High-frequency oscillatory ventilation in neonatal RDS: initial volume optimization and respiratory mechanics

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Kalenga, Masendu, Oreste Battisti, Anne François, Jean-Paul Langhendries, Dale R. Gerstmann, and Jean-Marie Bertrand. High-frequency oscillatory ventilation in neonatal RDS: initial volume optimization and respiratory mechanics. *J. Appl. Physiol.* 84(4): 1174–1177, 1998.—To determine whether initial lung volume optimization influences respiratory mechanics, which could indicate the achievement of optimal volume, we studied 17 premature infants with respiratory distress syndrome (RDS) assisted by high-frequency oscillatory ventilation. The continuous distending pressure (CDP) was increased stepwise from 6–8 cmH_2O up to optimal CDP (OCDP), i.e., that allowing good oxygenation with the lowest inspired O_2 fraction. Respiratory system compliance (Crs) and resistance were concomitantly measured. Mean OCDP was 16.5 ± 1.2 cmH_2O. Inspired O_2 fraction could be reduced from an initial level of 0.73 ± 0.17 to 0.33 ± 0.07. However, Crs (0.45 ± 0.14 $ml \cdot cmH_2O^{-1} \cdot kg^{-1}$ at starting CDP point) remained unchanged through lung volume optimization but appeared inversely related to OCDP. Similarly, respiratory system resistance was not affected. We conclude that there is a marked dissociation between oxygenation improvement and Crs profile during the initial phase of lung recruitment by early high-frequency oscillatory ventilation in infants with RDS. Thus optimal lung volume cannot be defined by serial Crs measurement. At the most, low initial Crs suggests that higher CDP will be needed.

newborn; optimal lung volume; static pulmonary compliance; respiratory distress syndrome

ALVEOLAR COLLAPSE resulting from a primary deficiency in pulmonary surfactant is one of the cornerstones of the pathophysiology of neonatal respiratory distress syndrome (RDS). A reduced functional residual capacity (FRC) is characteristic (18). This is associated with a decreased lung compliance and a disordered gas exchange. Assisted ventilation aims to reexpand atelectatic lung units, so as to increase gas-exchange surface and to improve ventilation-perfusion matching. Today, growing evidence suggests that, compared with conventional mechanical ventilation (CMV), high-frequency oscillatory ventilation (HFOV) is associated with better clinical outcomes (4, 7, 9). From experimental studies, it has been shown that HFOV induces a more homogeneous alveolar recruitment while reducing the risk of bronchopulmonary injury (5, 15, 16, 19). For these reasons, HFOV has become the standard mode of ventilation for neonatal RDS in our unit (Neonatal Intensive Care Unit, Rocourt, Belgium). As soon as HFOV is initiated, and before administering surfactant, we use an optimal lung volume strategy whereby gradual increases in inflating pressure are utilized to achieve lung recruitment and improvement in oxygenation.

The aim of the present study was to evaluate the profile of pulmonary mechanics and its potential clinical implications during this early phase of lung volume optimization (LVO).

METHODS

Entrance criteria and study design. This was a prospective clinical study protocol approved by the Ethics Committee of our medical institution. Preterm infants with a clinical picture suggesting primary surfactant deficiency as the main cause of their RDS were eligible for the trial if they were to be assisted by HFOV within the first 12 h of life. Patients with evidence of pulmonary infection, meconium aspiration or air leak syndromes, severe congenital malformation, or other life-threatening conditions were excluded. To minimize technical bias, entry into the trial was also dependent on the availability of the investigator (MK) in charge of pulmonary function testing.

HFOV strategy. Respiration support was provided with the 3100A HFOV ventilator (SensorMedics Critical Care, Yorba Linda, CA) through an endotracheal (ET) tube sized 2.5 or 3.0 mm. Because the 3100A provides a quasi-constant inflating pressure at the alveolar level, we use the term of continuous distending pressure (CDP) instead of mean airway pressure, as is used with CMV. Sedation was not used during LVO. The starting HFOV settings were as follows: CDP of 6–8 cmH_2O; inspired O_2 fraction (FI_{O_2}) between 0.6 and 1; pressure amplitude of oscillations (ΔP) adjusted to provide good chest vibrations with normocapnia (transcutaneous CO_2 tension between 40 and 45 mmHg); oscillatory frequency of 10 Hz; and inspiratory-to-expiratory ratio of 1:2. Prolonged apnea due to hypocapnia was avoided by lowering ΔP. An initial chest radiograph was performed to confirm the pulmonary diagnosis and to adjust the tip of the ET tube to at least 2 cm above the carina. CDP was increased stepwise, and optimal CDP (OCDP) was defined as that allowing good oxygenation (i.e., an O_2 saturation between 90 and 95% with a transcutaneous O_2 tension between 50 and 80 mmHg) with the lowest possible FI_{O_2}. At this point, another chest radiograph was obtained to check for lung expansion. If lung expansion corresponded to less than eight or nine posterior ribs on the right lung without evidence of lung overinflation, CDP was further increased, provided oxygenation did not deteriorate. This optimization phase usually required <1 h. Ventilator settings were adjusted independently of the results of any pulmonary function testing. All data were obtained before surfactant administration, a therapy we applied when the product OCDP × FI_{O_2} was 3 or more.

