64 patients with LBBB and 93 with ventricular pacemakers who participated in the ADVANCE MPI 1 and 2 trials.¹⁰ We observed a HR increase of 25 bpm and 15 bpm in LBBB patients with regadenoson and adenosine, respectively. The increase was blunted in patients with ventricular pacemakers, 12 vs 8 bpm, with regadenoson and adenosine, respectively. This difference did not produce an increase in visually or quantitative assessed septal or LAD territory defects, when comparing perfusion with regadenoson to perfusion with adenosine and using each patient as their own control.

The mechanism for the increase in HR with vasodilator stress was originally assumed to be reflex tachycardia secondary to their hypotensive effect. However, the chief mechanism is actually related to the existence of A2a receptors in the carotid body and that their stimulation causes not smooth muscle relaxation and vasodilation, as it does with endothelial A2a receptors, but a release of norepinephrine (NE).^{11–13} As

See related article, <https://doi.org/10.1007/s12350-019-01762-4>.

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J Nucl Cardiol 2021;28:978–80.

1071-3581/\$34.00

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Figure 1. Intravenous regadenoson nearly doubles plasma norepinephrine in the rat model ($n = 6$) and does so almost immediately. This increase in sympathetic tone is the primary cause of the heart rate increase seen with the vasodilator A2a stimulation. Reprinted with permission from Dhalla et al.¹⁴.

seen in the Figure 1, Dhalla demonstrated that NE nearly doubles within one minute in the rat model.¹⁴ The observation in the same study that metoprolol abolishes the HR increase provides further evidence that the HR increase is a result of an increase in sympathetic tone (NE release). This increase in NE is also the likely cause of the startle-like feeling that patients often feel early during regadenoson and adenosine infusion.¹⁵

Unlike adenosine, regadenoson is not weight based but given as a fixed dose. Thus, a large dose is needed to be able to accommodate larger patients. The greater selectivity for A2a receptors than adenosine and the fixed dose are the likely reasons for its greater HR increase.

In the present study, in the *Journal of Nuclear Cardiology*®, Iskander et al observed an annualized MACE rate (cardiac death/myocardial infarction) in patients with normal perfusion of 0.8% in LBBB patients and 1.0% in ventricularly paced patients.¹ MACE increased in a stepwise fashion with increasing SSS and SDS in both sets of patients but with greater absolute increases in the ventricular pacing group. The latter group also had a lower resting EF (49% vs 52%), greater estimated left ventricular end diastolic volume (178 mL vs 143 mL) and greater SSS and SDS.

As with adenosine MPI,^{16,17} adding low-level exercise to regadenoson^{18,19} has been shown to decrease side effects and improve image quality. Following ASNC guideline recommendations,²⁰ Iskander et al did not perform low-level exercise in LBBB or V-paced patients in their study so as not to increase HR with low-level exercise. The greater increase in HR observed following regadenoson relative to adenosine and dipyridamole reinforce the importance of this recommendation.

It should be remembered that while ischemia cannot be effectively evaluated by exercise testing in patients with LBBB, patients with right bundle branch block (RBBB) can be evaluated by ECG (and adjunctive MPI

if needed) with exercise stress. If adequate exercise is obtained in RBBB patients, ST depression in leads V4-V6 predicts ischemia.^{21–24} While the QRS interval is wide in RBBB, the QT interval is not significantly prolonged. Therefore, the duration of the ST segment depression is relatively shorter in RBBB because the wide S wave encroaches on the ST segment. Tanaka et al. demonstrated that the ST depression must be manifested in the lateral precordial leads (V4-V6) to be significant in RBBB patients, as patients with ST depression in V1 to V3 had normal coronaries on angiography.²² In fact, ST depression is often seen in V2 and V3 in RBBB patients secondary to repolarization changes related to the wide R' typically present in these leads. Overall, the sensitivity of exercise testing to detect CAD in patients with RBBB using the criteria of ST depression in V4-V6 appears modestly less than the sensitivity of exercise testing in patients with normal ECGs.²⁵

In sum, Iskander et al. add to the literature demonstrating the prognostic power of regadenoson stress in patients with conduction abnormalities associated with LBBB and ventricular pacing.¹ Studies have yet to be performed on the impact of vasodilator or regadenoson stress in patients with biventricular pacing, though mechanistically vasodilator stress should not be compromised with such pacing.

Disclosure

Gregory S. Thomas acknowledges royalties from *Ellestad's stress testing: Principles and practice*, Oxford University Press, and serving on the Speakers bureau of Astellas Pharma. Arash Taghavi has no disclosures.

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