Eur Respir J 2012; 39: 3–4
DOI: 10.1183/09031936.00119811

EDITORIAL

Pulmonary hypertension in patients with sickle cell disease: not so frequent but so different

G. Simonneau and F. Parent

Until recently, the prevalence and characteristics of pulmonary hypertension (PH) in adults with sickle cell disease remained uncertain. In previous studies, the prevalence of PH, as defined by a tricuspid valve regurgitant jet velocity (TRJV) of $\geqslant$2.5 m·s^{-1}, has been reported as high as 30% [1, 2]. However, in these studies, the diagnosis of PH was not systematically confirmed on right heart catheterisation (RHC), a procedure that is recommended in international guidelines as the standard of care [3]. Moreover, recent screening programmes for PH in high-risk populations have shown that using a TRJV of $\geqslant$2.5 m·s^{-1} to define PH results in a substantial number of false-positive cases not confirmed on RHC [4–6]. The use of RHC also makes it possible to accurately distinguish between pre-capillary and post-capillary PH, which is especially important in this setting, since the presence of post-capillary PH due to associated left heart disease has been frequently reported in adult patients with sickle cell disease [7, 8].

Two simultaneous studies, one recently published in the *New England Journal of Medicine* [9] and the other in this issue of *European Respiratory Journal* [10], have addressed this issue using the same methodology. All patients with sickle cell disease underwent Doppler echocardiography, with measurement of TRJV. RHC was performed in all patients in whom PH was suspected on the basis of TRJV of $\geqslant$2.5 m·s^{-1}. PH was defined as a mean pulmonary arterial pressure of $\geqslant$25 mmHg [3].

The results of these two studies performed in France [9] and in Brazil [10] are remarkably similar, showing a prevalence of PH of 6.2% and 10%, respectively; lower than expected. Interestingly, post-capillary PH was the most frequent cause, with a prevalence of 3.3% and 6.2%, respectively, whereas the prevalence of pre-capillary PH was only 2.9% and 3.8%. In addition, these two studies clearly demonstrate that, when a threshold TRJV of $\geqslant$2.5 m·s^{-1} was used to define PH, the positive predictive value of echocardiography for the detection of PH was only 25% and 32%, respectively.

In some studies involving patients with sickle cell disease, a TRJV of $\geqslant$2.5 m·s^{-1} independently predicted an increased risk of death [1, 2]; however, the proportion of these patients with confirmed PH with a mean pulmonary arterial pressure of $\geqslant$25 mmHg at RHC is unknown. FONSECA *et al.* [10] report only a trend for a worse survival in patients with a TRJV of $\geqslant$2.5 m·s^{-1} compared with patients with a TRJV of $<$2.5 m·s^{-1}. In contrast, what really makes the difference in term of prognosis is to have PH confirmed by RHC. In the study of FONSECA *et al.* [10], these patients showed a worse survival compared with the remaining patients, regardless of the TRJV measured. PARENT *et al.* [9] reported, in the supplement to their manuscript, similar observations. A difference between the Brazilian and French studies is the rate of death observed in patients with confirmed PH; this rate was 37% (three deaths among eight patients) and 12.5% (three deaths among 24 patients), respectively. Such a difference has to be interpreted with caution due to the small sample size in the two studies. The mean follow-up periods were similar in the two studies. Age and main patient characteristics were also roughly similar. The difference in mortality rate between the two cohorts can be partially explained by exclusion of patients with severe lung or liver disease or renal insufficiency in the French cohort. Lastly, patients in the French study were followed on a regular basis in three referral centres for sickle cell disease.

In their initial report, GLADWIN *et al.* [1] observed that patients with PH associated with sickle cell disease had elevations of presumed markers of haemolysis, especially elevated serum lactate dehydrogenase, and speculated that scavenging of nitric oxide by increased level of plasma haemoglobin makes an important contribution to its pathogenesis. This theory has been recently questioned [11]. FONSECA *et al.* [10] observed, in the group with confirmed PH when compared to patients without PH, a decrease in haemoglobin level and an increase in lactate dehydrogenase and aspartate aminotransferase levels, suggesting a hyper-haemolysis. However, other important markers of haemolysis, including reticulocyte count and unconjugated bilirubin level, were similar in the two groups. Moreover, lactate dehydrogenase and aspartate aminotransferase levels may be also influenced by liver dysfunction. In the study of PARENT *et al.* [9], data regarding biological markers of haemolysis and the presence of PH were also discordant. Further studies are needed in order to clarify the role of haemolysis in the pathogenesis of PH in patients with sickle cell disease.

