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Chronic Lung Disease (CLD): Prevention is the Cure

Rob Graham, R.R.T., N.R.C.P.

I dedicate this column to the late Dr. Andrew (Andy) Shennan, the founder of the perinatal program at Women's College Hospital (now at Sunnybrook Health Sciences Centre). To my teacher, my mentor and the man I owe my career as it is to, thank you. You have earned your place where there are no hospitals and no NICUs, where all the babies do is laugh and giggle and sleep.

Like the obnoxious uncle everyone hopes will be a no-show, CLD keeps crashing our party, just as it has since we first started resuscitating premature infants over 60 years ago. Today, antenatal steroids are given. With lung-protective ventilation, moderate to severe CLD is largely avoidable in the ≥25-week PMA (post-menstrual age) cohort. This is generally not the case in the more premature population, particularly those born ≤ 24 weeks PMA, antenatal steroid administration notwithstanding. Despite our best efforts to minimise lung injury, these infants will likely develop at least mild CLD.

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CLD is characterised by dysplastic changes throughout the lungs and airways, which collectively reduce their ability to function normally and efficiently. Airways may be hyper-reactive but generally have high resistance, even if not. Alveoli are not as numerous, and the surface area for gas exchange is significantly reduced due to a lack of secondary crests. Failure of appropriate apoptosis results in decreased diffusion gradient because thickened walls increase the distance between pulmonary contents and the capillaries, which must collect oxygen and carbon dioxide for distribution and removal. Lungs are often not evenly recruited and may have areas of collapse, while others may be overinflated due to a combination of gas trapping and volumes being delivered preferentially to areas of higher compliance. Ventilation-perfusion mismatching occurs, further reducing ventilatory efficiency.

Judicious use of non-invasive ventilation and limiting invasive ventilation as much as possible are critical mitigators of pulmonary damage. Anyone familiar with previous columns will know that when invasive ventilation is required, I strongly recommend high-frequency jet ventilation (HFJV) and/or oscillation (HFO), the latter utilizing volume targeting, if available, as a first-line mode in tiny babies.

If ventilating with conventional ventilation (CV), lung protective strategies must be followed: volume targeting of 3–4 ml/kg in tiny babies and 4–5 ml/kg in larger infants, pressure support mode if tolerated and, most critically, maintaining adequate inflation with PEEP. PEEP may need to be increased when switching from assist-control to pressure support as the inherently shorter inspiratory time produces less mean airway pressure (MAP). Regardless of ventilation mode, FiO_2 should be the lowest attainable to reduce oxidative stress; this occurs at optimum compliance, where lung injury is least likely.

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Permissive hypercapnia is a common strategy to reduce lung injury, but evidentiary support for it is inconclusive, and many studies advise against the practice. Given the wide variations

in ventilatory practice, this might not be surprising. One study terminated prior to completion as evidence favoured the control group. However, this study started on post-natal day 1 (1). This is not surprising since the risk of cerebral bleeds is highest during the first 72 hours of extrauterine life when CO_2 should be carefully maintained in a relatively narrow range, and hypercapnia avoided. Another meta-analysis showed no significant difference in a range of hypercapnia outcomes but found no benefit (2). Actual $PaCO_2$ is not mentioned in the analysis.

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Hypercapnic effects are not limited to the brain and pulmonary system; the cardiovascular system responds independently. Mild hypercapnia increases cardiac output multi-factorially, but this response is unpredictable, and a good thing can lead to bad things quickly (3).

The net harmful effect(s) of hypercapnia appears to be time- and severity-weighted. Brain-injured patients with hypercapnia do not seem to be harmed if pH is corrected within 24 hours (3). Extrapolated within reason, incremental increases in $PaCO_2$ of 7 mmHg may not have significant harmful effects if pH is compensated—one guideline for an upper $PaCO_2$ in the adult population is 70 mmHg (3). Premature infants are less able to respond to rapid changes in pH. Thus, $NaHCO_3$ correction is risky. Unless severe, acidosis should not be corrected aggressively with ventilation; hypocarbia-accompanied acidosis is a bad combination. Since the chemical reaction balance shifts toward CO_2, adequate ventilation is essential if there is to be an improvement in pH when giving $NaHCO_3$.

