



The Wisdom of the PHAROS

In *The Hermetica: The Lost Wisdom of the Pharaohs*, Timothy Freke and Peter Gandy present a translation of the Greco-Egyptian sage Hermes Trismegistus's writings¹. Thought to have been written around 3000 BC, these teachings encompass the mystical philosophy of ancient Egypt and have been ascribed as inspiration for artists, philosophers, and scientists such as Leonardo da Vinci, Carl Jung, and Sir Isaac Newton. While the current study in this issue of *The Journal* may not have the same far-reaching impact, the potential for advancement of our understanding of pulmonary vascular disease related to systemic sclerosis (SSc) is significant.

If the efficient study of rare diseases is quite challenging, the study of the intersection of 2 rare diseases is nearly impossible. SSc, with an estimated incidence of less than 20 persons per million per year in the United States, is significantly less common than other rheumatologic diseases such as systemic lupus erythematosus and rheumatoid arthritis, whose incidence in the US population is estimated at around 50 persons per million and over 300 persons per million, respectively^{2,3}. While the incidence of pulmonary arterial hypertension (PAH) remains unknown in the US, results from the national registry in France suggest an incidence of 2.4 cases per million; this estimate includes persons with various forms of PAH including those related to connective tissue diseases⁴. In cohort studies of patients with SSc, the prevalence of PAH ranges from 8% to 14% when the diagnosis is based upon right heart catheterization (RHC)⁵. Despite its relatively low prevalence, PAH remains the second most common cause of death in SSc⁶. However, our understanding of this complication of SSc, and importantly, identification of those persons likely to develop this complication, remain limited at best.

Despite recent advances in the medical therapy for PAH, survival in PAH related to SSc (SSc-PAH) remains poor, with a median survival of around 4 years⁷. However, similar to other forms of PAH, survival appears to be significantly better for patients with less severe symptoms as assessed by World Health Organization (WHO) functional classification

(FC); patients in FC I or II have a 3-year survival ranging from 70% to 85% versus 20%–45% for FC III or IV^{7,8}. Data from the EARLY study of bosentan (to date, the only randomized, placebo-controlled study of patients with PAH FC II) demonstrate significant reduction in pulmonary vascular resistance and a significant delay in clinical deterioration at 6 months of therapy, supporting a role for early treatment and thus, early diagnosis⁹. Unfortunately, as noted by Hachulla and colleagues, less than 20% of SSc-PAH patients present with FC II disease¹⁰. Therefore, systematic identification of high-risk individuals is imperative to ensure earlier detection of PAH.

To this end, Hinchcliff and colleagues present the baseline characteristics of the study population of the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) cohort¹¹. This collaborative, multicenter study based in North America was established to prospectively follow 2 groups of patients with SSc, those with incident PAH and those considered at high risk for developing PAH, a distinguishing feature of the study when compared to other SSc cohort studies. High-risk patients were selected based upon pulmonary function test (PFT) or echocardiographic criteria and followed prospectively. The goals of PHAROS are to (1) determine the incidence of PAH in a high-risk cohort, (2) identify risk factors for developing PAH, (3) characterize the types of pulmonary hypertension (PH) that develop in SSc, and (4) determine the effectiveness of PAH-specific therapies in patients with SSc. While the answers to many of these questions will remain elusive until the completion of the study, valuable data are presented in the current report. First, while many of the subject characteristics are comparable to prior data from the French registry regarding incident PAH cases, several notable exceptions are reported¹². The age of SSc diagnosis appears to be significantly younger in the PHAROS study (44 ± 18 vs 57 ± 13 years), while the proportion of patients with limited SSc and PAH appears higher (72% vs 56%) and the mean DLCO appears to be lower (mean DLCO% predicted 43 ± 18 vs 56 ± 23).

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Whether these differences represent inclusion of distinct phenotypes of SSc remains to be seen. Importantly, the PHAROS study collection of SSc-specific antibodies, including nucleolar antibodies, may offer insight into the natural history of the development of PH subtypes (i.e., PAH, PH related to left heart disease and PH related to interstitial lung disease), clinical associations, and response to PAH-specific therapy with respect to these antibodies.

Second, the study again reinforces the importance of RHC for the diagnosis of PH. Sixteen subjects in the pre-PAH cohort underwent RHC for evaluation of PH based upon symptoms, elevated right ventricular systolic pressure (RVSP) on echocardiogram, or PFT abnormalities; none were found to have PH. Further, low DLCO, previously demonstrated to be a strong predictor of the presence of PAH¹², was not only a feature of PAH and PH related to interstitial lung disease, but also of PAH related to left heart disease, suggesting that this parameter alone is insufficient to distinguish between WHO groups. Fortunately, PHAROS will follow patients with all forms of PH over time, allowing detailed characterization of the most common subtypes in the setting of SSc.

