Eur Respir J 2007; 30: 1–2
DOI: 10.1183/09031936.00055407

EDITORIAL

The burden of pulmonary hypertension

M. Humbert

A rare disease affects less than one in 2,000 individuals within the general population [1, 2]. By nature, rare diseases concern a low number of patients, families and healthcare providers. This often has negative consequences for the patients, who may suffer from less than optimal care [1, 2]. Rare respiratory diseases are no exception and it is time to improve awareness, as well as understanding of the epidemiology, pathophysiology and management, of these conditions [2]. In the current issue of the *European Respiratory Journal*, PEACOCK *et al.* [3] provide novel original data on the epidemiology of pulmonary arterial hypertension (PAH) in Scotland (UK). PAH describes a group of noninfectious, nonmalignant respiratory diseases causing breathlessness, loss of exercise capacity and death due to elevated pulmonary artery pressure and subsequent right heart failure [4]. A definite diagnosis of PAH requires strict right heart catheter criteria. Indeed, PAH is defined by an elevation of the mean pulmonary artery pressure >25 mmHg at rest and/or 30 mmHg during exercise without elevation of the pulmonary capillary wedge pressure (<15 mmHg), and elimination of frequent causes such as hypoxia, respiratory diseases and thromboembolic disease [4]. Half of all PAH cases referred to pulmonary vascular centres have no identifiable risk factor, corresponding to idiopathic (sporadic) and familial PAH. The other PAH subcategories include a number of associated conditions, such as connective tissue diseases, congenital heart diseases, portal hypertension and HIV infection [4].

Right heart catheterisation and pulmonary vasoreactivity testing are established and safe diagnostic tools that are mandatory in all PAH patients [4–6]. Less invasive tools, such as cardiac echo-doppler, are of interest for PAH screening: however, one has to bear in mind that a significant proportion of patients with echocardiography parameters compatible with PAH may have a strictly normal pulmonary circulation and/or another condition mimicking PAH, such as left heart diastolic disease [7]. This was well emphasised in a recent multicentre cross-sectional analysis of 599 patients with systemic sclerosis, where only 18 out of 33 patients with an echo-doppler compatible with PAH had a definite diagnosis of PAH after right heart catheterisation, while three out of 33 had diastolic left heart dysfunction and 12 had normal or near-normal values [7]. These data explain why pulmonary vascular specialists do not rely on inexpert PAH diagnosis, but require strict measurements to confirm the diagnosis.

One of the major interests of the study by PEACOCK *et al.* [3] was to provide ''administrative'' as well as ''robust'' data on PAH in Scotland. When analysing data from the Scottish Morbidity Record Scheme, a prevalence of 52 PAH cases per million population were obtained [3]. Despite the many limitations of this aspect of the study, the first comment is that this number, which may overestimate the true prevalence of the disease, still meets the criteria for a rare respiratory disease. Conversely, it is likely that the expert data based on gold standard procedures from the reference centre (Scottish Pulmonary Vascular Unit, Glasgow, UK) might underestimate the true frequency of the disease. Based on this expert centre experience the corresponding prevalence was 26 cases per million in Scotland [3].

PEACOCK *et al.* [3] also made a systematic comparison of their local data with the French PAH Registry [8]. In the French Registry, 674 patients with a strict catheter diagnosis of PAH were studied in a network of 17 university pulmonary vascular centres spread throughout France. Idiopathic, familial, anorexigen, connective tissue diseases, congenital heart diseases, portal hypertension and HIV-associated PAH accounted for 39.2, 3.9, 9.5, 15.3, 11.3, 10.4 and 6.2% of the population, respectively [8]. The resulting estimate of PAH prevalence was 15 per million [8]. As discussed previously, this prevalence is a low estimate. Indeed, PAH awareness is still insufficient, as demonstrated by marked differences in regional prevalence of the condition in France, ranging from 5–25 cases per million inhabitants, although PAH is considered to have a homogeneous distribution in the country [8]. This clearly indicates that many patients are either not identified or not referred to specialised regional PAH centres. In addition, availability of oral drugs may lead to late referral to pulmonary vascular centres, as suggested by the fact that most, if not all, patients treated with continuous *i.v.* prostacyclin infusion were followed in a pulmonary vascular centre, while this was the case in only two-thirds of PAH patients treated with oral endothelin receptor antagonists [8]. Thus, the data from expert centres are likely to represent a lower estimate of the disease. As stated by PEACOCK *et al.* [3], with expanding medical and surgical options in the field of pulmonary hypertension (PH) it is possible that specialist treatment centres will start to see a greater number of patients with PH. Indeed, PAH management should be provided in designated centres with multidisciplinary teams working in a shared care approach.

