Gas Exchange during High Frequency Flow-Interruption in Rabbits before and after Bronchoalveolar Lavage

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ABSTRACT. The performance of a high frequency flow-interrupter (HFFI) type neonatal ventilator was evaluated on nine adult rabbits (control) and on five adult rabbits after bronchoalveolar lavage (BAL). Tidal volumes and airway pressures were measured during conventional ventilation and during HFFI at rates of 4, 6, 8, 10, and 12 cycles/s. Tidal volumes were adjusted to maintain $PaCO_2$ between 35 and 42 mm Hg in control rabbits and 35–55 mm Hg in BAL rabbits; a positive end-expiratory pressure of 4 cm H_2O was applied to BAL rabbits to reduce atelectasis and improve gas exchange. The normalized tidal volume required to maintain $PaCO_2$ within the specified range during HFFI varied between 2.02 ml/kg (0.30 SD) and 2.55 (0.41) in control rabbits and between 2.65 (0.57) and 2.97 (0.51) in BAL rabbits. In neither group did the normalized tidal volume vary systematically with the rate of ventilation ($p < 0.05$). Mean airway pressures were lower during HFFI than during conventional ventilation in control rabbits but comparable in the BAL group. Peak inflation pressures were greater during HFFI than conventional ventilation in control rabbits but similar in the BAL group. End-expiratory lung volume was not affected by ventilation rate during HFFI in control rabbits. We conclude *1*) that HFFI can maintain gas exchange in rabbits suffering from acute respiratory distress with airway pressures that are comparable to those measured during conventional ventilation and *2*) the capacity of HFFI to ventilate the lungs with significantly lower airway pressures than conventional ventilation depends, in part, on the condition of the lungs. (*Pediatr Res* 24: 203–208, 1988)

Abbreviations

BAL, bronchoalveolar lavage
cps, cycles per second
FiO_2, fractional concentration of oxygen in inspired gas
HFFI, high frequency flow-interruption
HFJV, high frequency jet ventilation
HFV, high frequency ventilation
Pao, airway opening pressure
Paw, airway (tracheal) pressure
$\overline{Paw}$, mean airway pressure
P_D, dynamic pressure head
PEEP, positive end-expiratory pressure
PIP, peak inspiratory pressure
T_I/T_{TOT}, fractional duration of inspiration
V_{max}, peak flow

V_T, tidal volume
HFOV, high frequency oscillation
ANOVA, analysis of variation
a/A PO_2, arterial/alveolar PO_2 ratio

Mechanically assisted ventilation is the principal method of treatment for severe respiratory distress syndrome in newborn infants (2). In the large majority of infants who require ventilation therapy, a conventional time-cycled pressure limited ventilator is used. Ventilators of this sort typically operate at rates on the order of one cps and generate high airway pressures in order to achieve adequate V_T and sufficient gas exchange. Because large, phasic changes in airway pressure and lung volume are associated with an increased incidence of pulmonary barotrauma (2, 3), alternative modes of neonatal ventilation therapy including HFV are currently under investigation.

The three basic types of HFV are HFOV, HFJV, and HFFI (4). Each type differs from the others in the timing of the ventilator cycle, the flow-volume relationship and in whether expiration is passive or active. Whereas there is no doubt that HFV in general can maintain gas exchange with smaller V_T than conventional ventilators (5), it is not clear if HFV produces significantly lower airway pressures or reduces the incidence of lung barotrauma (6, 7). The uncertainty in this aspect of HFV may be due to the fact that the airway pressures and flows generated during the ventilation cycle vary considerably between different HFV devices (8). Thus, an important step in evaluating HFV involves characterizing the pressures and flows required to maintain gas exchange.

