Pharmacologic stress myocardial perfusion imaging in patients with pulmonary hypertension: What do we know, and what remains to be learned?

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PULMONARY HYPERTENSION

Pulmonary hypertension (PH) results from a large group of disorders, the common pathophysiology of which is to cause an elevation of mean pulmonary artery pressure above 25 mm Hg. The World Health Organization¹ currently has divided PH into five groups according to etiology: Group 1 includes patients with pulmonary arterial hypertension (formerly known as primary PH), as well as PH associated with collagen vascular disease, AIDS, portal hypertension, congenital heart disease. Group 2 comprises patients with PH resulting from left-sided heart disease. Group 3 patients have PH in association with severe parenchymal lung disease with or without hypoxemia. Group 4 patients include those with thromboembolic pulmonary vascular disease. Group 5 patients have multifactorial PH and include those with anemia, myeloproliferative disease, metabolic or glycogen storage disease.

Because of the large number and causes of PH, prognosis varies with severity of PH and etiology.^{2,3} However, ultimately, the disease results in symptoms of dyspnea on exertion and chest discomfort, which correlate with right ventricular enlargement and

hypertrophy and right-sided congestive heart failure.⁴ Cardiac decompensation and/or sudden cardiac death contributes to mortality in up to 50% of cases.⁴

Comparison of registry data of Group 1 patients with PH compiled at the NIH in 1991, vs 2006–2007 reveals an increase in mean age (36–45), although females still predominate. The increased age results in a significant percentage of patients having co-existing CAD.⁵ In a separate series from McGill that documented coronary disease prevalence,⁶ 162 patients with PH were evaluated with right and left heart catheterization. There were 28% who had significant CAD, which correlated with an older age group (mean age 66) and presence of hypertension and hyperlipidemia. Opitz et al⁷ reviewed data from 786 patients from the COMPERA European Registry of PH. They evaluated three groups of patients: those with idiopathic PH (≤ 2 standard coronary risk factors), those with “atypical PAH” (three or more coronary risk factors) and those with PH and left-sided heart failure with preserved ejection fraction. The atypical PH patients were older, and responded less well to targeted PH therapies. An accompanying editorial suggested that the atypical PH patients may represent a substantially different subgroup than idiopathic PH, possibly due to CAD.⁸

MYOCARDIAL PERFUSION IMAGING IN PULMONARY HYPERTENSION

The increasing age of PH patients, prevalence of chest pain and dyspnea as common symptomatology, the incidence of CAD of $\geq 25\%$ of patients, and the recognition that PH patients with coronary risk factors may represent a group with substantially different

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clinical response patterns, all suggest that myocardial perfusion imaging (MPI) for identification of CAD in PH may be potentially valuable.

Previous efforts to evaluate PH patients with MPI have been directed towards describing right ventricular morphology and identifying right ventricular ischemia. In 1976, Cohen et al⁹ compared resting planar thallium imaging in normal subjects, patients with CAD, and those with PH due to pulmonary parenchymal disease or left-sided heart disease. RV tracer visualization was present in all PH patients, but was rare in normals or those with CAD. Ohsuzu et al¹⁰ performed resting planar thallium imaging on PH patients with congenital heart disease. They described increased right ventricular uptake and straightening or bowing of the septum in pure RV pressure and volume overload, respectively. In 1991, DePuey et al¹¹ demonstrated RV ischemia in patients with CAD by masking the left ventricle (LV) on Tc-99m sestamibi SPECT imaging.

Gomez et al¹² studied 23 patients with pulmonary arterial hypertension, with an average PA systolic pressure of 99 mm Hg. Nineteen had stress dipyridamole MPI and four had exercise studies. Nine patients had reversible RV perfusion defects indicative of RV ischemia, which correlated with the presence of angina, and elevated right atrial and right ventricular diastolic pressure. Coronary angiography showed normal vessels in all patients. Ischemia was attributed to demand-supply imbalance and subendocardial hypoperfusion.¹² Movahed et al retrospectively reviewed eight patients with “straightening” of the inter-ventricular septum on stress SPECT MPI.¹³ Patients had congenital heart disease or COPD, and pulmonary pressures were less than those in the study by Gomez, ranging from 45 to 52 mm Hg measured by echo-Doppler. In addition to changes in septal conformation, patients had prominent RV visualization and RV enlargement. This triad was recognized as the hallmark of PH in an editorial by Wackers.¹⁴

