Evaluating Operability in Adults with Congenital Heart Disease and the Role of Pretreatment with Targeted Pulmonary Arterial Hypertension Therapy

Konstantinos Dimopoulos, MSc, MD

Michael A. Gatzoulis, MD, PhD

Konstantinos Dimopoulos, MSc, MD
Michael A. Gatzoulis MD, PhD
Adult Congenital Heart Centre and
Centre for Pulmonary Hypertension
Royal Brompton Hospital and National Heart
and Lung Institute
Imperial College School of Medicine
London, United Kingdom

Despite recent advances in cardiac surgery that have allowed repair of congenital heart defects at a very young age, pulmonary arterial hypertension (PAH) secondary to congenital heart disease (CHD) remains a major problem. In its most severe form, the Eisenmenger syndrome, PAH and its complications result in a significant increase in morbidity and mortality and also greatly affect the quality of life of patients.

Pulmonary vasodilators aimed at attenuating PAH by decreasing pulmonary vascular resistance have been available for many years in intravenous formulations requiring continuous infusion.[1-5] This restricted their application to severely symptomatic patients in which the benefits from chronic vasodilator therapy outweigh the risk of complications and the limitation imposed on patient quality of life. In recent years potent oral vasodilators aimed at the pulmonary circulation have become available, with promising results.[1,6] Interestingly, vasodilators also appear to be effective in reducing pulmonary vascular resistance and symptoms in patients with near-systemic pulmonary pressures, previously thought to have irreversible pulmonary vascular disease.[6,7] This has led to a new dilemma and has opened new therapeutic options: could intracardiac communications that were previously considered inoperable due to severe or "irreversible" pulmonary vascular disease, become amenable after successful treatment with vasodilators? What would the potential benefits and risks of such an approach be? How significant should the drop in pulmonary vascular resistance be to allow safe closure of the defect? Could this approach be applicable to all types of shunt? Are there sufficient data to consider such an approach in any patient with PAH secondary to CHD?

In this article, we will attempt to address the potential merits and risks of a treat-and-repair approach using oral targeted pulmonary hypertension agents in PAH secondary to CHD.

Key Words—Pulmonary arterial hypertension; adult congenital heart disease; operability; vasodilator therapy.

Address for reprint requests and other correspondence: Professor M. A. Gatzoulis, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK (email: M.Gatzoulis@rbht.nhs.uk; Fax: +44 207 351 8629)

Pulmonary Arterial Hypertension Secondary to Congenital Heart Disease

The current definition of PAH relies on the presence of a mean pulmonary arterial pressure exceeding 25 mmHg at rest or 30 mmHg during exercise, a left atrial pressure below 15 mmHg, and a normal resting cardiac output, suggesting a resting pulmonary vascular resistance above 3 Wood units.[1,8] An estimated 5% to 10% of patients with CHD (mostly those with late or no repair) develop PAH.[1,9-11] In theory, all large communications that result in pulmonary overcirculation by means of a significant left-to-right shunt can produce progressive histologic and physiologic abnormalities in the pulmonary vascular bed, leading to a rise in pulmonary arterial pressure. According to the Venice classification, the congenital systemic-to-pulmonary shunt that can be associated with PAH can be divided into: 1) simple shunts, such as atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus, and unobstructed total or partial anomalous pulmonary venous return; 2) combined shunts; and 3) complex shunts such as truncus arteriosus, single ventricle with unprotected pulmonary circulation, and atrioventricular septal defects.[1,12] VSDs are the most common simple defects causing PAH, with an estimated 10% of all VSDs and 50% of large VSDs having the potential to cause Eisenmenger syndrome if not repaired by age 2.[13,14]

The Eisenmenger syndrome is the extreme end of the spectrum of PAH secondary to CHD. It includes all left-to-right shunts that result in significant PAH to systemic or near-systemic levels with subsequent reversal of the shunt, which may become right-to-left or bidirectional. Nowadays, approximately 4% of individuals with CHD followed in tertiary centers develop Eisenmenger syndrome, as opposed to 8% prior to the current operative era.[6]

