Emerging Therapy of Congenital Heart Disease Associated with Pulmonary Hypertension

Michael J. Landzberg, MD
Director, Boston Adult Congenital Heart (BACH)
and Pulmonary Hypertension Group
Children's Hospital
Brigham and Women's Hospital
Beth Israel Deaconess Medical Center
Harvard University
Boston, Massachusetts

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Pulmonary arterial hypertension associated with congenital heart disease (CHD-PAH), as discussed throughout this issue of Advances in Pulmonary Hypertension, is one of the most commonly occurring causes of significant or severe morbidity and untimely mortality in CHD patients.[1] Without surgical therapy, it is suggested that some 30% of CHD patients will develop PAH.[2] Early recognition and treatment of CHD is often discussed, therefore, as the most effective preventive treatment measure for patients at risk for pulmonary vascular disease. Epidemiologic estimates of occurrence of CHD-PAH have targeted approximately 15% of all CHD survivors as having PAH.[3]

CHD-PAH may occur in several differing scenarios, including "dynamic," or shunt-mediated PAH, appearing to be responsive to control of shunt flow; late postoperative PAH; postoperative "reactive" PAH; normal or mild elevation of pulmonary resistance in unusual congenital circuitry (cavopulmonary shunts); and shunt reversal (Eisenmenger physiology), all contributing to morbidity and mortality in affected patients. After onset of PAH, removal of the offending "trigger" (the anatomic change that led to flow or pressure imbalance) to CHD-PAH development may have little positive, and possibly negative, impact on outcome. Perhaps due to comorbid inherited or acquired medical states, the potential for sharing of systemic venous and arterial circulations, or the increased duration of disease seen in affected individuals with CHD-PAH, functional capacity and survival in children and adults with CHD often remain limited when compared with age-matched controls. This is due not only to primary pulmonary vascular effects on the subpulmonic ventricle or circulation, but also, in significant part, to residual defects, postoperative cardiac and noncardiac residua, or medical comorbidities.

Key Words—Congenital heart disease; pulmonary arterial hypertension; targeted pulmonary hypertension therapy.

Address for reprint requests and other correspondence: Michael J. Landzberg, MD, Children's Hospital, 300 Longwood Ave., Boston, MA 02116. (email: Michael.landzberg@cardio.chboston.org)

Shunt-mediated Pulmonary Arterial Hypertension

Animal studies of surgically induced shunt-mediated elevation in pulmonary blood flow and/or increased pulmonary arterial pressure suggest that both contribute to increased shear stress and structural inflammatory changes,[4,5] including overexpression of endothelin-1 and ET_B receptors with or without ET_A receptors,[6] VEGF with or without its Flk-1/KDR receptors,[7] TGFβ-1 and its ALK1 receptor,[8] calcium-dependent K channels,[9] PDE5,[10] inducible NO synthase, angiotensin-II and the angiotensin A and B receptors, angiopoietin-1, MCP-1, ICAM and tenascin, along with decreased expression of BMPR1A, BMPR2, and NO-cGMP signaling.[11-13] In humans, of all these mediators, the strongest body of evidence currently exists for endothelin being a key pathogenetic mediator in the development and sustenance of CHD-PAH.[14-17] In animal models of disease as well as in humans, anecdotal reports abound of use of various agents designed to limit disease occurrence or progression by altering these inflammatory mediators as preoperative conditioning prior to surgical intervention, with many carrying potential for more fruitful clinical trials.

Surgical experience has suggested that there is reversibility to the changes occurring with shunt-mediated PAH, as surgery is typically curative when pulmonary vascular changes are not "fixed." One of the key elements of this review is the notion that accurate catheterization-based calculation of pulmonary blood flow (Qp) may be required in these patients, with, at times, complex isolation of all sources of Qp, individualized measure of resistance in isolated lung segments, and direct measure of pulmonary venous pressure. These may be required to fully measure, calculate, and understand pulmonary vascular resistance and assess PAH reversibility and outcome success at the time of operation. Studies have not been performed pointing to testing or surgical timing that can tie to reversibility to "normal" of pulmonary pressures and resistance. Although it is often quoted that preoperative assessment of pulmonary vascular resistance of less than 15 indexed Wood units and pulmonary/systemic resistance ratios of 2/3 or less are tied to improved surgical outcome,[18] individual institutions tend