In our study we assessed the performance of a particular HFV known as the Infant Star (Infrasonics, San Diego, CA). This device is essentially a flow-interrupter type of HFV that uses a series of solenoid valves to introduce brief pulses of high velocity airflow into the central airways. At the onset of expiration, the Infant Star produces a transient but substantial drop in airway pressure (Fig. 1). To our knowledge there are no reports on the magnitudes of pressure and airflow that are necessary to maintain gas exchange with the Infant Star. Accordingly, we evaluated these characteristics during HFV of normal adult rabbits. To assess the relationship of lung function and ventilator performance, measurements were also performed on rabbits suffering from acute respiratory distress after bronchoalveolar lavage.

MATERIALS AND METHODS

Nine New Zealand White rabbits weighing between 2.1 and 2.6 kg (mean body weight = 2.28 ± 0.20 kg) were studied. Each rabbit was anesthetized with an injection of methohexitol sodium (50 mg/kg, intraperitoneally) and maintained under anesthesia with a continuous intravenous infusion (0.5 mg/kg/min). A
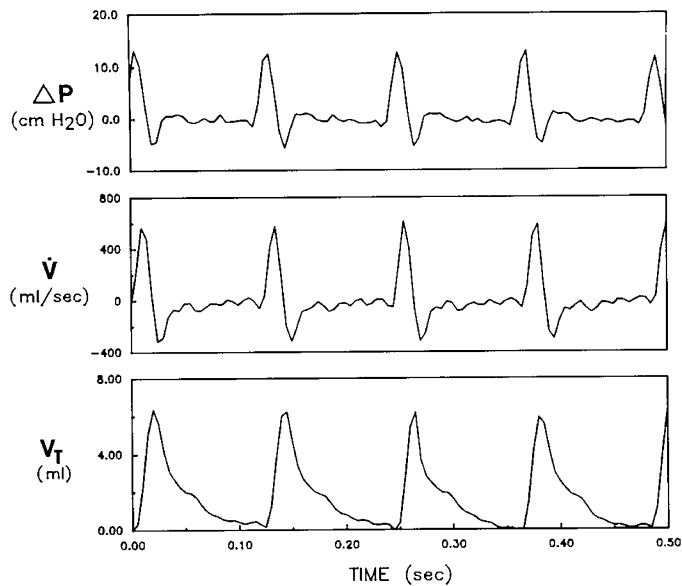
Fig. 1. Pressure, volume, and airflow waveforms produced by the Infant Star ventilator. Typical records of airway pressure P, flow V, and tidal volume V_T during HFFI at 8 cps. Note the negative swing in airway at the beginning of the expiratory phase and its effect on expiratory flow.

tracheotomy was performed below the level of the larynx and a short cannula (i.d. = 4.5 mm, internal volume 1.4 ml) was inserted and fixed in position using surgical thread and cyanoacrylate adhesive. The rabbit was placed supine inside a 22-liter whole-body plethysmograph and ventilated with air (F_{IO_2} = 0.21) at a conventional rate. Throughout the experiment spontaneous breathing was supressed by intermittent injections of pancuronium bromide (Pavulon 0.1 mg/kg, intravenously).

Paw was measured with a piezoresistive pressure transducer that has a flat frequency response up to 200 Hz (140PCO1D; Microswitch, Freeport, IL) and is connected to a side port on the cannula. Variations in plethysmograph pressure were measured with a negative differential pressure transducer (MP245; Validyne, Northridge, CA). The frequency response of the transducers and plethysmograph were determined by a variation of the method of Jackson and Vinegar (9) and were flat up to approximately 60 Hz. Mean arterial pressure was measured using a saline filled pressure transducer (DP15-32; Validyne, Northridge, CA) and catheter inserted into the femoral artery. Body temperature was monitored with a rectal probe (43TA; Yellow Springs Instrument Co., Yellow Springs, OH) and maintained at 38 ± 1° C with a radiant heat lamp.