SUPPORT STATEMENT: This manuscript is based, in part, on the 2006 Cournand lecture presented at the European Respiratory Society Congress in Munich, September 3, 2006. M. Humbert is supported by grants from Université Paris-Sud and INSERM (Paris, France).

STATEMENT OF INTEREST: A statement of interest for M. Humbert can be found at www.erj.ersjournals.com/misc/statements.shtml

CORRESPONDENCE: M. Humbert, Dept of Respiratory Medicine, Antoine-Béclère Hospital, 157, Rue de la Porte de Trivaux, 92140 Clamart, France. Fax: 33 146303824. E-mail: marc.humbert@abc.aphp.fr

Nevertheless, it is also very likely that nonspecialised centres will also see and attempt to treat cases in many countries. In that case it will be extremely important that strict procedures for management are implemented, in order to provide the best possible care for all patients [4, 5].

It remains widely believed that PH is a rare condition [4, 9]. Although true for PAH [3, 8], the global burden of PH as a whole is currently unknown and largely underestimated [10]. In the developing world, highly prevalent diseases, such as schistosomiasis in parts of South America and Africa or sickle cell disease in populations of African origin, are associated with a marked risk of PH [10–12]. In addition, hypoxia is a major worldwide risk factor for PH [13]. The predominant causes of hypoxia are inadequate oxygenation of arterial blood as a result of lung disease, such as chronic obstructive pulmonary disease, impaired control of breathing or residence at high altitude. Indeed, more than 140 million individuals live above 2,500 m worldwide, including 80 million in Asia and 35 million in South America, thus chronic mountain sickness is a public-health problem in the Andean mountains and other mountainous regions around the world [10, 13, 14]. Finally, up to 4% of all patients with acute pulmonary embolism may develop chronic thrombo-embolic disease and PH [15, 16].

Altogether pulmonary hypertension is certainly underestimated both in developing and developed countries and further well-designed studies are mandatory to better approach the burden of the disease in populations exposed to different risk factors.

REFERENCES

1 Orphanet, Rare diseases. www.orpha.net/consor/cgi-bin/home_info.php?Lng=FR&file=RareDisease. Date last accessed: May, 2007.
2 Le Pavec J, Humbert M. Reference centers for rare respiratory diseases. *Presse Med* 2007; [Epub ahead of print. PMID: 17442533].
3 Peacock AJ, Murphy NF, McMurray JJV, Caballero L, Stewart S. An epidemiological study of pulmonary arterial hypertension. *Eur Respir J* 2007; 30: 104–109.
4 Runo JR, Loyd JE. Primary pulmonary hypertension. *Lancet* 2003; 361: 1533–1544.
5 Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004; 351: 1425–1436.
6 Hoeper MM, Lee SH, Voswinckel R, *et al.* Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. *J Am Coll Cardiol* 2006; 48: 2546–2552.
7 Hachulla E, Gressin V, Guillevin L, *et al.* Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum* 2005; 52: 3792–3800.
8 Humbert M, Sitbon O, Chaouat A, *et al.* Pulmonary arterial hypertension in France: results from a National Registry. *Am J Respir Crit Care Med* 2006; 173: 1023–1030.
9 Simonneau G, Galiè N, Rubin LJ, *et al.* Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004; 43: Suppl. 12, 5S–12S.
10 Humbert M, Khaltaev N, Bousquet J, Souza R. Pulmonary hypertension: from an orphan disease to a public health problem. *Chest* 2007 (in press).
11 Lapa MS, Ferreira EM, Jardim C, Martins B, Arakaki JSO, Souza R. Pulmonary hypertension in two reference centers in Brazil: the importance of schistosomiasis as a differential diagnosis. *Proc Am Thorac Soc* 2006; 3: A418.
12 Gladwin MT, Sachdev V, Jison ML, *et al.* Pulmonary hypertension as a risk of death in patients with sickle cell disease. *N Engl J Med* 2004; 350: 886–895.
13 Penaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. *Circulation* 2007; 115: 1132–1146.
14 Bousquet J, Dahl R, Khaltaev N. Global alliance against chronic respiratory diseases. *Eur Respir J* 2007; 29: 233–239.
15 Pengo V, Lensing AW, Prins MH, *et al.* Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med* 2004; 350: 2257–2264.
16 Dartevelle P, Fadel E, Mussot S, *et al.* Chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2004; 23: 637–648.