Pulmonary vascular disease may complicate untreated congenital heart diseases as a result of increased pulmonary artery pressure, blood flow, or both. Typical lesions that predispose people to the development of pulmonary vascular disease include ventricular septal defect (VSD), patent ductus arteriosus (PDA), atrial septal defect (ASD), as well as more complex forms of congenital heart disease without congenital or acquired obstruction to pulmonary blood flow. There is a paucity of data to estimate accurately the number of children with congenital heart disease who have or are at risk for developing pulmonary vascular disease. We estimate that worldwide 3 million children are at risk for the development of pulmonary vascular disease due to congenital heart disease. The majority of children at risk globally will have a reparable heart defect, such as an isolated atrial septal or ventricular septal defect or patent ductus arteriosus. Cardiac repair in the first 2 years of life would prevent the development of Eisenmenger syndrome, the most advanced form of pulmonary vascular disease secondary to congenital heart disease. Worldwide, only a small fraction of those at risk are offered surgical repair. Thus, access to timely medical care would eliminate the vast majority of suffering, disability, and death from Eisenmenger syndrome. Globally, pulmonary vascular disease associated with congenital heart disease may be the most preventable cause of pulmonary artery hypertension and related mortality and morbidity.
with significant intracardiac or extracardiac shunt lesions receive curative intervention. For example in Papua New Guinea by the time surgical therapy is offered 20% of a cohort of children will be inoperable because of advanced pulmonary vascular disease. As a result, primarily because of insufficient access to specialist care, congenital heart disease is one of the most common causes of pulmonary vascular disease. In European adults the prevalence of pulmonary vascular disease due to congenital heart disease, derived from the French and Scottish registries, is estimated to be between 1.6 and 12.5 cases per million adults, with 25% to 50% of these patients suffering from Eisenmenger syndrome with a reversed shunt.

In this article, we discuss the pathophysiology of pulmonary vascular disease associated with congenital heart disease and focus on the global perspective and the interplay between environmental, genetic, and socioeconomic factors. We present how geographic location, genetic makeup, and environmental factors may conspire to affect and influence the phenotype of the disease.

It remains unequivocal that access to medical therapy is the single most important factor in the worldwide development of irreversible pulmonary vascular disease secondary to congenital heart disease. The stark reality is that developed regions account for 12% of the worldwide burden from all causes of death and disability and yet account for 90% of health-care expenditure worldwide. The inequality of access to medical care exists not only as a northern vs southern hemisphere divide or developed nation vs less developed but also as a result of economic disparity within countries. There are disadvantaged communities, for example indigenous peoples, within the developed world who share a greater burden of disease risk. Inequitable situations exist within poorer countries where expert medical therapy is available only to the privileged or affluent sector. In India, of the 14 pediatric cardiac centers, only one is a government hospital; the rest are in the private sector where the price of medical care is beyond the reach of most of the population. The disease burden due to pulmonary vascular disease from inadequate treatment of young infants with congenital heart disease is, to a large extent, avoidable. It shares similarities in global epidemiology with all illnesses for which poverty and poor access to medical care are at the heart of the matter. A huge population of children with simple shunt lesions will die in childhood, adolescence, and young adulthood after a life characterized by recurrent illness and growth failure. There is a stark contrast between the 85% of babies born with congenital heart disease in the United States who are expected to reach adulthood and the mortality rate of 11% for all children <5 years of age in Papua New Guinea.

It is sobering to remember that 10 million children die each year from preventable illness, such as diarrhea and pneumonia (Fig 1). We are cognizant that if access to clean water, good nutrition, and fundamental education for all children are a challenge globally, the development of expensive infant cardiac surgery programs will be neither a priority nor sustainable. The United Nations Children’s Fund report in 2001 advised that timely intervention in the first 3 years of life is paramount in the approach to many childhood diseases and disabilities. Congenital heart disease should be included in this list if we are to prevent the associated pulmonary vascular disease in later life.