Gas exchange. The V_T required to maintain normocapnia in control rabbits during HFFI was determined at ventilation rates of 4, 6, 8, 10, and 12 cps. These rates correspond roughly to between 4 and 12 times the rate of spontaneous breathing in the adult rabbit (10) and thus qualify as HFV according to guidelines recommended by Drazen *et al.* (5). At each rate, the ventilator was initially adjusted to produce changes in lung volume of between 1.0 and 3.0 ml/kg and the rabbit was ventilated continuously with air for 10 min. At the end of a 10-min period, a sample of arterial blood was withdrawn and blood gases and pH were determined using an automated blood gas analyzer (ABL2; Radiometer, Copenhagen). To verify that there was sufficient time for equilibration of blood gases (11), additional samples were drawn at 20- and 25-min intervals in one rabbit. We observed no further changes in blood gas tensions between 10 and 25 min of continuous ventilation. If $PaCO_2$ was between 35-42 mm Hg the ventilator was switched to a new rate. However, if $PaCO_2$ exceeded this range, the V_T was readjusted and the lung was ventilated for 10 min at the new setting before another blood sample was withdrawn. For all rabbits, the order

in which ventilation rates were studied was randomized to prevent any systematic effects due to ventilation history. In addition, at each rate, lung volume history was standardized by three large inflations to an airway pressure of 30-35 cm H_2O in order to reverse the atelectasis that may occur during positive pressure ventilation (12). No PEEP was applied to the normal rabbits during HFFI.

Blood gas tensions and pH were also measured during conventional mechanical ventilation at a frequency of 40 cycles/min (T_I/T_{TOT} = 0.3) and with a PIP of 8-10 cm H_2O. All ventilator pressure settings refer to Pao which is measured in the endotracheal tube connector and displayed on the ventilator console. No PEEP was applied to normal rabbits during conventional ventilation.

At each ventilation rate, alveolar oxygen tension was estimated using the alveolar gas equation:

$$PAO_2 = PIO_2 - PaCO_2 + [PaCO_2 * F_{IO_2}(1/R - 1)]$$

assuming R = 0.8, and the arterial to alveolar oxygen tension ratio, a/APO₂ (13) was calculated.

BAL. Gas exchange during HFFI was examined in five rabbits (body weight = 2.15 ± 0.14 kg) depleted of lung surfactant using the lavage technique described by Lachmann *et al.* (14). To wash out lung surfactant, the rabbit was ventilated for 10-15 min with 100% O₂, then hyperinflated to an airway pressure of 25-30 cm H_2O in order to promote release of surfactant (15). Isotonic saline (0.9 g/100ml, 30 ml/kg) at 37° C was instilled into the lung using airway pressures of less than 30 cm H_2O, while the thorax was gently massaged by hand to encourage distribution. By tilting the rabbit and manually compressing the thorax, saline-containing surfactant drained into the large airways and trachea from which it was removed by means of a suction catheter. The rabbit was then ventilated with 100% O₂ at a rate of 40 cycles/min (T_I/T_{TOT} = 0.3) and with a PEEP of 4 cm H_2O and PIP of 15-20 cm H_2O to facilitate transport of the saline remaining in the lung into the periphery. The lavage sequence was repeated until arterial PO₂ was 250 mm Hg or less after 20 min of conventional ventilation. As few as two and as many as eight separate lung lavages were required to obtain values of PaO₂ characteristic of acute respiratory distress (16).

After lung lavage, the effect of HFFI on gas exchange was assessed following the same protocol used for normal rabbits with the exception that PEEP was maintained at 4 cm H_2O and the F_{IO_2} equaled 1.0. For conventional ventilation of these rabbits, the rate was set at 40 cpm and PIP equaled 15-20 cm H_2O. Our choice of these settings was based on the previous study of BAL rabbits by Lachmann *et al.* (14). Because of their impaired lung function the BAL rabbits displayed elevated $PaCO_2$ that, in some cases, could be lowered by a moderate increase in V_T. Inasmuch as the risk of lung rupture and pneumothorax likely increases with this adjustment, we adopted the guidelines recommended by Stark and Frantz (1) and increased the upper limit of $PaCO_2$ to 55 mm Hg in this group. Accordingly, our evaluation of ventilator performance in BAL rabbits reflects its capacity to maintain blood gases at levels that are generally accepted for lungs in this condition.

