Eisenmenger syndrome (ES), the most advanced form of pulmonary arterial hypertension (PAH) associated with congenital heart disease, is a devastating condition that has a considerable impact on patients' lives. Patients who develop ES typically exhibit 1 or more of a range of cardiac defects, including ventricular septal defects, atrial septal defects, and patent ductus arteriosus. The nature of the congenital defect underlying ES is important because it has prognostic implications. Although ES shares similar morphological findings with idiopathic PAH, clinical differences exist between the 2 etiologies. Adults with ES exhibit increased survival and more favorable hemodynamics than those with idiopathic PAH. Treatment options for patients with ES have historically been limited; however, recent successes have been achieved with the use of therapies targeted against the pathophysiological pathways that underlie PAH. The dual endothelin receptor antagonist bosentan was demonstrated to improve hemodynamics and exercise capacity without compromising oxygen saturation, both in the short and long term. Improvements in hemodynamics also have been observed with the single endothelin receptor antagonist sitaxsentan. The phosphodiesterase type V inhibitor sildenafil may improve functional class, oxygen saturation, and hemodynamics in patients with ES, and beneficial effects of prostacyclin and prostacyclin analogs in patients with ES have been reported. The treatment of patients with PAH with the use of combinations of targeted therapies is becoming increasingly commonplace and may offer an alternative option for treatment of patients with ES. The authors of future studies may seek to investigate whether the pulmonary vascular remodeling in ES can be targeted and reversed. (J Am Coll Cardiol 2009;53:733–40) © 2009 by the American College of Cardiology Foundation

Eisenmenger syndrome (ES) represents the most advanced form of pulmonary arterial hypertension (PAH) associated with congenital heart defects (CHD) (1,2). Although patients with ES frequently survive into their third or fourth decades of life, the symptoms of this disease, which include dyspnea, cyanosis, fatigue, dizziness, and syncope, reduce life expectancy (3). In addition, cardiac arrhythmias, an important late complication of ES, are a frequent cause of sudden death in patients with ES (4).

During the past 50 years, the prevalence of ES in the Western world has reduced by an estimated 50%, resulting from advances in surgery and pediatric cardiology (4). Clinical management of patients with ES has traditionally focused on palliative and supportive treatment; however, an increased understanding of the pathophysiology of ES and the success of disease-specific treatment for PAH has offered new hope for patients with ES. This review provides an overview of the pathophysiology and natural history of ES, an evaluation of similarities and differences between ES and PAH, and a summary of key data on emerging treatments.

Pathophysiology
A wide range of cardiac defects can lead to pulmonary vascular disease, although the lesions most common to ES are ventricular septal defects (VSDs), atrial septal defects (ASDs), atrioventricular septal defects, and patent ductus arteriosus (2,4). Approximately 50% of all patients with large unrepaired VSDs, approximately 10% of patients with large unrepaired ASDs, and almost all patients with unrepaired truncus arteriosus are at risk of developing ES (5,6). The underlying defect in ES is important because it has prognostic implications. Evidence suggests, for example, that patients with ASDs differ in their evolution of pulmonary vascular disease compared with patients with VSDs (4).

Patients with ES may present with more complex underlying lesions, such as truncus arteriosus, transposition of
great vessels and VSD, or single ventricles with unobstructed pulmonary blood flow. The development of ES in patients with complex CHD is associated with a 10- to 12-fold increase in mortality (6).

Key stages in development of ES are outlined in Figure 1 (5). The mechanisms underlying the remodeling of the cardiopulmonary circulation have not been fully elucidated but are likely to involve vasoconstriction, inflammation, thrombosis, cell proliferation, and fibrosis (7). Implicated in these mechanisms is an errant expression of vasoactive mediators, including endothelin-1, thromboxane, prostacyclin, and nitric oxide (7). The apparent importance of such molecules in the development of ES emphasizes the similarities between this condition and other etiologies of PAH.

The 3 major pathophysiological pathways that represent important signaling cascades in PAH are illustrated in Figure 2 (8).

