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Original Article

Neonates with congenital cardiac defects and pulmonary hypertension

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Persistent pulmonary hypertension of the newborn can occur in association with a number of conditions such as congenital diaphragmatic hernia, congenital capillary alveolar dysplasia, congenital cardiac defects, meconium aspiration syndrome, premature intrauterine constriction of the ductus arteriosus, neonatal sepsis or thyrotoxicosis, or pulmonary arterial thrombosis. Alternatively, persistent pulmonary hypertension of the newborn can be strictly defined as severe hypoxemia shortly after birth, with right-to-left shunting across the ductus arteriosus and/or foramen ovale, in the absence of all these conditions.[1] This session focuses specifically on the management of neonates with pulmonary hypertension associated with congenital cardiac anomalies. In some instances, severe pulmonary hypertension present form birth constitutes a real problem in the management of these neonates. Since there has not been sufficient evidence for development of consensus recommendations on the subject, the session was prepared mainly on the basis of institutional views.

Pathogenic mechanisms

Pulmonary vascular resistance is relatively high in the fetus but normally falls rapidly at birth. In some neonates with congenital cardiac disease, failure of the elevated fetal vascular resistance to fall to lower postnatal levels requires prompt diagnosis and therapy. One theoretical basis for this delay in the fall of pulmonary vascular resistance is that there is endothelial and smooth muscle injury as a result of cardiac anomalies with increased pulmonary blood flow and shear stress.[2] In addition, there are concomitant physiologic and molecular alterations of the nitric oxide and endothelin signal pathways. In neonates with congenital cardiac disease, these derangements in endothelial function and regulatory pathways precede anatomic changes and pulmonary vascular remodeling.[3,4] Lastly, alterations in a myriad of biomolecular entities such as transforming growth factor beta, vascular endothelial growth factor, and vascular potassium channels as well as upregulation of collagens have been noted in animal models or children with congenital cardiac disease with increased pulmonary blood flow.[5–8]

Pulmonary hypertension associated with congenital cardiac disease in the neonate may be associated with several pathophysiological situations. Pulmonary hypertension may be caused by right-to-left shunts and pulmonary overcirculation, with increased pulmonary artery pressure (such as ventricular septal defect, patent ductus arteriosus, truncus arteriosus, aortopulmonary window, and common atrioventricular canal). Pulmonary venous hypertension may be associated with early development of arterial remodeling in total anomalous pulmonary venous drainage with obstruction, pulmonary venous stenosis, cor triatriatum, mitral stenosis, and hypoplastic left heart syndrome with a restrictive atrial septal defect.[9] Pulmonary hypertension may also occur in particular cases of cyanotic congenital cardiac disease. This includes anomalies

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that are usually not associated with severe pulmonary vascular abnormalities, such as transposition of the great arteries. Also included are patients with large aortopulmonary collaterals, or anomalous origin of a pulmonary artery from the ascending aorta.[10] Some patients with Ebstein anomaly of the tricuspid valve and mild to moderate elevation of pulmonary arterial pressure may present with severe hypoxemia due to "functional pulmonary atresia", although the concept of pulmonary hypertension is not applicable. Finally, some neonates with congenital cardiac disease and left ventricular dysfunction or noncompliance (such as aortic stenosis or coarctation of the aorta) can exhibit pulmonary venous hypertension and reflex pulmonary vasoconstriction.

The progression of pulmonary hypertension in neonates with congenital cardiac disease can be determined by three risk factors: magnitude of pulmonary blood flow, elevation of pulmonary arterial pressure, and arterial hypoxemia. Neonates with lesions such as truncus arteriosus or transposition of the great arteries with ventricular septal defect, lesions with the three risk factors listed above, can therefore develop irreversible pulmonary vascular disease earlier in life. Even in the presence of an intact ventricular septum, neonates with transposition of the great arteries are at risk for developing pulmonary vascular obstructive disease; indeed, abnormally elevated pulmonary arterial pressure has been observed not infrequently in these patients. Children with Down's syndrome and congenital cardiac disease also seem to have an added risk for pulmonary hypertension due to pulmonary hypoplasia. Additional risk factors for failure of the elevated fetal pulmonary vascular resistance to fall are congenital diaphragmatic hernia, omphalocele and gastroschisis.

Diagnosis

Routine tests such as chest radiography and electrocardiograms have limited use in estimating pulmonary vascular resistance in neonates, as they have right ventricular dominance during this period. Pulmonary biopsies are not routinely performed to determine the degree of pulmonary vascular abnormalities, in view of the inherent risks. In general, pulmonary arterial pressures in neonates with congenital cardiac disease are estimated noninvasively by echocardiography with Doppler interrogation of structures such as the patent ductus arteriosus, a ventricular septal defect, the regurgitation jet of the tricuspid valve and the interventricular septal position.