Pathophysiology of Pulmonary Arterial Hypertension

PAH is associated with important histologic alterations. The

histopathologic features of PAH include medial hypertrophy with hyperplasia of smooth muscle cells and increase in connective tissue and elastic fibers, intimal and adventitial thickening, and rarefaction of the arterial tree.[1,6,15-18] Complex (plexiform) lesions may also develop that are a focal proliferation of endothelial channels lined by myofibroblasts, smooth muscles cells, and connective tissue matrix.[1] Anatomic changes are progressive, relate to PAH severity and, though reversible when at an early stage, can become severe and irreversible should correction of the communication not occur.

The genesis of these changes is multifactorial.[6,7,14] Endothelial dysfunction and pulmonary vasoconstriction occur early in the pulmonary hypertensive process caused by the high pressure and flow through the pulmonary circulation. Vascular remodeling follows, with changes that involve many types of cells including endothelial cells, smooth muscle cells, and fibroblasts. Inflammatory cells also play a role, as do platelets and prothrombotic abnormalities. Genetic predisposition also plays an important role.[6,19,20]

The rate of progression of the pulmonary vascular disease secondary to CHD depends on the type and size of the defect and the severity and pressure of the shunt.[14] Individuals with large VSDs and patent ductus arteriosus are more likely to develop severe PAH at a faster rate (appearing in infancy), compared to patients with ASDs, in which, if PAH develops, it does so later in life, despite significant left-to-right shunting. Nevertheless, a genetic or other predisposition appears to be present in many patients who develop PAH earlier than others. Interestingly, despite similar physiology, PAH develops in only 4% of patients with secundum ASDs but in 16% of those with sinus venosus defects.[21]

Effect of Pulmonary Hypertension on Morbidity and Mortality in Adults with Congenital Heart Disease

The clinical effects of PAH relate to its severity. Adult CHD patients with significant PAH have a significant decrease in exercise capacity and functional status. The inability to adequately increase pulmonary perfusion and the right-to-left shunt result in significant ventilation/perfusion (V/Q) mismatch, ventilatory inefficiency, and greatly reduced tolerance to exercise.[9,22-25] Established right-to-left or bidirectional shunting is also associated with an increased risk of embolic events (stroke, cerebral abscess) and a propensity to bleeding and thrombosis. Cyanosis is also associated with dysfunction of peripheral organs such as the kidney and the liver, at least in part due to chronic hypoxia. Secondary erythrocytosis, a compensatory mechanism aimed at increasing tissue oxygenation, may also cause hyperviscosity symptoms such as headache, visual disturbances, and paresthesias.[26-29]

All the above result in a greatly reduced quality of life for these patients. Despite this, mortality in patients with Eisenmenger syndrome is not as high as previously thought and with adequate support and correct care, these patients can reach the 5th or 6th decade of life. In fact, life expectancy is significantly higher compared with that of patients with idiopathic PAH (iPAH), despite great similarities in pulmonary histology.[28,30,31] The reason for this difference in outcome remains unclear. It has been suggested that the right ventricle of patients with Eisenmenger syndrome is less likely to fail because of long-standing pressure and volume overload through a "training effect" or no regression of right ventricular hypertrophy after birth, or in merit of the right-to-left shunt that acts as a "relief valve" for the right ventricle.[32, 33]

Operability of Patients with Congenital Heart Disease and Pulmonary Arterial Hypertension

In current practice, referral for closure of an intracardiac communication responsible for the shunt largely depends on the status of the pulmonary circulation. In the case of large VSDs or patent ductus arteriosus, early repair is crucial for preventing irreversible pulmonary changes. Children diagnosed later in life, who have developed elevated pulmonary vascular resistance (exceeding 6 Wood units/m^2) and have poor vasodilator response are at high risk of sustained pulmonary hypertension, right heart failure, and hypertensive crises immediately after surgery.[14,34] Moreover, right-to-left shunting in the presence of severe PAH maintains cardiac output, at the expense of arterial hypoxia. Right-to-left shunting at the atrial level is a mechanism for relieving right atrial pressure in the presence of right ventricular failure.[10,35,36] ASDs are generally considered repairable by either interventional or surgical means unless significant PAH with no signs of reversibility has occurred.[37]

