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Original Article

Pulmonary hypertension associated with congenital diaphragmatic hernia

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Congenital diaphragmatic hernia is a cause of persistent pulmonary hypertension of the newborn that lacks an efficient therapy and as such, remains the most life-threatening cause of respiratory failure in newborns.[1,2] Congenital diaphragmatic hernia is a defect of the diaphragm allowing the abdominal content to ascend into the thorax, thereby compromising lung growth *in utero*. It occurs in 1/2000 live births.[3] The degree of lung hypoplasia and the severity of the pulmonary vascular abnormalities leading to persistent pulmonary hypertension are the two main factors determining outcome.[2,4]

Infants with congenital diaphragmatic hernia do not respond to our modern therapeutic armamentarium and strikingly, often present with refractory pulmonary hypertension resistant to inhaled nitric oxide.[5,6] When conventional therapy fails, the current treatment of last resort is extra-corporeal membrane oxygenation.[7,8] Experienced centers report improved survival with "gentle ventilation, permissive hypercapnia and hypoxemia".[9] As a result, more infants with severe pulmonary hypertension and hypoplastic lungs survive but suffer significant morbidity,[10–12] highlighting our limited success in managing newborns with this disorder.

Antenatal ultrasound diagnosis of congenital diaphragmatic hernia is feasible as early as 20 weeks gestation.[13] In order to optimize counselling for parents and management of patients, several echographic and more recently magnetic resonance-based predictors of lung and vascular hypoplasia have been proposed. Findings of these studies, however, remain inconsistent between centers.

Consequently, the present clinical guidelines tackled the following questions:

1. Are there antenatal predictors for severe persistent pulmonary hypertension of the newborn (including lung hypoplasia) that allow us to plan adequately the early postnatal assistance?
2. Is it possible reliably to confirm the diagnosis of persistent pulmonary hypertension in neonates with congenital diaphragmatic hernia?
3. What are the current recommendations for the management of neonates with pulmonary hypertension associated with congenital diaphragmatic hernia? Are there recommendations for the use of extra-corporeal membrane oxygenation?

Antenatal predictors

Standard echography

Most of the fetal echography specialists have attempted to quantify pulmonary hypoplasia based on either direct measurement of the size of the lungs or indirect indices assessing the mass of the herniated abdominal viscera (stomach herniation, liver herniation, polyhydramnios, mediastinal shift, abdominal circumference). These were extensively

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investigated in the early years of fetal ultrasound and reviewed by Keller.[14] Except for liver herniation, results vary between studies.

Fetal left ventricular size and its growth rate seemed to correlate with outcomes in small series, but have not been evaluated in recent studies.[15–17] The lung-head ratio is the most studied echographic parameter in recent years, and has been evaluated in all centers with extensive experience in managing patients with congenital diaphragmatic hernia. The inter-observer agreement is adequate in the center where this parameter was originally described (University of California, San Francisco). A multicenter study combining patients from European Centers and the University of California found that the lung-head ratio correlated with survival, especially when combined with liver herniation.[18] A recent meta-analysis, however, concluded that the prognostic value of lung-head ratio is not supported by current evidence.[19] Potential difficulties in the interpretation of this index, making extrapolation difficult from one center to another, have been well summarized by Keller[14] and include: methodology, the reported values, timing of measurement, site of delivery and neonatal care.

Magnetic resonance-based lung volume measurements

More recently, fetal magnetic resonance imaging has emerged as a new technique to measure volume of the lungs. In control fetuses, magnetic resonance estimates of pulmonary volumes correlate well with standard biometric data obtained by fetal ultrasound,[20] autopsy lung volumes[21] and the ratio of lung to body weights.[22] Current limitations, however, include the lack of reproducibility and the use of different equations for prediction of lung volumes between centers.

