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Review Article

Pulmonary arterial hypertension in congenital cardiac disease – the need for refinement of the Evian-Venice classification

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Abstract Pulmonary hypertension associated with congenital systemic-to-pulmonary shunts has been classified, in the Evian-Venice classification, as Pulmonary Arterial Hypertension, which includes a heterogeneous group of conditions. Emerging options for treatment of patients with pulmonary arterial hypertension are related to those with the idiopathic form of the disease, but may also improve quality of life and survival in patients with pulmonary arterial hypertension associated with congenital cardiac disease. Despite the evident similarities in pulmonary vascular disease, it is important also to recognise the differences between patients in whom pulmonary arterial hypertension is the consequence of systemic-to-pulmonary shunts as opposed to those with other conditions. Patients with pulmonary hypertension associated with congenital cardiac disease themselves constitute a heterogeneous population, in which generalisation may be hazardous. Specific considerations need to be given to the type of cardiac diagnosis, the prognosis and evolution of pulmonary vascular disease, and the circulatory physiology before embarking on new strategies for medical treatment in the individual patient. In this review, we highlight the features that require specific attention in these patients. In addition, we discuss briefly the data currently available on the effectiveness of the new anti-proliferative drugs in patients with the Eisenmenger syndrome.

Keywords: Congenital cardiac malformations; congenital shunts; Eisenmenger syndrome

Pulmonary hypertension is characterized by an increased pulmonary arterial pressure, defined as a mean pulmonary arterial pressure greater than 25 millimetres of mercury at rest, or 30 millimetres of mercury during exercise.[1] It may be a symptom of a variety of underlying conditions. During the successive World Symposiums on Pulmonary Hypertension held in Evian in 1998, and Venice in 2003, pulmonary hypertension was classified into 5 clinical categories, based on similarities in pathophysiological mechanisms, clinical presentation, and therapeutic options (Table 1).[2]

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The first category, pulmonary arterial hypertension, includes a heterogeneous group of conditions, all sharing a typical pulmonary vascular disease that is assumed to have common characteristics regarding morphological findings, clinical presentation and responsiveness to therapy. These characteristics are held to distinguish pulmonary arterial hypertension from the other 4 categories of pulmonary hypertension.

In a complex disease such as pulmonary hypertension, which occurs in a relative limited number of patients, such classification, although inevitably associated with limitations, has proven to be of utmost importance in the communication about individual patients, in standardizing diagnosis and treatment, in conducting trials with homogeneous groups of patients, and in analyzing novel

Table 1. Clinical classification of pulmonary hypertension, as proposed at the Third World Congress, Venice 2003.[2]

1. Pulmonary arterial hypertension
1.1 Idiopathic pulmonary arterial hypertension
1.2 Familial pulmonary arterial hypertension
1.3 Related conditions
1.3.1 Collagen vascular disease
1.3.2 Congenital systemic-to-pulmonary shunt
1.3.3 Portal hypertension
1.3.4 Human immunodeficiency virus infection
1.3.5 Drugs and toxins (including appetite suppressants)
1.3.6 Other (including thyreoid disorders, glycogen storage disease)
1.4 Associated with significant venous or capillary involvement
1.5 Persistent pulmonary hypertension of the newborn
2. Pulmonary venous hypertension
2.1 Left-sided atrial or ventricular heart disease
2.2 Left-sided valvular heart disease
2.3 Pulmonary venous obstruction
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Sleep-disordered breathing
3.4 Alveolar hypoventilation disorders
3.5 Chronic exposure to high altitude
3.6 Developmental abnormalities
4. Pulmonary hypertension resulting from chronic thrombotic and/or embolic disease
4.1 Thromboembolic obstruction of proximal pulmonary arteries
4.2 Thromboembolic obstruction of distal pulmonary arteries
4.3 Nonthrombotic pulmonary embolism
5. Pulmonary hypertension resulting from disorders directly affecting the pulmonary vasculature
e.g. Schistosomiasis, sarcoidosis, histiocytosis X, lymphangiomatosis
Compression of pulmonary vessels (tumor, fibrosing mediastinitis, adenopathy)

pathobiological abnormalities in well-characterized populations. Pulmonary hypertension associated with congenital systemic-to-pulmonary shunts is, according to the Evian/Venice classification, assigned to this category of pulmonary arterial hypertension.[2]

