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Combined high-frequency ventilation in children with severe adult respiratory distress syndrome*

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Abstract. Six children conventionally ventilated for acute pulmonary parenchymal failure developed severe hypoxemia (mean PaO_2 48±7 mmHg at an FiO_2 of 0.95±0.08) persisting for more than 6 h despite a progressive increase in positive end expiratory pressure (PEEP) to 14.7±1.5 cmH_2O. Combined high-frequency jet ventilation (HFJV, mean rate 225 b/min superimposed on small tidal volume conventional ventilation) resulted in a sustained increase in PaO_2 to 93±21 mmHg, $p<0.05$ while peak inspiratory pressure decreased from 47±8 to 35±6 cmH_2O and positive end expiratory pressure could be reduced to 5.8±4.5 cmH_2O, $p<0.05$ and FiO_2 to 0.88±0.10. This improvement occurred without new barotrauma nor deleterious effects on hemodynamic function or diuresis. After a mean of 62 h of combined HFJV, persistant improvement in gas exchange allowed us to resume conventional mechanical ventilation at lower airway pressures in 4 children who continued to improve and survived. The 2 other children maintained satisfactory gas exchange on combined HFJV, but ultimately died from multiple organ failure. We conclude that combined HFJV might prove helpful to relieve profound hypoxemia and possibly decrease the risk of barotrauma in children with catastrophic pulmonary failure.

Key words: Hypoxemia – Children – Adult respiratory distress syndrome – Combined high-frequency ventilation – PEEP

Hypoxemia unresponsive to oxygen therapy, a hallmark of adult respiratory distress syndrome (ARDS) is usually improved during conventional mechanical ventilation by raising positive end expiratory pressure (PEEP) [1] or inverting the inspiration/expiration time ratio and setting an inspiratory "plateau" [2]. These measures increase mean airway pressure, promote alveolar recruitment, reduce intrapulmonary shunt and improve PaO_2. In children with severe ARDS, application of increasing levels of PEEP has been shown to improve PaO_2 eventually [3] but often causes adverse cardiocirculatory effects [4] while being associated with a high incidence of barotrauma [5] and poor outcome.

Ventilation over a wide range of higher than physiologic frequencies has been proposed as a valuable alternative to maintain gas exchanges in adults [6–10]. However, clinical data [11] supporting this approach in the treatment of children presenting with severe pulmonary consolidation [12, 13] is lacking.

In this report, we describe our experience using combined high-frequency jet ventilation (i.e. high-frequency jet ventilation superimposed on the total respiratory cycle of small tidal volume conventional ventilation and low positive end-expiratory pressure) as a temporary rescue method to reverse severe hypoxemia that persisted in 6 children despite the use of high levels of PEEP.

Patients and methods

Over an 18-month period (June 1987 to December 1988), 14 children with ARDS according to clinical and radiological criteria described by Pfenninger et al. [14], were treated at the pediatric intensive care unit of our institution. Supportive treatment consisted of nasotracheal intubation with a cuffed endotracheal tube and ventilation with a Siemens Servo 900C ventilator in the volume controlled mode. PEEP, fractional inspired oxygen concentration (FiO_2) and inspiration to expiration time ratio (I:E) were adjusted to keep arterial oxygen saturation (SaO_2) above 85% with the lowest possible peak airway pressure and FiO_2. Patients were routinely paralyzed with pancuronium bromide 0.1 mg/kg when peak inspiratory pressure exceeded 30 cmH_2O. Midazolam at 0.1 mg/kg/h and morphine sulfate or nalbuphine at 0.1 to 0.2 mg/kg/h i.v. were used for sedation.

Maintenance fluids were administered with a mild restriction at 70 ml/kg/day. Broad antibiotic coverage was instituted early and adapted to the results of bacterial cultures.

