Eur Respir Rev 2010; 19: 118, 266–271
DOI: 10.1183/09059180.00008810

EUROPEAN RESPIRATORY UPDATE

Contemporary issues in pulmonary hypertension

C. Jardim, S. Hoette and R. Souza

In recent years, important contributions to the understanding of pulmonary hypertension (PH) have been published in core clinical journals [1]. Relevant and thought-provoking studies evidencing the high quality of research in the PH field have been carried out by specialists worldwide. We have decided to focus on special issues we believe to be, on the one hand, pertinent to the understanding of what has happened hitherto and, on the other hand, useful to lay the new foundations on which future research will be based.

Amongst the articles published in the last couple of years, we believe that the following groups of interest deserve special attention: the summary of the fourth World Symposium on PH; the guidelines on PH (both the American and the European); and the studies that shed new light on the discussion of survival in PH.

FOURTH WORLD SYMPOSIUM ON PH

In June 2009, the results of the discussion of working groups on specific issues of PH were published in 11 articles and one editorial in the *Journal of the American College of Cardiology* [2–13]. The articles covered a vast array of topics on PH, from basic research (comprising development, pathology, inflammation, genetics, and cellular and molecular basis of PH) to clinical issues, such as classification, diagnosis, the role of surgery and medical treatment in pulmonary arterial hypertension (PAH). Interestingly, there were also papers on end-points and clinical trials, and on future perspectives for the treatment of PAH.

The article entitled ''Updated clinical classification of pulmonary hypertension'' [3] aimed at grouping together different PH manifestations with similar pathophysiological mechanisms, clinical presentation and therapeutic options. In spite of the maintenance of the general architecture of the classification compared to the previous classifications (Second and Third World Symposium on Pulmonary Hypertension in 1998 (Evian, France) and 2003 (Venice, Italy), respectively) [14], some changes have been made to incorporate new knowledge on the disease.

The current classification of PH comprises the following groups, namely: 1) PAH, 1′) pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH), 2) PH owing to left heart disease, 3) PH owing to lung diseases and/or hypoxia, 4) chronic thromboembolic hypertension, and 5) PH with unclear and/or multifactorial mechanisms [3].

Most changes were incorporated in group 1, in which we find different subgroups. The first aspect to be highlighted is that the term idiopathic PAH (IPAH) was maintained, once again avoiding the use of primary and secondary PH; as stated since the Third World Symposium in PH (Venice, 2003) [14].

PAH may occur in a familial context and in this setting up to 70% of the patients may present with bone morphogenetic protein receptor (BMPR)-2 mutations [15, 16]. In addition, a mutation may be found in cases with no family history of PAH (up to 40% of such cases) [17]. Thus, it was reasonable to replace the term ''familial PAH'' by the term ''heritable PAH''. In this subgroup, identifiable mutations are acknowledged, such as BMPR2 and activin receptor-like kinase-1 or endoglin. Recently, the prognostic importance of identifying the presence of mutations has been highlighted [18, 19]. Mutation carriers not only present the genetic anticipation phenomena, in which symptoms start at earlier age as compared to the parents, but are also prone to present worse clinical course or a less favourable prognosis.

The role of drugs and toxins has been stressed and the categorisation of risk factors and the likelihood of developing PAH have been modified. In the previous classification, drugs and toxins were regarded as an associated condition, *i.e.* just as connective tissue disease [14]. However, recently published data suggest that the drugs act more like a trigger not necessarily influencing the clinical course of the disease [20]. We have also learnt that BMPR2 mutations can be found in anorexigen-induced PH [20, 21]. Based on these data, a subtle but significant change was made and instead of an associated condition, the classification now states ''drug and toxin-induced PAH''. In terms of epidemiology, this assumption allows the inclusion of this subgroup of patients together with patients with IPAH in clinical studies.

In the associated conditions, we have seen the incorporation of schistosomiasis as an associated condition for the development of PAH, and the limitation of the subgroup formerly generically called haemoglobinopathies [13] to the more specific subgroup of chronic haemolytic anaemia.