Although most MPI procedures in PH patients are performed to exclude conventional myocardial ischemia,¹⁵ studies of LV perfusion in PH patients are rare. El-Shafie et al evaluated exercise SPECT MPI on 20 patients with systemic lupus and 20 with scleroderma.¹⁶ Ten in each group had PH, with PA systolic pressures in the 40-50 mm Hg range. Subjects without PH had no perfusion defects. Six patients with PH, three each with lupus and scleroderma, had LV segmental perfusion defects. At coronary angiography, one patient with scleroderma had a borderline ostial lesion of the left anterior descending. All other patients had normal angiograms. The authors concluded that normal LV perfusion had a high negative predictive value. LV perfusion defects were not specific for CAD, and might

be caused by anatomic compression by dilated pulmonary arteries.

PHARMACOLOGIC STRESS TESTING USING SELECTIVE A2A RECEPTOR AGONISTS

The paucity of data on MPI in PH may be related, in part, to the challenges posed by performing stress testing in this group of patients. Early studies of the treatment of PH with pure vasodilators, such as hydralazine, showed inconsistent results, with some patients increasing cardiac output and reducing pulmonary pressures, while others developed peripheral vasodilation and marked hypotension.¹⁷ Other studies have shown a high incidence of sudden unexplained cardiac death in PH,^{4,18} difficulty of resuscitation, and their clinical fragility. These factors have contributed to a reluctance to perform exercise testing or administer vasodilators in this population. PH had, at one point, been considered a contraindication to stress testing.¹⁹

In patients with moderate degrees of PH, as in the study by El-Shafie et al,¹⁶ patients may be able to exercise to an adequate hemodynamic end point. However, as PH becomes more pronounced, as in the group represented by Gomez et al,¹² this becomes less likely, and pharmacologic stress testing is necessary. Other than the 13 patients of Gomez et al who underwent dipyridamole stress,¹² and 5 patients of Movahed who underwent adenosine stress,¹³ there is little experience reported in the literature on the safety of pharmacologic stress testing in PH.

PHARMACOLOGIC STRESS TESTING WITH SELECTIVE A2A AGONISTS

Coronary vasodilators generally work through stimulation of adenosine A receptors. Four receptors are recognized: A1, A2a, A2b, and A3. Stimulation of A1 causes sinus node slowing, AV nodal block, and bronchoconstriction. A2a agonism causes coronary and peripheral vascular vasodilation. A3 receptor stimulation causes mast cell degranulation and bronchial smooth muscle constriction.²⁰ Stimulation of the adenosine A receptors results in a fourfold increase in coronary blood flow. Regional differences in coronary blood flow are enhanced, and can be identified by radiotracer injection and perfusion imaging. Both dipyridamole, which inhibits metabolism of adenosine, and adenosine itself are non-selective adenosine A receptor agonists, and may cause bronchospasm. This may be problematic in testing Group 3 PH patients who have pulmonary disease and hypoxemia. Regadenoson is the first selective A2a receptor agonist approved for

vasodilator stress MPI. Accuracy in detecting coronary disease is equivalent to that of the other agents, but has a more favorable side-effect profile.²¹ A number of studies have documented the safety of the agonists in patients with moderate obstructive airways disease who have no clinically evident bronchospasm.²² Stimulation of the A2a receptor may cause pulmonary vasodilation, and regression of PH in an experimental model.²³

SAFETY OF REGADENOSON IN PH PATIENTS UNDERGOING STRESS MPI

In the current issue of the Journal, Moles et al posit that with increasing age and prevalence of coronary risk factors, PH patients are now at appreciable risk for CAD, and require safe, non-invasive testing.²⁴ Thus, they retrospectively reviewed the University of Michigan experience from 2008 to 2016 using regadenoson to perform stress SPECT MPI in 67 patients with PH. Group 2 PH subjects with left heart disease were excluded. There were seven subjects with Group 3 PH with severe lung disease. Mean age was 63, average PA pressure was 44 ± 12 mm Hg. There were 57 patients who had regadenoson alone, and ten had combined regadenoson low-level exercise. Most patients were female (67%), and obese (average BMI was 30), and had multiple coronary risk factors. Echocardiography generally showed right ventricular and atrial enlargement, with an average RV systolic pressure of 64 by Doppler. Symptoms and hemodynamic response to regadenoson were similar to those recorded in patients with CAD, with an increase in heart rate and systolic blood pressure, and mild decrease in diastolic blood pressure.^{21,22} There were seven patients who had a ≥ 10 mm Hg decrease in blood pressure or decrease in systolic blood pressure below 100 mm Hg. There were no hemodynamic or other predictors of this response, and no patient had symptomatic hypotension requiring fluid resuscitation. No serious arrhythmias were noted, and an ischemic ECG response was noted in only 4.4%. All patients received aminophylline, as was the routine protocol in their laboratory, but no patient required nitroglycerin, beta blockers, or Emergency Room Care to recover. There were no deaths, cardiac arrests, or hospital admissions related to the test. Perfusion imaging results were normal in 73% of patients, with normal average rest and stress LV ejection fractions.

