# Connective tissue disease-associated pulmonary arterial hypertension: "Beijing style"

Lorinda Chung[1,2] and Steven M. Kawut[3]

**Affiliations:** [1]Depts of Medicine and Dermatology, Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, USA. [2]Palo Alto VA Health Care System, Palo Alto, CA, USA. [3]Depts of Medicine and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA.

**Correspondence:** Lorinda Chung, 3801 Miranda Ave, Palo Alto VA Health Care System, Palo Alto, CA 94304, USA. E-mail: shauwei@stanford.edu

@ERSpublications
**Survival rates of CTD-APAH patients in China in the modern treatment era are similar to those in the USA and Europe** http://ow.ly/xXCZu

Patients with connective tissue disease (CTD)-associated pulmonary arterial hypertension (APAH) experience poorer outcomes than those with idiopathic PAH (IPAH) [1–6]. In the USA, patients with systemic sclerosis (SSc) are most commonly affected by CTD-APAH and have the worst survival [1]. Similarly, 74% of a large cohort with CTD-APAH in the UK had SSc, and these patients had poorer survival than those with systemic lupus erythematosus (SLE) or polymyositis/dermatomyositis [7].

Few published studies have described the clinical features and outcomes of patients with CTD-APAH in Asia. CHUNG *et al.* [8] found that Korean patients with SLE-pulmonary hypertension had much worse survival than those with IPAH, with 1- and 5-year survival rates of 51% and 17% for SLE-pulmonary hypertension compared with 77% and 68% for IPAH. A more recent study of 70 Japanese patients with CTD-APAH found that mixed connective tissue disease (MCTD) was the most common underlying CTD (43%), followed by SLE (29%), SSc (19%) and primary Sjogren's syndrome (10%) [9]. This study found no significant difference in survival among the different CTD-APAH subgroups, but did find improved survival rates in those diagnosed more recently.

In this issue of the *European Respiratory Journal*, HAO *et al.* [10] describe the clinical features and outcomes of 129 Chinese patients with CTD-APAH confirmed by right heart catheterisation between July 2006 and May 2011. It is known that the prevalence of SLE in the Chinese population is much higher than in Caucasians [11, 12], while SSc is more common in Caucasians than in the Chinese population [13]. Consistent with this epidemiology, SLE was the most common underlying CTD (49% of the study sample), followed by primary Sjogren's syndrome (16%), MCTD (9%) and SSc (6%). This study also included patients with Takayasu's arteritis (12%), an inflammatory vasculitis of the large vessels.

Compared with USA and European cohorts of CTD-APAH [1, 6, 7], the Chinese patients were younger, with a mean age of $39.3 \pm 12.3$ years compared with $57.1 \pm 13.7$ years in the REVEAL CTD-APAH group [1], possibly reflecting the patterns of underlying CTD in the different regions. Similar to western cohorts, the majority of patients were female. Although fewer patients were in World Health Organization (WHO) functional class III/IV (56.6% *versus* 73.5% in REVEAL), overall haemodynamics were comparable in the Chinese group compared with the REVEAL CTD-APAH patients. Diffusing capacity of the lung for carbon monoxide, a key prognostic factor in patients with SSc-APAH [14], was much higher in the Chinese CTD-APAH patients.

Received: May 16 2014 | Accepted after revision: June 05 2014

Conflict of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com

Overall survival at 1- and 3-years was 92% and 80%, respectively, with no significant differences amongst the CTD subgroups, and was similar to that of cohorts from the USA and Europe in the modern treatment era [1, 6, 7, 15]. Consistent with USA and European studies [7, 16], interstitial lung disease-pulmonary hypertension patients had poorer survival rates than those with isolated CTD-APAH in this Chinese cohort.

A 3 Wood unit increment in pulmonary vascular resistance was independently associated with a 34% increased risk for death in the multivariate analysis, consistent with studies in the USA [17]. This suggests that the severity of the pulmonary vascular disease itself in these patients is a critical determinant of outcome. The authors also found a 70% increase in mortality risk associated with a 50 $IU \cdot L^{-1}$ increment in alkaline phosphatase. While possibly reflecting the severity of congestive cardiac hepatopathy (as suggested by the authors), this finding should be interpreted with caution. The reported alkaline phosphatase values were all within normal limits in this population, and total bilirubin has been better linked with survival in other PAH cohorts [18, 19]. While potentially providing insight into pathogenesis, these associations are unlikely to be strong or discriminating enough to distinguish high- from low-risk patients at the bedside and should not be used for patient-level prognostication until data support their utility.

Unfortunately, this study did not record N-terminal pro-brain natriuretic peptide (NT-proBNP) or BNP levels. In the UK SSc-APAH cohort, a four-fold increased risk of death was associated with every order of magnitude increase in baseline NT-proBNP level, and BNP was discriminating for 2-year mortality in a recent study of a clinical trial population of patients with PAH [20, 21].

