should examine how the temporal behavior of the different markers over time, as a consequence of different therapeutic interventions, for instance, may influence or confirm a prognosis. It is likely that changes in these markers will prove useful for patient management and treatment decisions, such as choosing the appropriate time for combination therapy or referring a patient for transplantation. The French PAH network currently is conducting a prospective study that aims to evaluate the prognostic value of the changes in different prognostic markers, including invasive hemodynamic measurements, in the follow-up of patients with PAH.

Finally, it is important to highlight that Kane and colleagues[7] confirm that survival in PAH is still poor in the modern management era, despite valuable therapeutic advances. One-, 3-, and 5-year survival rates of 81%, 61%, and 48%, respectively, are similar to recently published rates,[6] illustrating that we are far from a cure for PAH and that there is still a lot to be done in the field.

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References

1. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med*. 2004;351(14):1425-1436.
2. Souza R, Jardim C. Trends in pulmonary arterial hypertension. *Eur Respir Rev*. 2009;18(111):7-12.
3. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med*. 1991;115(5):343-349.
4. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation*. 2010;122(2):156-163.
5. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation*. 2010;122(2):164-172.
6. Humbert M, Sitbon O, Yaïci A, et al; French Pulmonary Arterial Hypertension Network. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J*. 2010;36(3):549-555.
7. Kane GC, Maradit-Kremers H, Slusser JP, Scott CG, Frantz RP, McGoon M. Integration of clinical and hemodynamic parameters in the prediction of long-term survival in patients with pulmonary arterial hypertension. *Chest*. 2011;139(6):1285-1293.
8. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med*. 2004;23(13):2109-2123.
9. Galiè N, Hoeper MM, Humbert M, et al; Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC); European Respiratory Society (ERS); International Society of Heart and Lung Transplantation (ISHLT). Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2009;34(6):1219-1263.
10. Barst RJ, Gibbs JS, Ghofrani HA, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009;54(1 suppl):S78-S84.

Retro Is the Rage!

Ventilation-Perfusion Scanning Is Alive and Well in the Diagnosis of Pulmonary Embolism

In the past 2 decades, we have seen a changing pattern in the use of CT pulmonary angiography (CTPA) vs lung perfusion scintigraphy (ventilation-perfusion ratio [$\dot{V}/\dot{Q}$] scanning) in the investigation of pulmonary embolism (PE). $\dot{V}/\dot{Q}$ scanning was the imaging modality of choice, but it has largely been supplanted by CTPA in recent years.[1] CTPA has been shown to be accurate and safe when used as part of a diagnostic algorithm for suspected PE.[2-5] Further, CTPA can lead to additional diagnoses for patients who do not have PE, can provide prognostic information by focusing on the right ventricle, and is available 24 h a day at most institutions. Thus, CTPA currently is recommended as the primary imaging modality for suspected acute PE.[6]

A recently recognized limitation to CT imaging of the chest should bring a note of caution to this approach. The technique used in CTPA to obtain fine-cut images of the arterial tree exposes patients to a significant amount of radiation. The effective radiation dose after CTPA is between 3 and 5 mSv, which is equivalent to 1 to 2 years of background radiation exposure.[7] The lifetime attributable risk

of lung cancer from this exposure can be anywhere from 38 to 118 cases per 100,000 patients, depending on age and sex. The risk of breast cancer also is not negligible, especially in young women, where it can be as high as 503/100,000 excess cases.[7] Although new technology may lead to lower radiation exposure, the American College of Radiology emphasizes that both the primary clinician and the radiologist should be fully educated on the radiation risk of the imaging studies being ordered and interpreted. Part of this process should involve providing diagnostically equivalent options with less radiation exposure.[8]

$\dot{V}/\dot{Q}$ scanning, therefore, may still play an important role in the evaluation of suspected PE. Diagnostic algorithms using both imaging modalities have been demonstrated to safely rule out PE.[9] An important factor in clinician preference for CTPA, however, is the potential for indeterminate test results with $\dot{V}/\dot{Q}$ scans. A normal perfusion study has a negative predictive value close to 100% and effectively rules out PE, whereas a high-probability $\dot{V}/\dot{Q}$ scan has a positive predictive value $>90\%$ and confirms PE in patients with moderate or high probability of disease.[10] Unfortunately, many patients (up to 50% in some studies) do not fall into either of these categories and require further testing.[9] The diagnostic performance of $\dot{V}/\dot{Q}$ scintigraphy can be improved, however, by selecting patients without cardiopulmonary disease and normal chest radiograph.[11]

