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Review

Pulmonary arterial hypertension associated with congenital heart disease: Recent advances and future directions

Michael A. Gatzoulis [a,*], Maurice Beghetti [b], Michael J. Landzberg [c], Nazzareno Galiè [d]

[a] NIHR Cardiovascular BRU, Royal Brompton Hospital and the National Heart and Lung Institute, Imperial College, London, UK
[b] Children's Hospital, University of Geneva, Geneva, Switzerland
[c] BACH Pulmonary Hypertension Service, Departments of Paediatrics, Medicine and Surgery, Boston, USA
[d] Department of Experimental, Diagnostic and Specialty Medicine—DIMES, Bologna University Hospital, Bologna, Italy

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ABSTRACT

Congenital heart disease (CHD), the most common inborn defect, affects approximately 1% of all newborns worldwide. Advances in its diagnosis and treatment have led to a dramatic improvement in patients' quality of life and long-term survival prospects. However, recently it has been realised that many of these patients are affected by ongoing and life-long cardiac issues, namely residual and progressive haemodynamic lesions, arrhythmia and sudden cardiac death, as well as the development of chronic heart failure and pulmonary arterial hypertension (PAH) — all of which merit tertiary care. Unfortunately, many patients with CHD are lost to follow-up, due to the assumption that their initial response to surgical and or catheter intervention in childhood led to cure. Furthermore, there are many patients with undiagnosed or unoperated CHD in the developing world coming to medical attention during adulthood. Our article focuses on advances in the management of PAH associated with CHD, a common association with an adverse impact on quality of life and survival prospects that affects approximately 10% of patients with CHD. Much of the recent progress in PAH–CHD has focused on the extreme end of the disease spectrum, namely on Eisenmenger syndrome. Herein we discuss this progress and future directions for this emerging cardiovascular field.

1 . Introduction

Pulmonary arterial hypertension (PAH), defined as a pulmonary arterial pressure of ≥25 mm Hg at rest in the presence of normal pulmonary capillary wedge pressure (i.e. ≤15 mm Hg), is relatively common amongst patients with congenital heart disease (CHD) [1]. Recent prevalence data on PAH in adult CHD patients report rates between 4.2% (in a national CHD registry [2]) and 28% (in a cohort of tertiary European CHD centres) [3]. Although the exact prevalence of PAH in association with CHD (PAH–CHD) in the community remains unknown, many patients with CHD have sadly been lost to specialist follow-up [4]. Furthermore, severity of PAH and its rate of progression often remain largely unknown, even amongst patients with CHD who are currently under specialist cardiac care. This lack of information occurs because the urgency to prevent the development of PAH in infancy and early childhood in the developed world at least tends to relax once the diagnosis is made and early surgery or catheter intervention is performed. However, a proportion of patients who have received seemingly appropriate childhood therapy go on to develop late PAH for reasons that are not well understood. There may be an as yet undefined genetic susceptibility to develop PAH amongst patients with CHD, which persists even after haemodynamic intervention in early childhood. Furthermore, patients with anatomically complex CHD, who are now surviving into adulthood following improvements in palliative procedures and patients from developing countries, who have not received an early diagnosis (and repair) of CHD contribute to the pool of patients who go on to develop PAH.

Irrespective of pathogenetic mechanism(s), current evidence suggests that the presence of PAH in the CHD setting has an adverse impact on both quality of life and survival [3]. Eisenmenger syndrome (ES) represents the extreme end of the PAH–CHD spectrum and displays a prevalence of 1.1% to 12.3% amongst CHD patients [2,3], and a prevalence of 0.001% in the general population [5]. The exact number of patients with ES worldwide remains unknown [6]. We have observed a trend of an approximate 9% year-on-year increase in the number of patients with ES attending our designated tertiary CHD–PAH service over the past 8 years (personal communication, Professor Gatzoulis, Royal Brompton Hospital, London, UK). We submit this reflects improving awareness of the condition in the community and availability of therapy, rather than increasing numbers of patients with ES in the UK. Nevertheless, the anticipated growth in numbers and complexity of adult patients with CHD [7], including those with PAH, means the

* Corresponding author at: Adult Congenital Heart Centre and National Centre for Pulmonary Hypertension, NIHR Cardiovascular BRU, Royal Brompton Hospital and the National Heart and Lung Institute, Imperial College, Sydney Street, London SW3 6NP, UK. Tel.: +44 207 351 8602; fax: +44 207 351 8367.
E-mail address: M.Gatzoulis@rbht.nhs.uk (M.A. Gatzoulis).

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need for information on how to care for these patients will become increasingly relevant and pressing for cardiologists and other healthcare professionals alike.

Clinical and academic interest in PAH–CHD as a disease entity has grown in recent years [8]. Considerable progress has been made; but there remain multiple challenges concerning optimal classification, monitoring and therapy. A meeting was held in Vienna (February 2011) in which 63 PAH–CHD experts from around the world gathered to discuss the most salient of these issues. In this article, we, the Scientific Committee of the meeting, report on some of the meeting's debates and supplement this with our personal experiences and the very latest literature in this rapidly expanding field of cardiovascular medicine.

2 . Search strategy and selection criteria

We searched MEDLINE (01/01/2003–31/12/2013) using the search terms 'congenital heart disease' in conjunction with 'pulmonary arterial hypertension' or 'Eisenmenger syndrome' or 'Fontan circulation'. We selected publications from the past 5 years, but did not exclude older, commonly referenced and highly regarded publications. We also included well-known, relevant publications that we considered important, such as clinical guidelines that were not identified using the search strategy.