Assessment of respiratory mechanics. Static mechanics of the respiratory system, notably respiratory system compliance (Crs) and resistance (Rrs), were determined with the model 2600 pulmonary function machine (SensorMedics). Pulmonary mechanics algorithms with this computer-assisted device are based on the passive flow-volume method

in which the single-occlusion technique is used (13). A pneumatic slide valve, which included a 10 l/min pneumotachograph, was inserted between the ET tube and the ventilator circuit. The patient was visually checked for quiet breathing while oscillated, and brief occlusions of the ventilator circuit of at least 100-ms duration were performed in the manual mode of the valve at the end of inspiration. This training appeared to allow the patient to accommodate and remain relaxed during occlusion. Thereafter, the valve was automatically operated so as to allow passive exhalation through the pneumotacograph to ambient pressure and then to restore oscillation. At least 10 s were allowed between any two occlusions. Sequential mechanical variables were automatically computed and displayed along with the corresponding flow-volume curve. Well-shaped curves were accepted if the preceding pressure tracing showed a clearly defined and stable plateau of 100 ms after occlusion. For each patient, Crs and Rrs were calculated as means of a set of three to eight flow-volume curves (coefficient of variation ≤15%). The mean Crs of each set of occlusions was standardized for body weight.

The pulmonary mechanics evaluations were done after initiation of HFOV and after each CDP increment. The patient was retained in the study when a minimum of four measurement points (including OCDP) was obtained through a total CDP increase of at least 5 cmH_2O.

Data analysis. Ventilator settings (CDP, ΔP, and $F_{I_{O_2}}$) were recorded before each determination of pulmonary mechanics. Multiple mechanics measurements were made, but the profile of the optimization phase has been expressed by the following four data points: *1*) the starting point, i.e., where pulmonary function was determined for the first time; *2*) the midpoint, half-way between the starting and the OCDP point or approximately at midcourse of optimization; *3*) the OCDP minus 2 point (OCDP-2), i.e., 2 cmH_2O before OCDP; and *4*) the OCDP point. These points were chosen to detect any possible masking effect of lung overdistension on Crs at OCDP. Data are presented as means ± SD of the group. After repeated-measurements analysis of variance, the difference between points was tested with the Tukey-Kramer multiple-comparison test. The significance level was set at $P < 0.05$ with two-tailed probability. Additionally, a regression analysis was performed to test for correlation between Crs and ventilator settings.

RESULTS

Population. Of the 101 newborns assisted by early HFOV from June 1995 to August 1996, 17 premature babies with RDS met the entrance criteria and were enrolled in the present study. Their gestational age was 31.5 ± 1.6 wk (range 27–35 wk), and their birth weight was 1,744 ± 411 g (range 900–2,700 g). The age at HFOV institution was <6 h for all but three infants.

Ventilator settings and chest radiology. Table 1 presents the evolution of main ventilator settings over the optimization phase. CDP had to be progressively increased up to 16.5 ± 1.2 cmH_2O (OCDP level). All but two patients had an OCDP of ≥15 cmH_2O, with the highest value being 20.1 cmH_2O. Mean ΔP was 32.7 ± 6.2 cmH_2O at OCDP. The CDP increase was associated with a marked improvement in oxygenation, as indicated by a 51% reduction in $F_{I_{O_2}}$ between starting and OCDP points. $F_{I_{O_2}}$ at OCDP was ≤0.3 in 11 infants. OCDP corresponded to radiologically good lung expansion with attenuation of RDS features but without evidence of lung overdistension in any subject.

