World Journal of Pediatric Surgery

Lung-protective ventilation in the management of congenital diaphragmatic hernia

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To cite: Traynor M. Lung-protective ventilation in the management of congenital diaphragmatic hernia. *World J Pediatr Surg* 2024;**7**:e000789. doi:10.1136/wjps-2024-000789

Received 26 January 2024
Accepted 15 July 2024

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ABSTRACT

Prioritizing lung-protective ventilation has produced a clear mortality benefit in neonates with congenital diaphragmatic hernia (CDH). While there is a paucity of CDH-specific evidence to support any particular approach to lung-protective ventilation, a growing body of data in adults is beginning to clarify the mechanisms behind ventilator-induced lung injury and inform safer management of mechanical ventilation in general. This review summarizes the adult data and attempts to relate the findings, conceptually, to the CDH population. Critical lessons from the adult studies are that much of the damage done during conventional mechanical ventilation affects normal lung tissue and that most of this damage occurs at the low-volume and high-volume extremes of the respiratory cycle. Consequently, it is important to prevent atelectasis by using sufficient positive end-expiratory pressure while also avoiding overdistention by scaling tidal volume to the amount of functional lung tissue rather than body weight. Paralysis early in acute respiratory distress syndrome improves outcomes, possibly because consistent respiratory mechanics facilitate avoidance of both atelectasis and overdistention—a mechanism that may also apply to the CDH population. Volume-targeted conventional modes may be advantageous in CDH, but determining optimal tidal volume is challenging. Both high-frequency oscillatory ventilation and high-frequency jet ventilation have been used successfully as 'rescue modes' to avoid extracorporeal membrane oxygenation, and a prospective trial comparing the two high-frequency modalities as the primary ventilation strategy for CDH is underway.

HISTORICAL CONTEXT

Until well into the 1990s, standard management of neonates with persistent pulmonary hypertension (PHT), including those with congenital diaphragmatic hernia (CDH), involved aggressive hyperventilation to induce hypocapneic alkalosis. The intent was to improve oxygen delivery to critical organs through reduction or elimination of right-to-left shunt,[1] but outcomes were disappointing. In 1995, extrapolating from an earlier breakthrough in term neonates with both respiratory failure and persistent PHT,[2] Wung and colleagues reported successful management of neonates with CDH using permissive blood gas targets—a strategy previously thought dangerous in the context of PHT—to enable relatively low ventilator settings.[3] The authors described their approach as 'gentle ventilation' and when several subsequent retrospective analyses demonstrated greatly improved outcomes using similar techniques,[4–6] hypocapneic alkalosis was abandoned as a therapeutic strategy in CDH.

'Gentle ventilation' is predicated on the understanding that if systemic perfusion and preductal oxygen levels are adequate, moderate levels of hypercarbia and postductal hypoxemia are well tolerated by term infants, even in the presence of PHT. In contrast, aggressive mechanical ventilation and high inspired oxygen concentrations (FiO_2) injure the lung and adversely affect outcomes. A review of autopsy specimens from CDH neonates managed with hypocapneic alkalosis confirmed the presence of iatrogenic injury, with most specimens showing some combination of hyaline membrane formation, pulmonary hemorrhage, pulmonary interstitial edema, and even early bronchopneumonia. Evolving interstitial fibrosis was noted in specimens from infants who had survived long enough for it to develop.[7]

In addition to damaging lung tissue directly, high ventilator settings likely contributed to morbidity and mortality through other mechanisms. The intrathoracic pressures required to achieve hypocapneic alkalosis in some infants likely caused unnecessary cardiovascular instability and the effect of high mean airway pressures on pulmonary vascular resistance (PVR) and ventricular loading may have contributed to the failure of high-frequency oscillatory ventilation (HFOV) to improve outcomes not only in CDH[8], but also in acute respiratory distress syndrome (ARDS)[9]. An association has also been observed between the degree of hypocapnea achieved in the neonatal period and poorer neurological outcomes in CDH survivors,[10]

further validating the 'gentle ventilation' approach that is generally referred to as 'lung-protective ventilation' in the adult literature.