Third, the baseline data from PHAROS suggest reliance on the presence of dyspnea to trigger a diagnostic procedure may not be prudent. Even in the French registry, where referral for RHC was initiated for patients with SSc who (1) had a tricuspid regurgitant jet velocity (TR jet) greater than 3 meters per second, with or without dyspnea, or (2) had a TR jet between 2.5 and 3.0 meters per second on echocardiography and dyspnea, 17% of the incident cases had no dyspnea¹². In PHAROS, overall, 7% of subjects with RHC-proven PH had no dyspnea; a full 22% of PAH subjects had either no or minimal dyspnea. This should not be surprising given literature from other disease states demonstrating that perception of dyspnea varies greatly between individuals, even those with significant physiologic impairment¹³. Further, reliance on echocardiographic parameters such as RVSP or TR jet to prompt PAH evaluation also may be ill-advised; several studies in SSc populations have demonstrated an inability to acquire adequate acoustic signals to measure a TR jet and calculate a RVSP in up to 68% of patients, even in research protocols^{14,15,16}. The approach employed by the PHAROS study, enrolling subjects with either echocardiographic or PFT abnormalities, is more likely to identify PAH at an earlier stage. At our center, referrals for PH evaluation are generated based upon similar echocardiographic and PFT criteria, but not dependent upon the presence of dyspnea; nearly 50% of SSc-PAH patients are diagnosed in FC I or II, significantly different from the clinical experience reported by Hachulla and colleagues^{7,10}.

While there are many aspects of the PHAROS design that are laudable, there are several omissions that potentially would have strengthened the inferences that could be drawn from the study. In selecting a “high-risk” cohort from SSc,

the investigators did not include an elevated N-terminal pro-brain natriuretic peptide level as part of the inclusion criteria, despite studies demonstrating its prognostic significance in SSc-PAH^{17,18}. A noninvasive measure of right ventricular function, such as the tricuspid annular plane systolic excursion, would have enhanced the study by potentially providing a novel screening tool and/or outcome measure for SSc-PAH, for which there is an urgent need¹⁹.

Still, the PHAROS study remains an important addition to the observational cohort studies in SSc. Its focus on both a high-risk population within SSc and on incident cases of SSc-associated pulmonary hypertension offers the opportunity to study a range of pulmonary vascular disease at differing stages of progression. While it remains to be seen whether the wisdom of the PHAROS will be as enduring as that of Hermetica, the initial results are promising.

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REFERENCES

1. Freke T, Gandy P. The Hermetica: The lost wisdom of the pharaohs. New York: Tarcher-Penguin; 2008.
2. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009;11:229.
3. Mayes MD, Lacey JV Jr, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum* 2003;48:2246-55.
4. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006;173:1023-30.
5. Mathai SC, Hassoun PM. Pulmonary arterial hypertension associated with systemic sclerosis. *Exp Rev Respir Med* 2011;5:267-79.
6. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 2007;66:940-4.
7. Campo A, Mathai SC, Le Pavec J, Zaiman AL, Hummers LK, Boyce D, et al. Hemodynamic predictors of survival in scleroderma-related pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2010;182:252-60.
8. Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JS, Vrapai F, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. *Am J Respir Crit Care Med* 2009;179:151-7.
9. Galie N, Rubin LJ, Hooper M, Jansa P, Al-Hiti H, Meyer G, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008;371:2093-100.
10. Hachulla E, Launay D, Yaici A, Berezne A, de Groote P, Sitbon O, et al. Pulmonary arterial hypertension associated with systemic

- sclerosis in patients with functional class II dyspnoea: mild symptoms but severe outcome. *Rheumatology* 2010;49:940-4.
11. Hinchcliff M, Fischer A, Schiopu E, Steen V. Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): Baseline characteristics and description of study population. *J Rheumatol* 2011;38:2172-9.
 12. Hachulla E, Gressin V, Guillevin L, Carpentier P, Diot E, Sibilia J, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum* 2005;52:3792-800.
 13. Rabe KF. Improving dyspnea in chronic obstructive pulmonary disease: optimal treatment strategies. *Proc Am Thorac Soc* 2006;3:270-5.
 14. Murata I, Kihara H, Shinohara S, Ito K. Echocardiographic evaluation of pulmonary arterial hypertension in patients with progressive systemic sclerosis and related syndromes. *Jpn Circ J* 1992;56:983-91.
 15. Denton CP, Cailles JB, Phillips GD, Wells AU, Black CM, Bois RM. Comparison of Doppler echocardiography and right heart catheterization to assess pulmonary hypertension in systemic sclerosis. *Br J Rheumatol* 1997;36:239-43.
 16. Mathai SC, Sibley CT, Forfia PR, Mudd JO, Fisher MR, Tedford RJ, et al. Tricuspid annular plane systolic excursion is a robust outcome measure in systemic sclerosis-associated pulmonary arterial hypertension. *J Rheumatol* 2011;38:in press.
 17. Allanore Y, Borderie D, Avouac J, Zerkak D, Meune C, Hachulla E, et al. High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. *Arthritis Rheum* 2008;58:284-91.
 18. Mukerjee D, Yap LB, Holmes AM, Nair D, Ayrton P, Black CM, et al. Significance of plasma N-terminal pro-brain natriuretic peptide in patients with systemic sclerosis-related pulmonary arterial hypertension. *Respir Med* 2003;97:1230-6.
 19. Kowal-Bielecka O, Avouac J, Pittrow D, Huscher D, Behrens F, Denton CP, et al. Echocardiography as an outcome measure in scleroderma-related pulmonary arterial hypertension: a systematic literature analysis by the EPOSS group. *J Rheumatol* 2010; 37:105-15.

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