Classification of Pulmonary Hypertension

Pulmonary hypertension associated with congenital heart disease is classified in category 1, which includes also pulmonary arterial hypertension due to idiopathic (IPAH) and familial causes and related to or associated with other diseases, including connective tissue disease and HIV infection. The rationale for inclusion of pulmonary artery hypertension associated with congenital heart disease in category 1 is the observation that the histology and endothelial cell abnormalities of category 1 pulmonary arterial hypertensive diseases are indistinguishable from each other. The plexiform lesion is the epitome of severe disease in all category 1 diseases. There may be differences at cellular, genetic, and molecular levels between disorders in category 1 that remain to be elucidated. For instance, Lee et al have demonstrated that the plexiform lesions of patients with familial pulmonary arterial hypertension contain monoclonal proliferating endothelial cells in contrast to the polyclonal endothelial cell proliferation in secondary pulmonary hypertension due to congenital cardiac shunts. Mutations in bone morphogenetic receptor protein receptor type 2 are less common in patients with pulmonary hypertensive congenital heart disease than idiopathic pulmonary hypertension, but when present might have a profound impact on outcome. In addition, any globally relevant scheme of clinical classification cannot, and should not, lose sight of the prevalence of the disease state worldwide.

The Global Incidence of Pulmonary Vascular Disease Associated With Congenital Heart Disease

Published reports estimate the incidence of congenital heart disease at eight to 12 per 1,000 live births. The incidence is similar in all countries and between races. In addition, in school-aged children the prevalence

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of the common congenital heart diseases is similar and also constant around the world. VSDs are the most common lesions, followed by ASDs and PDAs. These lesions affect the sexes equally and make up about 60% of all heart defects encountered in school-aged children around the world; they appear to have remained constant over the last 30 years. 17,19,41 The prevalence of congenital heart disease in Québec, Canada is 12/1,000 population. In less-privileged countries the prevalence in school-aged children is estimated at about 3/1,000 population.22,24,41 This suggests significant infant attrition and/or incomplete case ascertainment. We calculate that there are approximately 3.2 million children worldwide with an isolated ASD, VSD, or PDA who if untreated and surviving infancy would develop pulmonary vascular disease and suffer the crippling morbidity of hypoxemia due to shunt reversal and a shortened life expectancy. In our estimate, we have made the following assumptions: the distribution of the heart malformations is similar to Québec worldwide, and pulmonary vascular disease develops in 10% of children with an ASD, 20% with a VSD, and 20% with a PDA.

Standard recommendation for children with large left-to-right shunts or evidence of an elevated pulmonary vascular resistance is operative closure of the defect in the first 12 to 18 months of life. In patients predisposed to pulmonary vascular disease, such as trisomy 21, earlier repair by 6 months of age is recommended. Patients with truncus arteriosus or transposition of the great arteries with VSD are repaired within the first month of life. This strategy has been effective at reducing the development of Eisenmenger syndrome or end-stage pulmonary vascular disease. For instance, the 35- to 45-year survival in Finland after surgical VSD closure is 79%, after PDA ligation 88%, and after ASD closure 95%, in a country where 95% of the general population can expect to live 45 years.42 In contrast, in Africa the mean age of referral of those children who do see a pediatric cardiologist is 17 months, and 5% to 10% of patients have Eisenmenger syndrome at referral.23,27,43 In Sudan, only 15% of children who need an operation receive one. The outcome for those operated on is extremely good.23,27 In Papua New Guinea, there is 21% mortality in those who need but do not receive an operation and, one presumes, a high rate of Eisenmenger syndrome.1,44

In the northern hemisphere the prevalence of Eisenmenger syndrome due to simple lesions has decreased considerably. The Eisenmenger patient of the future is likely to have complex cardiac lesions. Yet in the developing world, where 80% of the world population lives, the vast majority of patients now and for the near future will have Eisenmenger syndrome due to common and easily treated lesions. In North America, the evaluation of a child with straightforward cardiac lesions by cardiac catheterization to assess if the pulmonary vascular resistance is low enough for repair is performed only a handful of times per year, yet remains a frequent occurrence in India and accounts for between 5% to 25% of diagnostic cardiac

Figure 1. The global distribution of deaths in childhood. Each dot represents 5,000 deaths. (Reprinted with permission from Black et al.11)
catheterizations in selected pediatric cardiac units (personal communication, Drs S. Shrivastava, J. M. Tharakan, R. Krishnakumar, S. Maheswari).