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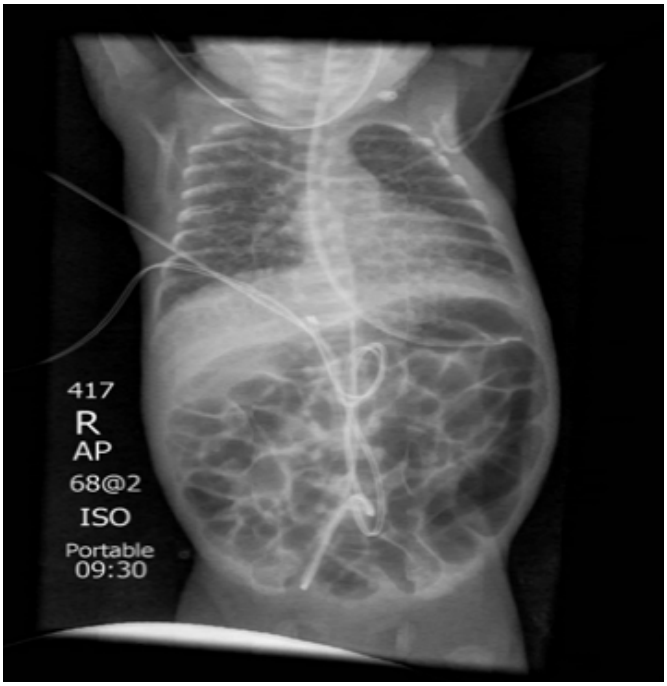

Figure 1. CXR of infant never intubated managed on CPAP

at all costs, particularly during the first 72 hours. The evidence supporting permissive hypercapnia is small relative to that against it, and I cannot recommend the practice.

CLD is most often thought of as a sequela to invasive mechanical ventilation, but it can develop in babies supported with non-invasive ventilation (NIV) (Figure 1).

This is especially true if clinicians fail to recognise that a baby is failing NIV until the lungs completely collapse and at which point intubation is the only option available to re-recruit them. This is a double whammy since the lungs are most prone to injury during recruitment/re-recruitment on top of atelectatic injury.

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Other contributory factors such as oxidative stress (4), infection (both antenatal and post-natal) (5), nutrition (6), genetics (7), and

even maternal body mass index (8) are all linked to increased risk of CLD. Ventilatory management (or mismanagement) that provides either too much or too little functional residual capacity, excessive tidal volume, and high FiO_2 are the primary drivers of lung injury. Hyperinflation usually gets much more air time than hypo-inflation, but atelectasis resulting from inadequate distending pressure is far from benign. Besides decreasing ventilatory efficiency and lung compliance, atelectasis increases pulmonary vascular resistance (PVR), thus decreasing cardiac output; damages the alveolar-capillary barrier; decreases pulmonary bioavailability of antibiotics; increases lung protein permeability; and triggers a local cellular inflammatory response (9). Alveoli are dependent on each other for structural integrity, and when adjacent to areas of collapse, they are damaged as they contort and expand into adjacent voids left by their collapsed neighbours.

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What should be done once a CLD diagnosis is made? How can ventilation be continued to facilitate pulmonary development and not to exacerbate damage already done? Different approaches to achieving these goals are emerging.

One method uses CV (SIMV + pressure support) and relatively high volumes (8–12 ml/kg). I cannot endorse this approach. Courtesy of our adult colleagues working with ARDS (Adult Respiratory Distress Syndrome), we know that high tidal volumes damage an adult's lungs, and it stands to reason that the same is true of the developing lungs of an infant. While babies with CLD do "want" higher tidal volumes, this is at least partly due to their higher physiological dead space, and a tidal volume of 7 ml/kg has been associated with lower work of breathing in infants with CLD (10). The high and varying conducting airway resistance plus non-homogenous lung compliance characteristic of CLD mean that volume will not be delivered to the lung evenly. 8–12 ml/kg at the patient wye may translate to 16–24 ml/kg where delivered.