PERMISSIVE HYPERCAPNEA

While ventilator settings other than FiO_2 may affect oxygenation to some degree, their influence on arterial carbon dioxide tension ($PaCO_2$) is greater and more direct. For this reason, lung-protective ventilation strategies generally allow $PaCO_2$ to rise above the normal range. Although safe bounds for $PaCO_2$ and arterial *p*H have not been definitively established, international guidelines recommend keeping $PaCO_2$ below 60-70 mm Hg and *p*H above 7.2-7.25.[11–13] A net benefit from permissive hypercapnea in this mild-to-moderate range has been established in several populations, and there are no reports directly linking mortality or significant morbidity to hypercapnea of this degree in mechanically ventilated patients.

Hypercapnea and the resulting hypercapneic acidosis (HCA) have generated significant interest as therapeutic strategies in their own right, although a comprehensive review from 2015 concluded that there was insufficient evidence to justify the clinical use of therapeutic hypercapnea.[14] Protective effects have been observed with hypercapnea in hypoxic, chemical, and physical models of epithelial injury in the lungs and gut, as well as hypoxic models of brain injury[14]; however, detrimental effects have also been noted, including blunting of the normal autoregulatory response to hypertension.[15] In the CDH population, cerebral blood flow that varies passively with changes in systemic blood pressure would be most worrisome in the small subsets born significantly preterm or requiring anticoagulation for extracorporeal membrane oxygenation (ECMO). In the general preterm population, trials examining the safety and efficacy of mild-to-moderate permissive hypercapnea are reassuring, with no evidence of increased intracranial bleeding,[16] but CDH-specific data are unavailable.

Given the prominent role of PHT in determining outcomes in CDH, the fact that hypercapnea (via HCA) can increase PVR has always worried clinicians. Paradoxically, animal studies show that hypercapnea mitigates hypoxia-induced PHT,[14] and the drop in ventilation pressures associated with permissive hypercapnea may decrease PVR by reducing physical compression of the pulmonary vasculature as long as atelectasis does not result—both excessive and inadequate lung inflation may elevate pulmonary vascular pressures.[8] There is no published evidence of an increased incidence of pulmonary hypertensive crisis in neonates with CDH since the adoption of gentle ventilation as standard of care, and despite reports of fairly extreme intraoperative hypercapnea during thoracoscopic repair of CDH, no associated pulmonary vascular instability has been noted.[17 18]

MECHANISMS OF VENTILATOR-INDUCED LUNG INJURY

While it is clear that ventilator-induced lung injury (VILI) contributes significantly to morbidity and mortality in various populations, most of the data on VILI are derived from adults with ARDS. Animal studies suggested that the maximal volumetric distention of the pulmonary acini is the principal cause of alveolar damage,[19] and when a large ARDS trial showed improved outcomes by simply using smaller tidal volumes,[20] the concept of 'volutrauma' gained traction. Unfortunately, mortality from ARDS remains substantial, and nagging inconsistencies in the available data—particularly the variable effects of positive end-expiratory pressure (PEEP)—have prompted a search for additional mechanisms.

Damage may also occur at the low-volume end of the respiratory cycle through repeated alveolar collapse and expansion (RACE).[21] Unfortunately, it remains unclear to what extent RACE occurs in healthy and diseased lungs, whether the collapse is literal (direct contact between epithelial cells on opposite sides of the lumen) or functional (friction related to tidal movement of foam in and out of these units), and how much damage actually results.[21–24] Damage from RACE has been dubbed 'atelectrauma' and recent data linking driving pressure (defined below) to outcomes in adults suggest that both volutrauma and atelectrauma play a role in the genesis of VILI. Oxygen toxicity may also contribute, and injury from any or all of these primary mechanisms is known to release inflammatory mediators that then cause further lung damage. Disruption of the alveolar-capillary barrier may also promote the translocation of inflammatory mediators and bacteria into the bloodstream, increasing the likelihood of multisystem organ dysfunction. Injury resulting from these secondary processes is referred to as 'biotrauma'[25] and is outside the scope of this review.