Schistosomiasis has been studied for decades and its association with PH has been described in the first half of the 20th Century [22, 23]. Formerly in group 4, schistosomiasis-associated PAH (Sch-PAH) has been reclassified into group 1. A recent study [24] confirmed earlier studies [25], demonstrating that in schistosomiasis most of the vascular injuries are not solely explained by egg embolism. In addition, the occurrence of

Pulmonary Dept, Heart Institute, University of São Paulo Medical School, São Paulo, Brazil.

CORRESPONDENCE: R. Souza, Pulmonary Dept, University of São Paulo Medical School, R. Afonso de Freitas 451 ap 112, São Paulo, Brazil, 04006-052. E-mail: rogerio.souza@incor.usp.br

Received: Sept 14 2010; Accepted after revision: Oct 13 2010

PROVENANCE: Submitted article, peer reviewed.

plexiform lesions in Sch-PAH might be indistinguishable from those seen in IPAH. Furthermore, there is growing evidence based on experimental models emphasising the role of inflammatory mechanisms on the pathogenesis of Sch-PAH [26]. Invasive haemodynamic assessment showed a PAH prevalence of 4.6% in patients with the hepatosplenic form of schistosomiasis. The development of PAH in this subgroup of patients may be related to inflammation, co-existence of porto-pulmonary hypertension and occasional increased cardiac output to the pulmonary circulation [27]. These multiple possible pathways may somehow explain the better clinical course of Sch-PAH. When compared to IPAH, Sch-PAH patients present with a better haemodynamic profile at diagnosis and better prognosis; nonetheless, they still have a 3-yr mortality rate of ~15% [28]. Since schistosomiasis is a highly prevalent disease worldwide and given the non-negligible mortality rate, the reclassification of Sch-PAH in group 1 based on pathological and haemodynamic studies may warrant trials with specific treatments for this highly prevalent condition.

PAH associated with chronic haemolytic anaemias, such as sickle-cell disease or thalassemia, remained in group 1, replacing the generic term haemoglobinopathies, which was present on the previous classification. The possible mechanisms for the development of PH in this group include a high cardiac output with consequential pulmonary vascular hyperflow and impaired nitric oxide action in the pulmonary vessels due to chronic haemolysis. Because one or more of these mechanisms may contribute to the elevation of pulmonary pressure in this setting, patients may present with either predominant pre- or post-capillary PH [29]. However, since a significant proportion of patients with PH and haemolytic anaemias have PAH, they were kept in group 1.

It is important to highlight that other conditions, such as connective tissue diseases [30] or schistosomiasis [31], may present pre- or post-capillary PH. Based on this, the classification cannot be done solely according to the baseline disease; it is absolutely indispensible to combine the clinical information and the results of the invasive haemodynamic evaluation in order to appropriately classify an individual with PH.

Finally, in group 1′ we find PVOD and PCH. Although presenting with different phenotypes, they have been placed together for occasionally having similar risk factors, genetic mutations and pathological findings, most of which they share with IPAH. However, when it comes to response to treatment, data is somewhat disappointing. In fact, some treatments to IPAH may actually be deleterious for these conditions if not used cautiously [32–35].

Group 2 comprises what is believed to be the most frequent cause of PH. In the previous classification, left ventricular heart disease was divided into atrial/ventricular or valvular disease [14]. In the current classification, PH owing to left heart disease was divided into systolic or diastolic dysfunction, maintaining valvular disease as a separate cause. There has been an increased interest of left ventricular dysfunction with normal ejection fraction. Specific algorithms have been proposed to better diagnose this clinical condition avoiding the possible deleterious effects that inadequate treatments strategies might cause when this condition is not recognised [4].

In group 3, a new category was added: mixed obstructive/restrictive disease. It has been recently recognised that patients presenting with upper lobe emphysema combined with lower lobes interstitial infiltrate have higher incidence of PH, with direct implication on prognosis [36, 37].