In this issue of *CHEST* (see page 1294), Salaun and colleagues[12] show us that even in unselected patients, $\dot{V}/\dot{Q}$ scanning remains an important diagnostic tool. The authors designed an algorithm that sequentially used clinical probability assessment, serum D-dimer levels, compression ultrasonography, and $\dot{V}/\dot{Q}$ scanning in all patients. CTPA was performed only if the diagnosis was still uncertain after these steps. A diagnosis was established in 76% of the patients. Even in patients with indeterminate scans, acute PE was excluded in patients with a low pretest probability of PE, and when combined with negative compression ultrasonography, it was excluded in patients with an intermediate pretest probability. Only 11% of the cohort ultimately required CTPA to assist in making a diagnosis. The rate of subsequent VTE in those not treated with anticoagulation was very low at 0.53% (95% CI, 0.09%-2.94%).

Although not all clinicians will want to revert to $\dot{V}/\dot{Q}$ scanning for all patients with suspected PE, there are clinical scenarios where it should be considered as the imaging test of choice. These scenarios include patients with a normal baseline chest radiograph (in which the likelihood of a diagnostic scan is high), young women, patients with a contrast dye allergy or impaired renal function, and patients who are claustrophobic and may not tolerate (or are obese and cannot be accommodated by) the CT scanner. $\dot{V}/\dot{Q}$ scanning also may offer the advantage of a test that can be repeated in follow-up to monitor for resolution. Further, in most settings, it is less costly than CTPA. We need to resist the temptation to get as much information as possible and focus instead on carefully selecting the test that will answer the question at hand. $\dot{V}/\dot{Q}$ scintigraphy, therefore, clearly still has a role in the diagnostic evaluation of acute PE, and I thank Salaun and colleagues for confirming that this approach is safe for our patients.

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References

1. Estrada YMRM, Oldham SA. CTPA as the gold standard for the diagnosis of pulmonary embolism [published online ahead of print August 6, 2010]. *Int J Comput Assist Radiol Surg*. doi:10.1007/s11548-010-0526-4.
2. Galipienzo J, García de Tena J, Flores J, Alvarez C, Alonso-Viteri S, Ruiz A. Safety of withholding anticoagulant therapy in patients with suspected pulmonary embolism with a negative multislice computed tomography pulmonary angiography. *Eur J Intern Med*. 2010;21(4):283-288.
3. Quiroz R, Kucher N, Zou KH, et al. Clinical validity of a negative computed tomography scan in patients with suspected pulmonary embolism: a systematic review. *JAMA*. 2005;293(16):2012-2017.
4. Stein PD, Fowler SE, Goodman LR, et al; PIOPED II Investigators. Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med*. 2006;354(22):2317-2327.
5. van Belle A, Büller HR, Huisman MV, et al; Writing Group for the Christopher Study Investigators. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA*. 2006;295(2):172-179.
6. Agnelli G, Becattini C. Acute pulmonary embolism. *N Engl J Med*. 2010;363(3):266-274.
7. Cronin P, Weg JG, Kazerooni EA. The role of multidetector computed tomography angiography for the diagnosis of pulmonary embolism. *Semin Nucl Med*. 2008;38(6):418-431.
8. Wells PS. Pulmonary embolism: a clinician's perspective. *Semin Nucl Med*. 2008;38(6):404-411.
9. Anderson DR, Kahn SR, Rodger MA, et al. Computed tomographic pulmonary angiography vs ventilation-perfusion

lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. *JAMA*. 2007;298(23):2743-2753.
10. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *JAMA*. 1990;263(20):2753-2759.
11. Calvo-Romero JM, Lima-Rodríguez EM, Bureo-Dacal P, Pérez-Miranda M. Predictors of an intermediate ventilation/perfusion lung scan in patients with suspected acute pulmonary embolism. *Eur J Emerg Med*. 2005;12(3):129-131.
12. Salaun P-Y, Couturaud F, Le Duc-Pennec A, et al. Noninvasive diagnosis of pulmonary embolism. *Chest*. 2011;139(6):1294-1298.

