Regadenoson in heart transplant recipients: Use without worries

Mouaz H. Al-Mallah, MS, MSc[a]

[a] Houston Methodist DeBakey Heart & Vascular Center, Houston Methodist Hospital, Houston, TX

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Cardiac allograft vasculopathy (CAV), a generalized coronary vasculopathy, is one of the leading causes of death post cardiac transplant. Thus, its detection is important from a diagnostic and prognostic standpoint to identify those transplant patients at risk of graft loss and poor outcomes.[1] However, screening for CAV in routine clinical practice is variable. There are no clear unified guidelines on how to detect this vasculopathy and manage it. Often treatment providers utilize coronary angiography as the test of choice to detect CAV and guide management and assess therapeutic responses. Myocardial perfusion imaging (MPI) has been suggested as a tool that can provide diagnostic and prognostic value. However, there have been several concerns about the use vasodilator stress in this patient population. This is in part due to the fact that the denervated sinus and atrioventricular nodes of the transplanted hearts have exaggerated responses to sympathomimetic amines.[2] A few single-center studies have suggested that adenosine in this patient population have acceptable risk. In a single-center study of adenosine MPI in transplant patients, adenosine infusion was found to be associated with a higher incidence of sinus pauses (4.9% vs 0%), second (11.8% vs 4.9%) and third degree AVBs (2.9% vs 0%) compared to the nontransplant patients. However, only 2% of the studies were terminated due to bradyarrythmia. It is important to note that baseline right or left bundle branch block, beta-blockers, calcium blockers, or digoxin were not associated with occurrence of AVB.[3]

However, there has been a shift toward the use of regadenoson in most nuclear cardiology laboratories given its improved tolerance and enhanced safety profile.[4–6] However, the safety of regadenoson in transplant recipients has not been well documented. A single-center study assessed the safety and tolerability of regadenoson in 40 orthotropic heart transplant patients. Both adenosine and regadenoson had similar side-effect profiles,. and there were no episodes of bradycardia and/or AV block with regadenoson. However, that study was limited by small sample size.[7] (Table 1).

In this issue of the journal, Lazarus et al[8] retrospectively report on the safety of regadenoson use in 123 orthotropic heart transplant patients who underwent positron emission tomography (PET) stress testing using rubidium imaging. The investigators evaluated the hemodynamics and ECG response as well as patient response and adverse events in response to regadenoson. As reported before, regadenoson was associated with increase in the heart rate and a drop in systolic, diastolic, and mean blood pressures. Of note, a larger proportion of OHT patients had hypotension (12%), but a similar proportion of OHT patients experienced large decreases in blood pressure (>35 mmHg; 24% vs 29%) Impotently, there were no documented second and third degree AV blocks. The authors concluded that regadenoson is safe in patients with prior heart transplantation.

This is the largest series of orthotropic heart transplant patients who underwent vasodilator or specifically regadenoson stress testing. These results have to be interpreted in the context used. Regadenoson was injected as per advised protocol. Almost none of the patients has any baseline heart block. In addition, beta blockers were stopped 24 hours prior to the stress test unless these patients had a myocardial infarction within the last three years or had systolic dysfunction that

Reprint requests: Mouaz H. Al-Mallah, MS, MSc, Houston Methodist DeBakey Heart & Vascular Center, Houston Methodist Hospital, 6565 Fannin Street, Smith-19, Houston, TX 77030; *mouaz74@gmail.com*

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Table 1. Comparison of the safety of vasodilator stress in patients with heart transplant patients

	Al-Mallah et al[3]	Cavalcante et al[7]	Lazarus et al[8]
Vasodilator	Adenosine	Regadenoson	Regadenoson
Number of patients	102	40	123
Second degree AV block	11.8%	0%	0%
Third degree AV block	2.9%	0%	0%
Sinus pauses	4.9%	2%	0%

Table 2. Adverse events of Regadenoson in patients with heart transplant in comparison to the general population

	Heart transplant patients[8] (%)	Heart transplant patients[7] (%)	ADVANCE registry[6] (%)
Dyspnea	67	68	25
Nausea	12	36	6
Flushing	12	12	17
Chest discomfort	3	19	11
Headache	3	21	29
Dizziness/lightheadedness	5	19	7

requires beta blocker therapy. It is interesting to note that in the few patients who used beta-blocker therapy, there was no effect on the heart rate or the presence of pauses. Most of these patients have presented more than five years after transplant. Thus, the safety of regadenoson in patients with transplants less than this duration is not known and regadenoson should be used carefully in this subgroup of transplant patients.

