Regadenoson-induced hyperemia for absolute myocardial blood flow quantitation by ^{13}N-ammonia PET and detection of cardiac allograft vasculopathy

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In this issue of the *Journal of Nuclear Cardiology*®, Miguel H. Pampolini and associates report on non-invasive quantitation of myocardial blood flow (MBF) by regadenoson positron emission tomography (PET) imaging for assessing cardiac allograft vasculopathy (CAV) in orthotopic heart transplantation (OHT) patients.[1] Non-invasive detection of post-transplant vasculopathy continues to be challenging, and PET quantitation of MBF may be uniquely positioned to address this challenge.

World-wide, there remains a large discrepancy between the need for OHT in patients with end-stage heart disease and available donors.[2] In the United States, the yearly number of OHT has been stable over the past 2 decades at ~2500 cases per year.[2] This paucity of available organs has led to the rise of ventricular assist devices implanted as destination therapy[3] and to a very rigorous transplant recipient selection process.[4] Following OHT, transplant recipients are exposed to a stringent surveillance program periodically screening for graft rejection, graft failure, infection, malignancy, and other complications.[2] CAV, or transplant vasculopathy, accounts for ~10% of deaths in OHT recipients starting at 1–3 years post-transplant.[2]

The pathophysiology of CAV involves activation of both the innate and adaptive immune responses in an attempt to reject the transplanted heart, leading to coronary inflammation, endothelial dysfunction, and migration and proliferation of vascular smooth muscle cells.[5] Contrary to atherosclerotic disease, CAV is characterized by the presence of an intact elastic lamina and a diffuse disease affecting the entire coronary tree with intimal hyperplasia composed of vascular smooth muscle cells.[6] Risk factors for the development of CAV include traditional risk factors associated with atherosclerosis, and additional transplant-associated risk factors such as donor-specific antibodies and cytomegalovirus infection.[7] The end-result of this disease process is the diffuse, concentric, and fibrotic intimal thickening of the coronary arteries, leading to extensive coronary artery disease (CAD) and myocardial ischemia.[5]

Given the transplanted heart is denervated—although not permanently—anginal symptoms are unreliable[8] and screening methods have to be utilized for coronary artery assessment. The diffuse nature of CAV often renders angiography insensitive and an

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alternative approach of intravascular ultrasound (IVUS) has been proposed[9] and is largely considered the reference standard. Serial invasive studies however are impractical, cumbersome to the patient, and not devoid of complication risk. In this setting, non-invasive imaging approaches to screen for silent CAV have garnered increased research and clinical attention.[10] Although echocardiography and single-photon emission-computed tomography (SPECT) have been the most studied, neither has established itself as an accepted alternative to IVUS in clinical practice.[10] PET, with its suitability for absolute MBF quantitation, has emerged as a viable imaging modality to fill this void.

Absolute MBF represents an integrated measure of epicardial CAD and microvascular disease.[11,12] Importantly, PET MBF can be assessed in an endothelial-dependent (cold-pressor test) and endothelial-independent (adenosine agonist family of vasodilators) manner in OHT patients.[13,14] Previous studies demonstrated that resting MBF is higher post-OHT than in matched controls, likely due to increased resting heart rate and rate-pressure product in the denervated heart.[13,14] Absolute MBF assessed by ^{13}N-ammonia PET is homogenous across diseased coronary territories, consistent with the diffuse nature of CAV, and abnormal coronary flow reserve (CFR) compared to control patients correlates with IVUS measures of CAV severity.[13–15]

In the present study, the authors assessed the suitability of regadenoson to induce hyperemia, stress MBF measurements, and CFR determination by ^{13}N-ammonia PET for the detection of CAV.[1] Twelve patients with no history of myocardial ischemia were enrolled ~5 years after OHT, and fifteen non-OHT patients with an intermediate pretest likelihood of CAD served as controls. As previously reported, the authors observed an elevated heart rate (78 bpm *vs* 66 bpm) and rate-pressure product (10,824 *vs* 7424) at rest in OHT compared to control patients. This was the main driving factor in the observed lower CFR (global mean CFR 2.05 *vs* 2.63) in OHT patients compared to controls, as hyperemic MBF was similar in both groups.

We now address the following three points: (1) safety of regadenoson in OHT patients, (2) efficacy of regadenoson to generate maximal hyperemia, and (3) adequate selection of PET radiopharmaceuticals for absolute MBF quantitation.