Table 1. *Evolution of ventilator settings during lung volume optimization*

	Starting Point	Midpoint	OCDP-2 Point	OCDP Point
CDP, cmH_2O	7.7 ± 0.8	12.4 ± 1.0†	14.2 ± 1.2†‡	16.5 ± 1.2†§
ΔP, cmH_2O	26.2 ± 4.1	30.5 ± 6.5	31.8 ± 7.2	32.7 ± 6.2*
$F_{I_{O_2}}$	0.73 ± 0.17	0.54 ± 0.13†	0.41 ± 0.12†‡	0.33 ± 0.07†§

Data are means ± SD (n = 17 infants). Time points as described in text. OCDP, optimal continuous distending pressure; CDP, continuous distending pressure; ΔP, pressure amplitude of oscillation; $F_{I_{O_2}}$, inspired O_2 fraction. *$P < 0.05$ and †$P < 0.001$ vs. starting point; ‡$P < 0.001$ vs. midpoint; §$P < 0.001$ vs. OCDP-2 point.

Respiratory mechanics. Overall, the single-occlusion technique was well tolerated, as no significant deterioration in oxygenation was observed during measurements. Crs and Rrs data are shown in Fig. 1. Mean Crs at the starting point was low (0.45 ± 0.14 ml·cmH_2O^{-1}·kg^{-1}) and remained unchanged through LVO. At OCDP, only four patients showed a Crs increase of ≥25% from baseline value. However, Crs still remained below 0.5 ml·cmH_2O^{-1}·kg^{-1} in three of these patients. In the fourth patient, Crs increased from 0.51 to 0.64 ml·cmH_2O^{-1}·kg^{-1}. In regard to the relationship between lung mechanics and ventilator settings, initial Crs was inversely correlated to OCDP ($r = -0.644$, $P = 0.005$). Because Crs remained unchanged, this negative correlation was also observed between final Crs and OCDP ($r = -0.680$, $P = 0.003$). Similarly, Crs was inversely related to ΔP at the OCDP point ($r = -0.577$, $P = 0.015$). Mean starting Rrs was 0.13 ± 0.04 cmH_2O·ml^{-1}·s. No consistent variation was observed in Rrs throughout the optimization phase.

DISCUSSION

Pulmonary function assessment during mechanical ventilation is a question of long-standing interest in clinical practice. In regard to newborns, the single-occlusion technique has proven to be a noninvasive and reliable bedside method of respiratory mechanics evaluation, especially for sick ventilated infants (10, 12, 13, 22). Previous studies on the subject have been essen-

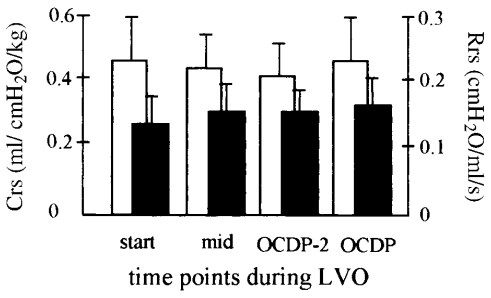

Fig. 1. Profile of respiratory mechanics during lung volume optimization (LVO). Data are means ± SD (n = 17 infants) for respiratory system compliance and resistance [Crs (□) and Rrs (■), respectively] measured during LVO. Starting, mid-, optimal continuous distending pressure (OCDP)-2 and OCDP points are as described in text.

tially conducted under CMV. Using primary HFOV for premature infants with RDS, we found that brief occlusions of airways at the end of spontaneous inspiration were well tolerated and yielded adequate and reproducible flow-volume curves. The computed Crs and Rrs closely approximated those previously reported in similar patients treated with CMV (6, 13, 22). In regard to the main question of the present study, we found that initial stepwise CDP increase to recruit lung volume, while associated with a marked improvement in oxygenation, did not result in any consistent modification of Crs or Rrs.

Several studies using CMV have previously addressed the question of the relationship between the optimal lung inflation and pulmonary compliance. Although controversial results have been reached, some authors have reported lung compliance improvement with positive end-expiratory pressure (PEEP) optimization in both children (20, 21) and adults (11, 21) with various pulmonary diseases. More related to neonatal surfactant deficiency is the study by Mathe et al. (14), who used pressure-volume (P-V) curves to determine the appropriate PEEP in premature infants with hyaline membrane disease. Patients were paralyzed and their lungs continuously inflated beginning at FRC up to a total volume of 10 ml/kg. An inflection of the P-V curve was observed as the inflating pressure approximated 9 cmH_2O, suggesting an improvement in compliance. In each patient, the pressure at the inflection point was applied as appropriate PEEP, which helped improve oxygenation.