In neonates with left-to-right shunts and pulmonary overcirculation, pulmonary hypertension is presumed if the ventricular septal defect or patent ductus arteriosus are unrestrictive. Pulmonary hypertension is always present in truncus arteriosus and common atrioventricular canal due to the large unrestrictive ventricular septal defect present in those lesions. In patients with pulmonary venous obstruction, diagnosis of pulmonary hypertension can be made by Doppler interrogation as mentioned above. Extreme hypoxemia can exist in these lesions and would strongly imply elevated left atrial and pulmonary arterial pressures. Neonates with cyanotic cardiac disease and varying degrees of pulmonary arterial hypoplasia or medial hypertrophy are diagnosed by the presence of hypoxemia, although sometimes the diagnosis of elevated pulmonary vascular resistance in this category can be elusive. Lastly, in neonates with congenital cardiac anomalies and left ventricular dysfunction or noncompliance, an obligatory increase in pulmonary arterial pressure accompanies the elevated left ventricular end-diastolic pressure. As in the other conditions discussed above, noninvasive echocardiographic techniques can be utilized to estimate pulmonary arterial pressures. Of note, when pulmonary hypertension occurs in neonates with transposition of the great arteries, the clinical phenomenon of reverse differential cyanosis occurs.

Pulmonary artery pressure in neonates with congenital heart disease can be estimated noninvasively by Doppler interrogation of structures such as the patent ductus arteriosus, a ventricular septal defect, or the regurgitation jet of the tricuspid valve, as well as the interventricular septal position.

Class: IIa. *Level of evidence: C.*

Management

Medical therapy

Medical therapy alone for most neonates with congenital cardiac disease and pulmonary hypertension is usually futile or even contraindicated as surgical and/or catheter intervention is necessary to ameliorate the clinical and hemodynamic abnormalities. For a few clinical situations such as transposition of the great arteries with pulmonary hypertension or Ebstein's anomaly with significant tricuspid valve regurgitation and functional pulmonary atresia, medical therapy for pulmonary hypertension can be instituted.

For neonates with left-to-right shunting and pulmonary overcirculation, there is no medical indication for lowering pulmonary vascular resistance, as pulmonary overcirculation will be exacerbated and heart failure will ensue. Similarly, for neonates with pulmonary venous obstruction, the use of vasodilators is contraindicated, as this will increase the severity of

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clinical and hemodynamic disturbances. For cyanotic heart disease and pulmonary arterial hypoplasia or medial hypertrophy, individualized therapy to lower pulmonary vascular resistance may be indicated, but should be planned on a case-by-case basis. If the pulmonary arterial anatomic issues are not transient, surgical therapy such as an aortopulmonary shunt may be more appropriate to overcome the elevated pulmonary vascular resistance in these neonates. Lastly, for neonates with congenital cardiac defects and concomitant left ventricular dysfunction or noncompliance with elevated pulmonary arterial pressures, medical therapy is of limited utility prior to catheter or surgical palliation or correction. The use of vasodilator and inotropic agents such as milrinone may be efficacious in selected neonates. Inhaled nitric oxide, which will increase preload to the left ventricle as a result of lowering of pulmonary vascular resistance, can potentially elevate left atrial pressure and worsen hemodynamic and clinical abnormalities in neonates with pulmonary venous obstruction.[11]

In general terms, manipulation of pulmonary vascular resistance in the few neonates for whom therapy is warranted parallels that for pulmonary hypertension in the neonate without congenital cardiac disease, as well as the neonate with residual pulmonary hypertension after surgical correction of the anomalies. There are only a few case reports focusing on this patient population. Sedation and paralysis can be instituted to minimize surges in endogenous catecholamines. In addition, correction of acidosis, hypercarbia, hypothermia, and polycythemia can help maintain lower pulmonary vascular resistance. Ventilation strategies are directed at maintaining adequate oxygenation while minimizing mean airway pressure at functional residual capacity. However, it is worthwhile to emphasize that it is the pH and not the elevated PCO_2 that increases pulmonary vascular resistance. Pulmonary vasodilating agents including prostacyclin (intravenous or inhaled), prostaglandin E-1 (intravenous), Iloprost (inhaled or intravenous), milrinone, sodium nitroprusside, isoproterenol, and more recently sildenafil (enteral or intravenous) can be judiciously administered to lower pulmonary arterial pressures. Dopamine has potential deleterious effects on pulmonary vascular resistance at higher doses and is usually not utilized. Inhaled nitric oxide (at doses of 2–40 ppm) as well as inhaled prostacyclin can also be efficacious in the neonate with congenital cardiac disease and pulmonary hypertension. Inotropic support for a failed right (and/or left) ventricle is an essential part of supportive therapy.