Three-dimensional ultrasound techniques

Three-dimensional ultrasound seems useful in predicting the size of the lungs. Ipsi-and contralateral pulmonary size is decreased in congenital diaphragmatic hernia.[18,23] By comparison with postmortem pulmonary volumes, the accuracy of measurements is 85% for fetuses with congenital diaphragmatic hernia, and 91% for controls.[24]

Direct antenatal assessment of the pulmonary vasculature

Very few studies have attempted to assess the size and function of the pulmonary vasculature in congenital diaphragmatic hernia. These prenatal parameters include: main pulmonary artery and branch diameter, pulmonary arterial Doppler, pulmonary arterial reactivity to oxygen, and the pulmonary arterial branch acceleration time/ejection time ratio.[14] Most of these studies, however, do not include pathological correlations to verify the accuracy of the diagnosis of pulmonary/vascular hypoplasia. Instead, measures have been obtained as antenatal predictors of survival and other outcomes.

The main limitation of these assessments is the inconsistency to predict reliably outcomes between centers. This may be due to several factors: small single center series, variability in the technique and gestational timing of measurement, the range of severity of pulmonary hypoplasia and the confounding effects of other factors influencing survival (i.e. associated anomalies, gestational age at delivery and postnatal management strategies). Future studies should focus on the development of algorithms that combine several antenatal predictors of outcomes, preferably on a multicentric basis.

1. Currently, the lung-head ratio in combination with liver position appears to be the most reliable predictor of outcome in congenital diaphragmatic hernia.

Class: IIb. *Level of evidence: B.*

2. Fetal magnetic resonance-based measurement of lung volume and assessment of pulmonary vasculature require further studies for validation.

Class: IIb. *Level of evidence: B.*

Diagnosis of persistent pulmonary hypertension in the newborn with congenital diaphragmatic hernia

The gold standard in the diagnosis of persistent pulmonary hypertension of the newborn is cardiac ultrasound. Apart from the clinical observation of a significant preductal-postductal saturation difference, the amount and direction of shunting (right-to-left versus bidirectional or left-to-right) can be evaluated by echo Doppler.[25] Cardiac ultrasound reveals in the classical situation of persistent pulmonary hypertension of the newborn, right-to-left shunting through the ductus arteriosus and/or the foramen ovale. Estimating pulmonary vascular resistance relative to the mean systemic blood pressure is important. In addition to the direction of the shunt, tricuspid regurgitation is often observed and can be quantified. Other features such as shift of the interventricular septum, "ballooning" of the right atrium as well as a compromised left ventricle are frequently observed.

So far, no single ultrasound parameter has been identified as an appropriate predictor of outcome. Especially the co-occurrence of a critical coarctation is a major challenge in the clinical management.[26] Differences in size between the aorta and pulmonary arterial trunk have been suggested as a measure

of pulmonary hypertension, the so-called McGoon index, but not confirmed in multicenter studies. Ejection fraction and other dynamic parameters of the right ventricle are of value in the evaluation of goal-directed therapy to diminish the workload of the right ventricle.

Depending on the availability of pediatric cardiology service, repeated cardiac ultrasound should be used as a parameter of right ventricular function. In the ideal situation, the initiation of new treatments such as inhaled nitric oxide, sildenafil and milrinone should be guided by cardiac ultrasound.

In case of weaning difficulties of extra-corporeal membrane oxygenation, repeated cardiac evaluation can provide some insight on the magnitude of pulmonary hypertension and response of inhaled nitric oxide later in the treatment algorithm. Objective criteria guiding therapy are not available nowadays, neither are ultrasound guided drug protocols. In principle, there is no indication for invasive cardiac evaluation such as catheterization in the acute phase of therapy of persistent pulmonary hypertension associated with congenital diaphragmatic hernia.