Ventilation parameters. For each combination of ventilation frequency and V_T that produced acceptable gas exchange, mean and peak airway pressures were computed along with peak inspiratory and expiratory flows. To assess if HFV caused an elevation of end-expiratory lung volume, the ventilator was momentarily turned off during HFFI. This caused airway pressure to rapidly fall to atmospheric pressure and lung volume to return to its resting volume. If lung volume was elevated during HFFI, the resting lung volume would fall below the end-expiratory volume and the change in volume could be determined from the change in plethysmograph pressure. This procedure was repeated three times at each frequency in six of the normal rabbits. No measurements of this sort were performed on BAL rabbits.

Data acquisition and analysis. The output signals from airway

and plethysmograph pressure transducers were low pass filtered with a cutoff frequency of 100 Hz (902LPF; Frequency Devices, Haverhill, MA) and passed into a computer (PDP 11/73; Digital, Maynard, MA) for A/D conversion. For each trial, 1200 data points were collected from each signal at a rate of 400 Hz. Variations in plethysmograph pressure were converted into changes in lung volume using a suitable calibration factor obtained by calibrating and plethysmograph several times throughout each experiment. The dimensions of the plethysmograph and the rate of the pressure changes within it insured that all measurements and calibrations were performed under essentially adiabatic conditions (17). Airflow was computed by numerical differentiation of the digitized volume signal.

All variables are presented as means ± 1 SD. Within group differences were tested using one-way ANOVA. Between groups differences were compared using two-way ANOVA (18). Differences were considered significant if $p < 0.05$.

RESULTS

Gas exchange. The effects of HFFI on blood gas tensions and pH in normal and BAL rabbits are shown in Table 1. For the nine normal rabbits, arterial PO_2, PCO_2, and pH were within acceptable limits at all ventilation frequencies. PaO_2 was not significantly different between HFFI and conventional ventilation nor did it vary with the rate of ventilation. The a/A PO_2 (Fig. 2) increased slightly with HFV but the change was not significant.

For the BAL group, arterial PCO_2 varied between 39.2 and 52.7 during HFFI with the highest level occuring at the lowest frequency. The relatively high value of $PaCO_2$ at 4 cps was due to poor ventilation that occurred in one rabbit. Inasmuch as this animal was also the largest in the group (2.4 *versus* 2.09–2.11 kg for the remaining four) it is possible that its ventilatory requirements exceeded the capacity of the ventilator at this rate of HFFI. Despite the high value in this animal, the mean $PaCO_2$ did not vary significantly with ventilation rate. Mean arterial PO_2 during HFFI was maintained at levels comparable to PaO_2 during conventional ventilation although there was greater intra-group variation in PaO_2 during HFFI. As in the normal group, there were no differences in PaO_2 or a/A PO_2 between conventional and HFFI and neither PaO_2 nor a/A PO_2 varied with the rate of HFFI.

The relationship between normalized V_T and the rate of ventilation is shown in Figure 3. For both normal and BAL rabbits, the V_T required to maintain $PaCO_2$ during HFFI were approximately 40–50% of the V_T used during conventional ventilation and were independent of rate up to 12 cps. For normal rabbits during HFFI, V_T/kg body weight varied between 2.02 and 2.55 ml whereas in the BAL group, V_T were slightly larger. Differences between groups during HFFI were not significant except at 10 and 12 cps.

