

Hypoplastic Left Heart Syndrome With Intact or Highly Restrictive Atrial Septum

Outcome After Neonatal Transcatheter Atrial Septostomy

Antonios P. Vlahos, MD; James E. Lock, MD; Doff B. McElhinney, MD; Mary E. van der Velde, MD

Background—Hypoplastic left heart syndrome (HLHS) with intact or very restrictive atrial septum is a highly lethal combination. We review our 13-year institutional experience treating this high-risk subgroup of patients with emergent catheter therapy.

Methods and Results—Infants with HLHS requiring catheter septostomy within the first 2 days of life were compared with a matched control group with adequate interatrial communication. Preoperative, early postoperative, and medium-term survival were evaluated. Earlier experience was compared with recent results to assess the effect of changes in catheterization and surgical and intensive care unit management strategies over the study period. From 1990 to 2002, 33 newborns with HLHS (11% of newborns with HLHS managed during this period) underwent urgent/semiurgent catheterization to create or enlarge an interatrial communication before surgical palliation. Preoperative and early postoperative mortality were high (48%) compared with control HLHS patients, regardless of prenatal diagnosis and despite successful catheter-based atrial septostomy with clinical stabilization. Mortality trended down during the later part of the study period. Those who survived the neonatal period had late survival, pulmonary artery pressure, and resistance similar to those of control subjects.

Conclusions—Neonatal mortality in the subgroup of HLHS patients with intact or highly restrictive atrial septum remains high despite successful urgent septostomy. Persistently poor outcomes for these patients have prompted efforts at our center to develop techniques for fetal intervention for this condition, in the hope that prenatal relief of left atrial and pulmonary venous hypertension may promote normal pulmonary vascular and parenchymal development and improve both short- and long-term outcomes. (*Circulation*. 2004;109:2326-2330.)

Key Words: heart defects, congenital ■ pediatrics ■ catheterization ■ pregnancy

Although the surgical management of hypoplastic left heart syndrome (HLHS) has continued to improve during the past decade,¹⁻⁷ morbidity and mortality remain high in the subset of patients with an intact or very restrictive atrial septum.⁸ These patients present with severe cyanosis and hemodynamic instability at birth and require urgent postnatal cardiac catheterization or surgery to relieve the septal obstruction and improve oxygenation.⁹ There is limited published information describing outcomes in this high-risk population and none assessing the impact of prenatal diagnosis of intact or restrictive atrial septum on short- and intermediate-term outcome.

We have increasingly used urgent catheter-based creation of an atrial septal defect (ASD) as the first management step in these infants. In recent years, we have also attempted to detect intact or very restrictive atrial septum in prenatally diagnosed HLHS, implementing an aggressive management strategy of planned delivery with immediate transfer for

catheter-based left atrial decompression. In a case-control study, we examined our experience from 1990 to 2002 to assess the impact of prenatal diagnosis and of evolution in catheterization techniques and critical care management on outcome.

Methods

Patient Identification

A computerized search of the cardiology department database was used to identify patients with HLHS born from 1990 through 2002 who underwent urgent or semiurgent transcatheter atrial septostomy at Children's Hospital, Boston, Massachusetts, within the first 2 days of life. A control group composed of patients with HLHS and an adequate ASD was selected by random computerized selection after matching to study patients by year of birth and prenatal diagnosis.

Data Analysis

The primary outcome variable was freedom from death by Kaplan-Meier analysis, and the secondary outcome measure was death before stage I palliation. Independent variables assessed for association with outcomes included intact or very restrictive atrial septum,

Received October 8, 2003; revision received February 6, 2004; accepted February 10, 2004.

From the Departments of Cardiology, Children's Hospital, and Pediatrics, Harvard Medical School, Boston, Mass. Dr van der Velde is now at the Division of Pediatric Cardiology, University of Michigan Health System, Ann Arbor.

Correspondence to Mary E. van der Velde, MD, Associate Professor of Pediatrics, Division of Pediatric Cardiology, University of Michigan Health System, L1242 Women's, Box 0204, 1500 East Medical Center Dr, Ann Arbor, MI 48109-0204. E-mail mvdvelde@med.umich.edu

© 2004 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000128690.35860.C5

prenatal diagnosis, year of admission (continuous and 1990 to 1996 versus 1997 to 2002), age at surgery, the presence of decompressing veins from the left atrium to the systemic venous circulation, and septostomy method. Categorical variables were compared by Fisher's exact test. Continuous variables were compared by 1- or 2-tailed *t* test analysis. Survival analysis was performed according to the Kaplan-Meier product limit method. Data are presented as mean $\pm$ SD unless otherwise specified.