Patients with pulmonary hypertension associated with congenital cardiac disease are a growing population, and themselves form a heterogeneous group, in which simplification may be hazardous and misleading. There is no such thing as a typical patient with this condition. Patients with cardiac defects with systemic-to-pulmonary shunts and pulmonary hypertension distinguish themselves from those with cardiac defects lacking such shunts. Patients with restrictive shunts will have a different natural history compared to those in whom the shunt is non-restrictive. This applies not only to the natural history of the cardiac defect, and the risk for development of pulmonary hypertension, but also to prognosis once pulmonary hypertension is established. Similarly, patients in whom the original shunt is surgically closed will face other sequels of pulmonary arterial hypertension compared to patients in whom the shunt was not closed. It is obvious that, when discussing or evaluating options for treatment, these different types of patients cannot be regarded as one single group.[3,4]

Thus, although the Evian/Venice classification has introduced a standardized approach to pulmonary hypertension, which can be regarded as a major achievement, it may require refinement for its application to patients in whom pulmonary hypertension co-exists with congenital cardiac disease. In these patients, additional specific considerations are required in order to make appropriate decisions on diagnosis and treatment. In this review, we highlight several aspects of clinical presentation, diagnosis, and treatment that require specific attention in such patients with pulmonary hypertension seen in the setting of congenital cardiac disease.

The rationale of the classification

The term "pulmonary arterial hypertension associated with congenital cardiac disease" is itself misleading. This terminology, used frequently in recent literature, is confusing. In our opinion, it hampers appropriate clinical decision making and adequate research. Patients with congenital cardiac disease may have different types of malformation, and may demonstrate different types of pulmonary hypertension, associated with different clinical courses and prognoses. It is essential, therefore, when describing those with so-called "pulmonary hypertension associated with congenital cardiac disease" to describe in detail the morphology of the cardiac anomaly and the medical history, including previous interventions and present co-morbidity, the latter including left ventricular function, thrombo-embolic events, respiratory or pulmonary complications, and use of medications. Also in these patients it is important to search for the underlying condition that causes the pulmonary vascular disease, since that cause may not always be the presence of the cardiac malformation itself.

The reason for classifying a heterogeneous group of diseases into one group was the presumption of common characteristics regarding morphological findings, clinical course, and responsiveness to therapy. But does this presumption hold for those with pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts?

Pulmonary vascular pathology

All forms of pulmonary arterial hypertension have a common characteristic histopathological pattern of vascular remodelling that was first recognised

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in patients with large systemic-to-pulmonary shunts.[5] This typical remodelling process was called plexogenic arteriopathy, indicating the potency to develop the characteristic plexiform lesion, which is unique for pulmonary arterial hypertension. The vascular lesions are characterized by increased muscularization of muscular arteries, and extension of muscularization to normally non-muscularized arterioles. This is followed by formation of typical intimal lesions, including concentric laminar intimal fibrosis and plexiform lesions, leading to occlusion of small arteries, and associated with progressive and irreversible disease. The latter lesions do not occur in other forms of pulmonary hypertension.[5]

Clinical course

Pulmonary arterial hypertension shows a progressive and ultimately fatal course. The period of evolution, however, differs significantly in those with congenital shunts compared to other forms.[6] In children with congenital cardiac disease associated with a non-restrictive left-to-right shunt, pulmonary arterial hypertension initially appears to be reversible when the shunt can be closed timely and adequately.[4] This is the only form of pulmonary arterial hypertension in which a reversible stage can be recognised clinically. Only after a certain time period, which may vary widely in individuals, will a point of no return be reached, where the pulmonary arteriopathy will be progressive even after correction of the defect. Ultimately, when pulmonary vascular resistance has increased to systemic level in the un-operated patient, the original left-to-right shunt will reverse so that flow is from right-to-left, leading to cyanosis. This condition is called the Eisenmenger syndrome.

Life-expectancy in patients with this syndrome is far more favourable than in other forms of pulmonary arterial hypertension. In contrast to idiopathic pulmonary arterial hypertension, for which, if the patient is untreated, median survival is 2.8 years, the median survival for those with the Eisenmenger syndrome may be to an age between 40 and 50.[7] This contrast in survival must be taken into account when interpreting outcomes of clinical trials with populations of mixed patients, and when assessing the cost-effect balance of the options for treatment.

Responsiveness to treatment

Although at the time of the conception of the Evian-classification, definite similarities had been recognised between the different forms of pulmonary arterial hypertension, justifying a common classification into one group, it is surprising that this criterion was introduced. At that time, in 1998, there was limited data regarding the response to therapy for different forms of pulmonary arterial hypertension. Most of this data was derived from patients with the idiopathic form, where the differences between pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and other forms of pulmonary arterial hypertension could be expected to affect the response to therapy. At that time, there was no reliable data for patients with the Eisenmenger syndrome.