It is important to note that this study does indicate a lower incidence of headache and a significantly higher incidence of dyspnea in the heart transplant population compared to the nontransplant patients included in different registries and randomized controlled trial.[8] (Table 2) The etiology of this dyspnea is unknown and no obvious pharmacologic interaction between immunosuppression medications and regadenoson. This finding of increased dyspnea is not unique to this study and has been described before.[7] (Table 2)

These results are reassuring and will be reassuring to providers who refer transplant patients MPI for the assessment of possible transplant CAV. In the current practice, many patients are referred to invasive coronary angiography directly. For example, in the study institution, since 2006, approximately 350 adult patients have undergone heart transplantation. PET stress imaging, dobutamine stress echocardiography, and coronary angiography are used to screen for coronary angiography based on patient comorbid conditions and physician preference. Of these 350 heart transplant patients, only 150 of these patients (40%) have undergone a total of 319 PET studies during the study period. This variation in practice patterns is due to many factors including patients' preferences, practitioners' preferences as well as renal function status.

In addition, there is also ambiguity among clinical practice guidelines on the best way to assess for CAV. In addition to the technique mentioned above. There is growing evidence is for coronary computed tomography to detect CAV.[9] In a study of 138 patients, the patient level sensitivity, specificity, and positive and negative predictive values of 98%, 78%, 77%, and 98%, respectively, for diagnosis of CAV with any degree of stenosis. None of the 61 patients with normal cardiac CT angiographic results had CAV on the basis of invasive angiography images.[10] A meta-analysis of 13 studies evaluating 615 patients showed patient-based analyses comparing CCTA versus angiography for the detection of any CAV (> luminal irregularities) and significant CAV (stenosis $\geq$ 50%), showed mean weighted sensitivities of 97% and 94%, specificities of 81% and 92%, a

negative predictive value of 97% and 99%, a positive predictive value of 78% and 67%, and diagnostic accuracies of 88% and 94%, respectively.[11] However, CT angiography is limited by the need to control the heart rate. It cannot be safely performed in patients with renal insufficiency, a common co-morbidity in heart transplant patients.[9]

PET also allows for comprehensive assessment of patients with suspect CAV. In addition to accurate stenosis assessment, coronary flow reserve assessment is helpful in these patients. In a study of 40 transplant recipients undergoing invasive adenosine hemodynamics and dipyridamole rubidium PET, CAV was detected in 32 patients (80%) by intravascular ultrasound. PET derived coronary flow reserve correlated significantly with invasive coronary flow reserve assessment and fractional flow reserve. Patients with CAV or microvascular dysfunction had reduced coronary flow reserve and stress myocardial blood flow.[12,13] The sensitivity, specificity, positive, and negative predictive value of semiquantitative PET perfusion alone for detecting moderate-to-severe CAV were 83% [52-98], 82% [69-91], 50% [27-73], and 96% [85-99], respectively.[14] Coronary flow reserve also adds prognostic value in this patient population. In 94 heart transplant recipients undergoing vasodilator PET, the annualized event rate was 5%, 9%, and 25% in patients with normal, mildly, and moderate-to-severely abnormal PET CAV grading ($P < 0.001$), respectively.[14]

With the current study, the data are now available to confirm the safety of PET MPI and allow the clinicians to utilize this important tool in the care of these patients. As many of these patients require frequent screening for CAV, regadenoson PET appear to be the ideal test with the maximum safety profile and optimal risk stratification.

Disclosure

The author has no conflict of interest to disclose.

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