Occasionally, a neonate with congenital cardiac disease and concomitant pulmonary hypertension can potentially benefit from a brief stabilization period prior to surgery. An example is a neonate with transposition of the great arteries and pulmonary hypertension. In these instances, medical therapy after balloon atrial septostomy can include the aforementioned pulmonary vasodilators as well as inhaled nitric oxide. The stabilization period allows the pulmonary vascular resistance to fall and mitigate any potential postoperative elevation of pulmonary vascular resistance. Another example is Ebstein's anomaly and functional pulmonary atresia. In these patients, one can argue that judicious use of intravenous pulmonary vasodilators or inhaled nitric oxide can minimize pulmonary vascular resistance and maximize pulmonary blood flow prior to any palliative surgical or catheter intervention. As it would be rare for a neonate with congenital cardiac disease to have pulmonary hypertension that requires chronic oral therapy rather than surgical or catheter intervention, there is a paucity of reported experiences with long-term therapy such as sildenafil, bosentan, or epoprostenol in this patient population.

Surgical strategy

Timing of surgery is usually accelerated to avoid further deterioration during the preoperative period and to minimize risk of postoperative pulmonary hypertension. However, the experience of the surgical team as well as the neonatal intensive care unit must be taken into account for decision between corrective and palliative procedures. In neonates with heightened pulmonary pressure due to left-to-right shunts and pulmonary overcirculation, corrective surgery is performed in a timely manner as medical therapy is not indicated (even contraindicated). Timing of surgery is usually not in the first month of life for ventricular septal defect or common atrioventricular canal as heart failure can usually be controlled with medical therapy, but can be earlier for truncus arteriosus, aortopulmonary window, or patent ductus arteriosus. Not infrequently, leaving an atrial shunt is life saving for the perioperative period; subsequently, as pulmonary arterial pressure falls weeks postoperatively, the atrial shunt will close spontaneously or will not be significant from the hemodynamic point of view. In neonates with pulmonary venous obstruction, surgical or catheter intervention to relieve the anatomic cause of the obstruction is performed as early as feasible since there is no role for medical therapy. An example is hypoplastic left heart syndrome with restrictive atrial septal defect. In this defect, an adequate atrial septal opening is urgently created either in the catheterization laboratory or in the operating room. It is theorized that even successful relief of pulmonary venous obstruction early in congenital cardiac disease may be followed by continued risk for pulmonary hypertension and poor

outcome, as arterial and venous structural changes may not be entirely reversible. In neonates with cyanotic heart disease and varying degrees of pulmonary arterial hypoplasia or medial hypertrophy, an appropriate surgical procedure such as an aortopulmonary shunt can be performed with improvement in oxygenation. Lastly, the neonate with left ventricular dysfunction or noncompliance secondary to lesions such as aortic stenosis or coarctation can have the appropriate catheter or surgical interventions to lower left ventricular end-diastolic pressure and thus pulmonary arterial pressure.

Mechanical support

In the neonate with intractable pulmonary hypertension and congenital cardiac disease, mechanical support with extracorporeal membrane oxygenation may be life-saving. Reported experience with preoperative extracorporeal oxygenation in neonates with congenital cardiac disease is limited to a few cases,[12,13] as the advent of inhaled nitric oxide has reduced its role in this patient population. Neonates with congenital cardiac disease and concomitant left ventricular dysfunction or noncompliance associated with pulmonary hypertension may benefit from the institution of extracorporeal membrane oxygenation if the end-diastolic pressure is exceedingly high.

Medical therapy alone for most neonates with congenital heart disease and pulmonary hypertension is usually futile or even contraindicated, as surgical or catheter intervention is necessary to ameliorate hemodynamic and clinical disturbances. Timing of surgery is determined to minimize the likelihood of postoperative pulmonary hypertension.

Class: IIa. *Level of evidence: C.*

Conclusion

For the vast majority of neonates with pulmonary hypertension associated with congenital cardiac disease, catheter interventions and early establishment of surgical strategies are required for prompt amelioration of hemodynamic changes due to structural abnormalities. Occasionally, a neonate can benefit from a brief period of stabilization. In such instances, medical management is carried out with therapies similar to those used in neonates without congenital cardiac defects, or those with persistent pulmonary hypertension following repair of cardiac anomalies.

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