Variation in structural cardiac malformations and its implications

The evolution of pulmonary vascular disease may differ in patients with congenitally malformed hearts depending on the type of underlying cardiac lesion. It appears that increased flow of blood to the lungs is obligatory in the development of pulmonary arterial hypertension. In patients with structurally malformed hearts not associated with such increased flow to the lungs, characteristic pulmonary arterial hypertension does not develop. Other forms of pulmonary hypertension should then be considered.

The haemodynamic condition characterised by both an increased pulmonary arterial pressure and an increased flow of blood to the lungs is detrimental to the pulmonary vascular bed.[8] This situation occurs in patients with a non-restrictive left-to-right shunt at post-tricuspid level. In more than half of these cases, they develop irreversible, and progressive, pulmonary vascular disease in the first years of life,[4,9] resulting eventually in progression to the Eisenmenger syndrome. Examples of these lesions are large ventricular septal defects, atrioventricular septal defects with common atrioventricular junction, or functionally univentricular hearts. Obviously, an additional right-sided obstructive lesion in these defects, such as pulmonary stenosis, may reduce both pulmonary flow and pressure, and will potentially prevent or delay the development of pulmonary vascular disease.

In cardiac lesions with a left-to-right shunt at the pretricuspid level, with an isolated increase in flow of blood to the lungs, pulmonary vascular disease develops significantly less often and much later in life. Untreated, only from one-tenth to one-fifth of patients with a haemodynamically important interatrial communication will eventually develop pulmonary vascular disease, mostly in their 3rd or 4th decade.[3] A similar situation may occur in patients with a shunt at post-tricuspid level that is limited in size, and therefore restrictive. Then, the pulmonary vascular bed is not exposed to systemic arterial pressure, and the development of pulmonary vascular disease will be prevented or delayed.

The optimal prevention of progression of pulmonary vascular disease in those with congenitally malformed hearts is correction of the original defect. When intervention is correctly timed and successful, early pulmonary vascular disease will regress. After a certain point of no return, pulmonary vascular remodelling will progress even after closure of the original cardiac defect. In other words, the possibility for interventional closure of the defect is determined by the developmental stage of the vascular disease process. Thus, timing of correction is critical. Once advanced pulmonary vascular disease has developed, the temptation to close a present defect should be resisted. Closure in such patients will have detrimental effects. In general, patients with a closed defect combined with advanced pulmonary arterial hypertension have a worse outcome than those with the physiology induced by the Eisenmenger syndrome.[10] This is because the pulmonary vascular disease will continue to progress, the subpulmonary ventricle will miss the opportunity to unload, and it will not be possible to maintain cardiac output.

Patients may also have a residual shunt after correction of their cardiac defect. The consequences of this shunt depend on its extent, whether it is located at pre- or post-tricuspid level, and whether it is restrictive or non-restrictive. As a rule of thumb, in contrast to a non-restrictive shunt, the physiology produced by a restrictive shunt is not believed to contribute considerably to further progression of the disease.

An exceptional challenge is formed by those with a functionally univentricular heart. These patients eventually require conversion to the "Fontan-circulation" as final palliation, where systemic venous return is directed to the lungs without an interposed ventricular pump.[11] Consequently, the slightest increase in pulmonary vascular resistance can jeopardize the total circulation.

The type and size of the cardiac defect may not be the only determinants of the severity of pulmonary vascular disease in those with congenitally malformed hearts. Occasionally, patients with non-restrictive shunts at post-tricuspid level develop accelerated endstage plexogenic arteriopathy, whereas others show delayed, or no development, of advanced pulmonary arterial hypertension. As already stated, of the patients with shunts at pre-tricuspid level, only from one-tenth to one-fifth will eventually develop pulmonary arterial hypertension. These epidemiologic observations suggest an individual susceptibility in these patients.[12] Genetic factors, such as mutations in the bone morphogenetic protein receptor type 2, activin-like kinase type 1, or the 5-hydroxy tryptamine transporter, might play a role in this individual susceptibility.[13] Moreover, children with Down's syndrome and congenitally malformed hearts are believed to develop pulmonary arterial hypertension more frequently, and at an earlier stage, than chromosomally normal children with comparable cardiac malformations,[14] suggesting an increased susceptibility in those with trisomy 21. In patients with a cardiac defect with mild haemodynamic consequences, the question should be raised whether the defect itself is the cause of the pulmonary vascular disease, or if the patient may have another type of pulmonary arterial hypertension independent of the cardiac abnormality.