Importantly, the data presented by FONSECA *et al.* [10] provide some additional information regarding the haemodynamic characteristics of sickle cell disease patients suffering from pre-capillary PH. Pulmonary arterial hypertension (PAH) is characterised by the presence of pre-capillary PH in the absence of left-sided heart disease, lung disease or chronic thromboembolism. In the updated clinical classification of PH [8], sickle cell disease appears in the

Université Paris-Sud, Faculté de Médecine, Kremlin-Bicêtre, Centre National de Référence de l'Hypertension Pulmonaire Sévère, Service de Pneumologie et Réanimation Respiratoire, and INSERM U999, Hôpital Antoine Béclère, AP-HP, Clamart, France.

CORRESPONDENCE: G. Simonneau, Service de Pneumologie et Réanimation Respiratoire, Hôpital Antoine Béclère, AP-HP, Université Paris-Sud 11, 157 rue de la porte de Trivaux, 92140 Clamart, France. E-mail: gerald.simonneau@abc.aphp.fr

group 1 (PAH) as a separate entity in subgroups of PAH associated with identified diseases. An important finding of FONSECA *et al.* [10] is that patients with sickle cell disease and pre-capillary PH have a distinct haemodynamic profile, characterised by a less marked increase in mean pulmonary arterial pressure, a higher cardiac output and lower pulmonary vascular resistance than patients with idiopathic PAH. In addition, response to specific PAH therapies also appears to be different in these patients. Specific therapies approved for the treatment of PAH include prostacyclin derivatives, endothelin receptor antagonists and phosphodiesterase-5 inhibitors [12]. However, none of these agents are currently approved for the treatment of PAH associated with sickle cell disease due to the lack of data in this specific population. Recently, the effect of bosentan was assessed in a randomised, double-blind, placebo-controlled trial of patients with sickle cell disease and PH. Overall, bosentan appeared to be well tolerated, although the small sample size precluded an analysis of its efficacy [13]. Another randomised, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of sildenafil was prematurely halted after interim analysis showed that sildenafil-treated patients were likely to have more acute sickle cell pain crises (35%) compared with placebo-treated patients (14%) [14]. Furthermore, there was no evidence of treatment-related improvement at the time of study termination. Thus, the optimal management of this severe complication remains to be properly evaluated. Finally, pre-capillary PH associated with sickle cell disease appears quite different from the other forms of PAH in terms of both its haemodynamic profile and response to specific PAH therapies. These observations call into question the rationale for keeping sickle cell disease in group 1 (PAH) of the clinical PH classification system.

STATEMENT OF INTEREST

None declared.

REFERENCES

1 Gladwin MT, Sachdev V, Jison ML, *et al.* Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med* 2004; 350: 886–895.

2 Ataga KI, Moore CG, Jones S, *et al.* Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. *Br J Haematol* 2006; 134: 109–115.

3 Galie N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; 34: 1219–1263.

4 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.

5 Sitbon O, Lascoux-Combe C, Delfraissy JF, *et al.* Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. *Am J Respir Crit Care Med* 2008; 177: 108–113.

6 Lapa M, Dias B, Jardim C, *et al.* Cardiopulmonary manifestations of hepatosplenic schistosomiasis. *Circulation* 2009; 119: 1518–1523.

7 Anthi A, Machado RF, Jison ML, *et al.* Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. *Am J Respir Crit Care Med* 2007; 175: 1272–1279.

8 Simonneau G, Robbins IM, Beghetti M, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009; 54: S43–S54.

9 Parent F, Bachir D, Inamo J, *et al.* A hemodynamic study of pulmonary hypertension in sickle cell disease. *N Engl J Med* 2011; 365: 44–53.

10 Fonseca GHH, Souza R, Salemi VMC, *et al.* Pulmonary hypertension diagnosed by right heart catheterisation in sickle cell disease. *Eur Respir J* 2012; 39: 112–118.

11 Bunn HF, Nathan DG, Dover GJ, *et al.* Pulmonary hypertension and nitric oxide depletion in sickle cell disease. *Blood* 2010; 116: 687–692.

12 Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004; 351: 1425–1436.

13 Barst RJ, Mubarak KK, Machado RF, *et al.* Exercise capacity and haemodynamics in patients with sickle cell disease with pulmonary hypertension treated with bosentan: results of the ASSET studies. *Br J Haematol* 2010; 149: 426–435.

14 Machado RF, Barst RJ, Yovetich NA, *et al.* Hospitalization for pain in patients with sickle cell disease treated with sildenafil for elevated TRV and low exercise capacity. *Blood* 2011; 118: 855–864.