**ES Versus Other Forms of PAH**

Structural changes in the pulmonary vasculature are qualitatively similar in all forms of PAH, including ES (9). In the Venice classification, PAH associated with CHD (PAH-CHD) is grouped with idiopathic, drug-, connective tissue disease- and human immunodeficiency virus–related etiologies (10). Notable clinical differences, however, are reported to exist between ES and idiopathic pulmonary arterial hypertension (IPAH). For example, patients with ES may experience hemoptysis, cerebrovascular incidents, brain abscesses, secondary erythrocytosis, and coagulation abnormalities, as well as sudden death, cardiac arrhythmia, and other problems associated with insufficient tissue oxygenation that are uncommon in IPAH (3,5).

Adult patients with ES exhibit increased survival and a more favorable hemodynamic profile and prognosis versus untreated patients with IPAH (11). Several vascular differences between patients with ES and IPAH also have been reported (12). These differences may result from the initial preservation of right ventricular function and relief of excess pressure via the right-to-left shunt. Consequently, patients with ES may exhibit better life expectancy but poorer quality of life in comparison with patients with IPAH.

**Treatment of ES**

Historically, management options for patients with ES have been limited to palliative measures or heart-lung transplantation, the latter of which is suitable only for a small subgroup of patients. Pharmacological treatment often involved the use of digitalis, diuretics, antiarrhythmics, and/or anticoagulants; however, none of these approaches significantly modified survival or risk of deterioration (3). Right heart failure is a potential complication of ES, for which digoxin may be beneficial, although evidence supporting this application is weak (13). Digoxin may, however, be of greater utility in the treatment of arrhythmias. Diuretics have been used for symptomatic relief of congestion (5) but carry the risk of worsening hyperviscosity. A better understanding of the molecular biology underlying right heart failure will hopefully reveal novel therapeutic targets for right ventricular failure in ES.

The use of anticoagulants in ES is controversial because of the increased risk of hemoptysis, stroke, and hemorrhage (14). The prevalence of pulmonary artery thrombosis in ES is estimated to be 20%, with increasing risk correlating with increasing age, biventricular dysfunction, dilation of the pulmonary arteries, and concomitantly decreased pulmonary flow velocity (15). Although the use of anticoagulants may be beneficial in patients with IPAH, no prospective studies have addressed their value in ES; therefore, no recommendations for their use can be given.

Patients with long-standing cyanosis may develop bronchial collaterals that lead to hemoptysis. Our own experience in treating chronic thromboembolic pulmonary hypertension and ES suggests that percutaneous closure of these vessels may be a potential therapeutic option in ES.

The efficacy of calcium-channel blockers in patients with ES is neither proven nor recommended because their use...
may decrease systemic arterial pressure and increase right-to-left shunting, leading to syncope and sudden death (5).

Long-term therapy with oxygen administered for at least 12 to 15 h/day may improve symptoms but has not been shown to influence survival (14). Tailored oxygen therapy is indicated if there is evidence of significant desaturation.

Phlebotomy with isovolumic replacement is used in the management of hyperviscosity syndrome associated with the increased production of red blood cells; however, only patients with definite signs of hyperviscosity should be phlebotomized (4).

Patient education, behavioral modifications, and awareness of potential medical risk factors are important aspects of management. Patients with ES are at particular risk during surgery, anesthesia, dehydration, chest infection, pregnancy, high altitude, and intravenous lines (4,6). Patients are advised to avoid strenuous exercise and competitive sports (6), although light exercise may be beneficial.

Heart–lung transplantation or lung transplantation with surgery to correct the cardiac defect are options for some patients with severe ES (16). Transplant surgery is, however, associated with high perioperative mortality (17).

Survival rates for ES patients are similar to those reported in non-ES recipients (18,19). The prolonged survival of patients with ES compared with IPAH complicates the decision of whether or not to list ES patients for transplant surgery. Given the paucity of suitable donor organs, the small number of suitable recipients, and prognosis following transplantation, any means to delay the need for heart–lung transplantation in ES patients is advantageous. A recent
A retrospective analysis suggested that ES patients who received novel, advanced, targeted therapies, including prostacyclin analogs and endothelin receptor antagonists, benefitted from significantly longer mean times to death or listing for transplant than patients receiving standard care (20).