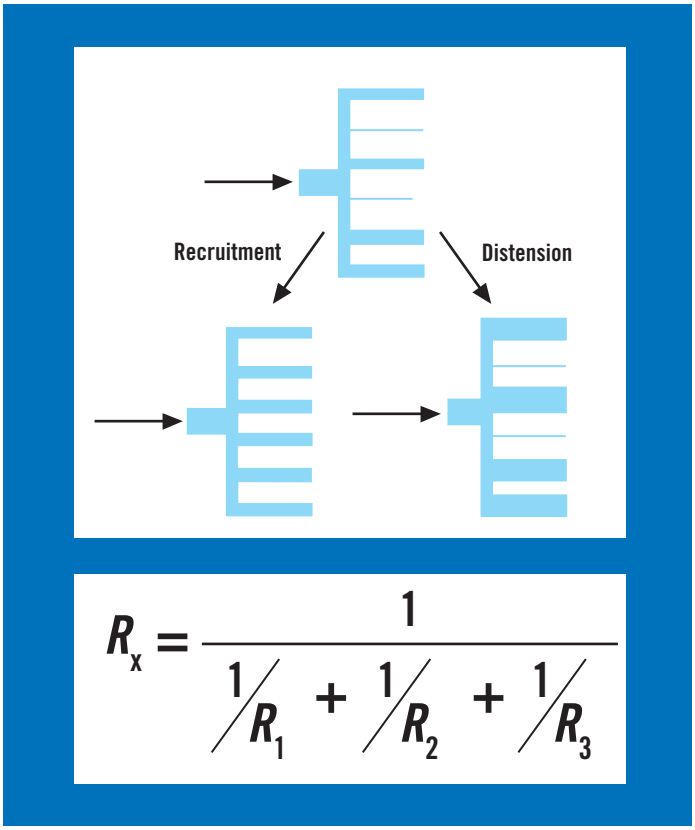

Figure 1. Increased flow both recruits and distends pulmonary vessels in parallel, with total resistance calculated as 1 / (sum of inverse of individual resistances).

to have regional variation and lesion-specific limits to tested pulmonary vascular resistance, tested both de novo and with maximal acute vasodilation, prior to proceeding with surgery, with or without medical or surgical preoperative conditioning of the pulmonary vasculature. If chosen, these strategies in highest risk patients must never be fixed and should involve periodic reassessment of hemodynamics and therapies, with potential to halt or reverse anatomic interventions if such becomes indicated. Unusual circumstances (particularly in more youthful individuals) may arise where reduction of pulmonary blood flow (at the expense of increased intracardiac shunt-mediated cyanosis) is created by means of surgical or catheter-based restriction, so as to decrease pulmonary vascular flow and pressure, with potential to enable vascular remodeling.[19,20] If such occurs and is evidenced by later change in measured hemodynamics after months or longer, further surgical correction may be considered.

The important concept that pulmonary vascular resistance is flow-dependent, with distention and recruitment of vascular beds in parallel (**Figure 1**), needs more routine application when planning therapy for individuals with shunt-mediated CHD-PAH, particularly at borderline levels of operability. It is tempting to rely on strict application of hemodynamically derived shunt calculations, implying direct reduction of pulmonary pressures if shunt flow is surgically eliminated (assuming "fixed" resistance and pulmonary vascular resistance = [PA mean – LA mean]/Qp). However, it must be recognized that in "reversible" circumstances of shunt-mediated CHD-PAH, shunt flow recruits additional vascular beds in parallel (thereby reducing pulmonary vascular resistance). With elimination of shunt flow, these additionally recruited vascular beds may no longer be utilized to similar extents (thereby raising measured pulmonary vascular resistance). Thus, it is not uncommon to see substantively less drastic pulmonary arterial pressure reduction than expected, given that pulmonary vascular resistance may rise as flow decreases, balancing measured reduction in pressure.

Table 1. Additional "Triggers" of Pulmonary Hypertension in CHD-PAH

Abnormal subpulmonary or subsystemic ventricular loading conditions
Valvular dysfunction
Diastolic abnormalities of systemic or pulmonary atrioventricular function
Pulmonary venous hypertension or obstruction
Constrictive pericardial disease
Restrictive pulmonary disease (skeletal, muscular, or parenchymal)
Procoagulation due to viscosity, iron deficiency, systemic venous hypertension, or liver disease
Portal hypertension due to long-standing cardiac congestion