Interrogation of medical records and computerized hospital databases was approved by the Children's Hospital Institutional Review Board, and the procedures followed were in accordance with institutional guidelines for retrospective record review and protection of patient confidentiality.

Results

Patients

Between 1990 and 2002, 300 neonates with HLHS were admitted to Children's Hospital, Boston, Massachusetts. Of these, 33 (11%) underwent urgent or semiurgent transcatheter atrial septostomy. HLHS had been diagnosed by fetal echocardiography in 18 of these 33 patients (55%), including 16 who were also diagnosed in utero as having an intact or restrictive atrial septum by color and/or pulsed-wave Doppler examination. Decompressing veins from the left atrium or pulmonary veins to the systemic venous circulation were diagnosed in 7 patients (21%), 4 by prenatal and/or postnatal echo and 3 at subsequent catheterization. A 34th patient was diagnosed prenatally to have HLHS and intact atrial septum, but this patient died very soon after birth, before catheterization could be performed. All other candidates presenting during the study period underwent catheterization with intent to create or enlarge the ASD.

The control group consisted of 66 patients with HLHS and an unrestrictive ASD.

Catheter Intervention

Catheter septostomy was performed at a median age of 0 days for prenatally diagnosed infants and 1 day for those diagnosed postnatally ($P=0.03$). A variety of methods, and in some cases more than 1 method, were used to create or enlarge the interatrial communication, including transseptal puncture in 27 patients (82%), balloon dilation in 28 (85%), traditional balloon atrial septostomy in 7 (21%), and blade septostomy in 1 (3%). Stents were placed in the created ASD in 4 patients.

Before septostomy, the mean left atrial pressure was 24.8 ± 6.1 mm Hg, falling to 13.6 ± 4.3 mm Hg after septostomy. Of note, in all 7 patients with a decompressing vein to the systemic circulation, the decompressing vein was restrictive, and in all but 1 of these patients, the left atrial pressure was >25 mm Hg. Among patients with a highly restrictive interatrial septum ($n=20$), the mean instantaneous interatrial pressure gradient was 14.7 ± 6.5 mm Hg (true instantaneous gradients were not determined in the 13 patients with an intact atrial septum) before septostomy, falling to 4.3 ± 3.1 mm Hg after septostomy. One patient had undergone an unsuccessful attempt at septostomy at another institution and died in our catheterization laboratory before a repeat septostomy could be performed. No patient undergoing septostomy at Children's Hospital required repeat catheterization before stage I (Norwood) surgery or went urgently to the

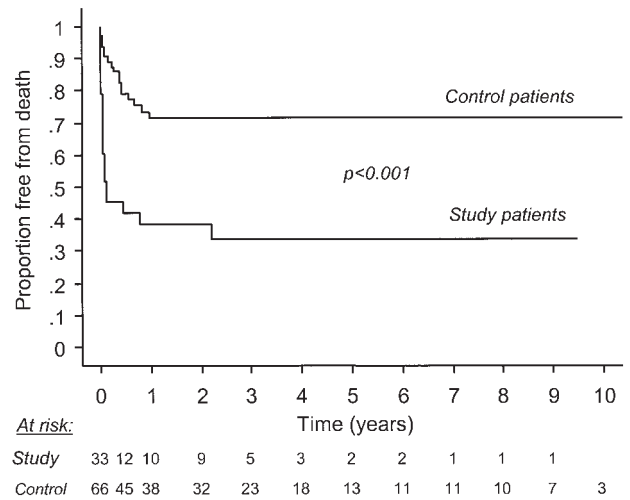


Figure 1. Kaplan-Meier curves demonstrating estimated survival (freedom from death) over time among study and control patients. Numbers of patients at risk are indicated below abscissa.

operating room for left atrial decompression. One patient who developed hemopericardium during catheterization was placed on extracorporeal membrane oxygenation and underwent urgent repair of a left atrial perforation.