Pulmonary artery banding before cardiac surgery may be effective in younger patients with CHD but not in older adults (21,22). The use of flap-valve closure of congenital defects was reported to gradually decrease pulmonary vascular resistance (PVR) in some patients with large VSDs without unreasonable mortality and morbidity (23,24).

**Targeted therapies.** A number of vascular mediators have been implicated in the pathophysiology of PAH, including prostacyclin, thromboxane A2, endothelin-1, and nitric oxide (7). Evidence also is emerging suggesting that PAH-CHD is associated with altered expression of serotonin, pulmonary potassium channels, and transforming growth factor beta and its receptors (4). Given the similarities between the pulmonary vascular changes observed in ES and other forms of PAH (25), disease-targeting therapies that have proved successful in IPAH have been investigated for the management of ES. Demonstrating prognostic benefit in ES versus IPAH patients is, however, challenging, given that patients with ES exhibit a more favorable hemodynamic profile and prognosis than those with IPAH. A long-term comparison of prognosis using end points such as “time to clinical worsening” in treated patients versus historical data, therefore, may be needed.

As a precursor to pharmacological therapy, tests for pulmonary vasoreactivity have an established role in selecting appropriate therapy for patients with IPAH (16,26). Although a proportion of patients with PAH-CHD are responsive to acute vasodilator testing with nitric oxide (27,28), this response is generally only minimal. Available treatment guidelines have been derived primarily from studies in IPAH and PAH associated with connective tissue disease (16,26); therefore, care should be taken in extrapolating data for patients with ES.

**ENDOTHELIN RECEPTOR ANTAGONISTS.** Endothelin-1 plays a major role in the structural and functional abnormalities in the pulmonary vasculature and in the progression of PAH-CHD and ES. The authors of several small-scale, open-label studies with the oral dual endothelin receptor antagonist, bosentan, suggested that efficacy in functional class, oxygen saturation, clinical status, and pulmonary hemodynamics was possible in patients with ES (29–31). The double-blind, placebo-controlled BREATHE-5 (Bosentan Randomized Trial of Endothelin Antagonist Therapy-5) study, the only such study in patients with ES, demonstrated that bosentan significantly reduced PVR and improved exercise capacity versus placebo (Fig. 3) (25). Bosentan was well tolerated and did not adversely affect systemic arterial oxygen saturation (25). A 24-week, open-label, follow-up study demonstrated further improvements in exercise capacity (Fig. 4) and functional class (32). A post hoc analysis of patient subgroups with ASDs, VSDs, or both ASDs and VSDs showed no changes in efficacy or systemic pulse oximetry between these patient subgroups (33). Most, but not all, long-term data suggest that clinical improvements observed in ES patients treated with bosentan can be maintained for at least 2 years, without safety or tolerability issues (34–39).

A retrospective review of 14 patients with ES treated with the single endothelin receptor antagonist, sitaxsentan, showed evidence for improvements in the ratio of PVR to systemic vascular resistance with no risk of significant decreases in resting oxygen saturation (40). Further investigation of the potential benefits of sitaxsentan is warranted.

**PHOSPHODIESTERASE TYPE-5 INHIBITORS.** To date, there have been limited studies in which phosphodiesterase type-5 inhibitors were used in patients with ES. During a
prospective, open-label trial of sildenafil, significant improvements in functional class, oxygen saturation, and cardiopulmonary hemodynamics were observed after 6 months. Improved exercise capacity (Fig. 5) and reduced cyanosis, with few significant side effects, also were observed (41).

Other small studies of phosphodiesterase type-5 inhibitors, alone and in combination with prostanoids, have shown improvements in exercise capacity, functional class, and hemodynamic parameters without safety issues (42–47). Although these data increase confidence in the potential safety and efficacy of phosphodiesterase type-5 inhibitors in ES, their value is limited by the small size of the studies and methodological shortfalls. Ultimately, these encouraging efficacy data require validation by large, randomized, placebo-controlled trials. Currently, patients are being recruited to participate in such a trial in Germany.