The study of Moles et al has significant limitations: it is retrospective, and from a single center. However, its strength lies in the fact that it represents the largest series of patients with PH undergoing pharmacologic stress testing to date. Although PA pressures in their cohort were lower than those of Gomez et al,¹² the

population is similar to that in the REVEAL Registry, and representative of the current population undergoing treatment and evaluation of PH. Their principle finding was that regadenoson was generally safe, with hemodynamics and side effects analogous to those found in a general population with suspected coronary disease.^{21,22}

Higher risk patients were included in the study: seven patients had Group 3 PH, due to lung disease (which was not further characterized). Most patients with PH from pulmonary processes have severe ventilatory dysfunction, a group in whom regadenoson use is usually proscribed. Regadenoson has been shown to be safe only in stable patients with mild-to-moderate obstructive lung disease.²⁵ A preliminary report has suggested that regadenoson combined with low-level exercise may be feasible in patients with severe COPD.²⁶ These two studies suggest that even PH patients with severe lung disease might be considered as candidates for pharmacologic stress testing. However, the number of total PH patients tested still remains small, and caution should still be employed when determining suitability for stress testing.

NEXT STEPS

The central question that must still be addressed is: even if pharmacologic MPI stress testing in PH is safe, is the procedure accurate enough in this group to add value in the diagnosis of CAD? In Moles et al, 73% of images were interpreted as normal and 27% abnormal. However, patients did not undergo angiography, so sensitivity, specificity, and predictive values were not available. In the study of El-Shafie et al,¹⁶ only one of six patients with LV segmental perfusion defects had CAD at angiography, for a positive predictive value of only 16%. This suggests that there remains much to be learned about the interpretation of MPI in PH patients.

Typical MPI findings in a PH patient are depicted in a 30-year-old patient presented by Ohira et al,¹⁵ (shown in Figure 1), and illustrate the difficulties in interpretation. In that figure, the MPI scintigrams show increased RV uptake, and bowing of the septum into the LV. The septum and apex appear to be hypoperfused, with some reversibility at the apex. The LV is crescent shaped. These findings were all attributed to PH, as described by Movahed et al¹³ rather than coronary disease, because of the patient's age. However, a stress/rest polar coordinate map in this patient, compared to a normal database, would most likely show severe, partially reversible perfusion defects of the septum and apex, with a high-summed stress score. Clearly, more work needs to be done, either through Registry data, or prospective studies, to compile a profile of normal and abnormal perfusion limits in PH

Figure 1. A patient who underwent stress perfusion SPECT scan prior to the diagnosis of PH. A 32-year-old male with dyspnea, dizziness, and palpitations on exertion. The patient was referred for pharmacological ^{99m}Tc -tetrofosmin with SPECT to rule out ischemia. Increased RV tracer uptake (white arrows), flattening of the interventricular septum (IVS), (red arrows) and dilated RV (pink arrows) indicate the presence of RV pressure overload and right ventricular hypertrophy (RVH). Subsequent transthoracic echocardiography (TTE) revealed the presence of significantly elevated RV systolic pressure (RVSP 88 mm Hg). A small reversible change in the apical segment of interventricular septum (IVS) is likely due to pressure overload in the RV. (Reprinted with permission from American Society of Nuclear Cardiology; originally published as Figure 3 in [15]).

patients that will help prove the diagnostic value of MPI in this population.

CONCLUSIONS

PH is caused by a diverse group of disorders, the demographics of which have changed over the last two decades. Now a disease often of middle age and older patients, coronary risk factors have increased in prevalence, and the possibility of complicating CAD has become significant. Previous non-invasive nuclear imaging has focused on characterizing the appearance of right ventricular hypertension, so there is only scant data on the safety and efficacy of MPI. The study by Moles et al provides data suggesting that using A2a receptor agonists for pharmacologic stress testing in PH may have a safety profile comparable to the general CAD population. Further data are necessary to determine the accuracy of MPI in PH, and whether this will prove a valuable method of diagnosis.

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