Article Reviews

Todd M. Bull, MD, FACP

Francisco Soto, MD, MS

Section Editors: **Todd M. Bull, MD, FACP,** and **Francisco Soto, MD, MS**

Summaries and commentaries from the section editors and invited reviewers present a clinical context for practitioners' application of the latest published research relevant to care of patients with pulmonary hypertension.

Condliffe R, Kiely DG, Peacock AJ, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. *Am J Respir Crit Care Med.* 2009; 179(2):151-7.

This interesting and important article examines the outcomes and characteristics of pulmonary arterial hypertension (PAH) associated with connective tissue disease (CTD-PAH) in the modern era treated in the United Kingdom. Historically CTD-PAH is believed to have a poor prognosis, but there are few good studies specifically examining this patient population. Because the management of all adult CTD-PAH cases in the UK is centralized to 1 of 5 pulmonary hypertension centers, the authors were able to examine the clinical data in a large number of incident cases over a 5-year time period (2001-2006). The strengths of this paper include the use of right heart catheterization data to make the diagnosis of PAH (lacking in earlier cohort studies), inclusion of only incident cases, robust clinical data, and follow up on a large number (484) of patients. The data set is predominately composed of patients with systemic sclerosis (315, 74%) but also included patients with PAH due to other connective tissue diseases such as systemic lupus erythematosus (SLE) (35, 8%), mixed connective tissue disease (28, 8%), and others in smaller numbers. The analyses are subdivided into those with concomitant respiratory disease (FVC <60% or fibrosis on CT scan) and there is also a group of patients with exercise-induced PAH examined over the course of the study. Some of the interesting observations include 1- and 3-year survival rates for SSc-PAH of 78% and 47% respectively, and a 3-year survival rate of 75% for patients with SLE-PAH (significantly better then those patients diagnosed with SSc-PAH, *P*=0.01). It is also interesting to note that 19% of the patients with exercise-induced PAH progressed to PAH at rest over the time period of the study, and there was an appreciable mortality even in this group of patients. — TMB

Address for reprints and other correspondence: todd.bull@ucdenver.edu

Tunariu N, Gibbs SJ, Gin-Sing W, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. *J Nucl Med.* 2007; 48(5):680-4.

The association of chronic thromboembolic pulmonary hypertension (PH) has been well described in the literature and carries a significant morbidity and mortality. A large number of studies have examined imaging modalities for the diagnosis of acute pulmonary embolism; however, there are few studies that investigate the detection of chronic thromboembolic pulmonary disease (CTEPD). This article is the first to explore the utility of ventilation perfusion (V/Q) scintigraphy vs multidetector CT angiography for detecting CTEPD in a head-to-head fashion.

The authors of the article retrospectively reviewed the results of 500 patients diagnosed with PH that had both a V/Q scan and CTPA performed at Hammersmith Hospital, London. Of the initial 500 patients screened, 227 fulfilled the inclusion criteria. Interpretation of V/Q scintigraphy was made according to modified PIOPED criteria. Mutidetector CTPA performed was suggestive of CTEPD if there was visualization of the thrombus, calcified thrombus, recanalization, sudden change in vessel caliber, strictures, poststenotic dilatation, webs, or perfusion abnormality. Pulmonary DSA was performed on 61 of the 227 patients.

Ninety percent of patients had the V/Q scan and CTPA performed within 10 days of each other, with 73% of both studies within 48 hours. The investigators separated out the participants into 2 groups: *Group A*, 78 patients with CTEPH; the diagnosis was confirmed in 61 patients with pulmonary digital subtraction angiography (DSA). The remaining 17 patients were either not fit for pulmonary endarterectomy or did not consent. *Group B* patients were those with non-CTEPH, 149 patients whose clinical and imaging picture did not suggest thromboembolic phenomena, so no DSA was performed.

This small, retrospective study is the first to make a head-to-head comparison of V/Q scintigraphy and CTPA in the evaluation of CTEPD. It showed that V/Q scans have a higher sensitivity and lower specificity than CTPA for detection of clot. It is important to note that the allocation of intermediate V/Q scan patients impacted the results of the V/Q scan groups. When intermediate V/Q scans were grouped along with high probability scans the sensitivity increased by 1.2%, decreased specificity by 4.6%, and decreased positive predictive value (PPV) by 6.8% and had a negligible effect on the negative predictive value (NPV). The authors concluded that grouping the intermediate probability patients with low probability V/Q scans (using only high probability scans as positive scans) would maintain a high sensitivity and NPV improve specificity, PPV. One major limitation of this study is that not all patients enrolled had a DSA for confirmation of pulmonary embolism. Group B patients were thought to have non-CTEPH based upon CT or V/Q scan, and no DSA was used to confirm lack of embolism. In addition, the remaining members of group B (17 patients) did not have a definitive study either, due to inability to consent or patients were not considered suitable candidates for thrombectomy. Lack of DSA in these groups affect

the sensitivity and specificity of V/Q scan in detection of CTEPD. A potential future direction would include a larger scale study in which patients all patients enrolled received DSA, V/Q scan, and CTPA.— TMB