PROSTACYCLIN AND PROSTACYCLIN ANALOGS. Data on prostanoid therapy in patients with ES are limited to case reports and small studies (43,48–57). Continuous intravenous epoprostenol was reported to significantly improve functional class, oxygen saturation, and exercise capacity and to decrease PVR in 8 patients with ES after 3 months of therapy (49). The potential benefits and risks of potent pre-operative vasodilator therapy also have been illustrated in case studies in which continuous prostacyclin improved hemodynamics sufficiently to enable ES patients with ASD to undergo surgical repair of the cardiac lesion (50,51). The use of prostanoids in similar “inoperable cases” merits further investigation.

Safety of continuous prostanoid therapy is an important issue, particularly with respect to increases in SVR and PVR, reduced arterial oxygen, and long-term catheter use (49,52). Inhaled and oral prostanoids offer
advantages over epoprostenol in terms of the safety of long-term administration, but their efficacy and safety has not been comprehensively investigated in patients with ES.

**Future Aspects**

In recent years, advances in targeted therapies for PAH have challenged the dogma that ES is a stable disease, not amenable to treatment (25). In the future, surgical and other therapeutic approaches aimed at reversing vascular remodeling and regenerating the pulmonary microvasculature may be of benefit to our understanding of ES and the optimal management of ES.

Early data suggest that the repair of systemic-to-pulmonary shunts during childhood may be sufficient to reverse the development of pulmonary vascular disease for some patients (58). In other patients, PAH may develop even after closure of a septal defect and may result from an increased burden on the right ventricle due to remodeling of the pulmonary vasculature before surgery (59). Not all patients with CHD and particularly ASD, corrected or otherwise, develop PAH, and some may exhibit a genetic predisposition. Research is ongoing to identify those patients at greatest likelihood of developing pulmonary vascular disease.

Recent studies in animal models of PAH have demonstrated reversibility of vascular remodeling in response to long-term iloprost inhalation (60), inhibition of phosphodiesterase-1 (61), activation of soluble guanylate cyclase (62), and gene transfer of angiogenic factors (63). The reversal of monocrotaline-induced PAH and prolonging of survival using gene therapy targeting survivin, an inhibitor of apoptosis, also has been shown in a pre-clinical rodent model (64).

Imatinib, a selective antagonist of the platelet-derived growth factor receptor, was effective in the case of a single patient with severe treatment-refractory familial PAH (65), suggesting that such antiproliferative drugs may reverse pulmonary vascular remodeling, thus alleviating pulmonary hypertension. Treatment with the use of vasoactive intestinal peptide also may elicit beneficial effects in PAH (66) and warrants further investigation.

Increased levels of endothelin-1 produced by the pulmonary vascular endothelium may contribute to systemic dysfunction in PAH-CHD, although the clinical relevance of this is unclear in ES (67). Whether current PAH therapies targeting endothelin-1 can improve systemic circulation, and other complications in ES, remains to be elucidated.

The use of combinations of targeted oral therapies for the treatment of PAH is becoming increasingly commonplace, and benefits of early diagnosis and treatment of PAH recently have become apparent (68,69). Further investigation will be needed to elucidate the benefits of these novel approaches in ES and the optimal time for initiating treatment.

**Conclusions**

Eisenmenger syndrome is a severe and devastating condition that is associated with considerable morbidity and mortality. The identification of pathophysiological similarities between PAH and ES has led to the evaluation of targeted therapies, including endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, prostacyclin, and prostacyclin analogs, in patients with ES. Improvements in exercise capacity, functional class, and hemodynamics without compromising oxygen saturation using these treatments have challenged the notion that ES is a stable disease, not amenable to treatment. Continued research to quantify the value of earlier intervention, combined regimens of targeted therapies, and the potential to reverse pulmonary vascular remodeling in PAH-CHD is warranted.

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