In other words, in order to understand the relation between coexisting pulmonary hypertension and a congenital cardiac malformation in the individual patient, and to define appropriately prognosis and treatment, it is necessary to assess the progression of the vascular disease, and also adequately to characterise the cardiac malformation from a morphological and physiological point of view. It has been recognized before that the heterogeneity of congenital cardiac diseases, and the complex haemodynamic and pathophysiological interactions, requires a more detailed description than the restricted one that is currently provided in the Evian-Venice classification, specifically "associated with congenital systemic-to-pulmonary shunt".[2] Based on these considerations, previous adaptations or refinements of the Evian-Venice classification have been proposed.[2,15] Until now, however, these suggestions have received little attention, have not been generally accepted, nor have they been included in the common practise of physicians treating pulmonary hypertension. Based on these considerations, we propose a checklist for the clinical characterization of patients with congenitally malformed hearts and coexisting pulmonary hypertension (Table 2).

Current therapies

Until 10 to 15 years ago, no therapy, other than of a supportive nature, was available for patients with pulmonary arterial hypertension. In the last decade, however, insight has evolved concerning the pathobiological mechanisms of the disease, and a growing number of disease-specific therapies is becoming available. Although not curative, these drug therapies have been demonstrated to improve outcome in patients with pulmonary arterial hypertension. Therapies include different prostacyclin-analogues, dual or selective endothelin-receptor-antagonists, and phosphodiesterase-5 inhibitors.

Clinical trials have, in the majority of cases, included patients with idiopathic pulmonary arterial

Table 2. Characterization of pulmonary hypertension associated with congenital cardiac disease.

Presence of a systemic-to-pulmonary shunt.
Yes/No
Previously (age, duration)
(note: if such a shunt does not exist – nor has it existed in history – then another form of pulmonary hypertension than that described in the first group of the Venice classification should be considered)
Location of the shunt.
Pre-tricuspid level – interatrial communication or abnormal pulmonary venous drainage
Post-tricuspid level – interventricular communications, patent arterial duct, functionally univentricular hearts.
Direction of the shunt.
Systemic-to-pulmonary
Pulmonary-to-systemic
Bidirectional
Size of defect. (Anatomical and functional, both at present and at early age):
Quantification of the shunt in terms of ratios of pulmonary to systemic flows
Restriction: is there a pressure drop over the (post-tricuspid) defect
State of repair.
Correction of shunt and age at correction
Pulmonary arterial banding: age at and duration of the banding
Presence, type and duration of surgical shunts (Pott's, Waterston, Blalock-Taussig)
Residual shunting (quantification and location)
Associated cardiac anomalies.
Affecting pulmonary haemodynamics, such as pulmonary stenosis
Affecting pulmonary venous outflow, such as divided left atrium, mitral stenosis, or left ventricular dysfunction
Affecting ventricular function and/or cardiac output
Associated extracardiac anomalies.
Including syndromes, chromosomal abnormalities, airway anomalies, metabolic disorders, and so on
NB. A full description of pulmonary haemodynamics at the time of examination and, if available, at early age is recommended, as is a full history regarding interventions and timelines, in order fully to establish the impact of the cardiac malformations on the development of pulmonary arteriopathy

hypertension. The beneficial effects of therapies in these patients, however, cannot automatically be translated to patients with pulmonary arterial hypertension associated with systemic-to-pulmonary shunts. The reasons for this include differences in the nature of the cardiac disease, the nature of the evolution of the pulmonary vascular disease, the variable prognosis, as discussed before, but also the circulatory pathophysiology of different intracardiac shunts and its consequences for vasodilating therapy. Finally, consideration should be given to the multi-organ involvement in Eisenmenger syndrome. It is vital, therefore, to describe in detail the specific congenital cardiac malformation, along with the state of correction and its functional haemodynamic consequences, before it is possible adequately to assess potential options for treatment. For example, in patients with non-restrictive shunts at post-tricuspid level, the direction and magnitude of the flow across the defect depends directly on the ratio of the pulmonary and systemic vascular resistances. Since a truly selective pulmonary vasodilator does not exist, this has direct consequences for the effect of potentially vasodilating agents: When the effect of the vasodilating agent is more pronounced on the systemic than on the pulmonary vasculature, the net effect will be an increase in right-to left shunting, inducing progressive hypoxaemia and clinical deterioration of the patient. This is in contrast to patients with shunts at pre-tricuspid level, in which the flow across the defect is a mainly diastolic phenomenon, and depends mostly on the diastolic properties of both ventricles. Although patients with congenitally malformed hearts have been included in several large trials, insufficiently powered numbers and lack of appropriate definition of the cardiac malformations have hampered interpretation of the results for this specific group of patients.[16–18]