In group 4 we find chronic thromboembolic pulmonary hypertension (CTEPH). Formerly, all causes of thromboembolic disease were subclassified in proximal and distal obstruction [38]. Since CTEPH may be an operable form of PH with potential cure (or significant improvement in right ventricle function), the new classification avoids the distinction between proximal end distal obstruction, to underline the need of specific multidisciplinary assessment of such cases in experienced reference centres in order to evaluate operability.

Finally, in group 5 we find PH with unclear multifactorial mechanisms. Haematological, systemic and metabolic disorders are described in this group, recognising the relationship between these conditions and PH; however, expressing the uncertainties about pathophysiology, treatment and outcome. The classification working team has fortunately found an adequate name for this set of conditions within group 5 instead of simply calling it ''PH caused by disorders directly affecting the pulmonary vasculature'' or ''miscellaneous'', as in previous classifications [14].

The definition of resting PH has not changed, being defined as the presence of mean pulmonary artery pressure ($\bar{P}_{pa}$) $\geqslant$25 mmHg. A resting $\bar{P}_{pa}$ between 8 and 20 mmHg should be considered normal. The authors consider that further studies are needed to determine the natural history of individuals with a resting $\bar{P}_{pa}$ between 21 and 24 mmHg. The definition of exercise PH is still awaiting better evidence to support it, therefore, being excluded from the current classification [39].

A thorough search of the literature and a strict classification of the levels of evidence of each intervention were performed to put together an algorithm to treat patients in group 1, in each functional class [12]. General interventions, such as anticoagulants, oxygen and diuretics, were incorporated into the algorithm as expert opinion level of evidence. When it comes to specific treatment, the following data are presented for the same level of recommendation, in alphabetical order, not in order of importance (all oral therapy, unless otherwise stated).

PAH class II: Level of recommendation A: ambrisentan, bosentan, sildenafil; level of recommendation B: sitaxsentan, tadalafil.

PAH class III: Level of recommendation A: ambrisentan, bosentan, epoprostenol (intravenous), iloprost (inhaled), sildenafil; level of recommendation B: sitaxsentan, tadalafil, treprostinil (subcutaneous); level of recommendation C: beraprost; expert opinion B: iloprost (intravenous), treprostinil (intravenous).

PAH class IV: Level of recommendation A: epoprostenol (intravenous); level of recommendation B: iloprost (inhaled); level of recommendation C: treprostinil (subcutaneous); expert opinion B: iloprost (intravenous), treprostinil (intravenous), initial combination therapy; expert opinion C: ambrisentan, bosentan, sildenfil, sitaxsentan, tadalafil.

It is also interesting to note that in the event of lack of clinical response, a sequential combination therapy is considered with either three classes of drugs available (phosphodiesterase-5 inhibitors, endothelin receptor antagonists and prostanoids). This treatment approach has been reported in different settings and with different combinations of drugs [40–42]; no specific combination is formally recommended.

The relevance of this article is to organise the available data on treatment in an evidence-based algorithm, considering the incorporated practice of combination therapy, either upfront (for the most severe cases) or add-on (in the event of lack of clinical response).

THE EUROPEAN SOCIETY OF CARDIOLOGY/EUROPEAN RESPIRATORY SOCIETY AND THE AMERICAN COLLEGE OF CHEST PHYSICIANS/AMERICAN HEART ASSOCIATION GUIDELINES

Following the publication of the summary of the Fourth World Symposium on PH, joint guidelines from the European Society of Cardiology/European Respiratory Society [43] for the diagnosis and treatment of pulmonary hypertension were published, as was the American College of Chest Physicians (ACCP)/American Heart Association (AHA) expert consensus on pulmonary hypertension [44]. These guidelines offered another unique opportunity to propose useful approaches to issues in clinical practice. Some aspects of both documents deserve closer attention.

