Myocardial perfusion imaging with regadenoson stress in advanced lung disease

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Many patients suffering from a chronic lung disease may also have coronary artery disease (CAD) due to shared comorbidities between lung disease and atherosclerosis.[1] In particular, these diseases share common risk factors, most notably smoking. Lung transplantation is a treatment option for advanced lung disease.[2] Lung transplantation is a complex therapy with a significant risk of perioperative morbidity and mortality.[2–4] Therefore, it is important to consider comorbidities influencing surgical risk, including CAD.[2–4] Cardiovascular disease accounts for 12% of deaths in the first 30 days after lung transplantation and about 7% of deaths in the long-term.[5] Almost half of the patients considered for lung transplantation have some degree of CAD.[6,7] CAD associated with significant myocardial ischemia remains a relative contraindication for lung transplantation in the recent consensus statement for patient selection.[2]

The role of myocardial perfusion imaging (MPI) in preoperative risk assessment in patients undergoing major non-cardiac surgery has been evaluated in several studies.[3,4] The studies show that moderate to large reversible perfusion defects, which reflect myocardial ischemia, carry an increased risk of perioperative cardiac death or myocardial infarction. An abnormal MPI study is associated with a high sensitivity for detecting patients at risk for perioperative cardiac events. Several meta-analyses have shown the clinical utility of pharmacological stress testing in the preoperative evaluation of patients undergoing non-cardiac surgery.

Performing a stress test in patients with an underlying lung disease requiring evaluation of CAD may be challenging.[8] Not only are such patients often unable to reach sufficient increases in heart rate and blood pressure via exercise protocols, but also the use of pharmacologically induced stress is a concern to physicians due to the risks associated with the available stress agents. The two most commonly used vasodilatory agents, adenosine and dipyridamole, may cause bronchoconstriction mediated by adenosine receptors A_{2B} and/or A_3, which is a particular concern to physicians testing patients with asthma or chronic obstructive pulmonary disease (COPD).[8,9] In addition to non-invasive testing, this relates to invasive functional evaluation of coronary stenosis by measurement of fractional flow reserve (FFR) that is performed during adenosine stress.

Regadenoson is a selective agonist of the A_{2A} adenosine receptor which mediates the vasodilative effect of adenosine.[8] While many of the milder side effects of regadenoson are similar to the nonselective agonists, the incidence of bronchospasm is low. Indeed, the past decade has brought forth a growing amount of evidence supporting the safety of regadenoson for patients with chronic lung diseases. In the present issue of the Journal, Schiopu et al. bring their contribution to this matter by assessing the safety and accuracy of single photon emission computerized tomography (SPECT) MPI with regadenoson in patients with end-stage lung disease being considered for lung transplantation.[10]

The safety of regadenoson in patients with lung disease has been evaluated in randomized, double-blind, placebo-controlled trials.[11–13] The RegCOPD trial studied patients with COPD and showed that there were no differences in the lung function parameters, including

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forced expiratory volume at 1 second (FEV1) after administration of regadenoson as compared to the placebo group.[11] The study of Leaker et al. focused on asthmatic patients with a known hypersensitivity towards inhaled AMP and found no changes in the lung function parameters after administration of regadenoson.[12] Furthermore, there was no difference in the incidence of bronchoconstrictive reactions between the regadenoson and placebo groups in these trials. The study by Prenner et al. studied patients with either COPD or asthma who presented likely candidates for MPI due to known CAD or the presence of risk factors for CAD.[13] The severity of lung disease among patients varied over a wide range, but a common requirement was a stable stage in the disease prior to the study. Regadenoson was administered to 672 patients out of which 356 had asthma and 316 COPD. The results of this study were in line with the two previous studies. There was no statistically significant difference in the deterioration of lung function (measured as at least 15% decrease in FEV1 up to 24 hours after baseline) between patients receiving regadenoson and the placebo group. Milder side effects such as dyspnea were observed after regadenoson administration. Similar results have been seen in observational studies in patients with lung disease undergoing MPI for evaluation of CAD.[14,15] In these studies including 228 and 116 patients, no clinically apparent bronchospasm or exacerbation of lung disease was observed immediately after regadenoson infusion. In all of the above mentioned studies, the severity of the lung diseases has been limited to mild or moderate in the majority of patients. Therefore, the study of Schiopu et al. in patients with advanced lung disease is timely.

The study of Schiopu et al. in this issue of the Journal [10] evaluated retrospectively the safety of regadenoson in 102 patients referred for lung transplantation due to advanced lung disease. All patients had both SPECT MPI and invasive coronary angiography as part of the pre-transplantation evaluation according to a local protocol. The patients were more than 50-years of age and had either interstitial lung disease (ILD, $n = 51$) or COPD ($n = 51$). Patients with COPD had mean FEV1 $< 30\%$ of predicted, consistent with stage 4 disease severity according to the GOLD criteria.[13] Diffusing capacity of the lung for carbon monoxide (DLCO) was on average $< 30\%$ of predicted in patients with either COPD or ILD. Long-term oxygen therapy was used by 88%, and pulmonary hypertension defined as the mean pulmonary artery pressure of ≥ 35 mmHg was present in 8% of patients.