Late Postoperative Pulmonary Hypertension

Perhaps one of the most devastating sequelae of surgical correction of CHD is the development of late postoperative pulmonary hypertension. Typically, causation is attributed to late timing of anatomic shunt correction, miscalculation of surgical potentials, or to long-standing effects of stable but elevated subpulmonary ventricular afterload, and therapies tend to focus on long-term use of standard pulmonary vasoactive agents or pulmonary transplantation. However, it should be recalled that individuals with congenital cardiac defects harbor multiple additional triggers to pulmonary hypertension relatable, in part, to sequelae of their intrinsic physiology (**Table 1**). These factors may be equally as common, if not more so, as progression of underlying poorly understood intrinsic CHD-PAH; the frequency of their occurrence has been highlighted by the unexpected frequency of exclusion criteria due to comorbid non-CHD pulmonary hypertension triggers witnessed by some centers in tightly controlled medical trials for CHD-PAH (personal correspondence: BREATHE-5 trial[21]). Treatable additional triggers, therefore, should be sought in all CHD patients, regardless of correction status, when PAH presents or worsens.

Perhaps typical of medical diagnostics, recognition of additional CHD-PAH triggers and targeting interventions for such is dependent on clinician and center experience and awareness of disease potential. Anatomic and physiologic definition at timing of catheterization is requisite (**Table 2**) to identify additional treatable contributors to subpulmonic ventricular or circulatory afterload (including mechanical or

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Table 2. Anatomic Considerations for Noninvasive and Invasive Diagnosis and Surgical or Transcatheter Therapies for Additional Contributors to Pulmonary Hypertension in CHD-PAH

Diagnosis
Mechanical or pulmonary parenchymal etiologies of pulmonary venous desaturation
Peripheral pulmonary stenosis or thrombosis/intravascular obstruction
Pulmonary venous or baffle obstruction
Subsystemic or subpulmonary atrial or ventricular outflow obstruction
Valvular regurgitation
Coronary arterial compression or obstruction
Constrictive pericardial disease
Therapy
Balloon, stent, or surgical atrial or ventricular septostomy
Restriction of pulmonary blood flow (pulmonary arterial band)
Transplantation (lung or heart/lung)

parenchymal etiology of pulmonary venous desaturation, or recognition and therapy of pulmonary arterial obstruction due to peripheral pulmonary stenoses or thrombotic sequelae, pulmonary venous or baffle obstruction, pulmonary venous hypertension, subsystemic ventricular failure, coronary arterial compression or obstruction, or constrictive pericardial disease).

It remains unclear whether use of balloon- or stent-mediated limited septostomy (using right-to-left shunting as a means of improving loading conditions of the pulmonary circulation and subpulmonary ventricle) is better tolerated or effective in patients previously exposed to intravascular shunting.

Immediate Postoperative Pulmonary Hypertension

It has long been recognized that in the immediate postoperative phase of cardiopulmonary surgery, pulmonary vascular reactivity is heightened, with potential to precipitate marked increase in pulmonary vascular resistance with resultant decrease in pulmonary blood flow, hypotension, academia, myocardial ischemia and increase in airway resistance, bronchoconstriction, ventilation perfusion mismatch and alveolar edema.[22] Central to the understanding of such abnormalities is the occurrence of pre- and perioperative endothelial cell dysfunction, with attendant alterations in eiscosanoid production,[23,24] nitric oxide synthesis,[25] and endothelin synthesis and clearance.[26] Improvements in understanding of such triggers and conditioning, as well as use of management strategies that decrease adrenergic tone and recognized vasospactic stimuli and enhance postoperative right ventricular and atrioventricular valve function (including use of appropriate sedation agents, avoidance of respiratory or metabolic acidosis, overcoming alveolar hypoxia or mechanical atelectasis, treating painful stimuli and correcting anemia or myocardial demand abnormalities, and rapid potential to seek unanticipated residual anatomic abnormalities) have nearly eliminated mortality related to postoperative pulmonary hypertension in most large centers. Additional use of standard pulmonary vasoactive agents (most typically inotropes, inhaled nitric oxide, nitric oxide donors, or phosphodiesterase III or V inhibitors) may be required to treat and terminate such events. When such crises do occur, however, morbidity, including prolonged hospitalization, ICU stay, and mechanical ventilation, clearly remains increased.[22,25]