In the European guidelines, an interesting approach to the likelihood of the presence of PH based on echocardiogram findings was presented. Since echocardiogram is usually the first assessment to detect the possibility of PH [45], it may be reasonable to consider combined parameters to establish the likelihood of PH. By combining the tricuspid regurgitation velocity to other echocardiographic variables suggestive of PH an arbitrary criteria suggest the stratification in PH unlikely, possible and likely. The interesting aspect of this stratification is its combination to the presence of symptoms or associated baseline conditions in order to obtain a rational use of right heart catheterisation or to propose the follow-up approach for a given patient. Although arbitrary, these recommendations are from an expert consensus and may represent innovative ways for daily practice or at least suggest new approaches to be addressed in future studies [46].

Conversely, the ACCP/AHA consensus suggests a practical approach on diagnosing PH with a table of pivotal and contingent tests. For instance, ventilation/perfusion scans are considered to be pivotal test, whereas computed tomography angiograms are considered to be contingent in the investigation process. By such a diagnostic approach, a more reasonable use of the diagnostic tools is possible, based on the probability of diagnosis, timesaving and resources.

These provocative suggestions might be considered when adapting the diagnostic algorithms to a specific socio-geographical condition, putting together the regional characteristics and the availability of the different diagnostic tools.

SURVIVAL

In 2009, we emphasised the role of contemporary registries in PAH not only to better characterise the disease itself but also to recognise that regional characteristics have to be identified in order to appropriately extrapolate and/or adapt international guidelines for diagnosis and treatment [1]. Interestingly, over the past year, the survival data of some of these registries have become available. One of the problems of dealing with an orphan disease is its low prevalence. Consequently, an important part of the gathered knowledge results from a small observation series, precluding the generalisation of the findings [47]. One alternative to bypass this obvious limitation is to set up multicenter registries. However, significant caveats may take place in such an approach and should be taken into consideration when analysing data coming from registries of rare diseases. Retrospective cohorts have the limitation imposed by missing data and reliable diagnosis, while prospective cohorts may limit the inclusion criteria too much in order to homogenise the study population [48]. Both characteristics may limit the extrapolation of data and should be carefully considered. Nevertheless, three different registries had their survival data published during the last year and from all of them new prediction equations have emerged. This is particularly interesting since it reinforced a common feeling that the National Institute of Health equation, published in the early 1990s [49], was no longer accurate to evaluate contemporary data, considering the significant development in knowledge and available therapies that has taken place in the past decades.

THENAPPAN *et al.* [50] published a large monocentric registry of PAH patients. One of the findings that was also confirmed by the other registries is that current PAH patients present at an older age compared to earlier studies. While in the late 1980s the mean age at diagnosis was 37 yrs [51], in this study the authors found a mean age of 48 yrs (patients were even older in the other published registries). Moreover, older age at diagnosis was independently associated with long-term survival. Of note, the majority of patients presented in functional class III or IV at diagnosis, although the predominant retrospective nature of the study may have biased this finding. The authors also described that connective tissue disease, functional capacity, right atrial pressure, cardiac index and pulmonary vascular resistance were predictors of survival. Surprisingly, the authors decided to build a prediction equation based not on the prognostic variables found in their study but only on the same hemodynamic variables used in the National Institute of Health equation alleging their intention to make a direct comparison to the previously described equation. The proposed model was certainly a step further in the analysis of survival data in PAH; however, by excluding significant parameters the authors may have limited the extrapolation of their prediction model.

In 2006, baseline data from the French National Registry on PAH were published evidencing a PAH incidence of 2.4 cases per 1 million adult inhabitants per year and a prevalence of 15 cases per 1 million inhabitants for PAH (5.9 cases per 1 million inhabitants for IPAH) [52]. The study included 674 cases from 17 different reference centres. By that time, the authors had already described older age at diagnosis and a less preserved functional class (III or IV) for the vast majority of the patients, reinforcing the concept that even with the development obtained in recent years the diagnosis was still late on the disease progression.