In the past, operability was decided based on lung biopsy.[6,14-18,37] Nowadays, it is decided based on determination of the severity of PAH and the degree of vasoreactivity of the pulmonary circulation. Precise determination of the reversibility of the PAH is essential and agents used to elicit such reaction should ideally have an effect on pulmonary vascular resistance but not on the systemic circulation.[1,14,34] Inhaled 100% oxygen was the most commonly used agent. It is now recommended that acute vasodilator testing be performed using short-acting vasodilators such as inhaled nitric oxide, intravenous epoprostenol, or adenosine. Adenosine and nitric oxide have a half-life of seconds (5 to 30 seconds) and epoprostenol has a half-life of 3 minutes. An acute reduction of the mean pulmonary arterial pressure of 10 mmHg or greater with a resultant mean pulmonary arterial pressure of 40 mmHg or less without a fall in cardiac output is considered a positive response to acute vasodilator testing. In patients with evidence of vasoreactivity during acute testing but high pulmonary vascular resistance and bidirectional shunting, balloon test occlusion may provide additional information on the suitability for closure and the post-repair outcome. A drop in cardiac output and/or increase in RV filling pressures with temporary occlusion may suggest a low likelihood to benefit from permanent repair, as well as a higher perioperative risk.[34]

Steele et al in 1987 reported the outcome at 4 years of 40 patients with an ASD and pulmonary vascular disease (greater than 7 Wood units/m^2) treated either medically (n = 14, mean age 44 years) or surgically (n = 26, mean age 47 years). All patients who were not treated surgically had progression of their disease. Those who underwent surgical correction and had a preoperative pulmonary vascular resistance between 9 and 14 Wood units/m^2 showed no signs of disease progression and those between 7 and 9 Wood units/m^2 improved.[38] No vasoreactivity was performed prior to closure.

The INOP test I was a multicenter study that gathered data on preoperative hemodynamics, including reversibility with oxy-

gen and nitric oxide, in CHD patients with PAH (ratio of pulmonary to systemic resistance [Rp/Rs] ≥ 0.33).[39] Data on a total of 124 patients (median age 28 months, range 1 month to 47 years) from 10 institutions were collected. Of these, 74 patients underwent corrective surgery or transplantation. An Rp/Rs < 0.42 with oxygen alone and one of < 0.27 with oxygen plus nitric oxide were identified as optimal cut-off values for determining operability (reduced risk of death or right ventricular failure after surgery).

Vasodilator Therapy for Pulmonary Arterial Hypertension

A recent major breakthrough in the treatment of patients with PAH has been the availability of oral endothelin antagonists (eg, ambrisentan, bosentan, and sitaxsentan [Europe, Canada]) and the applications of sildenafil, a type-5 phosphodiesterase inhibitor. Endothelin antagonists are potent pulmonary vasodilators with limited side-effects and a proven beneficial effect when administered to patients with iPAH. It is currently recommended that selective pulmonary vasodilators be administered to highly symptomatic patients with PAH (NYHA functional class III or IV).[1] These recommendations are not specific for Eisenmenger patients, though there are recent data to support the use of such medication also in this cohort of patients. In BREATHE 5, a randomized controlled study of bosentan versus placebo, bosentan was effective in reducing pulmonary vascular resistance and improving NYHA functional class and the 6-minute walk test distance in Eisenmenger patients with severe PAH.[6]

A major advantage of oral formulations is that they allow long-term administration. Contrary to intravenous vasodilators requiring continuous infusion (eg, epoprostenol), oral agents are not associated with complications such as line infections, endocarditis, and paradoxical emboli, and do not impose the limitations that continuous intravenous infusion imposes on the quality of life of these patients.[5-7,24,40-54] Data on the long-term safety and persistent efficacy of such agents are, nevertheless, scarce at present.