Normal to Mildly Abnormal Pulmonary Ventricular Resistance States

Similar to outcomes in states of acute right ventricular dysfunction (pulmonary embolism, right ventricular infarction), most successful outcome in special circumstances in congenital cardiac postoperative care lend themselves to lowest potential pulmonary vascular resistance. Prototypical of these circumstances is the situation of surgical creation of cavopulmonary anastomoses (Glenn shunt and its variants, Fontan palliation and its variants) for individuals with tricuspid atresia or similar single-ventricle physiologies. These circulations are unique, without pulsatile flow to the pulmonary vasculature and with direct continuity between cerebral and pulmonary circulations (the superior vena cava directly communicates to the pulmonary arteries with the Glenn shunt, with inferior vena cava incorporation into this circulation via construction of a baffle in individuals with complete cavopulmonary Fontan anastomosis). These circulations may have vasoactive triggers acting in opposition in differing but now connected vascular beds, due to varying actions on cerebral versus pulmonary vasculature. For example, hypercapnea, acidemia, and hypoxia decrease cerebral vascular resistance and increase cerebral blood flow, but act to decrease pulmonary flow, with cerebral effects taking precedence (pulmonary flow decreases). Likewise, hypocapnea, alkalosis, and oxygen increase cerebral vascular resistance and decrease cerebral blood flow, but act to decrease pulmonary vascular resistance and increase pulmonary blood flow, again, with cerebral effects taking precedence (pulmonary blood flow increases).[27,28] Despite hopes for substantive improvement in functional outcomes given recognized long-term morbidities related to adequacy of pulmonary flood flow, there remains considerable debate as to overall effects of adding pulmonary vasoactive therapies into these circulations, though study of such potentials continues[29-31].

Similar unknowns exist regarding potential for benefit of administration of pulmonary vasoactive agents in individuals with right ventricle-dependent functional outcomes, such as with Ebstein's disease and tetralogy of Fallot (TOF). Given the increasing morbidities seen with aging in such affected patients, further study of such potential interventions is expected.

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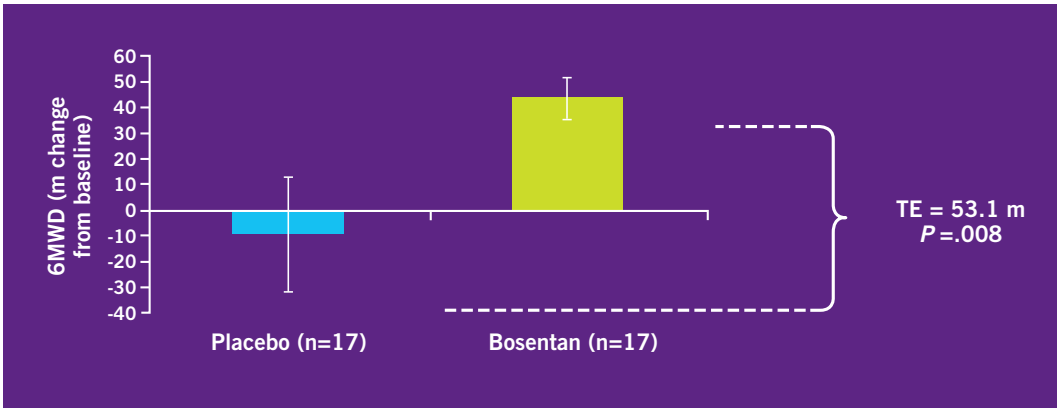

Figure 2. Improved functional capacity, as evidenced by improved 6-minute walk distance (6MWD), after short-term therapy with bosentan in Eisenmenger physiology patients when compared with use of placebo in a randomized controlled study. Treatment effect (TE) was greater than 50 m improvement compared with controls. (Reprinted with permission from Galie N, Beghetti M, Gatzoulis MA, et al.[21])

Eisenmenger Physiology

Patients with Eisenmenger physiology have additional complications as compared with patients with idiopathic or other forms of secondary PAH, as outlined elsewhere in this issue. Organ damage may result, predominantly noted in the blood elements, cerebrovasculature, kidneys (glomerular, tubular, and interstitial function may be altered), liver (elevated central venous pressure and low systemic cardiac output), peripheral musculature, and chest.

Hence, as outlined, emphasis has been on educated consumerism within a medical team framework, with advocacy of avoidance of destabilizing situations (volume shifts, alteration of catecholamines, extreme fatigue, high-altitude exposure, contact with cigarette smoke, changes in renal or hepatic function or use of medications that may modulate flow to or function of these organs, pregnancy, and iron deficiency), prompt therapy of arrhythmia or infection, and use of specific medical teams versed in pulmonary vascular management strategies for cardiac and noncardiac surgery.