12% of this Chinese cohort had Takayasu's arteritis. Takayasu's arteritis is a systemic inflammatory vasculitis involving the aorta and its main branches that initially demonstrates granulomatous inflammation in the adventitia and medial wall of involved vessels, with subsequent progression to fibrosis and stenosis/occlusion in the lesions [22]. Pulmonary artery involvement has been found in 20–56% of Takayasu's arteritis patients on autopsy and is more common in those with active disease [22, 23]. Pulmonary artery involvement is typically limited to segmental and subsegmental branches, especially in the upper lobes, but larger branches may also be involved [24]. Pulmonary hypertension occurs in approximately 13–15% of Takayasu's arteritis patients and can be related to: 1) pulmonary artery vasculitis; 2) pulmonary artery sclerosis and development of stenoses; or 3) elevated left ventricular filling pressure [22, 25]. The definition of pulmonary hypertension in published studies was not standardised, so true estimates of this complication in Takayasu's arteritis are not known. Treatment of pulmonary artery involvement in Takayasu's arteritis typically focuses on controlling inflammation with glucocorticoids and other immunosuppressive therapies, as well as angioplasty and stent implantation for stenotic lesions, an approach distinct from that taken in other forms of CTD-APAH [23, 26].

Takayasu's arteritis has not been included in prior observational cohorts of CTD-APAH or in clinical trials of PAH-specific medications. Given the difference in the pathological vascular findings between Takayasu's arteritis and other CTDs (at least in some forms of Takayasu's arteritis), pulmonary hypertension from Takayasu's arteritis may be better classified in WHO group V pulmonary hypertension [27]. The classic pathological findings of pulmonary hypertension complicating Takayasu's arteritis in the active phase, including lymphoplasmacytic infiltration and multinucleated giant cells, are not seen in other CTD-APAH [28]. Thus, whereas glucocorticoids and additional steroid-sparing immunosuppressive therapies are the mainstay of treatment for pulmonary hypertension complicating Takayasu's arteritis, the utility of immunosuppression in the treatment of traditional forms of CTD-APAH is still debated. Small, uncontrolled studies indicate that immunosuppression may be useful in the treatment of SLE-APAH and MCTD-APAH, with minimal efficacy in SSc-APAH [29, 30]. Interestingly, in this study, a higher percentage of patients in the SLE-APAH and SSc-APAH subgroups were treated with such agents than in the Takayasu's arteritis group.

In the late phase of pulmonary hypertension complicating Takayasu's arteritis, transmural sclerosis with minimal inflammation is seen, which is more consistent with the vasculopathy observed in SSc-APAH [28]. Takayasu's arteritis patients had pulmonary hypertension-associated symptoms many years prior to the diagnosis of pulmonary hypertension in this study. This suggests that these patients may indeed have been in the late phase of disease, but the authors do not provide data on inflammatory markers or extrapulmonary disease activity to support this assumption. Pulmonary artery systolic pressure was significantly higher (and diastolic pulmonary artery diastolic pressure lower) in pulmonary hypertension complicating Takayasu's arteritis compared with other forms of CTD-APAH, implying differences in pulse pressure and impedance. This may indicate more significant involvement of the large vessels in pulmonary hypertension complicating Takayasu's arteritis compared with the other forms.

Survival was not different in the Takayasu's arteritis patients compared with the other CTD-APAH patients, and the relatively high frequency of pulmonary hypertension in Takayasu's arteritis patients makes it possible


DOI: 10.1183/09031936.00090814

that screening could be useful in this population. Additional studies focused particularly on pulmonary hypertension in Takayasu's arteritis patients are warranted to determine the best clinical approach.

In summary, epidemiological and clinical differences exist between CTD-APAH patients from different countries and ethnic origins. The severity of pulmonary vascular disease is an important determinant of outcome in these patients; however, patient-level predictors of survival and the most effective treatment regimens are still unknown. Large international cohort studies of CTD-APAH patients will be helpful to better understand these differences and the implications for screening and treatment, as well as to identify novel biomarkers of risk prediction.