In newborns with surfactant deficiency, lung inflation starting at ambient pressure, like in the paralyzed patients of the study just cited, is characterized by an initial inflection of the P-V curve. This inflection corresponds to the opening of peripheral lung units and is usually observed between 5 and 10 cmH_2O (14, 17). In our study, it is clear that airway occlusions were performed over the inflation limb of the P-V curve. As Crs did not improve with gradual CDP increase, it is suggested that HFOV optimization was started at a pressure equal to or just above the inflection point, where most peripheral airways were already patent. The rest of volume optimization was then operated over a linear portion of the P-V curve and allowed a further expansion of terminal air spaces. The ensuing increase in gas-exchange surface resulted in an improvement in oxygenation. However, it is important to remember that, based on animal models of surfactant deficiency treated by HFOV, improvement in Crs can be observed if measurements are obtained on the deflation P-V curve following a volume recruitment maneuver such as sustained inflation (1, 2, 23). These interesting observations were not evaluated in our study, as sustained inflation is not part of our current HFOV strategy.

We presumed that in all our patients surfactant deficiency was the main cause of gas-exchange impairment due to collapse of terminal lung units. This was strongly supported by the prompt improvement in oxygenation on LVO as well as by the rapid clearing of chest radiographs. The results of the present study clearly show that optimization of alveolar expansion with HFOV does not favorably influence pulmonary mechanics as long as the underlying cause, i.e., surfactant deficiency, is not reversed. This will occur by a gradual synthesis of endogenous surfactant over hours or days, or after exogenous surfactant instillation. Interestingly, an optimal-volume strategy stabilizing terminal air spaces tends to prolong the effectiveness of exogenous surfactant (8).

It is noteworthy that we found that Crs was inversely related to OCDP and ΔP. It is unlikely that inadvertent lung overinflation was the reason why patients with high OCDP had low Crs, because CDP was increased in a progressive manner starting from low level. Moreover, lack of progressive Crs deterioration implies that LVO was not operated up to the upper flat portion of the P-V curve, which means that the used LVO procedure induces an appropriate lung expansion. Clearly, low Crs was an indication of the severity of lung disease. In one study using HFOV in a rescue mode, Chan and his colleagues (3) also reported an inverse correlation between OCDP and Crs obtained just before start of HFOV. Relevantly, it has been previously shown that pulmonary compliance measured during artificial ventilation (CMV) was directly related to the surfactant deficit determined by lecithin-to-sphengomyelin ratio in tracheal aspirate (24).

In conclusion, the single-occlusion technique is an applicable and well-tolerated method of determining pulmonary mechanics in infants with RDS, assisted by HFOV. The initial LVO by gradual CDP increase, which markedly improves oxygenation, does not affect pulmonary mechanics. Consequently, optimal lung volume achievement is not detectable by serial Crs measurements during the early phase of HFOV. At the most, low initial Crs appears to indicate that higher distending pressure is needed.

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REFERENCES

1. **Bond, D. M., J. McAloon, and A. B. Froese.** Sustained inflations improve respiratory compliance during high-frequency oscillatory ventilation but not during large tidal volume positive-pressure ventilation in rabbits. *Crit. Care Med.* 22: 1269–1277, 1994.
2. **Byford, L. J., J. H. Finkler, and A. B. Froese.** Lung volume recruitment during high-frequency oscillation in atelectatis-prone rabbits. *J. Appl. Physiol.* 64: 1607–1614, 1988.
3. **Chan, V., A. Greenough, and F. Giffin.** Disease severity and optimum mean airway pressure level on transfer to high-frequency oscillation. *Pediatr. Pulmonol.* 17: 178–182, 1994.
4. **Clark, R. H., D. R. Gerstmann, D. M. Null, Jr., and R. A. deLemos.** Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. *Pediatrics* 89: 5–12, 1992.
5. **DeLemos, R. A., J. J. Coalson, D. R. Gerstmann, D. M. Null, M. B. Ackerman, N. B. Escobedo, J. L. Robotham, and T. J. Kuehl.** Ventilatory management of infant baboons with hyaline membrane disease: the use of high-frequency ventilation. *Pediatr. Res.* 21: 594–602, 1987.
6. **Dreizzen, E., M. Migdal, J. P. Praud, M. A. Saby, B. Chambille, M. Dehan, and C. Gaultier.** Passive total respiratory