Ventilation parameters. $\overline{Paw}$ during HFFI for normal and BAL rabbits are shown in the *top* of Figure 4. For normal rabbits, $\overline{Paw}$ was significantly lower during HFFI than during conventional ventilation. For BAL rabbits, however, there was no significant difference in $\overline{Paw}$ between HFV and conventional modes of ventilation. During HFFI in normal rabbits PIP were about twice the value found with conventional ventilation (Fig. 4, *bottom*) but for BAL rabbits, PIP did not differ significantly between high frequency and conventional ventilation. In both groups neither $\overline{Paw}$ nor PIP varied with the rate of HFFI.
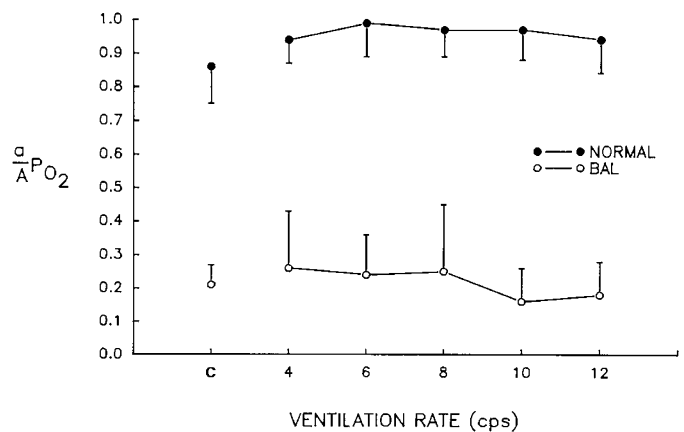

Fig. 2. Arterial-alveolar oxygen tension ratios in normal and BAL rabbits. Mean a/A PO_2 ratios during conventional ventilation (*C*) and HFFI. *Closed circles,* normal rabbits; *open circles,* BAL rabbits. Data points are group means, bars denote 1 SD. The a/APO_2 ratios in BAL rabbits during HFFI are similar to those obtained from infants suffering respiratory distress (29).

Table 1. *Blood gas and pH in normal and BAL rabbits**

Rate (cps)	C	4	6	8	10	12
Normal (n = 9)						
PaO₂	95	101	106	107	106	101
mm Hg	(11)	(9)	(7)	(10)	(11)	(11)
PaCO₂	39.1	41.5	39.9	38.1	39.4	41.4
mm Hg	(3.1)	(2.2)	(1.6)	(2.8)	(1.3)	(1.7)
pH	7.32	7.35	7.35	7.36	7.34	7.33
	(0.03)	(0.03)	(0.04)	(0.04)	(0.03)	(0.04)
BP	84	84	90	88	87	84
mm Hg	(9)	(8)	(8)	(7)	(7)	(7)
BAL (n = 5)						
PaO₂	135	177	165	172	106	125
mm Hg	(41)	(112)	(84)	(135)	(68)	(70)
PaCO₂	44.0	52.7	39.5	38.1	41.0	39.2
mm Hg	(4.4)	(16.0)	(2.7)	(1.3)	(12.1)	(3.0)
pH	7.27	7.27	7.36	7.38	7.37	7.34
	(0.04)	(0.09)	(0.02)	(0.02)	(0.03)	(0.02)
BP	78	76	80	79	79	79
mm Hg	(16)	(12)	(11)	(11)	(10)	(10)

* Values of arterial PO_2, PCO_2, and pH obtained from normal and BAL rabbits during conventional ventilation (C) and HFFI. BP, mean arterial pressure. Group mean values are presented with 1 SD in parentheses. In both normal and BAL groups, arterial blood gases, pH, and BP were unaffected by ventilation rate.

Peak inspiratory and expiratory flows ($\dot{V}_{max}$) during HFFI are shown in Figure 5. Peak flows during HFFI were similar in both groups. The peak inspiratory flows were about five times greater during HFFI than during conventional ventilation whereas the peak expiratory flows were about three times greater.

In six normal rabbits, changes in the end-expiratory lung volume when HFV was suddenly interrupted varied between 0.20 and 0.73 ml and were not significantly different from zero.