Advanced therapies for PAH are now being increasingly used to reduce the risk of developing and for treating postoperative PAH in patients around and after surgical repair for CHD or acquired valve disease.[55,56] Postoperative pulmonary hypertension is, in fact, a major determinant of perioperative morbidity and mortality in patients undergoing cardiac surgery. Pulmonary hypertensive crises are characterized by an acute increase in pulmonary vascular resistance, which precipitates right ventricular failure and causes a drop in cardiac output. Older patients with elevated pulmonary arterial pressure preoperatively are at higher risk of developing postoperative PAH.[57,58] Advanced PAH therapies have the potential to produce a reduction in pulmonary vascular resistance, even in patients with advanced pulmonary disease, lowering perioperative risk and possibly widening the range of cases amenable to repair.

Surgical Repair after Vasodilator Therapy in Previously Inoperable Patients

Eisenmenger syndrome has been synonymous with inoperability as patients are perceived to have irreversible obstructive pulmonary disease that puts them at high perioperative risk, at low likelihood of benefiting from the procedure, and at high risk of postoperative right ventricular failure. Right-to-left shunting in patients with PAH can, in fact, act as a safety valve and forms the basis of practicing atrial septostomy in patients with PAH.[36,59-63]

Nevertheless, despite the established long-standing pulmonary vascular disease with evidence of significant anatomic obstruction, Eisenmenger patients often respond favorably to advanced therapy.[7] It has been demonstrated that almost one third of Eisenmenger patients maintain some degree of pulmonary vasoreactivity despite the presence of obstructive pulmonary hypertension.[64] Moreover, it has been suggested that endothelin receptor antagonists may have antiproliferative effects causing reverse remodeling in the pulmonary circulation.[7,65] Could vasodilators then be used as pretreatment to bring a subset of previously inoperable patients to a point where repair of the intracardiac communication can be performed safely, abolishing cyanosis and the symptoms related to it?

Arguments for Repair of Previously Inoperable Patients Who Respond to Advanced Therapies

Cerebrovascular events (strokes/abscesses) are major, devastating, and debilitating complications of Eisenmenger syndrome and are directly related to right-to-left shunting. Moreover, cyanosis is a major cause of exercise limitation, triggers erythrocytosis, and is associated with hemostatic problems. Systemic arterial desaturation may also aggravate pulmonary vascular obstruction and cause peripheral organ failure. It is thus conceivable that abolishing the right-to-left shunt may produce a symptomatic improvement in highly symptomatic patients. The palliative Mustard procedure is an interesting model of the benefits derived from reduction of hypoxia in patients with PAH secondary to CHD. In this procedure, patients with transposition of great arteries and a large ventricular communication, in which oxygen saturations in the pulmonary artery are higher than that in the aorta, undergo an atrial switch without VSD closure.[66,67] The increase in arterial oxygen saturation resulting from redirection of flow provides significant symptomatic relief and increase in quality of life in patients with severe cyanosis-related symptoms.

It has been suggested that treatment with advanced therapies without correction of the underlying anatomical defect may lead to further insult on the pulmonary circulation. In the case of patients with large VSDs, for example, the drop in pulmonary vascular resistance induced by such therapies leads to an increase in flow and shear stress in the pulmonary circulation, while high pressures through the defect persist.[14] Should advanced therapies aggravate the histological changes in the lung, this could result in short-term benefits, which over the long term could have deleterious effect on the pulmonary circulation and ultimately on its ability to respond to advanced therapy. This could lead to deterioration after the initial short-term improvement. It could, thus be necessary to address this issue by limiting the communication or fenestrating the patch shortly after a drop in pulmonary vascular resistance with vasodilator therapy is documented. Certainly, in less advanced lesions prompt closure of the defect could limit further progression of disease.