THE EVOLUTION OF LUNG-PROTECTIVE VENTILATION IN ADULTS

It is important to understand that all recommendations relating to mechanical ventilation in the CDH population are currently based on limited evidence[11–13]. The only indisputable fact is that avoiding VILI improves outcomes, so until better CDH-specific data become available it is important to monitor the expanding body of evidence relating to lung-protective ventilation in other populations. The majority of such evidence is currently derived from adults with ARDS.

The 'baby lung' model

In ARDS, changes in epithelial permeability result in leakage of plasma from pulmonary capillaries into adjacent alveoli. Gattinoni and Pesenti observed that during ventilation with tidal volumes normalized to predicted body weight, the compliance of the respiratory system correlates directly with the amount of aerated lung tissue on CT imaging.[26] This led to the understanding that while dependent regions in ARDS are fluid filled and

therefore not ventilated, the remaining lung, although reduced in size, has normal physical properties. The authors chose to refer to the total volume of aerated lung as the 'baby lung' to emphasize that it is not actually stiff—just small. When tidal volumes are set using size-based norms for healthy adults, the respiratory system compliance measured at the airway inlet is diminished, but this is only because the delivered tidal volumes push the plateau pressure above the upper inflection point of the pressure-volume curve of the relatively small (but not stiff) 'baby lung'.[26]

Although a consensus is forming that lung tissue strain is a common denominator in the pathogenesis of VILI, the etiology of this strain—overdistention, RACE, or a combination—is hotly debated[24 27]; nevertheless, the paradigm shift from thinking of ARDS as a homogeneous entity ('stiff lungs') to thinking of it as a reduction in the volume of functional lung tissue has clearly reduced mortality. A low tidal volume strategy has become standard of care after an ARDSNet trial comparing low tidal volumes (6 mL/kg) to volumes that had traditionally been used (12 mL/kg) showed a significant reduction in mortality with smaller tidal volumes, confirming that iatrogenic damage to the 'baby lung' had been contributing to poor outcomes.[20]

The 'open lung' ideal

Recognizing the importance of the amount of lung that is open and participating in tidal ventilation has encouraged research on how to actively recruit flooded alveolar units. Although all agree that the more of the lung that can be opened—and kept open—the better, opinions differ regarding the degree to which this can safely be achieved given the heterogeneity of lung mechanics and lack of alveolar stability (surfactant inactivation) in ARDS. Those more concerned with RACE argue that after optimizing end-inspiratory lung volume, further reducing VILI can only be achieved by decreasing the amount of lung subject to RACE,[24] that recruitment of alveolar units increases the size of the baby lung—which in turn reduces its susceptibility to both overdistention and RACE—and that a lower shunt fraction minimizes exposure to inspired oxygen concentrations high enough to cause injury. Those more concerned with overdistention point to the fact that achieving a fully open lung necessarily involves measures that increase airway pressure (recruitment maneuvers, higher PEEP, longer inspiratory times) and therefore some risk of both overdistention injury and hemodynamic compromise.[23]

Mortality in ARDS remains significant despite various attempts to recruit flooded areas and restore alveolar stability so that the lung remains open after recruitment, with only modest further gains since the improvement that followed the widespread adoption of the ARDSNet low tidal volume protocol. Apart from prone positioning[28] and early paralysis,[29] attempts to further minimize VILI have not shown significant benefit in the ARDS population and, in the case of HFOV, there is some evidence of harm.[9 30 31] Trials examining PEEP have yielded conflicting results, but recent work suggests that it has an important role in placing 'baby lung' on the steep portion of its pressure-volume curve and therefore reducing the damage at both ends of the respiratory cycle.

Driving pressure

A multilevel mediation analysis of data from nine randomized trials in patients with ARDS showed that adjustments in tidal volume and PEEP were not beneficial unless the net effect was a reduction in the 'driving pressure', defined as the tidal volume divided by the static compliance of the respiratory system.[32] A subsequent meta-analysis of adult trials involving mechanical ventilation for surgery under general anesthesia demonstrated a similar phenomenon—while altering tidal volume or PEEP had variable effects on the risk of postoperative respiratory failure, they consistently decreased the risk when they resulted in lower driving pressure.[33] Although this methodology cannot confirm causality, a recent hospital registry study examining data from almost 100 000 surgical patients demonstrated that the association between driving pressure and the rate of postoperative respiratory failure is independent of baseline respiratory characteristics.[34]