The Eisenmenger syndrome, originally defined by Paul Wood as all systemic-to-pulmonary shunts leading to pulmonary hypertension and resulting in a reversed or bidirectional shunt,[19] also includes a heterogeneous selection of lesions, including shunts at both pre- and post-tricuspid level. For reasons of homogeneity, we prefer to use the term "true Eisenmenger syndrome" for those patients with non-restrictive systemic-to-pulmonary shunts at post-tricuspid level, in which increased pulmonary vascular resistance has resulted in reversal of the shunt. In the sections that follow, we will discuss the considerations regarding conventional and new therapies in this specific group.

Supportive therapy

Adequate supportive care in patients with the true Eisenmenger syndrome is symptomatic, and is directed at avoiding or treating harmful interventions, complications associated with hypoxia, haematological or haemostatic abnormalities, disturbances of rhythm, infection, and congestive cardiac failure. Although this care has been the hallmark for the treatment of these patients for over 40 years, virtually no reliable studies have been performed on the effects of this approach, including diuretics, treatment with oxygen, or digoxin. Diuretics are thought to be beneficial in the treatment of patients with right ventricular failure and systemic venous congestion. Diuretics should be used with great care in those with the true Eisenmenger syndrome, however, since these patients depend on their preload for adequate circulation.[10] Care should be taken not to dehydrate

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such patients too much. Furthermore, increasing hyperviscosity might lead to the occurrence of thrombo-embolic events.

Phlebotomy with replacement of fluid may alleviate symptoms of hyperviscosity due to erythrocytosis in these patients. It may also lead to iron depletion, resulting in relative microcytic anaemia, often unrecognized because levels of haemoglobin are still elevated, but low in relation to the magnitude of hypoxaemia. The microcytic erythrocytes are believed to increase the risk for cerebrovascular accidents.[20] The use of frequent phlebotomy in those with the true Eisenmenger syndrome, therefore, should be discouraged. If used at all, it should be directed by symptoms of hyperviscosity rather than the level of the haematocrit. Iron supplementation and adequate hydration are mandatory.[10,20]

The risk-benefit ratio of elective, non-cardiac, surgery should be weighed carefully in these patients, since they can be particularly susceptible to relatively small disturbances in their fragile haemodynamic, ventilatory, and haematological balance. These interventions should preferably be performed in centres that are familiar with the specific requirements of the patients.

In the last decade, new effective options for treatment have emerged for the treatment of idiopathic pulmonary arterial hypertension. Anticoagulants,[21,22] calcium-channel-antagonists,[22] prostacyclins,[23] endothelin-receptor-antagonists[24,25] and 5-phosphodiesterase inhibitors[26] have been shown to be beneficial. Although these results cannot automatically be translated to patients with the true Eisenmenger syndrome, these therapies may also be applicable, and encouraging results in this respect are slowly becoming available.

Anti-coagulation

Patients with the true Eisenmenger syndrome are cyanotic, and they experience increased general tendencies to bleed, and have abnormal platelet counts and function. Up to one-tenth of the mortality in such patients has been suggested to be related to haemoptysis,[7] which seems to be clinically more important than in idiopathic pulmonary arterial hypertension. Anticoagulation, therefore, has been considered for a long time contra-indicated in these patients. Paradoxically, evidence exists for a local prothrombotic state at the pulmonary endothelium in these patients[27] and, moreover, chronic proximal pulmonary thrombosis has been demonstrated in one-fifth.[28] This data indicates the need for reconsidering the use of anticoagulants in the Eisenmenger syndrome, and for clinical trials focused on this topic.

Calcium-antagonists

Calcium-channel blockers are systemic vasodilators. They may decrease systemic vascular resistance and increase right-to-left shunting, as already discussed. By definition, those patients with the true Eisenmenger syndrome are unable to fulfil the definitions of the acute responder, as described by Sitbon et al.,[29] because the unrestricted defect leads to equalisation of pulmonary and systemic arterial pressures. Although an incidental study has reported a beneficial haemodynamic effect of calcium-blockade in children with the true Eisenmenger syndrome,[30] in general this therapy has not been accepted by the experts for the use in these patients.