Outcomes

Of 33 patients in the study group, 7 (21%) died before stage I surgery, compared with none of the 66 control patients ($P=0.03$). Four of these 7 patients had a prenatal diagnosis of HLHS, including 3 in whom the intact or very restrictive atrial septum was noted in utero. There was a trend toward lower initial pH on arrival in the catheterization laboratory in these 7 patients (7.24 ± 0.18 versus 7.32 ± 0.13 , $P=0.18$). Left atrial pressure was the same, and the transseptal gradient after septostomy was actually significantly lower than in patients who survived to undergo stage I (1.7 ± 2.4 mm Hg versus 4.7 ± 3.2 mm Hg, $P=0.04$). All 7 were thought to have a poor prognosis because of either multiorgan damage ($n=6$) or multiple congenital anomalies ($n=1$). Other than an intact or very restrictive atrial septum, no risk factors for death before stage I palliation were identified among the variables analyzed.

Among patients undergoing stage I palliation, surgery was performed at a younger age in study patients than in control subjects (controls) (4.3 ± 2.3 versus 6.3 ± 5.4 days, $P=0.03$ by 1-tailed *t* test). Ten of the 26 (38%) patients who survived to undergo a stage I procedure died within 35 days after surgery. Thus, early survival among the 33 study patients was 48%. There was no significant difference in early mortality between those born with an intact atrial septum ($n=13$) and those with a patent but highly restrictive interatrial communication ($n=20$).

Kaplan-Meier freedom from death at 1, 6, and 12 months was 52%, 42%, and 34% among study patients and 91%, 79%, and 72% among controls (Figure 1). Survival was significantly worse among study patients than controls ($P<0.001$). Overall (including both study and control patients), freedom from death was lower among patients born

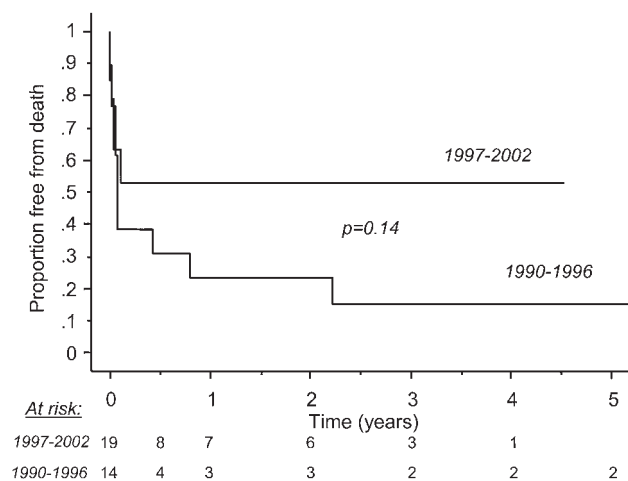


Figure 2. Kaplan-Meier curves demonstrating estimated survival (freedom from death) over time among study patients born between 1990 and 1996 and those born between 1997 and 2002. Numbers of patients at risk are indicated below abscissa.

before 1997 ($P=0.02$). This difference appeared to hold true within both the study and control groups, although the statistical power to determine an independent effect of this variable within the study group was limited by the number of patients (Figure 2). None of the other independent variables analyzed were found to correlate with survival overall or within the study group, including prenatal diagnosis.

All 16 stage I survivors underwent bidirectional Glenn anastomosis at a mean age of 6.1 ± 2.3 months (versus 7.4 ± 4.2 months in control patients, $P=0.25$). There were 3 early postoperative deaths (19%) and a fourth death 14 months after the Glenn procedure. Among patients who survived to undergo a bidirectional Glenn anastomosis, Kaplan-Meier survival after bidirectional Glenn was worse among study patients than controls (47 control patients had undergone bidirectional Glenn) to a degree that approached significance ($P=0.065$; eg, 79% versus 90% at 6 months). At pre-Glenn catheterization, mean pulmonary artery pressure was higher in study patients than in controls (20.8 ± 8.3 versus 17.5 ± 4.3 mm Hg, $P=0.08$), but this reflected higher left atrial pressure (12.1 ± 5.7 versus 10.1 ± 2.9 mm Hg, $P=0.09$) rather than a higher transpulmonary pressure gradient (8.6 ± 4.7 versus 7.4 ± 2.9 mm Hg, $P=0.24$) or pulmonary vascular resistance (1.9 ± 1.2 versus 2.0 ± 1.0 WU, $P=0.69$), which did not differ between study patients and controls. Pulmonary artery pressure and pulmonary vascular resistance were similar in study patients who died after the Glenn procedure and those who survived.