Driving pressure can be calculated—in mechanically ventilated patients without spontaneous respiratory effort—by simply subtracting PEEP from plateau pressure (airway inlet pressure measured during a brief inspiratory pause introduced to generate quasistatic conditions).[35] Because respiratory system compliance is directly proportional to the size of the 'baby lung' in ARDS,[26] normalizing tidal volume using compliance instead of predicted body mass seems to effectively scale ventilation to the amount of functional lung, providing a simple way for clinicians to tailor tidal volume and PEEP to the individual patient and point in time by minimizing the mechanical power to which the lungs are exposed.[35]

APPLICABILITY TO CONGENITAL DIAPHRAGMATIC HERNIA

Although the fundamental principles of lung-protective ventilation are probably consistent across populations, as illustrated by the similarity of the impact of driving pressure in ARDS and in surgical patients, there are significant pathophysiological differences between infants with CDH and adults at risk of VILI. This context must be kept in mind when extrapolating from the adult data, but the CDH-specific evidence currently available is insufficient to provide an adequate alternative.

Vulnerability of the hypoplastic lung

In infants with CDH, the fibroelastic structure of the lung tissue in the more hypoplastic regions may be stiffer than normal,[36] resulting in preferential distribution of tidal volume into the rest of the lung and exposure of these less hypoplastic areas to injury in the same manner as

the 'baby lung' in ARDS and surgical patients. However, the flooded alveoli in ARDS and the collapsed alveoli in surgical patients may be relatively protected from VILI because they are not subject to overdistention, and because any RACE would be confined to the distal airways entering the affected acini.[21 37] In contrast, all of the alveoli in babies with CDH, regardless of the degree of regional hypoplasia, remain open throughout the respiratory cycle and are fully exposed to whatever ventilation pressures are applied.

Little is known about the intrinsic susceptibility of hypoplastic lung tissue to VILI, although autopsy data from babies managed before the 'gentle ventilation' era show that both lungs are damaged by aggressive ventilation.[7] This may simply reflect the very high peak pressures used during this epoch, but increased susceptibility to damage in the most hypoplastic areas—from overdistention, RACE or both—cannot be ruled out. Mechanical ventilation in CDH may therefore need to be individualized differently than in ARDS, with the best possible settings representing a compromise between optimal protection of the ipsilateral and contralateral lungs. Despite some interesting theoretical work in this domain,[38] no clinical parameters such as driving pressure have been tested directly in the CDH population.

Recruitability

The fact that the poorly compliant regions of lung tissue in CDH are hypoplastic—rather than flooded or collapsed—also suggests that they are non-recruitable, a hypothesis that is indirectly supported by data showing that measures designed to prioritize an open lung or maintain alveolar stability do not add further benefit to standard gentle ventilation protocols in the wider CDH population: a small study examining two levels of PEEP in spontaneously breathing infants immediately after CDH repair favored the lower value (2 cm H_2O vs 5 cm H_2O)[39]; exogenous surfactant administration has not proven useful in CDH[40 41]; and the only randomized controlled trial examining any aspect of ventilation in CDH failed to show any benefit to using HFOV (at a relatively high mean airway pressure) over conventional gentle ventilation.[42]

An important caveat to the idea that CDH lungs are fundamentally non-recruitable is that *atelectasis* adds an element of recruitability when allowed to occur. Atelectasis increases intrapulmonary shunt fraction, raises PVR, and promotes VILI by decreasing the size of the 'baby lung'. Unfortunately, the balance between the inward pull of the lung tissue and the outward recoil of the chest wall is heavily tilted toward collapse in neonates, such that functional residual capacity (FRC) in the absence of muscle tone lies below closing capacity.[43] This imbalance obliges all neonates to actively maintain FRC and avoid atelectasis.[43] Intubation, anesthesia, and paralysis all interfere with this active maintenance of FRC, implying that some degree of PEEP will be necessary after intubation in all neonates, including those with CDH, to maintain an open lung.