Regadenoson is a selective adenosine 2A (A2A) receptor agonist, with associated improved patient tolerability and reduced side effect profile compared to the more traditional vasodilators adenosine and dipyridamole.[16–18] Following manufacturer instructions, a 0.4 mg dose of regadenoson in 5 mL solution was administered over 15–20 seconds into a peripheral vein, followed by a saline flush. Approximately 30 seconds thereafter, ^{13}N-ammonia was injected and dynamic PET images obtained synchronously and continued for 15 minutes. The authors did not report any adverse events with regadenoson in OHT patients. Previous work with regadenoson stress in OHT patients also demonstrated its safety in this population.[19] These are important observations, given the well-known hypersensitivity of the denervated sinus and atrioventricular nodes to adenosine in OHT patients[20] with the ensuing risk of sinus pause or arrest and high-degree atrioventricular block. In a larger study of 102 OHT patients compared to age- and gender-matched non-OHT controls, adenosine infusion was associated with a significantly higher incidence of sinus pause, and 2nd and 3rd degree atrioventricular block.[21] However, these effects of adenosine were transient and not associated with significant adverse events in OHT patients.[21]

In the present study, the authors compared the degree of hyperemia achieved with regadenoson in OHT patients with hyperemia in an intermediate CAD risk population. The relative extent of the hyperemia itself, and adequacy of the regadenoson protocol, was not studied. Recently, the duration of regadenoson injection and timing of PET tracer injection to achieve optimal results have been evaluated in several studies. A previous study compared absolute MBF and CFR in low CAD risk patients stressed with either regadenoson or dipyridamole, and found similar results.[22] Relative perfusion results were also found to be similar when stressing the same patients sequentially with regadenoson and dipyridamole, albeit with the caveat that absolute MBF quantitation was not assessed in that study.[23] Recent work by Nils P. Johnson and K. Lance Gould in non-OHT patients demonstrated that compared to dipyridamole, regadenoson administered to the same patients achieved only 80% of maximal hyperemia when following the manufacturer's recommendation,[24] similar to the protocol in the present study. This is of concern to the interpreting physician, given a suboptimal hyperemic stimulus underestimates the true physiologic severity of disease and also alters tracer kinetics of absolute MBF quantitation. Using multiple regadenoson timing protocols compared to PET radiotracer injection, they concluded that the optimal delay between regadenoson and radiotracer injection was 65–70 seconds, resulting in a significant increase in hyperemia with regadenoson to 90% of the one achieved with dipyridamole.[24] Recent work by Timothy M. Bateman *et al.* suggested an even longer delay from 60 up to 120 seconds to induce maximal hyperemia with regadenoson stress prior to radiotracer injection, leading to optimization of absolute MBF quantitation by PET.[25] Additional work further addressed concerns for dynamic PET imaging studies not only of the timing of

regadenoson injection, but also its duration,[26,27] determining that increasing the regadenoson injection duration to 30 seconds in a canine preclinical study produced a more stable peak hyperemic response, comparable to the one achieved by a standard adenosine infusion. In the present study, despite likely achieving submaximal hyperemia with a standard protocol of regadenoson administration, the authors were able to demonstrate significant differences in CFR with an intermediate-risk CAD group, which would have likely been further accentuated had they included a low-risk CAD group.

In addition to the choice of vasodilatory agent and induction of maximal hyperemia, the selection of the PET radiopharmaceutical is also critical. To optimize absolute MBF assessment by PET, an ideal radiopharmaceutical should exhibit a high first-pass cardiac extraction fraction with absence of 'roll-off'—or plateauing—at high flows.[12,28] This is the case of ^{13}N-ammonia chosen by the investigators (~80%),[12] and also of the novel PET radiopharmaceutical ^{18}F-flurpiridaz (~94%), which should be studied for suitability in CAV assessment in future studies using relative perfusion and absolute MBF quantitation.[29]

Whereas the present study is limited by a small number of patients, it is a welcome addition in our understanding of the optimal CAV screening strategies in OHT recipients, and adds to the body of literature on the safety of the selective A2A agonist regadenoson in these patients. The optimal timing and duration of regadenoson to achieve maximal hyperemia need to be further studied in both CAD and CAV patients to maximize the yield of PET relative perfusion determination and absolute myocardial blood flow quantitation.

Disclosure

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