DISCUSSION

In this study we have used standard measurements of gas exchange and ventilation to assess the operating characteristics of the Infant Star neonatal ventilator. Our results indicate that this ventilator can maintain adequate gas exchange in normal and BAL rabbits during HFV. Paw during HFFI were comparable or less than those measured during conventional ventilation for the same PEEP; PIP during HFFI were equal to or greater than those measured during conventional ventilation. An interesting result of our analysis was that the performance of HFFI depended on the condition of the lungs. Specifically, when compared with conventional ventilation, the mean airway pressures necessary for adequate gas exchange during HFFI were greater in lungs depleted of surfactant than in normal lungs.

The Infant Star ventilator incorporates microprocessors to monitor and control the Pao in the endotracheal tube connector. During HFFI the mean value of Pao is equal to the applied PEEP. For normal rabbits during HFFI, Paw measured in the trachea was the same as mean Pao. However, for the BAL rabbits Paw was greater than mean Pao which equaled the applied PEEP of 4 cm H_2O (Fig. 4, *top*). This phenomenon has been observed during HFJV in normal rabbits (6) as well as in rabbits suffering from respiratory distress induced by oleic acid lung injury (10). Frantz and Close (6), reported that Paw in the trachea during HFJV may exceed Pao by as much as two to three times and noted that the elevated Paw corresponded well with the mean alveolar pressure and an increase in end-expiratory lung volume. Our finding that Paw during HFFI was greater than Pao in sick rabbits but comparable to Pao in normal rabbits suggests that intrinsic-PEEP can develop in sick lungs during HFFI that is not apparent from measurements of Pao. In view of previous observations (6, 10), this finding underscores the importance of airway (*i.e.* tracheal) pressure measurement in evaluating the performance of HFV.

Another interesting characteristic of HFFI is that the V_T re-

Fig. 4. Comparison of mean and peak airway pressures in normal and BAL rabbits. *Top*, Paw during conventional ventilation (*C*) and HFFI. *Bottom*, PIP. *Closed circles*, normal rabbits; *open circles*, BAL rabbits. Data points are group means; bars denote 1 SD; * significant difference between C and HFFI.

Fig. 5. Comparison of peak inspiratory and expiratory airflows in normal and BAL rabbits. Maximum inspiratory and expiratory flows ($\dot{V}_{max}$) during conventional ventilation (*C*) and HFFI. *Closed circles* and *triangles*, normal rabbits; *open circles* and *triangles*, BAL rabbits.
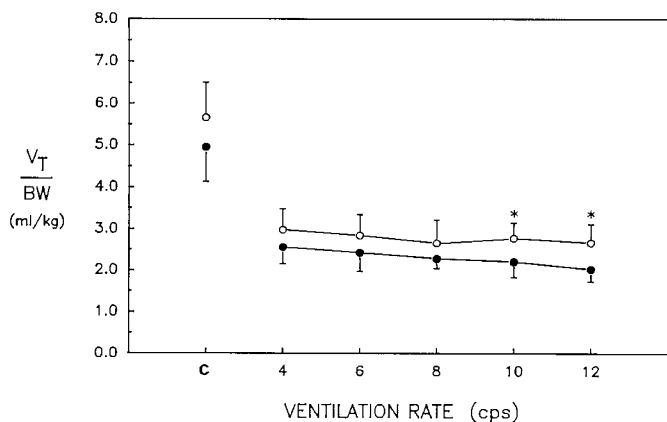