Sedation and paralysis

When feasible, maintenance of spontaneous ventilation may provide favorable hemodynamic conditions and an intubated (but unparalyzed) neonate will still contribute to the preservation of FRC as long as reasonable synchrony with the ventilator is maintained. Unfortunately, synchrony can be difficult to achieve, making atelectasis a common problem in mechanically ventilated neonates. While this is a compelling reason to avoid intubation in those babies who can manage without it,[44] it also explains why gas exchange commonly improves when, after struggling with asynchrony for a while, clinicians eventually resort to using a muscle relaxant. As long as PEEP is raised sufficiently to negate the accompanying drop in transpulmonary pressure,[45] the consistency of respiratory system mechanics resulting from pharmacological paralysis (which need not be complete) may make avoidance of both collapse and overdistention more feasible and may therefore assist with providing ventilation that is both effective and safe.[46]

Consistency of conditions was the principal mechanism proposed by the authors of a trial that demonstrated improved outcomes with up to 48 hours of paralysis early in ARDS.[29] Likewise, a trial in adults with acute hypoxemic respiratory failure found that titrating a cisatracurium infusion to achieve partial neuromuscular blockade always succeeded in meeting lung-protective ventilation targets while allowing some spontaneous respiratory effort, even when other measures were insufficient.[47] It is important to acknowledge, however, that the utility of paralysis as part of a lung-protective approach in adults may also be due, at least in part, to a reduction in the power of inspiratory efforts made by the patient. The compliant neonatal chest wall seems to mitigate overdistention injury in analogous situations such as laryngospasm as a complication of general anesthesia, perhaps reducing any potential benefit from paralysis.

In addition to providing stable and possibly lung-protective pulmonary mechanics, pharmacological paralysis during the preoperative period may reduce gaseous distention of intrathoracic bowel—distention that can further hamper ventilation and that, on rare occasions, may even cause hemodynamic compromise.[48] Despite these potential benefits, all current consensus guidelines for managing CDH[11–13] warn against routine deep sedation and paralysis without any mention of context—delivery room, preoperative stabilization period, or postoperative recovery. The limited evidence for this merits closer inspection.

Terui and colleagues retrospectively reviewed their experience using 'fetal stabilization' (FS), which they hoped would reduce PHT in newborns with CDH.[49] To achieve FS, midazolam and fentanyl were administered to the mother during cesarean section such that the babies were delivered in a sedated state. Despite similar

pulmonary pressures, the oxygenation index evaluated shortly after initial stabilization was slightly higher (worse) in FS newborns than in non-FS controls. Unfortunately, the authors do not specify whether higher ventilation pressures were permitted in the FS group to counter the sedation-induced loss of FRC. Additional work on the FS approach was abandoned by these authors based on these findings.

An observational study from 2013 provides a possible explanation for this observed drop in oxygenation index and suggests it may be avoidable. Murthy and colleagues employed respiratory function monitoring in the delivery room to demonstrate reduced respiratory system compliance after paralysis in newborns with CDH.[50] The difference in compliance was sustained after five minutes of ventilation, but there is no mention of specific measures to maintain FRC. If FRC was indeed allowed to drop and tidal volumes were not adjusted to match the reduced amount of lung available to ventilate, then a corresponding fall in the compliance of the respiratory system is not unexpected because tidal ventilation would then extend past the upper inflection point of the pressure-volume curve. The authors recommend avoiding paralysis in neonates with CDH based on their observations, but their rationale invokes 'stiff lungs' rather than 'small lungs' and may therefore need to be rethought with a modified version of the 'baby lung' model in mind. There is no biologically plausible reason for a decrease in compliance after paralysis other than a drop in FRC, so rather than strictly avoiding paralysis we should perhaps be focusing on optimizing ventilatory parameters under various conditions—including paralysis—in individual patients with CDH.

MODES OF MECHANICAL VENTILATION

Volume-targeted ventilation

Volume-targeted ventilation (VTV) has recently supplanted pressure-control ventilation (PCV) as the default mode in many neonatal settings. Respiratory system compliance changes frequently in ventilated neonates, especially those who are awake, alert, and breathing spontaneously. Alterations in compliance result in plateau pressure variability during VTV, rather than the fluctuations in tidal volume that are expected during PCV. Our current understanding of the pathophysiology of VILI holds that high pressure only causes injury insofar as it results in excessive distention, implying that VTV should be less likely than PCV to cause lung injury. A systematic review supports this hypothesis in the general neonatal population,[51] but evidence in infants with CDH is lacking. Another theoretical advantage of VTV over PCV is that large, rapid changes in $PaCO_2$—and the associated swings in cerebral blood flow—may be less common when tidal volume is the parameter being directly controlled, something which may be relevant in preterm infants.