In the study of Schiopu et al., a total of 14 patients reported symptoms related to regadenoson, but only 2 patients required medical treatment with bronchodilators.[10] Furthermore, clinical exacerbations of the lung disease were not observed after regadenoson administration. Based on this, the authors concluded that regadenoson is well tolerated in end-stage lung disease patients. The prevalence of obstructive CAD defined as $\geq 50\%$ stenosis in the left main coronary artery or $\geq 70\%$ stenosis in any other major coronary artery by invasive coronary angiography was 20%.[6] SPECT MPI was abnormal in 5 (25%) patients with obstructive CAD by angiography. Among patients with normal SPECT but obstructive CAD on invasive coronary angiography, only 1 patient was revascularized. As authors discuss, evaluation of the accuracy of SPECT MPI is limited by small sample size, but it is notable that revascularization decisions largely followed the combined information about coronary anatomy and ischemia provided by invasive coronary angiography and SPECT MPI, respectively. Authors conclude that demonstration of myocardial ischemia by SPECT MPI with regadenoson may be helpful in guiding decisions on revascularization prior to lung transplantation.

The study by Schiopu et al.[10] is associated with some weaknesses related to the relatively small number of patients with obstructive CAD and retrospective design, such as lack of systematic follow-up of lung function after administration of regadenoson and possible exclusion of some patients with an unstable lung disease. However, the study provides valuable information about the safety profile and feasibility of performing SPECT MPI with regadenoson in patients with advanced lung disease that are being considered for lung transplantation. The results provide evidence that regadenoson is well tolerated even in patients with advanced lung disease and therefore, may be an option for evaluation of myocardial ischemia in such patients.

Disclosures

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References

1. Decramer M, Janssens W. Chronic obstructive pulmonary disease and comorbidities. Lancet Respir Med 2013;1:73-83.
2. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant cadidates: 2014: An update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Hear Lung Transplant 2015;34:1-15.
3. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: Cardiovascular assessment and management: The Joint Task Force on

non-cardiac surgery: Cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J 2014;35:2383-431.
4. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Developed in collaboration with the American College of Surgeons, American Society of Anesthesiologists, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Vascular Medicine Endorsed by the Society of Hospital Medicine. J Nucl Cardiol 2015;22:162-215.
5. Yusen RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Levvey BJ, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third adult lung and heart-lung transplant report-2016; focus theme: Primary diagnostic indications for transplant. J Heart Lung Transplant 2016;35:1170-84.
6. Nathan SD, Basavaraj A, Reichner C, Shlobin OA, Ahmad S, Kiernan J, et al. Prevalence and impact of coronary artery disease in idiopathic pulmonary fibrosis. Respir Med 2010;104:1035-41.
7. Khandhar SJ, Althouse AD, Mulukutla S, Kormos R, Toma C, Marroquin O, et al. Postoperative outcomes and management strategies for coronary artery disease in patients in need of a lung transplantation. Clin Transplant 2017;31:e13026.
8. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ. ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. J Nucl Cardiol 2016;23:606-39.
9. Cerqueira MD, Verani MS, Schwaiger M, Heo J, Iskandrian AS. Safety profile of adenosine stress perfusion imaging: Results from the adenoscan multicenter trial registry. J Am Coll Cardiol 1994;23:384-9.
10. Schiopu SRI, Zacherl M, Todica A, Bartenstein P, Milger K, Leuschner G, et al. Feasibility and accuracy of SPECT myocardial perfusion imagin in end-stage lung disease. J Nucl Cardiol 2019. https://doi.org/10.1007/s12350-019-01851-4.
11. Thomas GS, Tammelin BR, Schiffman GL, Marquez R, Rice DL, Milikien D, et al. Safety of regadenoson, a selective adenosine A2A agonist, in patients with chronic obstructive pulmonary disease: A randomized, double-blind, placebo-controlled trial (RegCOPD trial). J Nucl Cardiol 2008;15:319-28.
12. Leaker BR, O'Connor B, Hansel TT, Barnes PJ, Meng L, Mathur VS, et al. Safety of regadenoson, an adenosine A2A receptor agonist for myocardial perfusion imaging, in mild asthma and moderate asthma patients: A randomized, double-blind, placebo-controlled trial. J Nucl Cardiol 2008;15:329-36.
13. Prenner BM, Bukofzer S, Behm S, Feaheny K, McNutt BE. A randomized, double-blind, placebo-controlled study assessing the safety and tolerability of regadenoson in subjects with asthma or chronic obstructive pulmonary disease. J Nucl Cardiol 2012;19:681-92.
14. Husain Z, Palani G, Cabrera R, Karthikeyan AS, Dhanalakota S, Pathmanathan S, et al. Hemodynamic response, arrhythmic risk, and overall safety of Regadenoson as a pharmacologic stress agent for myocardial perfusion imaging in chronic obstructive pulmonary disease and bronchial asthma patients. Int J Cardiovasc Imaging 2012;28:1841-9.
15. Garcia CS, Heffernan AJ, Sanchez De Mora E, Ramos Font C, Lopez Martin J, Rivera de los Santos F, et al. Comparative study of the safety of regadenoson between patients with mild/moderate chronic obstructive pulmonary disease and asthma. Eur J Nucl Med Mol Imaging 2014;41:119-25.