The 3-yr survival data for idiopathic, heritable and anorexigen-associated PAH have been addressed in two publications this year [12, 48]. The first study demonstrated 1-, 2- and 3-yr survival rates of 82.9%, 67.1% and 58.2%, respectively [53]. These results, when compared to the results of the National Institute for Health registry, suggest that survival has been significantly but still too modestly improved, reinforcing the concept that PAH is still a devastating clinical condition. Of note, the authors identified three independent prognostic factors: cardiac output and 6-min walk test (6MWT) distance at diagnosis, and sex. Male patients notably presented with worse prognosis compared to the predominant female subgroup. The possible mechanisms that justify this association of male sex and prognosis in IPAH are not clear but this now constitutes a new issue to be addressed in future studies. Some methodological aspects of this study deserve better attention. The authors decided to limit their observations to a more homogeneous population; for this, not only did they limit the population to patients with idiopathic, heritable and anorexigen-induced PAH but also decided to consider only the data obtained at diagnosis, in an attempt to deal with a more robust data set. Another important aspect was the distinction between newly diagnosed patients (incident) and prevalent patients (diagnosed before study enrolment). It is well known that the inclusion of prevalent cases in observational studies may impose a significant bias if the mortality rate is not constant during time, which is the case for PAH.

By distinguishing both populations, the authors tried to minimise this bias. However, the arbitrary cut-off for combining the prevalent and incident groups in order to perform the survival analysis (the authors joined prevalent patients diagnosed <3 yrs of study enrolment and performed a left truncation analysis) still imposed a bias to the analysis. It is important to notice that no specific treatment algorithm, besides the international guidelines available at the time [54], was imposed; thus the study tried to reflect ''real life'' in PAH management.

In another study, the authors analysed the significant difference on survival between incident and prevalent cases [55]. In addition, the trend in survival was associated with the time from diagnosis in the prevalent population; the shorter the time from diagnosis the more the prevalent subgroup resembled the incident group, with worse prognosis. This study also reinforced the concept that different diagnoses within group 1 have different survival rates. We also have to consider that there are different survival rates in different groups of PAH, *e.g.* a worse prognosis in connective tissue disease-PAH and a better prognosis in HIV-PAH, congenital heart disease-PAH and Sch-PAH [56–58].

Moreover, a new prognostic equation for idiopathic, heritable and anorexigen-induced PAH was proposed based on the three prognostic markers found on the multivariate analysis (sex, 6MWT and cardiac output), thus incorporating markers other than the common haemodynamic ones, possibly increasing the representativeness of the equation. This assumption, however, has to be properly validated in a different population prior to being accepted.

Another important registry whose data have been published this year is the REVEAL registry (Registry to Evaluate Early and Long-Term PAH Disease Management). The registry comprises the efforts of 54 different centres in the USA and has been evaluated in three articles addressing different characteristics of this comprehensive study on PAH [59–61].

The first article described the baseline demographic characteristics of the 2,967 patients included in the registry [59]. This study confirmed the shift toward older age at diagnosis in PAH. 46% of included patients presented with IPAH; considering patients with associated causes for PAH, connective tissue disease associated-PAH accounted for almost half of the cases. It is interesting to note the low prevalence of HIV associated-PAH in the REVEAL study (~2.2%) as compared to the prevalence found in the French Registry (6.2%). How much of this can be attributed to lower awareness about the association in the US as compared to France where a quite recent multicenter prevalence study was performed [62] is still a matter of debate.

An interesting comparison between the REVEAL registry and other historic or non-US contemporary registries recently became available, reported by FROST *et al.* [61]. In this study the authors selected the subgroups within the REVEAL registry that could be directly compared to other studies. In addition, different aspects of the registry not previously addressed were analysed. One peculiar aspect is the behaviour of the female/male ratio increasing with survival post-diagnosis. One might link this finding to a worse prognosis for the male sex found in the French Registry [53], strengthening the need to address the role of sex in PAH survival in a specific study with an appropriate design.

The incidence for idiopathic and familial PAH found in the registry was 1.1 cases per million while the prevalence of PAH was 12.4 cases per million which is comparable to the previously described rates [52] providing consistent data for contemporary use.