Prostacyclins

Limited data exists on the use of intravenous epoprostenol in patients with pulmonary arterial hypertension caused by congenital cardiac lesions, mostly derived from patients with various types of defects in various states of correction.[31,32] These observational studies showed improved haemodynamics and exercise tolerance after one year of treatment. Only one small series studied the effect in patients with true Eisenmenger physiology,[33] and showed beneficial effects in terms of haemodynamics and exercise tolerance. Of note, however, were the serious adverse effects reported, including cerebrovascular accidents, probably related to the use of a central venous catheter in the presence of a right-to-left shunt. Because of the median survival to 40 or 50 years of age of patients with the true Eisenmenger syndrome, the ratio of risk to benefit of continuous intravenous treatment with epoprostenol will differ from patients with idiopathic pulmonary arterial hypertension.[20] Prostacyclin analogues, such as inhaled iloprost or subcutaneous treprostinil, are conceptually attractive because of their non-intravenous modes of delivery. Their efficacy in these patients, however, has not yet been sufficiently studied.

Endothelin receptor antagonists

The rationale for treatment with endothelin antagonists in patients with Eisenmenger syndrome has been well reviewed.[34] Recently, the first randomized placebo-controlled clinical trial was performed in patients with Eisenmenger physiology, known as BREATHE-5. The trial included patients with shunts at both pre- and post-tricuspid levels, showed that, after 16 weeks of treatment, bosentan did not worsen hypoxaemia, but increased exercise capacity and decreased pulmonary vascular resistance.[35] Improvements in functional class and exercise capacity persisted after 40 weeks of treatment.[36] Long term

results will have to show whether this effect will be lasting, and whether bosentan will be able to improve quality of life and survival in these patients in the long term.

Phosphodiesterase-5 inhibitors

Preliminary data on the efficacy of two 5-phosphodiesterase inhibitors, namely sildenafil and tadalafil, from different reports, suggests beneficial effects.[37–39] These results indicate that phosphodiesterase-5 inhibition with these drugs may be promising, warranting further study in this subgroup of patients.

Combination therapy

The described groups of drugs target different pathobiological pathways. Combinations of these drugs, therefore, may have synergistic effects. On the other hand, caution is required with regard to potential toxicity and interaction of the agents. Although studies are under way, at present data suggesting the additional value of combination therapy in pulmonary arterial hypertension is scarce, in fact non-existent in patients with true Eisenmenger syndrome.

Transplantation

Lung transplantation, generally reserved for patients failing other therapies, has been successful in patients with idiopathic pulmonary arterial hypertension.[40,41] Lung transplantation is limited by availability of donors, rejection of the graft, bronchiolitis obliterans, and complications of immunosuppressive therapy. For selected patients with the Eisenmenger syndrome, lung transplantation with repair of the cardiac defect, or combined heart-lung transplantation, may improve quality of life and possibly survival. With a 10 year survival rate below 50% after combined heart lung transplantation, however, the majority of patients with the true Eisenmenger syndrome will have better prospects for survival without transplantation. The difficulties in clinical decision making regarding timing of transplantation in these patients are emphasized by reports from Charman et al.,[42] and Waddell et al.[43]

Conclusion

At present, patients with progressive, advanced pulmonary arterial hypertension associated with congenitally malformed hearts, including the true Eisenmenger syndrome, cannot be cured. Appropriate conventional management, nonetheless, can reduce their morbidity and mortality. The rapidly increasing knowledge of pathobiological mechanisms, and new options for treatment, largely obtained from patients with idiopathic pulmonary arterial hypertension, are expected to be of great value for these patients. Patients with "pulmonary arterial hypertension associated with congenital heart disease", however, make up a markedly heterogeneous group, in which differences in the specific lesion, along with its clinical course and prognosis, will clearly affect the choices for treatment in the individual patient. The Evian-Venice classification for pulmonary hypertension has been a major achievement in the approach to patients with pulmonary hypertension. It does not fully acknowledge the complex haemodynamic, constitutional and pathophysiological interactions present in the setting of congenital cardiac disease. Rather, the heterogeneity of cardiac morphology, and its functional consequences, requires a customized classification, including a detailed description of morphology, the state of surgical repair, and its functional haemodynamic consequences. Establishing such a clinical phenotype is of crucial importance for correct diagnosis in terms of the nature and course of the pulmonary vascular disease, for appropriate stratification of risk and clinical decision-making in the individual patient, and finally, but no less important, for adequate design and interpretation of clinical research in this heterogeneous group of patients.

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