VTV may be useful in the CDH population, but selecting an appropriate tidal volume is complicated by the fact that optimal volume varies not only with body weight but also with the degree of pulmonary hypoplasia. In a small study using respiratory monitoring in the delivery room, te Pas and colleagues showed that in newborns with CDH, asynchronous positive pressure breaths yield the smallest tidal volumes, assisted spontaneous breaths yield the largest tidal volumes, and unassisted spontaneous breaths generate tidal volumes somewhere in between.[52] They speculated that volumes achieved during unassisted spontaneous breaths might provide a safe starting point. Although very reasonable, the hypothesis that the infant naturally achieves optimal FRC and tidal volume when allowed to breathe spontaneously has not been proven and would only be valid once the normal alveolar recruitment process that occurs at birth is (at least mostly) complete. If paralysis is employed, adult evidence suggests adjusting tidal volume and PEEP to keep the driving pressure less than 15 cm H_2O,[35] an extrapolation that would require validation in the CDH population. It is possible that antenatal imaging could be used to estimate optimal tidal volume, perhaps relating it to lung-head ratio, but this has not been tested. In the absence of a reliable method for determining optimal tidal volume, 4–6 mL/kg is a reasonable starting point in most neonates with CDH[8] with adjustments then made to meet blood gas targets while keeping peak inspiratory pressures within recommended limits.

High-frequency ventilation

Elimination of CO_2 can be challenging in CDH because tidal volumes must be small to avoid VILI while the ratio of anatomical dead space to functional alveolar volume imposes a lower limit to effective tidal volume when conventional frequencies are used. High-frequency modes produce a continuous circuit of air within the conducting airways and rely on agitation of the acini to promote the mixing of alveolar gas with the fresh gas stream. Air movement is not tidal, so anatomical dead space is irrelevant and CO_2 removal is very efficient; however, the exponential relationship between the degree of alveolar agitation and the efficiency of CO_2 elimination means that minor changes in respiratory system compliance or ventilator settings can produce significant and unpredictable variations in $PaCO_2$.

A 1994 review of the theoretical basis behind high-frequency ventilation explains in detail the motivation for its use.[53] Lung volume stays very close to FRC at all times, so the risk of damage both from overdistention and from RACE is, in theory at least, minimized. Unfortunately, no studies have demonstrated a definite reduction in VILI using high-frequency modes in CDH or any other population. While the reasons for these disappointing results remain unclear, then it may be related to the relatively high total kinetic energy of the alveolar agitation.

The two most commonly used high-frequency modes are HFOV and high-frequency jet ventilation (HFJV),

and both have proven effective in a 'rescue' role to avoid ECMO[54–56] in CDH. Because alveolar pressures with HFJV are very low, it is a useful mode for air leaks and is often employed when CDH is complicated by pneumothorax. HFJV can be used at lower mean airway pressures than those required with conventional ventilation and has been shown to improve hemodynamics in preload-dependent populations.[57 58] Lower mean airway pressures help minimize overdistention and some have speculated[8 33] that high mean airway pressures may explain why routine use of HFOV has proven disappointing when compared with conventional ventilation in both ARDS[9 30 31] and CDH.[42] If this is true, then HFJV may prove more effective than HFOV in CDH. A randomized controlled trial comparing HFOV and HFJV in the CDH population is ongoing.[59]