Finally, a third study analysing survival of PAH patients included in the REVEAL registry has been published [60]. The authors decided not to limit their study population, including all forms of PAH now within group 1 of the classification and available at the time of the study initiation [14]. By doing so, the authors tried to make the analyses reproducible in all subgroups; as if a proposition of this approach is of indubitable value, it may impose limitations to the analysis itself. Another methodological issue that has to be accounted for is the fact that the data used in the analyses was collected within a certain period of time and not necessarily at the diagnosis. In addition, prevalent and incident cases were considered together which could have resulted in somehow optimistic survival rates. The authors, however, carefully included time from diagnosis in the analysis in order to categorise the patients; nevertheless, no statistical significance was found regarding this dichotomisation of the study population. Of note is the fact that the comparison was made between patients diagnosed within 90 days prior to study enrolment and patients diagnosed >90 days before enrolment, a rather small time-frame to properly distinguish the two study populations if the results of the prevalent population from the French study is considered [55]. This is particularly important since the vast majority of the REVEAL population comprises prevalent patients.

This large cohort allowed the identification of multiple prognostic factors, such as the origin of PAH (different diagnoses within group 1), age, functional class, 6MWT distance, cardiac function, B-type natriuretic peptide, echocardiographic finding of pericardial effusion and diffusing capacity of the lung for carbon monoxide. Based on these variables, the authors were able not only to develop a prognostic equation but to create a ''stratification of risk'' considering 1-yr survival. This stratification confirmed a concept suggested in 2006 in an article by MCLAUGHLIN and MCGOON [63] in which the authors described several conditions that could be reflecting a higher risk of death. The REVEAL study allowed the proper validation of the concept and also identified the group of variables that should be considered in this matter.

Taken together, these registries brought important information to the field by identifying subgroups with worse prognosis that should be better addressed in terms of treatment strategies. There are certainly numerous possibilities to explore in the future, such as upfront combination therapy and earlier indication for epoprostenol. These studies provided us with goals to be reached in order to possible interfere in the prognosis of PAH patients.

In summary, the last couple of years have been quite prolific in terms of baseline concepts that will allow the delineation of better studies in the near future. Besides the development of new therapies, the advances to be reached will depend on strong foundations regarding concepts and understanding of the natural course of the disease; doubtlessly these recent studies represent a significant step forward in this sense.

STATEMENT OF INTEREST

None declared.