Fig. 3. Comparison of normalized V_T from normal and BAL rabbits during conventional ventilation and HFFI. The V_T normalized per kg body weight (V_T/BW) during conventional ventilation (*C*) and HFFI. *Closed circles*, normal rabbits; *open circles*, BAL rabbits. In both groups inflation volumes were independent of ventilation rate during HFFI. Data points are group means; bars denote 1 SD; * significant difference between normal and BAL rabbits.
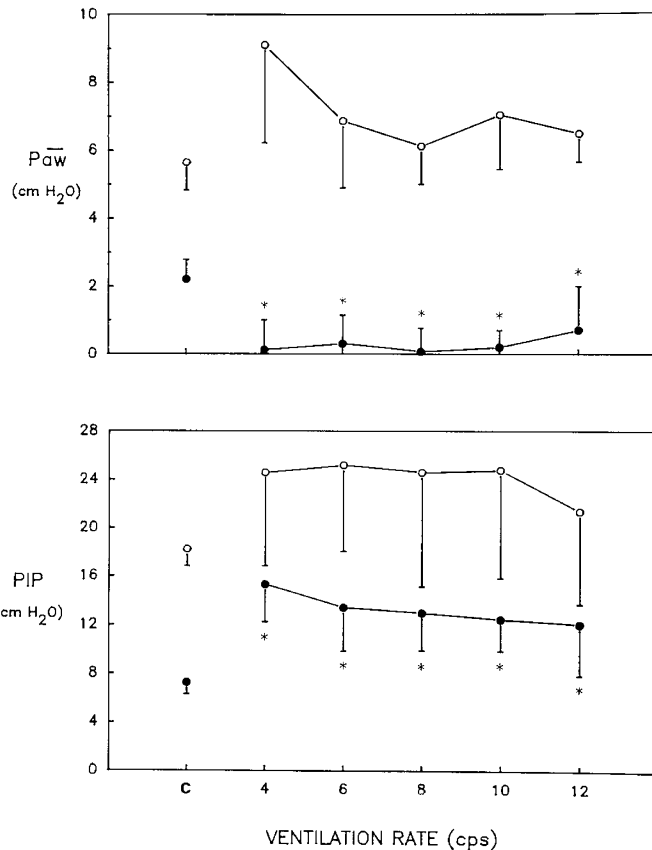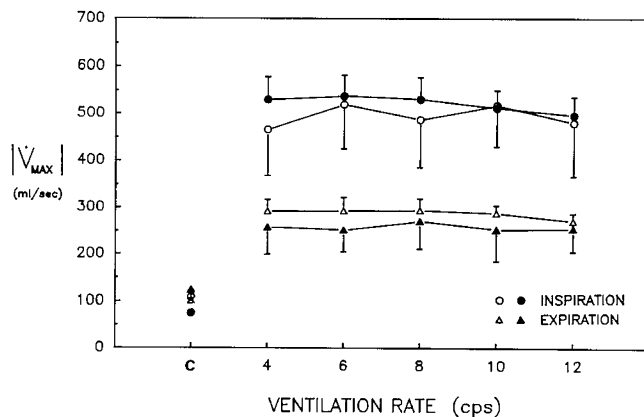
quired to maintain $PaCO_2$ in normal rabbits during HFFI exceeded the estimated dead space of the respiratory system (about 1.7 ml/kg; from Ref. 19). This characteristic is not confined to HFFI ventilation because V_T larger than dead space have also been reported during jet ventilation (6, 20, 21). However, unlike other forms of HFV, in which V_T decreases with increasing ventilation rate (9, 22, 23), the V_T recorded HFFI were independent of ventilation rate (Fig. 3). The practical significance of this feature of HFFI is that high rates of ventilation may not be .necessary to obtain acceptable gas exchange in neonates. Al-

though we are not yet able to understand why this occurs, a possible mechanism may involve manner in which HFFI is produced.

For the Infant Star, the duration of inspiration during HFFI is fixed and the rate can only be varied by adjusting the duration of expiration. Because of the fixed inspiratory timing the V_T delivered with each cycle is determined entirely by the rate of the inspiratory flow. Owing to the short (12 ms in this model) duration of inspiration, these flows are quite large and, like the corresponding V_T, appear to be independent of ventilation rate (Fig. 5). It should be noted, however, that the later models of this ventilator incorporated a longer inspiratory duration (18 ms). To achieve airflows of this order the gas within the large central airways must be subjected to considerable acceleration and the resulting flows are governed predominantly by gas inertia. Under these conditions, fresh gas may move into the lung periphery through a process of bulk convection. An empirical and theoretical analysis of gas transport by this mechanism has revealed the rate of CO_2 washout from a physical model depends primarily on V_T and is relatively unaffected by ventilation rate (24).