HFJV is ideal for overcoming the obstacles CLD presents. It is less affected by airway resistance and does not deliver gas preferably to areas of higher compliance; thus, overdistention of these areas is avoided. Of any mode of invasive ventilation, HFJV is least likely to produce gas trapping, mitigating another problem when ventilating CLD. If lung protection is the goal, HFJV will likely hit that target.

So why not HFJV in CLD? HFJV's gentleness and relatively low pressures are generally considered lung protective. The mean airway pressure generated is sufficient to maintain airway and alveolar stability but insufficient to recruit areas needing it. Recruitment maneuvers do what the name implies, but in practice, recruitment maneuvers are discouraged once the task is accomplished. This is in recognition of the potentially damaging effects of larger tidal volumes. In the case of older babies with CLD, this may not be the best approach.

As damaged as they are, the lungs of these babies are still developing. New alveoli cannot participate meaningfully in gas exchange unless recruited; as mentioned above, HFJV does not do this well. I suggest a hybrid approach to ventilating CLD that will take advantage of the protective nature of HFJV and recruit new alveoli as they are formed. Using recruitment maneuvers at a low rate or applied intermittently may offer the best of both worlds.

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Conventional breaths used with HFJV have traditionally been referred to as "sigh breaths" and used pressures and inspiratory times used in conventional ventilation. More recently, the term "recruitment maneuvers" (RMs) has been coined to reflect a gentler approach to their delivery. Instead of high peak pressures and inspiratory times of 0.4 to 0.5 seconds, a lower peak pressure of 5-6 cmH_2O above PEEP and a longer inspiratory time of 2–3 seconds are used. Utilizing a lower peak pressure affords some protection to areas of the lung with higher compliance (where gas delivered by CV will go first), while the longer inspiratory time provides time for pendelluft to occur and allows the lower pressure to exert an effect that a shorter inspiratory time cannot do. The lower peak pressures are also important in reducing sheer forces on lungs held at higher end-expiratory volumes than those typically found with CV.

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In a hybrid approach, a continuous low rate (2–3/minute) of RMs or giving them for a short time every few hours may be helpful in both recruiting new lung growth as well as aiding in oxygenation (the primary difficulty in CLD) and maintaining airway and alveolar stability.

RMs may also allow using a lower PEEP level while maintaining overall MAP, thus improving venous return while maintaining oxygenation. Another possible benefit of using HFJV is that

the lungs can be held at higher inflation. This may improve gas exchange via several mechanisms: slightly stretched alveoli, combined with MAP, may increase diffusion gradient while avoiding shear forces associated with the larger tidal volumes of CV. Activation of stress receptors may also decrease air hunger.

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As the PMA of our patients becomes ever lower, gentle, lung-protective ventilation is essential given that the success rate of NIV in the sub-25-week PMA cohort is very low, and invasive mechanical ventilation is all but unavoidable. How well invasive mechanical ventilation is practised will determine how often we are presented with the myriad of problems we face when ventilating CLD babies. One of those problems is our impatience. Healing damaged lungs takes time, and clinicians may be too quick in pronouncing an intervention ineffective.

Given the 30+% rate of CLD that has persisted over the years, all the hopeful technological advances notwithstanding, for 60 years, we'd best up our game. I submit HFJV is an excellent place to start.

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Corresponding Author

Rob Graham, R.R.T./N.R.C.P.
Advanced Practice Neonatal RRT
Sunnybrook Health Science Centre
43 Wellesley St. East
Toronto, ON
Canada M4Y 1H1
Email: rcgnrcp57@yahoo.ca
Telephone: 416-967-8500