REFERENCES

1 Souza R, Jardim C. Trends in pulmonary arterial hypertension. *Eur Respir Rev* 2009; 18: 7–12.
2 Humbert M, McLaughlin VV. The 4th World Symposium on Pulmonary Hypertension. Introduction. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S1–S2.
3 Simonneau G, Robbins IM, Beghetti M, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S43–S54.
4 Hoeper MM, Barbera JA, Channick RN, *et al.* Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S85–S96.
5 Hassoun PM, Mouthon L, Barbera JA, *et al.* Inflammation, growth factors, and pulmonary vascular remodeling. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S10–S19.
6 Machado RD, Eickelberg O, Elliott CG, *et al.* Genetics and genomics of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S32–S42.
7 Keogh AM, Mayer E, Benza RL, *et al.* Interventional and surgical modalities of treatment in pulmonary hypertension. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S67–S77.
8 McLaughlin VV, Badesch DB, Delcroix M, *et al.* End points and clinical trial design in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S97–S107.
9 Morrell NW, Adnot S, Archer SL, *et al.* Cellular and molecular basis of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S20–S31.
10 Ghofrani HA, Barst RJ, Benza RL, *et al.* Future perspectives for the treatment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S108–S117.
11 Badesch DB, Champion HC, Sanchez MA, *et al.* Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S55–S66.
12 Barst RJ, Gibbs JS, Ghofrani HA, *et al.* Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S78–S84.
13 Tuder RM, Abman SH, Braun T, *et al.* Development and pathology of pulmonary hypertension. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S3–S9.
14 Simonneau G, Galie N, Rubin LJ, *et al.* Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004; 43: Suppl. 12, 5S–12S.
15 Cogan JD, Pauciulo MW, Batchman AP, *et al.* High frequency of BMPR2 exonic deletions/duplications in familial pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006; 174: 590–598.
16 Aldred MA, Vijayakrishnan J, James V, *et al.* BMPR2 gene rearrangements account for a significant proportion of mutations in familial and idiopathic pulmonary arterial hypertension. *Hum Mutat* 2006; 27: 212–213.
17 Machado RD, Aldred MA, James V, *et al.* Mutations of the TGF-beta type II receptor BMPR2 in pulmonary arterial hypertension. *Hum Mutat* 2006; 27: 121–132.
18 Girerd B, Montani D, Coulet F, *et al.* Clinical outcomes of pulmonary arterial hypertension in patients carrying an ACVRL1 (ALK1) mutation. *Am J Respir Crit Care Med* 2010; 181: 851–861.
19 Sztrymf B, Coulet F, Girerd B, *et al.* Clinical outcomes of pulmonary arterial hypertension in carriers of BMPR2 mutation. *Am J Respir Crit Care Med* 2008; 177: 1377–1383.
20 Souza R, Humbert M, Sztrymf B, *et al.* Pulmonary arterial hypertension associated with fenfluramine exposure: report of 109 cases. *Eur Respir J* 2008; 31: 343–348.
21 Humbert M, Deng Z, Simonneau G, *et al.* BMPR2 germline mutations in pulmonary hypertension associated with fenfluramine derivatives. *Eur Respir J* 2002; 20: 518–523.
22 Shaw AP, Ghareeb A. The pathogenesis of pulmonary schistosomiasis in Egypt with special reference to Ayerza's disease. *J Pathol Bacteriol* 1938; 46: 401–424.
23 Souza R, Fernandes CJ, Jardim CV. Other causes of PAH (schistosomiasis, porto-pulmonary hypertension and hemolysis-associated pulmonary hypertension). *Semin Respir Crit Care Med* 2009; 30: 448–457.
24 Pozzan J, Souza R, Jardim C. Histopathological features of pulmonary vascular disease in chronic Schistosomia mansoni infection are not different from those in idiopathic pulmonary hypertension. Presented at the American Thoracic Society Annual Congress, Toronto, Canada; 2008: A443.
25 Chaves E. The pathology of the arterial pulmonary vasculature in manson's schistosomiasis. *Dis Chest* 1966; 50: 72–77.
26 Graham BB, Mentink-Kane MM, El-Haddad H, *et al.* Schistosomiasis-induced experimental pulmonary hypertension: role of interleukin-13 signaling. *Am J Pathol* 2010; 177: 1549–1561.
27 Hovnanian A, Hoette S, Fernandes CJ, *et al.* Schistosomiasis associated pulmonary hypertension. *Int J Clin Pract Suppl* 2010; 165: 25–28.
28 dos Santos Fernandes CJ, Jardim CV, Hovnanian A, *et al.* Survival in schistosomiasis-associated pulmonary arterial hypertension. *J Am Coll Cardiol* 2010; 56: 715–720.
29 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.
30 de Groote P, Gressin V, Hachulla E, *et al.* Evaluation of cardiac abnormalities by Doppler echocardiography in a large nationwide