Hagger D, Condliffe R, Woodhouse N, et al. Ventricular mass index correlates with pulmonary artery pressure and predicts survival in suspected systemic sclerosis-associated pulmonary arterial hypertension. *Rheumatology (Oxford)*. 2009. Jul 14. [Epub ahead of print]

Pulmonary arterial hypertension (PAH) is a major cause of morbidity and mortality in patients with systemic sclerosis (SSc). There is great clinical interest in developing effective means of screening these patients for evidence of PAH in hopes of initiating therapy earlier and perhaps impacting outcomes. In this interesting study by Hagger et al, MRI is examined as a possible screening tool for PAH in patients with SSc. Earlier studies have shown that the MRI measured ventricular mass index (VMI), defined as the ratio of the right and left ventricular diastolic mass, correlate strongly with the mean pulmonary arterial pressure (mPAP). The authors have now examined the utility of the VMI in the SSc spectrum of disease. Forty patients, 28 of whom were diagnosed with PAH at rest, were included in the study. Ventricular mass index was found to be elevated in SSc patients with PAH as compared to those with normal PA pressures (0.89 ± 0.3 vs 0.55 ± 0.1, $P<0.001$). The VMI correlated strongly with mPAP in these patients (r=0.7). Receiver operating curves were used to identify optimal diagnostic threshold levels for PAH using VMI. The 2-year survival rate for patients with a VMI <0.7 vs ≥0.7 was 91% vs 43%. While intriguing, it is notable that all patients entered in this study were referred for a suspicion of PAH. The findings may be different in an unselected population. It is also notable that the tricuspid gradient as measured by echocardiography also had excellent correlation with mPAP measured at cardiac catheterization. Therefore, echo remains a more appropriate initial tool for screening. Still, there are scenarios where an adequate tricuspid regurgitant jet can not be measured and a previous echo study by Mukerjee et al (*Rheumatology* 2004, 43:461-6) could not identify a lower threshold for a tricuspid gradient that excluded the diagnosis of PAH in patients with SSc. MRI could then be considered as a screening tool in patients where echo was nondiagnostic but suspicion remains high. Further prospective studies should be considered with this rationale.— TMB

Nickel N, Kempf T, Tapken H, et al. Growth differentiation factor-15 in idiopathic pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2008;178(5):534-541.


Michael Risbano, MD

There is a great need for novel and useful biomarkers to both assist with diagnosis and track disease progression in patients with pulmonary arterial hypertension (PAH). The authors of this manuscript demonstrate that growth differentiation factor-15 (GDF-15) may play such a role. GDF-15 is a member of the TGF-ß cytokine superfamily. Several studies have demonstrated that GDF-15 can be induced in cardiac tissue during pathologic periods of stress such as acute coronary syndrome, chronic left-sided heart failure, and pulmonary embolism. Right ventricular overload has been noted to increase in GDF levels, which led the authors to investigate GDF-15 expression in idiopathic pulmonary arterial hypertension (IPAH).

The authors examined the diagnostic and prognostic utility of GDF-15 in the evaluation of patients with IPAH. This involved the evaluation of a retrospective cohort of 76 patients with IPAH from 1999-2004. A second prospective group included 22 consecutive IPAH patients over a 1-year period with follow-up right heart catheterization at baseline and 3-6 months, during which response to medical therapy was evaluated.

Fifty five percent of patients in the first cohort had elevated GDF-15 levels at presentation. Furthermore, elevated GDF-15 levels are associated with a poor prognosis in patients with IPAH. In the first patient cohort those patients who died (39/76) or underwent transplantation (3/76) had a significantly higher median GDF-15 at baseline compared to those who did not have these adverse events.

Interest in using panels of biomarkers for prognostication or diagnosis in a variety of diseases, including PAH, has arisen recently. GDF-15, in combination with NT-proBNP, identified patients at risk for adverse outcomes (death or transplantation). However, it was not demonstrated to be useful in monitoring response to treatment in this study.

The take-home messages of this study were that GDF-15 might be a novel useful biomarker for predicting outcomes in patients with IPAH. The source of GDF-15 in this patient population remains unclear. — Michael Risbano, MD, Pulmonary Hypertension Fellow, University of Colorado, Denver, and TMB ■