**Pathophysiology**

The currently accepted paradigm for the development of pulmonary vascular disease associated with congenital heart disease is that increased pulmonary blood flow and pressure conspire to trigger unfavorable vascular remodeling. Endothelial cell dysfunction, abnormal shear stress, circumferential wall stretch, and an imbalance in vasoactive mediators, involving the prostacyclin, thromboxane, endothelin, nitric oxide, cyclic guanosine monophosphate, transforming growth factor-β1, vascular endothelial growth factor, and fibroblast growth factor-2 pathways, promote vasoconstriction, inflammation, thrombosis, cell proliferation, impaired apoptosis, and fibrosis. 45-58

**Histologic Correlates**

Heath and Edwards 59 published the seminal work in 1958 that described six grades of pulmonary vascular disease. Grade 1 is the mildest form, characterized by medial hypertrophy, extension of smooth muscle into normally nonmuscular arteries, and adventitial thickening and fibrosis. Grades 4 to 6 represent severe disease and are typified by the sequential appearance of medial thinning, plexiform lesions, medial fibrosis, and finally necrotizing arteritis. 59 As mentioned previously, these changes seem to unify pulmonary vascular disease from various etiologies. However, the Heath-Edwards classification is less useful to characterize the earliest changes frequently seen in infants and children undergoing cardiac surgery. Therefore, a morphometric approach was studied by Rabinovitch et al., 60, 61 Haworth, 62 and Haworth and Hislop. 63 The morphometric approach quantifies and grades from A to C the degree of abnormal distal extension of smooth muscle, the thickness of the medial hypertrophy, and the density of small pulmonary arteries relative to the number of alveoli. The results of the morphometric analysis of lung biopsy specimens may be predictive of late outcome, but lung biopsy is used rarely in the routine assessment of operability. Nevertheless, the morphometric approach has emphasized that young age and preservation of small pulmonary arteries are the best indicators of good pulmonary hemodynamics postoperatively. 60, 61

**Development and Reversibility of Pulmonary Vascular Disease**

Early in the disease, in children younger than about 2 years of age, the abnormal pulmonary vascular remodeling is generally reversible if the congenital heart defect is repaired. 61 However, not all lesions have the same propensity to cause pulmonary vascular disease. For instance, pulmonary vascular disease may be advanced at birth and persist despite neonatal repair in patients with transposition of the great arteries, emphasizing the importance of prenatal conditions (eg, atrial septal or ductal restriction *in utero*) and developmental pulmonary vascular influences. 64-69

It is suggested that lesions with both a high flow and high pressure develop pulmonary vascular changes sooner and with more certainty than those with increased flow alone. Yet, clinical observations suggest that even with high flow and pressure lesions there is variability in the propensity to develop pulmonary vascular disease. Compare, for example, patients with transposition of the great arteries and a VSD or truncus arteriosus who develop severe pulmonary vascular disease during the first year of life (and inevitably if unrepaired) 70-74 with patients with an isolated large VSD or PDA, the majority of whom may develop pulmonary vascular disease over time but in whom it is distinctly unusual to do so before 2 years of age.

There is also a subset of patients with a small shunt from left to right who, nevertheless, develop pulmonary vascular disease of such severity that it is out of keeping with the anatomic size of the defect. There remains ongoing speculation as to whether those patients with small ASDs and pulmonary hypertension have an additional predisposition, which, coupled with a small shunt, promotes the development of pulmonary vascular disease, or whether they suffer from IPAH with an irrelevant shunt.