PROMPT SURGICAL REPAIR AS A LUNG-PROTECTIVE STRATEGY

Mechanical ventilation via an endotracheal tube is inherently risky,[8] so expeditious surgical repair once the transition from the fetal to the neonatal circulation has reached a stable plateau is likely helpful. The sooner the endotracheal tube can be removed, the lower the risk of VILI and other ventilator-associated morbidity such as pneumothorax, pneumonia, vocal cord damage, subglottic stenosis, and even potential neurological injury from large swings in $PaCO_2$. The degree of exposure to opioids and other sedatives is also directly related to duration of mechanical ventilation, making unnecessary delays undesirable. Although reducing the hernia does not immediately improve ventilatory mechanics,[60 61] it does eliminate certain risks: the mass effect of intrathoracic viscera can interfere with both ventilation and circulatory dynamics, and there have been (rare) reports of strangulated bowel, both in utero[62] and after delivery.[48 63 64] Finally, reducing the hernia allows the use of the gut for both medications and nutrition. A recent retrospective analysis of left-sided CDH suggested that repair between 24 and 48 hours of life is associated with the best overall survival,[65] supporting the notion that while it is important to let the PVR settle before operative intervention, this generally does not take more than 48 hours and further delay may result in morbidity and mortality related to duration of therapy.

LOCAL CLINICAL APPROACH

At the author's institution, babies with antenatally diagnosed CDH are intubated immediately on delivery, without sedation or paralysis. Although extremely common worldwide, this practice has (justifiably) been questioned.[66] While we do not yet have a protocol in place for a trial of spontaneous ventilation without intubation for babies with an antenatal diagnosis of mild CDH, we are following reports of success with interest.[44]

Once intubated, conventional ventilation is begun using a volume-targeted mode. Initially, tidal volumes are set to 5 mL/kg and PEEP is set to 5 cm H_2O. Light sedation is used to ensure relative comfort during mechanical ventilation and the targets recommended by the Canadian CDH Collaborative are used to fine-tune ventilator settings.[12] The targets for $PaCO_2$ (45–60 mm Hg), pH (7.25–7.40), and preductal SpO_2 (>85%, but not >95% if any supplemental oxygen is used) can generally be met fairly quickly; however, it is important to recognize that the transition to extrauterine circulation in the CDH population is slower than normal and that some patience is required in the first few hours after birth. PEEP is adjusted only to correct overinflation or atelectasis on the chest radiograph—stepwise titration to systemic oxygenation is complicated by variable shunting due to PHT, may result in overdistention of the contralateral lung, and is not generally required to meet ventilation targets.

Pharmacological paralysis is not used routinely but is added without hesitation if accumulation of gas in the intrathoracic bowel is significant or if asynchrony interferes with ventilation. The need for an increase in PEEP is anticipated if paralysis is required, and although the corresponding rise in peak inspiratory pressure does not change transpulmonary pressure and thus should not increase VILI risk, HFJV is generally employed if standard targets cannot be met with a peak inspiratory pressure less than 25 cm H_2O after paralysis. PEEP on HFJV is adjusted to lung volumes as assessed by radiography, with careful attention paid to avoiding overdistention of the contralateral lung. Because consistency of respiratory mechanics is critical to preserving adequate FRC when using HFJV, some degree of paralysis is generally maintained after surgical repair until weaning back to conventional ventilation is initiated.

Surgical repair is undertaken as soon as the transition from intrauterine to extrauterine circulation is essentially complete and the PVR has stabilized. If used preoperatively, HFJV is continued in the operating theater. Weaning from HFJV to conventional ventilation after closure of the diaphragmatic defect rarely requires more than 48 hours. Although all patients are assessed for ECMO suitability, it is infrequently required.

CONCLUSION

Providing adequate gas exchange while avoiding VILI is the primary objective when mechanically ventilating neonates with CDH today. Defining adequate gas exchange during the dynamic transition from intrauterine to extrauterine life is not straightforward and the blood gas targets currently recommended in international guidelines are based primarily on retrospective data and expert opinion. Nonetheless, standardization of care around these targets will undoubtedly help generate some of the data required to refine them further. The comparatively small size of the CDH population makes randomized controlled trials comparing lung-protective ventilation strategies challenging, but efforts to obtain high-quality, prospective, CDH-specific data must

continue and collaboration across international networks will likely be required to make significant progress in this area. Until such data become available, lung-protective strategies validated in other populations are the main tools available to clinicians caring for neonates with CDH.

Contributors Michael Traynor: Sole author of this article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analyzed for this study.

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