Achieving Adherence to Positive Airway Pressure Therapy

Modifying Pressure and the Holy Grail

Dingo: Where are you going?
Sir Galahad: I seek the Grail! I have seen it, here in this castle!
Dingo: No, oh no! Bad, bad Zoot!
Sir Galahad: What is it?
Dingo: She has been setting a light to our beacon, which, I've just remembered, is Grail shaped. It's not the first time we've had this problem.
Sir Galahad: It's not the real Grail?

Monty Python and the Holy Grail[1]

Adherence to continuous positive airway pressure (CPAP) treatment for obstructive sleep apnea syndrome (OSAS) continues to be a subject of intense interest to practitioners who treat these patients; indeed, the search for techniques that would ensure compliance could be likened to the search for the Holy Grail, a quest spoken of in medieval mythology. Of the many aspects of CPAP treatment that have been implicated as a cause of reduced adherence, patient complaints about the difficulty of exhaling against pressure are sometimes mentioned, although less often than one might suppose: Only 18% of 204 patients in an often-quoted survey by Engleman et al[2] noted it, and it was not even listed as a side effect in several other studies.[3-5] More common are symptoms that are almost certainly closely related to the level of pressure, such as mask leaks, aerophagia, and chest discomfort, and those symptoms that are attributable to the magnitude of airflow necessary to maintain a set pressure, such as nasal congestion, sneezing, and rhinorrhea; oral/nasal desiccation; and blower noise.[2-5] In addition, problems with mask discomfort and fit often are related to the degree of tightening necessary to prevent leaks, and such complaints are legion among CPAP users (roughly one-half of respondents in most reports[2,3,5]), although it is likely that advances in mask design have somewhat mitigated this situation. Finally, a complaint of claustrophobia is frequently heard, and some of these patients may actually be reacting to the difficulty they experience in exhaling against pressure.

There is also a high degree of face validity to the contention that the degree of pressure is a major impediment to CPAP use, since exhaling against pressure is one of the more obvious attributes of this therapeutic approach. Hence, a variety of alternative modalities of pressure delivery have been developed and proposed to enhance compliance in some patients by reducing positive airway pressure under certain conditions: bilevel positive airway pressure (bilevel PAP; pressure is reduced during the entire expiratory phase), auto-titrating CPAP (pressure is varied depending on what is actually required to maintain airway patency), and pressure-relief CPAP. Interestingly, another option that has been proposed involves detecting wakefulness using respiratory pattern analysis and reducing pressure whenever the patient is awake[6]; to my knowledge, no published reports of this technology being incorporated into a CPAP generator have yet appeared. Pressure-relief CPAP involves a brief reduction in pressure at the start of exhalation to ameliorate the sensation of resistance to breathing out, and several vendors offer their own proprietary versions. Whether these techniques represent a useful advance in improving adherence in the treatment of OSAS or are just a marketing tool remains controversial, although studies of bilevel PAP and auto-titrating CPAP for this purpose have not been particularly promising thus far.[7] It may well be that pressure-related complaints do not occur with great enough frequency to show an overall benefit for a study group of patients who are unselected for this attribute. Indeed, complaints of nasal and pharyngeal symptoms and lack of subjective perceived benefit from treatment represented more common reasons for noncompliance in one case-control study.[8]

The literature thus far does not consistently support the overall usefulness of pressure-relief CPAP. One small, nonrandomized study suggested better treatment adherence with CPAP plus pressure-relief CPAP compared with CPAP alone,[9] whereas a second, larger, randomized trial found no difference in long-term compliance.[10] A third study examining auto-titrating CPAP with and without pressure relief in experienced CPAP users found a subjective preference for the pressure relief mode in this group of patients but only a nonsignificant trend in terms of greater subjective comfort with the pressure relief modality.[11] Other outcome measures showed no significant differences (eg, apnea-hypopnea index, sleep efficiency, mean oxyhemoglobin saturation). Additional crossover and parallel studies published since