On the one hand, few patients <1 to 2 years old have a severely elevated pulmonary vascular resistance (pulmonary-to-systemic vascular resistance [Rp:Rs] ratio of >0.75). On the other hand, older patients with severely elevated pulmonary vascular resistance index (PVRI) are at risk for sustained pulmonary hypertension or a progressive increase in PVRI after repair. 73 The exact level of PVRI that precludes safe closure of a defect is controversial and varies with each lesion. In the first US Natural History Study, patients with an Rp:Rs <0.2 uniformly did well. 76 Closure of a VSD in the first 2 years of life, even when PVRI is markedly elevated, usually results in normal or near-normal pulmonary vascular resistance at follow-up. The likelihood of favorable pulmonary vascular remodeling is high if operation is performed in the first year of life. 61, 77 Although an occasional older child or adult with substantially elevated PVRI has a marked decrease after repair, most patients beyond the first few years of life with increased PVRI preoperatively have the same or increased PVRI postoperatively. 75, 78-85 Even if PVRI is normal at rest after closure of a high-resistance VSD, it is well
documented that abnormal responses to exercise persist and the pulmonary vascular resistance not only fails to decrease with exercise-induced flow but increases. However, it is worth noting that many of these studies predate improvements in preoperative treatments, cardiac surgical techniques, and postoperative care, and more recent series may have improved results. An elevated pulmonary vascular resistance >7 Wood units (WU/m²) and age >5 years were important risk factors for death on long-term follow-up over 30 years. It is prudent to offer repair of a VSD or PDA in the first 2 years of life. Pulmonary vascular disease is rare in children with ASDs, and asymptomatic ASDs are usually closed between 3 and 5 years. Significantly increased pulmonary vascular resistance also increases the risk of mortality immediately after operation because of right ventricular dysfunction compounded by pulmonary vascular lability.

For patients with high, but not systemic-level, pulmonary vascular resistance, we do not have a sufficiently sensitive and specific method for determining who will respond favorably to operation. Wood suggested 50 years ago that surgical repair is indicated for those whose PVRI is not >10 WU/m² and whose pulmonary-to-systemic flow ratio is at least 2:1. A contemporary approach to determining operative suitability is to consider the reactivity of the pulmonary circulation to vasodilators. Some patients with an Rp:Rs between 0.2 and 0.5 may have progression of pulmonary vascular disease on follow-up if they are >2 years old at repair, and general guidelines suggest that if pulmonary vascular resistance can be decreased to 6 to 8 WU/m² and an Rp:Rs ratio <0.3 that a good outcome after repair of VSD can be expected. Thus, with rare exceptions end-stage pulmonary vascular disease is preventable by early intervention to repair congenital heart defects in the first 2 years of life.

**Eisenmenger Syndrome**

Eisenmenger syndrome is the name given to the most severe spectrum of pulmonary vascular disease secondary to congenital shunt lesions. Although the disease bears the name of Victor Eisenmenger, it was Paul Wood who most elegantly characterized the disease in a masterly account that remains germane today. Wood defined Eisenmenger syndrome as pulmonary hypertension at the systemic level, due to high PVRI (>800 dyne s/cm² or 10 WU/m²) with reversed (ie, right-to-left) or bidirectional shunt. These patients have severely remodeled pulmonary vasculature and seldom respond to vasodilators with a large decline in PVRI, especially if the shunting is purely right to left. In general at this stage closure of the pulmonary-to-systemic connection is contraindicated and associated with a worse outcome than the natural history of Eisenmenger syndrome.