Arguments against Repair of Previously Inoperable Patients Who Respond to Advanced Therapies

There are serious concerns when taking into consideration closure of cardiac defects in patients with established PAH. The mainstay of this approach is an effective decrease in pulmonary vascular resistance by advanced therapies, the long-term results and tolerability of which remain unknown. Moreover, no data are available on the long-term response of the right ventricle to closure of intracardiac communications in patients with right-to-left shunting. Once the defect is closed, a pathophysiologic situation more similar to iPAH could become established, which is associated with a much worse long-term outcome compared to Eisenmenger patients. It has been hypothesized that the striking difference in outcome between Eisenmenger and iPAH patients is due to the presence of the defect that permits unloading of the right ventricle by means of right-to-left shunting and thus preservation of right ventricular function. Thus, closure of the defect without marked reduction of pulmonary arterial pressure and abolition of the right-to-left shunt could alter the natural history of Eisenmenger syndrome to resemble that of iPAH. It is, nevertheless, important to remember that, different from iPAH, the pulmonary circulation of a child who develops PAH due to CHD does not grow normally.[68] In fact, intra-acinar arteries are reduced, and endothelial dysfunction and smooth muscle cell hyperplasia are present early after birth. Therefore, fundamental differences in pathophysiology are likely to be present in Eisenmenger and iPAH patients.

An additional reason for concern when contemplating surgery in patients with PAH is the high perioperative risk. Hypertensive crises can be triggered by hypoxia, acidosis, and cardiopulmonary bypass itself.[69,70] Moreover, endotracheal suctioning causes sympathetic stimulation and significant rise in pulmonary vascular resistance, which can be attenuated by adequate pretreatment with high doses of narcotics.[71] Postoperative V/Q mismatch may result in alveolar hypoxia and trigger vasoconstriction.[34]

Cases and Evidence in the Literature

Available data on closure of intracardiac communications in the presence of severe PAH, with or without the use of vasodilators, are scarce and still limited to case reports. Frost et al described the case of a 29-year-old woman with near-systemic PAH in which an ASD was closed after a dramatic drop in pulmonary arterial pressure with continuous intravenous epoprostenol and the subsequent detection of a 3:1 left-to-right shunt.[72] After closure of the defect there was a gradual decrease in pulmonary arterial pressure and the patient was weaned off epoprostenol. At 8-year follow-up, she remained in NYHA functional class II with nifedipine therapy.

Yamauchi et al reported on a 35-year-old woman with an ASD and systemic levels of PAH (systolic pulmonary arterial pressure 110 mmHg, mean 65 mmHg) who underwent ASD closure based on histologic findings on lung biopsy (Heath-Edwards class III).[73] Treatment with oral prostacyclin was started immediately after surgery. At 2 years post-op, the patient had symptomatic improvement, with a significant drop in pulmonary arterial pressure (systolic 65 mmHg) on therapy.

Schwerzmann et al described a highly symptomatic (NYHA class III) 38-year-old woman with a large ASD and significant PAH (mean pulmonary arterial pressure 53 mmHg, pulmonary vascular resistance 8 Wood units/m^2).[51] The right ventricle was dilated and there was a D-shaped left ventricle. Resting saturations were 92% and dropped to 79% during exercise. Lung biopsy revealed plexiform lesions (Heath Edwards grade IV/VI). Therapy with intravenous prostacyclin was started, with significant symptomatic improvement at 1 year (NYHA class I) and reduction of mean pulmonary arterial pressure to 32 mmHg and no desaturation during 6-minute walk testing. Pulmonary vascular resistance dropped to 2.8 Wood units/m^2, further reduced to 1.3 Wood units/m^2 with temporary balloon occlusion. The ASD was closed percutaneously. One year later prostacyclin was weaned off because of side-effects and bosentan therapy was started. A further reduction in pulmonary arterial pressure was noted at follow-up and RV size and function had returned to normal.

Imanaka et al reported on a 51-year-old patient with a secundum ASD and severe PAH.[74] Despite high pulmonary arterial pressure and pulmonary vascular resistance, there was a Qp/Qs of 2 for which he underwent ASD closure. He had a rocky post-op period with recurrent pulmonary hypertensive crises and was treated with nitric oxide. At 2 years, systolic pulmonary arterial pressure had dropped from 96 to 52 mmHg and pulmonary vascular resistance from 14 to 10 Wood units/m^2.