system compliance and gas exchange in newborn with hyaline membrane disease. *Pediatr. Pulmonol.* 6: 2–7, 1989.
7. **Froese, A. B., P. O. Butler, W. A. Fletcher, and L. J. Byford.** High-frequency oscillatory ventilation in premature infants with respiratory failure: a preliminary report. *Anesth. Analg.* 66: 814–824, 1987.
8. **Froese, A. B., P. R. McCulloch, M. Sugiura, S. Vaclavik, F. Possmayer, and F. Moller.** Optimizing alveolar expansion prolongs the effectiveness of exogenous surfactant therapy in the adult rabbit. *Am. Rev. Respir. Dis.* 148: 569–577, 1993.
9. **Gerstmann, D. R., S. D. Minton, R. A. Stoddart, K. S. Meredith, F. Monaco, J. M. Bertrand, O. Battisti, J. P. Langhendries, A. François, and R. H. Clark.** The Provo multicenter early high-frequency oscillatory ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome. *Pediatrics* 98: 1044–1057, 1996.
10. **Guslits, B. G., R. A. Wilkie, S. J. England, and A. C. Bryan.** Comparison of methods of measurement of compliance of the respiratory system in children. *Am. Rev. Respir. Dis.* 136: 727–729, 1987.
11. **Kuckelt, W., J. H. Schgarfenber, H. Mrochem, R. Daubersc-midt, G. Petrakov, W. Kassil, and M. Meyer.** Effect of PEEP on gas exchange, pulmonary mechanics, and hemodynamics in adult respiratory distress syndrome (ARDS). *Intensive Care Med.* 7: 177–185, 1981.
12. **Kugelman, A., T. G. Keens, R. deLemos, and M. Durand.** Comparison of dynamic and passive measurements of respiratory mechanics in ventilated newborn infants. *Pediatr. Pulmonol.* 20: 258–264, 1995.
13. **LeSouëf, P. N., S. J. England, and A. C. Bryan.** Passive respiratory mechanics in newborns and children. *Am. Rev. Respir. Dis.* 129: 552–556, 1984.
14. **Mathe, J. C., A. Clement, J. Y. Chevalier, C. Gaultier, and J. Costil.** Use of inspiratory pressure-volume curves for determination of appropriate positive end-expiratory pressure in newborns with hyaline membrane disease. *Intensive Care Med.* 13: 332–336, 1987.
15. **McCulloch, P. R., P. G. Forkert, and A. B. Froese.** Lung volume maintenance prevents lung injury during high-frequency oscillatory ventilation in surfactant-deficient rabbits. *Am. Rev. Respir. Dis.* 137: 1185–1192, 1988.
16. **Meredith, K. S., R. A. deLemos, J. J. Coalson, R. J. King, D. R. Gerstmann, R. Kumar, T. J. Kuehl, D. C. Winter, A. Taylor, R. H. Clark, and D. M. Null, Jr.** The role of lung injury in the pathogenesis of hyaline membrane disease in premature baboons. *J. Appl. Physiol.* 66: 2150–2158, 1989.
17. **Pfenninger, J., and C. Minder.** Pressure-volume curves, static compliances and gas exchange in hyaline membrane disease during conventional mechanical and high-frequency ventilation. *Intensive Care Med.* 14: 364–372, 1988.
18. **Richardson, P., C. L. Bose, and J. R. Carlstrom.** The functional residual capacity in infants with respiratory distress syndrome. *Acta Paediatr. Scand.* 75: 267–271, 1986.
19. **Simma, B., G. Luz, R. Trawöger, C. Hörmann, G. Klima, A. Kreczy, and M. Baum.** Comparison of different modes of high-frequency ventilation in surfactant-deficient rabbits. *Pediatr. Pulmonol.* 22: 263–270, 1996.
20. **Sivan, Y., T. W. Deakers, and C. J. L. Newth.** Effects of end-expiratory pressure on respiratory compliance in children with acute respiratory failure. *Pediatr. Pulmonol.* 11: 103–107, 1991.
21. **Suter, P. M., H. B. Fairley, and M. D. Isenberg.** Effect of tidal volume and positive end-expiratory pressure on compliance during mechanical ventilation. *Chest* 73: 158–162, 1978.
22. **Thomson, A., and M. Silverman.** Single-breath measurement of lung mechanics in very low birth weight infants. *Crit. Care Med.* 13: 4–8, 1985.
23. **Walsh, M. C., and W. A. Carlo.** Sustained inflation during HFOV improves pulmonary mechanics and oxygenation. *J. Appl. Physiol.* 65: 368–372, 1988.
24. **Wilkie, R. A., M. H. Bryan, and W. O. Tarnow-Mordi.** Static respiratory compliance in the newborn. II. Its potential for improving the selection of infants for early surfactant treatment. *Arch. Dis. Child.* 70: F16–F18, 1994.