Of the 12 surviving study patients, 10 have undergone a fenestrated Fontan procedure, and 2 are awaiting completion of the Fontan circulation. At pre-Fontan catheterization, there was no difference between study and control patients (32 control patients had undergone Fontan completion) in mean pulmonary artery pressure (12.7 ± 6.5 versus 12.6 ± 3.6 mm Hg, $P=0.94$) or pulmonary vascular resistance (1.9 ± 0.9 versus 1.9 ± 1.0 WU, $P=0.93$).

Lung Pathology

Ten of the 22 study patients who died underwent postmortem microscopic examination of lung tissue. Eight of the 10 died

within the first month of life, 4 after stage I surgery and 4 without surgery. Four of these 8 were found to have dilated and/or prominent pulmonary lymphatic vessels on microscopic histopathology. The 2 autopsies performed on older patients did not describe abnormal lymphatic vessels.

Discussion

HLHS is characterized by hypoplasia of the left ventricle associated with stenosis or atresia of the mitral and aortic valves. Thus, all or most of the pulmonary venous return must be shunted to the right atrium to reenter the circulation. Accordingly, relatively unrestricted communication at the atrial level is necessary for oxygenated blood to be delivered to the body and to avoid pulmonary venous congestion. However, $\approx 6\%$ of patients with HLHS have an intact atrial septum, and up to 22% have some degree of restriction of left-to-right flow through the ASD.^{7,8} Significant limitation of interatrial communication in such patients results in hemodynamic instability postnatally, with severe cyanosis, acidosis, and pulmonary venous congestion requiring an urgent intervention to create or enlarge the communication.^{8,9} In some patients with HLHS, a levoatrial cardinal vein or other channel between the left atrial and systemic circulation may provide adequate left atrial decompression,^{8,10} although the mere presence of such a communication does not guarantee adequate decompression, as demonstrated by the fact that all 7 patients with a levoatrial cardinal vein in our series had severe left atrial hypertension.

Survival of infants born with HLHS has improved steadily in recent years.¹ However, as our study and previous smaller studies have confirmed, outcomes among patients with HLHS and a restrictive or intact atrial septum are significantly worse than among the group as a whole despite aggressive early management strategies aimed at relieving atrial septal obstruction.^{2,8,11} Among patients managed during the first half of our study period (1990–1996), early survival (6 of 14, 43%) was slightly better than that of neonates with HLHS and an intact atrial septum who were sent directly to the operating room as an alternative form of management at The Children's Hospital of Philadelphia during the same era (6 of 18, 33%).⁸ Although we noted a trend toward improved outcome in more recent years compared with our earlier experience, the early survival was still only 53% for the period 1997 to 2002. Improved survival parallels improvements in survival among all patients with HLHS and corresponds with improving outcomes for HLHS reported by other centers, which are most likely at least in part because of perioperative management strategies that extend to the particularly ill subset of patients with a restrictive or intact atrial septum.^{1,3–7} The increasing use of extracorporeal membrane oxygenation may have contributed to improved survival.

In concert with the advances in operative and perioperative strategies that have occurred in recent years, significant progress has been achieved in transcatheter techniques.^{9,12} In our cohort, the majority of patients underwent transseptal puncture followed by balloon dilation of the atrial septum, with or without stenting of the interatrial communication. Although surgery was performed at a younger age in study patients than in controls, none of the patients who underwent

transcatheter creation/enlargement of an interatrial communication required emergent surgical relief of atrial septal obstruction. Clearly, pre-stage I catheter-based palliation of an intact or very restrictive atrial septum is a feasible and effective means of decompressing the hypertensive left atrium.

Other centers have advocated urgent surgery over catheter septostomy in these infants. This approach subjects the critically ill neonate, often with multisystem organ dysfunction, to the additional risks of cardiopulmonary bypass and cardiac surgery. In addition, the elevated pulmonary vascular resistance may take several days to fall, complicating early postoperative management. Although catheter-based therapy may reduce morbidity in these patients, published data on a comparable patient population undergoing urgent surgical treatment in the same era are not available for comparison.