Eisenmenger syndrome is a multisystem disorder causing hemoptysis, cerebrovascular stroke, brain abscesses, secondary erythrocytosis, coagulation abnormalities, cardiac arrhythmia, and sudden death. Many patients with Eisenmenger syndrome can expect to live longer than patients with IPAH because of preserved right ventricular function. The preservation of right ventricular function is explained by the congenital adaptation of a right ventricle exposed to systemic level of pressure since birth and the advantage of a shunt that prevents right ventricular pressure from reaching suprasystemic levels. For many years the disease was regarded as a therapeutic orphan. However, the observation that even patients with established Eisenmenger syndrome have a small but quantifiable degree of vasodilation in response to inhaled nitric oxide and the recent emergence of oral pulmonary hypertension-specific therapies has raised awareness of the disease. Beneficial effects of treatment with endothelin receptor antagonists, type 5 phosphodiesterase inhibitors, and prostacyclin analogs have been reported to improve symptoms in patients with Eisenmenger syndrome. However, until recently only type 5 phosphodiesterase inhibitors were available and affordable outside of Europe and North America. Endothelin receptor antagonists manufactured locally have just become available in India. The benefits of drug therapy in established Eisenmenger syndrome pale in comparison with the advantage of early repair. Although there is a great deal of interest in treating Eisenmenger syndrome with pulmonary artery-specific therapy and reassessing operability, it is unclear whether any currently available medical therapy can reverse the vascular changes. Caution is required with this approach because some patients >2 years of age with an elevated pulmonary vascular resistance at repair may have progression of the pulmonary vascular disease with a worse outcome than children with IPAH.

**The Global Interplay of Congenital Heart Disease and General Health of Children**

It is unknown how other factors common in children with limited access to medical care might exacerbate the pulmonary vascular disease from congenital heart disease. For instance, in of a group of children evaluated in Africa, 53% were anemic, 47% underweight, and 33% marasmic compared with a control group without congenital heart disease, of whom none were marasmic and 14% were underweight.
High altitude has profound and fascinating effects on normal neonatal pulmonary vascular transition that is related not only to altitude but also to ancestry. Thus, ethnic groups with recent migration to high altitude have lower oxygen saturations and higher pulmonary artery pressures than those with a long ancestry of high-altitude living, such as native Tibetans or Andean residents. In addition, the incidence of congenital heart disease increases at higher altitude, there is delayed closure of the ductus arteriosus, and the ductus is larger, with a higher pulmonary-to-systemic blood flow ratio for any given pulmonary vascular resistance. Thus, operability assessment and management decisions are different at high altitude.

The Scope of Inequalities

The American College of Cardiology recommends one pediatric cardiac program per 5 million people. This level of primary care, let alone subspecialist care, is not available in most countries. In Malawi, for instance, a single cardiologist saw 4,000 new patients in 5 years. In India, with a population of 1.2 billion, there are 14 pediatric cardiac centers or one center per 85 million people. Some countries with populations between 15 and 70 million have no access at all to pediatric cardiac care. It should not be surprising, therefore, that an estimated 15 million children die or are crippled annually by potentially treatable or preventable cardiac diseases.

Extraordinary and innovative solutions have evolved in response to the dearth of pediatric cardiac services. In São Paulo, 800 congenital cardiac cases are operated on per year, and the operations are funded mostly through social security provided by the government rather than the private sector. Individual efforts to train personnel in infant cardiac disease in Guatemala have yielded remarkable results. In Sudan, the combined efforts of visiting and local surgical teams yield a surgical mortality of only 8.3%. Teams of pediatric cardiac specialists, often led by a cardiac surgeon, visit countries and perform operations with excellent short- and medium-term results.

Summary

Pulmonary vascular disease secondary to congenital heart disease is a preventable illness, especially if repair is offered to children < 2 years of age. The collective efforts of many people and collaboration between the worldwide medical communities will be required to eradicate the suffering due to Eisenmenger syndrome. The United Nations Children’s Fund, reported in the State of the World’s Children that:

Attention to the youngest children is most needed where it is most difficult to guarantee: in countries where the seemingly intractable grip of poverty, violence and devastating epidemics seriously challenge parents’ hopes and dreams for their children.
This is germane to all illness with origins in childhood. Globally, pulmonary vascular disease associated with congenital heart disease may represent the most preventable cause of pulmonary artery hypertension and the morbidity and fatal sequelae.

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