multicentric cohort of patients with systemic sclerosis. *Ann Rheum Dis* 2008; 67: 31–36.
31 Lapa M, Dias B, Jardim C, *et al.* Cardiopulmonary manifestations of hepatosplenic schistosomiasis. *Circulation* 2009; 119: 1518–1523.
32 Montani D, Jais X, Price LC, *et al.* Cautious epoprostenol therapy is a safe bridge to lung transplantation in pulmonary veno-occlusive disease. *Eur Respir J* 2009; 34: 1348–1356.
33 Montani D, Price LC, Dorfmuller P, *et al.* Pulmonary veno-occlusive disease. *Eur Respir J* 2009; 33: 189–200.
34 Montani D, Jais X, Dorfmuller P, *et al.* Goal-oriented therapy in pulmonary veno-occlusive disease: a word of caution. *Eur Respir J* 2009; 34: 1204–1206.
35 Palazzini M, Manes A. Pulmonary veno-occlusive disease misdiagnosed as idiopathic pulmonary arterial hypertension. *Eur Respir Rev* 2009; 18: 177–180.
36 Cottin V, Le Pavec J, Prevot G, *et al.* Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. *Eur Respir J* 2010; 35: 105–111.
37 Cottin V, Nunes H, Brillet PY, *et al.* Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Eur Respir J* 2005; 26: 586–593.
38 Dartevelle P, Fadel E, Mussot S, *et al.* Chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2004; 23: 637–648.
39 Kovacs G, Berghold A, Scheidl S, *et al.* Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J* 2009; 34: 888–894.
40 Humbert M, Barst RJ, Robbins IM, *et al.* Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004; 24: 353–359.
41 Hoeper MM, Markevych I, Spiekerkoetter E, *et al.* Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J* 2005; 26: 858–863.
42 Galie N, Negro L, Simonneau G. The use of combination therapy in pulmonary arterial hypertension: new developments. *Eur Respir Rev* 2009; 18: 148–153.
43 Galie N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; 34: 1219–1263.
44 McLaughlin VV, Archer SL, Badesch DB, *et al.* ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009; 53: 1573–1619.
45 Vachiéry J-L, Coghlan G. Screening for pulmonary arterial hypertension in systemic sclerosis. *Eur Respir Rev* 2009; 18: 162–169.
46 Montani D, O'Callaghan DS, Jaïs X, *et al.* Implementing the ESC/ERS pulmonary hypertension guidelines: real-life cases from a national referral centre. *Eur Respir Rev* 2009; 18: 272–290.
47 McLaughlin VV, Suissa S. Prognosis of pulmonary arterial hypertension: the power of clinical registries of rare diseases. *Circulation* 2010; 122: 106–108.
48 Provencher S, Souza R. Predicting survival in pulmonary arterial hypertension: time to move forward. *Eur Respir J* 2010; 35: 958–959.
49 D'Alonzo GE, Barst RJ, Ayres SM, *et al.* Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991; 115: 343–349.
50 Thenappan T, Shah SJ, Rich S, *et al.* Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. *Eur Respir J* 2010; 35: 1079–1087.
51 Rich S, Dantzker DR, Ayres SM, *et al.* Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987; 107: 216–223.
52 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.
53 Humbert M, Sitbon O, Chaouat A, *et al.* Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010; 122: 156–163.
54 Galie N, Seeger W, Naeije R, *et al.* Comparative analysis of clinical trials and evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol* 2004; 43: Suppl. 12, 81S–88S.
55 Humbert M, Sitbon O, Yaici A, *et al.* Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010; 36: 549–555.
56 Degano B, Yaici A, Le Pavec J, *et al.* Long-term effects of bosentan in patients with HIV-associated pulmonary arterial hypertension. *Eur Respir J* 2009; 33: 92–98.
57 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.
58 Beghetti M, Tissot C. Pulmonary arterial hypertension in congenital heart diseases. *Semin Respir Crit Care Med* 2009; 30: 421–428.
59 Badesch DB, Raskob GE, Elliott CG, *et al.* Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest* 2010; 137: 376–387.
60 Benza RL, Miller DP, Gomberg-Maitland M, *et al.* Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010; 122: 164–172.
61 Frost AE, Badesch DB, Barst RJ, *et al.* The Changing Picture of Pulmonary Arterial Hypertension (PAH) Patients in the United States: How the REVEAL Registry Differs From Historic and Non-US Contemporary Registries. *Chest* 2010 [Epub ahead of print DOI: 10.1378/chest.10-0075].
62 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.
63 McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. *Circulation* 2006; 114: 1417–1431.