Previous studies have demonstrated that prenatal diagnosis of HLHS may improve preoperative and/or operative outcome by allowing planned delivery in a tertiary center specializing in the treatment of patients with HLHS.^{13–15} To accurately assess the effect of prenatal diagnosis, one would need to determine how many undiagnosed newborns died in outside hospitals before transfer to a tertiary care institution. Although diagnosing atrial septal restriction prenatally did not demonstrably improve our survival rate, earlier septostomies in prenatally diagnosed neonates presumably shorten the preintervention period of extreme cyanosis and acidosis.

It has been demonstrated that patients with HLHS and an intact or very restrictive atrial septum have pulmonary vascular and lymphatic abnormalities, presumably secondary to intrauterine left atrial hypertension, which place them at increased risk after surgical palliation or orthotopic heart transplantation.^{8,11,16} Thus, it is notable that among our small group of patients who survived the neonatal period and underwent subsequent bidirectional Glenn and Fontan operations, pulmonary vascular resistance and pulmonary arterial pressure were normal. Although it is not clear whether this is because of milder initial disease or natural regression after relief of left atrial hypertension, these patients had degrees of left atrial hypertension similar to that of patients who died in the neonatal period. Assuming that pulmonary vascular changes were present to a similar extent in this group, the fact that they had normal pulmonary vascular resistance at pre-Glenn and pre-Fontan catheterization is encouraging and suggests that any damage to the pulmonary vasculature in the setting of pulmonary venous hypertension in utero may be reversible over time. Nevertheless, the reversibility of the histopathological pulmonary vascular changes that have been observed in patients with HLHS and left atrial hypertension⁸ have not been documented definitively, and the effects of prenatal pulmonary venous hypertension and decreased pulmonary blood flow on the pulmonary vascular bed remain unstudied. However, data from other studies of pulmonary artery hypertension caused by pulmonary venous hypertension have found that pulmonary vascular changes may be reversible after relief of pulmonary venous hypertension, even after protracted elevation of left atrial pressure.^{17–19}

Conclusions and Implications for the Future

HLHS with intact or severely restrictive atrial septum continues to have a high mortality rate before and after stage I palliation, despite prenatal diagnosis and recent advances in interventional catheterization, surgical technique, and critical care management strategies. Beyond the high-risk neonatal perioperative period, early childhood survival may not differ from that of other HLHS patients, but the long-term outlook is unknown.

We and others have assumed that the primary source of increased mortality in these patients is the profound cyanosis caused by a reversible increase in pulmonary vascular resistance. However, elevated pulmonary vascular resistance and decreased pulmonary blood flow in utero may also prevent development of a normal pulmonary vascular bed and parenchyma. Diminished cross-sectional area of the pulmonary vascular bed, venous and arterial muscularization, and parenchymal abnormalities may not be rapidly or entirely reversible after birth, in which case refractory pulmonary edema and extreme cyanosis may persist despite effective left atrial decompression. It has been suggested that pulmonary venous relaxation may be an important factor in the normal adaptation of the pulmonary circulation to the postnatal environment and that pulmonary venous relaxation is blunted in piglets with pulmonary vascular hypertension.²⁰ This being the case, it stands to reason that pulmonary venous hypertension and remodeling in the fetus will have an important effect on the normal postnatal drop in pulmonary vascular resistance. Because mortality in patients with HLHS and a restrictive or intact atrial septum is highest in the newborn period, rapid normalization of the pulmonary vasculature seems essential to optimizing outcomes in this group of patients.

The findings of the present study, in conjunction with existing data on pulmonary vascular changes and lymphangiectasia in patients with HLHS and left atrial hypertension caused by interatrial restriction,⁸ support efforts to relieve pulmonary venous hypertension in utero. If the diagnosis of intact or severely restrictive atrial septum without an unrestricted decompressing vein can be made reliably in utero, as our study suggests it can, and if prenatal relief of obstruction can be shown to be technically possible and safely achieved for both mother and fetus, fetal atrial septostomy may be a means of altering the natural history of this condition. Lowering pulmonary venous pressure and increasing intrauterine pulmonary blood flow may reverse or reduce pathological pulmonary changes and promote development of the pulmonary vascular bed, thereby ideally improving early survival as well as long-term outcome.