## References


1 Chung L, Liu J, Parsons L, *et al.* Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. *Chest* 2010; 138: 1383–1394.
2 Clements PJ, Tan M, McLaughlin VV, *et al.* The pulmonary arterial hypertension quality enhancement research initiative: comparison of patients with idiopathic PAH to patients with systemic sclerosis-associated PAH. *Ann Rheum Dis* 2012; 71: 249–252.
3 Kawut SM, Taichman DB, Archer-Chicko CL, *et al.* Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. *Chest* 2003; 123: 344–350.
4 Lee WT, Ling Y, Sheares KK, *et al.* Predicting survival in pulmonary arterial hypertension in the UK. *Eur Respir J* 2012; 40: 604–611.
5 Humbert M, Sitbon O, Yaïci A, *et al.* Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010; 36: 549–555.
6 Escribano-Subias P, Blanco I, López-Meseguer M, *et al.* Survival in pulmonary hypertension in Spain: insights from the Spanish registry. *Eur Respir J* 2012; 40: 596–603.
7 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: 151–157.
8 Chung SM, Lee CK, Lee EY, *et al.* Clinical aspects of pulmonary hypertension in patients with systemic lupus erythematosus and in patients with idiopathic pulmonary arterial hypertension. *Clin Rheumatol* 2006; 25: 866–872.
9 Shirai Y, Yasuoka H, Okano Y, *et al.* Clinical characteristics and survival of Japanese patients with connective tissue disease and pulmonary arterial hypertension: a single-centre cohort. *Rheumatology (Oxford)* 2012; 51: 1846–1854.
10 Hao Y-J, Jiang X, Zhou W, *et al.* Connective tissue disease-associated pulmonary arterial hypertension in Chinese patients. *Eur Respir J* 2014; 44: 963–972.
11 Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. *Lupus* 2006; 15: 308–318.
12 Osio-Salido E, Manapat-Reyes H. Epidemiology of systemic lupus erythematosus in Asia. *Lupus* 2010; 19: 1365–1373.
13 Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. *Curr Opin Rheumatol* 2012; 24: 165–170.
14 Chung L, Domsic RT, Lingala B, *et al.* Survival and predictors of mortality in systemic sclerosis-associated pulmonary arterial hypertension: outcomes from the pulmonary hypertension assessment and recognition of outcomes in scleroderma registry. *Arthritis Care Res (Hoboken)* 2014; 66: 489–495.
15 Launay D, Sitbon O, Hachulla E, *et al.* Survival in systemic sclerosis-associated pulmonary arterial hypertension in the modern management era. *Ann Rheum Dis* 2013; 72: 1940–1946.
16 Mathai SC, Hummers LK, Champion HC, *et al.* Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: impact of interstitial lung disease. *Arthritis Rheum* 2009; 60: 569–577.
17 Campo A, Mathai SC, Le Pavec J, *et al.* Hemodynamic predictors of survival in scleroderma-related pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2010; 182: 252–260.
18 Kawut SM, Horn EM, Berekashvili KK, *et al.* New predictors of outcome in idiopathic pulmonary arterial hypertension. *Am J Cardiol* 2005; 95: 199–203.
19 Takeda Y, Takeda Y, Tomimoto S, *et al.* Bilirubin as a prognostic marker in patients with pulmonary arterial hypertension. *BMC Pulm Med* 2010; 10: 22.
20 Williams MH, Handler CE, Akram R, *et al.* Role of N-terminal brain natriuretic peptide (N-TproBNP) in scleroderma-associated pulmonary arterial hypertension. *Eur Heart J* 2006; 27: 1485–1494.
21 Fritz JS, Blair C, Oudiz RJ, *et al.* Baseline and follow-up 6-min walk distance and brain natriuretic peptide predict 2-year mortality in pulmonary arterial hypertension. *Chest* 2013; 143: 315–323.
22 Lee GY, Jang SY, Ko SM, *et al.* Cardiovascular manifestations of Takayasu arteritis and their relationship to the disease activity: analysis of 204 Korean patients at a single center. *Int J Cardiol* 2012; 159: 14–20.
23 Toledano K, Guralnik L, Lorber A, *et al.* Pulmonary arteries involvement in Takayasu's arteritis: two cases and literature review. *Semin Arthritis Rheum* 2011; 41: 461–470.
24 Kumar S, Moorthy N, Kapoor A. Takayasu's arteritis mimicking unilateral pulmonary artery agenesis in a child with severe pulmonary hypertension and right heart failure: a diagnostic dilemma. *Pediatr Cardiol* 2011; 32: 993–997.
25 Soto ME, Espinola-Zavaleta N, Ramirez-Quito O, *et al.* Echocardiographic follow-up of patients with Takayasu's arteritis: five-year survival. *Echocardiography* 2006; 23: 353–360.
26 Qin L, Hong-Liang Z, Zhi-Hong L, *et al.* Percutaneous transluminal angioplasty and stenting for pulmonary stenosis due to Takayasu's arteritis: clinical outcome and four-year follow-up. *Clin Cardiol* 2009; 32: 639–643.
27 Simonneau G, Gatzoulis MA, Adatia I, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62: Suppl., D34–D41.
28 Kerr KM, Auger WR, Fedullo PF, *et al.* Large vessel pulmonary arteritis mimicking chronic thromboembolic disease. *Am J Respir Crit Care Med* 1995; 152: 367–373.
29 Sanchez O, Sitbon O, Jaïs X, *et al.* Immunosuppressive therapy in connective tissue diseases-associated pulmonary arterial hypertension. *Chest* 2006; 130: 182–189.
30 Jais X, Launay D, Yaici A, *et al.* Immunosuppressive therapy in lupus- and mixed connective tissue disease-associated pulmonary arterial hypertension: a retrospective analysis of twenty-three cases. *Arthritis Rheum* 2008; 58: 521–531.