As modern understanding of pulmonary arteriolar hypertension and subpulmonary ventricular failure has increased, so has recognition that therapy of Eisenmenger physiology relies on modulation of primary pulmonary vascular inflammation and its ramifications (see earlier section on shunt-mediated PAH). Therapies for adults with shunt-associated pulmonary hypertension have been limited and have included oxygen, warfarin, diuretics, high-dose calcium-channel blockers, long-term continuous intravenous epoprostenol, oral prostacylin analogues, oral endothelin antagonists, oral phosphodiesterase inhibition, and lung or lung/heart transplantation.

The benefit of supplemental oxygen administration is debated, given conflict between recognized concomitant oxygen-responsive (Walker and colleagues have shown that oxygen delivery at FIO_2 = 40% improved mean systemic arterial saturation from 81.6% to 88.0% in Eisenmenger physiology patients) and oxygen-unresponsive components of hypoxemia in many patients and the lack of sufficient trial data to assess benefit.[32-34] Despite few data, calcium-channel blockers have shown limited results or have worsened well-being.[35] Transplantation has offered limited intermediate- and long-term survival benefit for this patient population (with 1-year survival rates after heart/lung transplantation and lung transplantation approximating 70% and 55%, respectively). However, given the unpredictability of transplant-free survival as well as significantly higher perioperative mortality in this cohort of patients, individual outcomes may warrant individual considerations.[36,37]

Anticoagulation with warfarin is widely employed in patients with PAH based on observational studies, in the absence of randomized controlled trials supporting benefit or evaluating risk. In adults with Eisenmenger physiology recognition of in vivo threatening prothrombosis,[38] contrasted with reports of in vitro abnormalities of coagulation in persons with cyanosis,[39] has led to debate over the potential benefit of oral anticoagulant therapy.

The theoretical possibility of worsening of right-to-left shunting raised questions about the safety of using pulmonary arterial modulating therapies that also have systemic vasodilator potential. Nevertheless, some of these agents (intravenous prostacyclin, subcutaneously administered treprostinil, oral beraprost, inhaled iloprost, oral bosentan, and oral sildenafil), have shown improvements in hemodynamics, exercise tolerance, and/or systemic arterial oxygen saturation in limited case study.[40-47] A potential for significant adversity due to these agents has been recognized. Randomized controlled trials showing benefit of many of these agents (intravenous prostacyclin, subcutaneously administered treprostinil, oral beraprost, and oral sitaxsentan) for patients with PAH have included smaller numbers of persons with Eisenmenger physiology. However, utility of these trials in guiding therapy for persons with Eisenmenger physiology is limited, given that the trials were not designed to test hypotheses specifically in persons with Eisenmenger physiology and such persons were not randomized to therapy within an Eisenmenger physiology subgroup.[44-46, 48-49] Results of BREATHE-5, the first randomized controlled trial of an agent for individuals with Eisenmenger physiology, tested oral bosentan compared with placebo and found that in short-term follow-up, bosentan not only was safe, but led to substantive and sustained improvement in catheter-measured hemodynamics as well as in both objective and patient-sensed functional outcome (**Figure 2**).[21] These relatively short-term results have been substantiated over longer-term follow-up.[50-51] Given the positive findings in this trial and the establishment of bosentan as a first therapy to improve functional capacity and potentially to impact on survival in the Eisenmenger physiology population, further studies of additional pulmonary vasoactive agents, both alone and in combination, to treat individuals with Eisenmenger physiology are likely in the future.

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The potential for medical PAH therapy combined with surgical- or catheter-based pulmonary flow restriction has yet to be studied.

Summary

CHD-PAH is a devastating multifactorial phenomenon, similar to all forms of severe PAH and pulmonary hypertension, that carries particular comorbidities and risks to affected patients due to frequently long-standing past or concurrent shunt effects on comorbid organ systems. All therapies aimed at limiting or eliminating effects of such CHD-PAH must take these comorbidities, as well as the potential for novel additional pulmonary hypertension triggers, into account. Anatomic and physiologic understanding of the mechanism of pulmonary hypertension may be complex, leading to multifactorial and multistaged therapies and reassessments based on anatomic and physiologic considerations. Medical therapies for PAH, long avoided because of concern for increased morbid risk and lack of data from randomized trials, are now showing improved outcomes in this population. Coordinated care strategies in centers with knowledge of and expertise in both CHD and PAH diagnostics and therapeutics are suggested. ■

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