1. *Every patient with congenital diaphragmatic hernia should be evaluated by cardiac ultrasound for structural abnormalities, presence and characteristics of shunting.*

Class: IIb. *Level of evidence: B.*

2. *Drug therapy for persistent pulmonary hypertension of the newborn with congenital diaphragmatic hernia should ideally be guided by repeated cardiac ultrasound evaluating the "workload" of the right ventricle.*

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

Management of persistent pulmonary hypertension in congenital diaphragmatic hernia

Due to the severity of respiratory failure in congenital diaphragmatic hernia, elective endotracheal intubation and nasogastric drainage to prevent interference with expansion of the lungs are performed almost universally, although in some centers, spontaneous breathing in the absence of muscular paralysis and moderate sedation are common practices. No protocols are available to determine the optimal ventilatory mode in congenital diaphragmatic hernia. Following the initiation of ventilation with positive end-expiratory pressure of 3–5 cm, relatively high frequencies of 40–100/minute and low peak pressures not exceeding 25 cm H_2O, most units would use a raising CO_2 as an indication for high frequency oscillatory ventilation as rescue therapy.

Routine cardiac ultrasound is an important diagnostic procedure in the first hours after delivery. Fluid restriction and adequate use of vasopressor drugs to sustain the systemic blood pressure and prevent right-to-left shunting due to the increased pulmonary vascular resistance, are unit-dependent measures. In the absence of appropriate designed protocols on optimal drug dosing, maintaining an appropriate systemic blood pressure is one of the primary goal-directed therapies in these patients. Accepting preductal saturations as low as 85% in the absence of metabolic acidosis and raising lactate is another therapeutic goal.

Prevention of acidosis, hypoxemia, hypercapnia as well as agitation and pain are keystones of supportive therapy in the prevention or reduction of pulmonary hypertension. Routine sedation and analgesia with either fentanyl or morphine are used in most units although, again, protocols are not available on optimal drug dosing.

If these measures are inadequate and progressive signs of right ventricular failure do occur, inhaled nitric oxide at the dosage of 20 ppm can be considered as the drug of choice. The initiation of extra-corporeal membrane oxygenation in case of failure of conventional therapy is controversial. The best trial so far in the literature is the United Kingdom collaborative trial. Underpowered for congenital diaphragmatic hernia, it determines the use of extra-corporeal membrane oxygenation in case of therapy-resistant pulmonary hypertension. Given that the procedure is unavailable in many institutions, and that treated patients have an overall survival rate not higher than 40% and high morbidity, its indication has been a matter of debate.[27]

Algorithm for pharmacological management

Pulmonary vascular resistance falls dramatically at birth with the onset of respiration. In infants with congenital diaphragmatic hernia, pulmonary vascular resistance often remains at supra-systemic levels, causing extra-pulmonary right-to-left shunting across the ductus arteriosus and severe hypoxemia. The persistence of high pulmonary vascular resistance may be due to a hypoplastic vascular bed with abnormal arterial muscular structure, and functional abnormalities of the pulmonary vasculature.[1,28] Although there is a number of available therapies to treat persistent pulmonary hypertension of the newborn, much of the information on pharmacotherapy is derived from observational studies rather than randomized controlled trials.

Inhaled nitric oxide

Nitric oxide is a major contributor to the postnatal decrease in pulmonary vascular resistance. Inhaled

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nitric oxide is very efficient in improving oxygenation in infants with persistent pulmonary hypertension. Infants with congenital diaphragmatic hernia, however, often present with refractory pulmonary hypertension often resistant to inhaled nitric oxide. A recent meta-analysis on inhaled nitric oxide for persistent pulmonary hypertension of the newborn (all causes) suggests that the outcome of infants with congenital diaphragmatic hernia is not improved, and recommends its use in term and near term infants with hypoxic respiratory failure who do not have diaphragmatic hernia.[6] The immediate short-term improvements in oxygenation, however, seen in some treated infants may be of benefit for transport, or until initiation of extra-corporeal membrane oxygenation.[4]

Phosphodiesterase inhibitors

Phosphodiesterase inhibition using dipyridamole results in transient improvement in oxygenation with some side effects on systemic blood pressure.[29–31] The relatively lung-selective Phosphodiesterase-5 inhibitor sildenafil has been successfully used in the treatment of adult pulmonary hypertension. Case reports in infants with congenital diaphragmatic hernia are emerging, suggesting some acute improvement in oxygenation or decrease in pulmonary vascular resistance either with sildenafil alone, or in combination with inhaled nitric oxide to potentiaties its pathway.[32–35] There are no randomized controlled trials or prospective studies on the use of sildenafil in infants with congenital diaphragmatic hernia.