3. Classification of patients with pulmonary arterial hypertension in association with congenital heart disease

A wide range of defects are often associated with PAH and patients with PAH–CHD represent a heterogeneous group. While it is necessary for CHD specialists to possess and apply a detailed descriptive classification system of PAH–CHD (please refer to Table 7 in the joint European Society of Cardiology/European Respiratory Society [ESC/ERS] guidelines for the diagnosis and treatment of pulmonary hypertension) [1] this can be overly complex and unworkable for the non-CHD expert. A simple, practical system of identifying PAH–CHD patients is clearly needed, so that cardiologists, pulmonologists and other healthcare professionals can readily recognise patients who have been lost to follow-up and refer them to specialist tertiary care. An example of a simplified classification system has been proposed by an expert consensus panel and categorises patients with PAH–CHD into four groups (please refer to Table 6 in the ESC/ERS guidelines) [1]. We have developed this system further and provide a modification of this table and a graphical representation of the four PAH–CHD patient groups (see Fig. 1) [1]. Furthermore, we also discuss the Fontan cohort, patients who do not fulfil the criteria for diagnosis of PAH, but nevertheless merit consideration.

3.1. Eisenmenger syndrome (Fig. 1A) and chronic cyanosis

3.1.1. Historical context

In 1897 Viktor Eisenmenger first described a typical example of the syndrome that would later bear his name with a detailed anatomical and clinical account of a man with cyanosis and a ventricular septal defect (VSD). It took more than 50 years for clinicians to recognise that the cyanosis present in this setting resulted from a bidirectional or reversed shunt caused by pulmonary hypertension. Accordingly, 'Eisenmenger complex' was defined as PAH with bidirectional or reversed shunt through a large VSD. Working in London in the 1950s, it was Paul Wood who realised that the position of the shunt, i.e. the type of defect, was of little relevance when it came to the clinical phenotype and physiology of a large and non-restrictive communication between the pulmonary and systemic circulation. Given the number of different anatomical cardiac defects that can lead to the same clinical course of progressive PAH–CHD with an eventual reversal of the shunt from left to right to right to left and the development of chronic cyanosis, he proposed that the term 'Eisenmenger syndrome' be extended to characterise this clinical entity, irrespective of the anatomy of the underlying cardiac defect [11,12].

Although the all-encompassing definition of ES bequeathed by Dr Wood is still in use today, there is some controversy as to whether simple atrial septal defects (ASDs) should be included in the ES group. It is true that the majority of patients with an ASD do not develop PAH early in life but it is also true that the prevalence of ASD is higher amongst patients with PAH than those without. Furthermore, there appears to be a cause and effect relationship between large left-to-right shunts and progression to ES over time, although this clinical course does not apply to all patients. We speculate that a permissive genotype, which remains to be determined, 'allows' a minority of patients with a large ASD to develop 'aggressive' PAH that eventually leads to ES. Furthermore, there is evidence that this group of ES patients with an ASD do respond to oral PAH-specific therapy in a similar manner to those with ES and a VSD [13].

3.1.2. Management and treatment options

Patients with ES display chronic cyanosis and, typically, multi-organ, multi-system involvement [14,15]. Chronic cyanosis has a detrimental effect on exercise capacity [16] but it is also a powerful stimulus for secondary erythrocytosis which, in turn, increases oxygen carrying capacity and, therefore, enhances tissue oxygenation and prevents, at least in part, hypoxic end-organ damage [14]. This desirable and naturally occurring adaptive mechanism of secondary erythrocytosis is often mislabelled as polycythaemia. This error is not simply an issue of semantics: polycythaemia affects all three haematopoietic cell lineages and is linked historically with complications such as hyperviscosity syndrome, pulmonary embolism and stroke [16]. Hyperviscosity syndrome in ES patients is relatively rare and presents with non-specific symptoms (headache, muscle weakness, fatigue etc.) that mimic those of iron deficiency, a common occurrence in ES. The long-standing and inappropriate practice of periodic venesection to counteract secondary erythrocytosis and ostensibly to convey shorter- or longer-term symptomatic relief in ES patients [17], lacks both rationale and evidence. Despite good intentions, venesections compromise oxygen tissue delivery, reduce exercise capacity and increase rather than decrease the risk of stroke [18].

Our practice has changed a great deal in this matter: routine venesections have been abandoned, iron deficiency is routinely investigated [19] (as it is common even in venesection-naïve patients [18]) and iron deficient patients routinely receive iron supplements. A recent pilot/intention-to-treat study [20] demonstrated an increase in haemoglobin levels following 3 months of iron supplementation, which was matched by improvements in 6-minute walk distance (6MWD) and quality of life scores based on the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) disease-specific questionnaire. The diagnosis of iron deficiency in ES should not be based on haemoglobin or mean cellular volume levels. We employ ferritin <20 mg/L or ferritin <50 mg/L and transferrin saturation of $<20\%$ as the main diagnostic markers for iron deficiency in this population; levels of expression of the transferrin receptor can also be used. There is, nevertheless, a need for further refining the diagnostic criteria for iron deficiency in this setting and for a greater understanding of the adaptive mechanisms between chronic cyanosis, secondary erythrocytosis, iron metabolism/utilisation and endothelial dysfunction [21], all of which may shed more light on pathogenesis and further improve therapy for this group of patients.

There is growing evidence for the prognostic significance of exercise in CHD in general [22,23], and especially in ES patients [24,25]. Furthermore, there was a recent report on the safety and benefits of exercise training in patients with PAH–CHD [26], reinforcing the potential benefits of exercise in this specific patient cohort [27]. Therefore, guided patient-specific exercise training and physical activity [28], as well as avoidance of smoking and obesity and the exclusion of associated sleep apnoea, should be considered and discussed with the patient at the clinic.