References

1. Tweddell JS, Hoffman GM, Mussatto KA, et al. Improved survival of patients undergoing palliation of hypoplastic left heart syndrome: lessons learned from 115 consecutive patients. *Circulation*. 2002;106(suppl I):I-82–I-89.
2. Jenkins PC, Flanagan MF, Jenkins KJ, et al. Survival analysis and risk factors for mortality in transplantation and staged surgery for hypoplastic left heart syndrome. *J Am Coll Cardiol*. 2000;36:1178–1185.
3. Drinkwater DC Jr, Aharon AS, Quisling SV, et al. Modified Norwood operation for hypoplastic left heart syndrome. *Ann Thorac Surg*. 2001;72:2081–2086.

4. Azakie T, Merklinger SL, McCrindle BW, et al. Evolving strategies and improving outcomes of the modified Norwood procedure: a 10-year single-institution experience. *Ann Thorac Surg*. 2001;72:1349–1353.
5. Mahle WT, Spray TL, Wernovsky G, et al. Survival after reconstructive surgery for hypoplastic left heart syndrome: a 15-year experience from a single institution. *Circulation*. 2000;102(suppl 3):III-36–III-141.
6. Poirier NC, Drummond-Webb JJ, Hisamochi K, et al. Modified Norwood procedure with a high-flow cardiopulmonary bypass strategy results in low mortality without late arch obstruction. *J Thorac Cardiovasc Surg*. 2000;120:875–884.
7. Forbess JM, Cook N, Roth SJ, et al. Ten-year institutional experience with palliative surgery for hypoplastic left heart syndrome: risk factors related to stage I mortality. *Circulation*. 1995;92(suppl II):II-262–II-266.
8. Rychik J, Rome JJ, Collins MH, et al. The hypoplastic left heart syndrome with intact atrial septum: atrial morphology, pulmonary vascular histopathology and outcome. *J Am Coll Cardiol*. 1999;34:554–560.
9. Atz AM, Feinstein JA, Jonas RA, et al. Preoperative management of pulmonary venous hypertension in hypoplastic left heart syndrome with restrictive atrial septal defect. *Am J Cardiol*. 1999;83:1224–1228.
10. Bernstein HS, Moore P, Stanger P, et al. The levoatriocardinal vein: morphology and echocardiographic identification of the pulmonary-systemic connection. *J Am Coll Cardiol*. 1995;995–1001.
11. Graziano JN, Heidelberger KP, Ensing GJ, et al. The influence of a restrictive atrial septal defect on pulmonary vascular morphology in patients with hypoplastic left heart syndrome. *Pediatr Cardiol*. 2002;23:146–151.
12. Cheatham JP. Intervention in the critically ill neonate and infant with hypoplastic left heart syndrome and intact atrial septum. *J Interv Cardiol*. 2001;14:357–366.
13. Tworetzky W, McElhinney DB, Reddy VM, et al. Improved surgical outcome after fetal diagnosis of hypoplastic left heart syndrome. *Circulation*. 2001;103:1269–1273.
14. Mahle WT, Clancy RR, McGaurn SP, et al. Impact of prenatal diagnosis on survival and early neurologic morbidity in neonates with the hypoplastic left heart syndrome. *Pediatrics*. 2001;107:1277–1282.
15. Satomi G, Yasukochi S, Shimizu T, et al. Has fetal echocardiography improved the prognosis of congenital heart disease? Comparison of patients with hypoplastic left heart syndrome with and without prenatal diagnosis. *Pediatr Int*. 1999;41:728–732.
16. Canter CE, Moorehead S, Huddleston CB, et al. Restrictive atrial septal communication as a determinant of outcome of cardiac transplantation for hypoplastic left heart syndrome. *Circulation*. 1993;88(suppl II):II-456–II-460.
17. Endo M, Yamaki S, Ohmi M, et al. Pulmonary vascular changes induced by congenital obstruction of pulmonary venous return. *Ann Thorac Surg*. 2000;69:193–197.
18. Naeije R, Lipski A, Abramowicz M, et al. Nature of pulmonary hypertension in congestive heart failure: effects of cardiac transplantation. *Am J Respir Crit Care Med*. 1994;149:881–887.
19. Wagenvoort CA. Morphological substrate for the reversibility and irreversibility of pulmonary hypertension. *Eur Heart J*. 1988;9(suppl J):7–12.
20. Arrioni FI, Hislop AA, Haworth SG, et al. Newborn intrapulmonary veins are more reactive than arteries in normal and hypertensive piglets. *Am J Physiol*. 1999;277:L887–L892.