Mizuhara et al reported two cases of adult patients with secundum ASDs who had near-systemic pulmonary arterial pressure but demonstrated some degree of reversibility after inhalation of 100% oxygen.[75] Both patients survived the operation and pulmonary vascular resistance decreased in both after repair.

Eicken et al reported the case of a 35-year-old woman with a nonrestrictive patent ductus arteriosus and PAH (mean pulmonary arterial pressure 66 mmHg).[76] The patient was highly symptomatic (NYHA class III) and there was exclusive left-to-right shunting. Vasoreactivity testing produced a significant drop in pulmonary resistance. The patent ductus arteriosus was occluded percutaneously, but at 4 months, pulmonary arterial pressure was still high (mean 50 mmHg) despite no residual shunting, but with evidence of vasoreactivity. Bosentan therapy was started and 5 months later the patient was in NYHA class II.

These initial case reports appear promising, but no conclusions can be drawn until stronger evidence is available. Moreover, follow-up in most cases was relatively short and the long-term response of the right ventricle to closure of the communication remains unknown. In fact, once the perioperative risk is overcome, the process of right ventricular dilation and failure can be slow and manifest itself years later.[77] Closure of intracardiac defects after a positive response to advanced PAH therapies cannot, therefore, be recommended until hard evidence of it safety, efficacy, and durability becomes available.

Selection of Patients Amenable to a Treat-and-Repair Strategy

An important step to adopting a treat-and-repair approach will be appropriate selection of patients who may benefit from it. Patients with less advanced pulmonary vascular disease and those who demonstrate a significant response to advance therapy are more likely to be potential candidates. In all cases,

careful assessment of the balance between the benefit of closing a large defect and abolishing shunting (and cyanosis if present) and the risk of causing deterioration of right ventricular function and cardiac output should be performed, based on available data. Unfortunately, no solid evidence onto which to base this assessment is currently available. Most reported cases of defect closure combined with vasodilator therapy had atrial communications. One would argue that these cases represent the best end of the spectrum, often with evidence of significant reversibility or left-to-right shunting. Mild forms of PAH are expected in older patients with atrial communications, in which mean pulmonary arterial pressure is expected to be approximately half the patient's age (eg, a 60-year-old patient should have a mean pulmonary arterial pressure of 30 mmHg).[78] Thus, provided that the patient is pink at rest and during exercise (ie, no shunting is present), an increased pulmonary arterial pressure in an elderly patient should not preclude ASD closure. Nevertheless, the cases described by Yamauchi et al and especially Schwerzmann et al also had evidence of advanced lung disease, the latter with plexiform lesions on lung biopsy.[51,73] Certainly, formal hemodynamic assessment with vasoreactivity testing is important, as patients with lower preoperative pulmonary vascular resistance and evidence of significant vasoreactivity are likely to be better candidates. Whether other patient groups (eg, with large VSDs) could be considered for this approach remains unknown.

Defect closure in patients with PAH should be undertaken only if the benefits of abolishing the shunt outweigh the risks of surgical or percutaneous closure. Obviously, it is more likely that this will be the case for defects amenable to percutaneous closure. Nevertheless, regardless of the closure technique, should restoration of the communication become necessary in patients who develop right ventricular failure or low cardiac output postoperatively, this may be difficult and carry additional risk to the patient.

Response to advanced therapy is another important issue that needs to be addressed. There is no uniform response to advanced treatment, as some patients demonstrate strong benefit, whereas others may show little or no change. Pretreatment with advanced therapies for a sufficient period to assess the hemodynamic and symptomatic effects as well as tolerance to long-term administration is thus strongly recommended.