Decreased left ventricular performance in patients with severe congenital diaphragmatic hernia is common, and is perhaps the most important determinant of outcome following nitric oxide administration. The markedly diminished left ventricular performance causes a right-ventricular-dependent systemic circulation. In this setting, both prostaglandin E1 to maintain ductal patency (thus enhancing right ventricular contribution to systemic blood flow), and milrinone for pharmacologic reduction of left ventricular afterload may be beneficial.[11]

Prostaglandins

Another emerging therapy takes advantage of the possibility, in this patient population, of relieving the right ventricle from excessive afterload by reopening the ductus arteriosus. Therefore, serial ultrasound to detect a restrictive ductus and initiate a trial of prostaglandin E1 to re-open the ductus and decrease right ventricular pressure overload is increasingly used in some centers.[1] There is also evidence that prostaglandin E1 augments the endogenous production of cyclic adenosive monophosphate and thus, could potentiate the effect of cyclic guanosine monophosphate-mediated vasodilatation. There are, however, no randomized controlled trials on the use of prostaglandin E1 in infants with congenital diaphragmatic hernia.

With improved management, infants with smaller lungs survive. Recent observations suggest that these infants present beyond the immediate neonatal period with late (weeks-months after birth), and chronic (years after birth) pulmonary hypertension, contributing to long-term morbidity and mortality.[11] The use of inhaled nitric oxide alone or in combination with sildenafil to treat pulmonary hypertension after extra-corporeal membrane oxygenation/endotracheal ventilation is a promising therapy in congenital diaphragmatic hernia. Moreover, the observation that sustained pulmonary vasodilatation can be achieved using delivery of inhaled nitric oxide by nasal cannula[36] suggests the potential for noninvasive chronic management of this population.

Ideally, pharmacological treatment of persistent pulmonary hypertension in congenital diaphragmatic hernia should be combined with an "optimal" management approach using gentle ventilation and permissive hypercapnia-hypoxemia, although evidence for this "best management" is scarce. Future trials are needed to define a "best management practice". Given the low numbers of patients with congenital diaphragmatic hernia in any given center, task forces regrouping several centers need to be established to tackle important outstanding questions.

1. *Inhaled nitric oxide does not improve long-term oxygenation and outcome in patients with congenital diaphragmatic hernia (Class: IIa; level of evidence: A). However, immediate short-term improvements in oxygenation seen in some treated infants may be of benefit for transport or until initiation of extra-corporeal membrane oxygenation (Class: IIb; level of evidence: B).*
2. *Serial ultrasound to detect a restrictive ductus arteriosus and initiate a trial of prostaglandin E1 to re-open the ductus and decrease right ventricular pressure overload may be beneficial (Class: IIb, level of evidence: B). Prostaglandin E1 may cause additional vasodilatation by activating cyclic adenosine monophosphate and thereby potentiating vasodilators acting on the cyclic guanosine monophosphate pathway.*
3. *Sildenafil may be useful either alone or in combination with inhaled nitric oxide in acute, chronic or late pulmonary hypertension (Class: IIb; level of evidence: B).*

Conclusion

Major limitations remain in our ability reliably to predict outcomes in patients with congenital diaphragmatic hernia. This is mainly related to pulmonary hypoplasia, persistent pulmonary hypertension after birth, and the lack of efficient postnatal therapies to decrease mortality and

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morbidity in severe cases. The literature reveals a paucity of randomized trials addressing these limitations. In view of the rarity of cases in single centers, future studies should focus on developing algorithms that combine several antenatal predictors of outcome on a multicenter basis. Until then, the best approach in the management of patients with congenital diaphragmatic hernia, as suggested by Logan et al.[9] should include: "… the development of uniform practices within centers, based on successful center reports, and monitoring the consistency of practices and physiologic and neuro developmental outomes…".

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