The large airflows during HFFI may generate additional effects within the airways. As shown in Figure 5, the peak inspiratory flows varied between 450 and 500 ml/s or roughly three to five times greater than the peak airflow during conventional ventilation. These high inspiratory flows produce a shear force at the wall of the large airways that can promote the movement of mucus in the direction of flow. For bidirectional flows, the net direction of mucus transport depends on the net shear force acting on the airway wall and is determined by the relative rates of inspiratory and expiratory airflows (25). An index of the magnitude of shear forces in the trachea is the P_D at the opening of the endotracheal tube. Estimated values of P_D for inspiratory and expiratory flows are given in Table 2. During inspiration, P_D, is about 20 times greater than the values obtained during conventional mechanical ventilation. Expiratory values are roughly 25–35% of the inspiratory values indicating that the net shear force is in the inspiratory direction. Conceivably, the active expiratory phase of the ventilator may reduce the net shear forces in the large airways and the effect of these forces on mucus clearance. However, because the high flow velocities produced during HFV are also implicated in the development of tracheal lesions (21, 26) and pose problems in the delivery of humidified air, it remains to be determined whether bidirectional flows of the magnitude produced by the Infant Star are beneficial to the infant.

Gas trapping can occur during HFJV if the duration of the expiratory phase is too short to allow for complete expiration to resting lung volume (27). The transient decrease in airway pressure and the corresponding airflows during the expiratory phase (Figs. 1 and 5) likely prevented elevation of end-expiratory lung volume and $\overline{Paw}$ in normal rabbits at high rates of HFFI. However, because $\overline{Paw}$ during HFFI in the BAL group exceeded

the applied PEEP suggests that the effect of the active expiratory phase does not counteract intrinsic PEEP in sick lungs.

Although we have reported on HFFI as an independent mode of ventilation, it should be noted that the ventilator offers the option of combining HFFI with conventional ventilation. A ventilation routine that consists of high frequency and conventional modes can improve oxygenation by increasing mean lung volume and yet maintain comparatively lower $PaCO_2$ and airway pressures than conventional ventilation alone (28). Intermittent conventional inflations, or sighs, combined with HFFI may improve gas exchange in neonates with respiratory distress syndrome but our data on BAL rabbits suggests that airway pressures may not be significantly reduced.

In summary, we found that the Infant Star flow interruption ventilator can maintain adequate gas exchange in normal as well as surfactant depleted rabbits both at conventional settings and during HFFI at rates of 4, 6, 8, 10, and 12 cps. The ventilator generates comparatively high peak airway pressures and airflows during HFFI primarily due to the short duration of its inspiratory phase. No gas trapping was observed in normal rabbits and a PEEP of 4 cm H_2O was needed to ventilate the rabbits with respiratory distress. The V_T required during HFV were independent of frequency as were the maximum inspiratory and expiratory flow rates. The peak inspiratory flow velocities exceeded the peak expiratory velocities by about 60% possibly influencing mucus clearance from the airways.

Table 2. P_D during conventional ventilation and HHFI*

Rate (cps)	C	4	6	8	10	12
Normal						
P_DInsp	0.34	6.61	6.81	6.63	6.17	5.77
P_DExp	0.24	2.01	2.02	2.03	1.95	1.73
Bal						
P_DInsp	0.27	5.11	6.36	5.58	6.31	5.42
P_DExp	0.36	1.55	1.49	1.73	1.51	1.53

* P_D computed from the flow velocity at the distal end of the tracheal cannula. C, conventional ventilation; Insp, inspiratory phase; Exp, expiratory phase. Units of P_D are cm H_2O. Note the large values of P_D during HFFI.

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