Partial-Repair Options: Defect Closure Allowing Atrial-Level Right-to-Left Shunting

Partial closure of a defect with a one-way flap that permits right-to-left shunting could be a way of allowing decompression of the right ventricle during periods of raised pulmonary vascular resistance, especially in the postoperative period, while limiting flow and pressure stress to the pulmonary circulation.[14, 23, 79] Subsequent complete closure of the defect could be performed should pulmonary vascular resistance fall in response to the advanced therapy. Another staged approach could be the application of a pulmonary arterial band once pulmonary vascular resistance starts to decrease in response to chronic vasodilator treatment in order to protect the pulmonary circulation from the pressure and flow stress.[14, 80] Should pulmonary vascular resistance decrease further, closure of the defect with debanding could be performed.

Finally, whether closure of a post tricuspid cardiac defect (VSD or patent ductus arteriosus) while allowing or creating an atrial communication could convene any hemodynamic, symptomatic, or prognostic benefits is purely speculative.

Other Applications of Advanced Therapies to Address Operability

The Fontan procedure is a complete cavopulmonary anastomosis offered to patients with univentricular heart and results in resolution of cyanosis and decreased volume load on the ventricle. Numerous modifications of the Fontan procedure are available, the most commonly used being total cavopulmonary connection. Patients with Fontan physiology have in common a passive flow of blood to the pulmonary circulation, on which even minor pulmonary vascular abnormalities can have disastrous effects. In fact, pulmonary vascular disease precludes surgery in unoperated patients and can be the cause of or contribute to a failing Fontan circulation.[81, 82] Plastic bronchitis or silent emboli could be the cause of an increase in pulmonary arterial pressure after Fontan operation.[81,83] Pulmonary vasodilators may have a role in this setting in reducing pulmonary vascular resistance, enhancing transpulmonary blood flow and left ventricular filling and, thus, potentially reversing failure of the Fontan circulation.

There is a case report in the literature of successful use of bosentan in a 14-year-old patient with a failing Fontan procedure who was on a transplant list for plastic bronchitis.[81] Takahashi et al have reported successful reduction of pulmonary vascular resistance in candidates for the Fontan operation that had a pulmonary arterial pressure greater than 20 mmHg or pulmonary vascular resistance greater than 3 Wood units, using beraprost.[84] Nemoto et al reported the case of an infant with early deterioration after bicavopulmonary shunt, treated successfully with oral sildenafil.[85] It thus appears that oral vasodilators may have a role in patients with Fontan physiology, both increasing the numbers of operable patients and treating postoperative PAH. Clearly, further studies are required.

The Need for Constant Vigilance

In all new experimental approaches in medicine, vigilance and close follow-up of patients is essential. This is especially true in this case, in which long-term outcome depends on the long-term efficacy of the advance therapies for PAH. These drugs have proven efficacious in alleviating symptoms and reducing pulmonary vascular resistance, but their effect is not curative, it is palliative. Moreover, tolerability to long-term, possibly lifelong, administration of such therapies needs to be established.[86]

Continuing care for adult CHD patients, especially those with concomitant PAH, is best offered in specialized tertiary centers. High levels of expertise in adult CHD and adequate resources are essential for optimal care. Other aspects of care such as the management of secondary erythrocytosis, the abolition of routine venesection, appropriate iron supplementation, and adequate support through noncardiac operation are equally important to the outcome of cyanotic patients. One cannot overemphasize the importance of competence and skills in the diagnosis and treatment of adult CHD, including advanced ther-

apies for PAH, interventional and surgical techniques, and diagnostic modalities such as echocardiography, cardiac magnetic resonance imaging, and exercise testing. Deep understanding of pathophysiology and determinants of outcome, a multidisciplinary approach, and commitment to research and development of new therapeutic modalities are essential.[87]

Conclusions

PAH in patients with adult CHD is a common and extremely debilitating condition, affecting both survival and quality of life. Oral advanced therapies have opened new therapeutic options for these patients, which need to be explored. Highly selected patients may be considered and benefit from a combination of advanced therapy and repair of the defect (partial or complete). Caution is, however, necessary as data on the long-term efficacy of advanced therapies are not yet available. The potential benefits of a treat-and-repair approach have to be carefully weighed against possible adverse hemodynamic effects, based on current knowledge of the natural history of unoperated intracardiac defects. ■

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Conflict of Interest Disclosures

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