Fresh frozen plasma or packed red cells were given to restore blood volume when required and to maintain hematocrit above 35%. Hemodynamic variables were assessed through central venous and peripheral arterial lines. Placement of a Swan-Ganz pulmonary artery catheter was felt to be justified for better control of cardiovascular state in 3 of the 14 children.

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During the course of their disease, 8 of these 14 children maintained adequate gas exchange (lowest mean PaO_2 74±24 mmHg at FiO_2 0.82±0.2 and PEEP of 10±3.2 cmH_2O) under conventional mechanical ventilation.

The other 6 developed severe and persisting hypoxemia (mean PaO_2 48±7 mmHg at FiO_2 0.95, $SaO_2 < 80\%$) despite a progressive increase in positive end expiratory pressure to 14.7±1.5 cmH_2O, an inverse inspiration to expiration ratio of 2:1 and a respiratory frequency of 35±15 breaths/min. At that time, all were clinically considered to be in the acute or subacute phase of their disease (range of time elapsed from acute respiratory failure, 24–192 h, median 38 h).

As deterioration in arterial oxygen saturation was observed on pulse oximetry on short attempts to lower PEEP and as no improvement was obtained in PaO_2 on the latest increase in PEEP of 2 cmH_2O, switching to combined HFJV was considered. The poor prognosis was explained to the parents along with the experimental nature of the proposed ventilatory mode. Their consent was obtained and combined high frequency jet ventilation was started.

Management of combined high-frequency ventilation

A commercially available universal jet ventilator, Model AMS-1000 (Acutronic Medical System, 8645, Jona-Rapperswil, Switzerland) was used. It consists in a high pressure gas source with a blender and a microprocessor-controlled pneumatic valve. Frequency and duty cycle can be selected stepwise, and tidal volume modified in a continuous manner by changing the driving pressure. The ventilator is coupled with a system (Model AMS-1020) providing continuous humidification and temperature control of the jet gas mixture. An adjustable roller pump dispenses 5 to 99 ml/h of distilled water into a heated chamber to produce vapour which is mixed with the breathing gas.

The tubing of the jet ventilator was connected to a 16 gauge venous catheter introduced in the endotracheal tube by a hole in a swivel connector and advanced to within 5 cm of the distal end of the endotracheal tube.

HFJV was started at a rate of 250/min applied during the whole ventilatory cycle of conventional ventilation, with a duty cycle of 30–40%, corresponding to an I:E ratio of 30/70 or 40/60 of HFJV. Driving pressure was raised to about 1.0 bar in a stepwise manner over a time period of 5–15 min while PEEP and conventional tidal volume were simultaneously reduced to avoid excessive peak airway pressures. PEEP was decreased as long as increasing the driving pressure resulted in a higher PaO_2. Ventilation by the Siemens 900C was decreased to the point where CO_2 retention started to occur. This corresponded to about 50% of the initial tidal volume and minute ventilation given by conventional mechanical ventilation (CMV). Changes in oxygenation were monitored continuously with a pulse oximeter while changes in pH and $PaCO_2$ were controlled by frequent arterial blood gas analysis.

Nursing care of the endotracheal tube required discontinuing combined HFJV and was attempted only when clinically indicated because hand ventilation of these very unstable patients usually resulted in rapid decrease in SaO_2 on the pulse oximeter.

Comparisons

The following periods of 6h of observation each were analyzed:

For all 6 children: (1) On CMV soon after intubation, period labeled “initial” to document ventilatory requirements on admission, (2) On CMV with high PEEP levels, just prior to transition to combined HFJV, period labeled “high PEEP”, (3) Soon after institution of combined HFJV, period labeled “early”.

For four children who survived: (4) On combined HFJV before switching back to CMV, period labeled “late”, (5) On CMV soon after stopping combined HFJV, period labeled “resumed”.

Periods 2–5 were used to assess the respective effects of combined HFJV and CMV, each patient serving as its own control.

For each period, 3 determinations, approximatively 2h apart, were averaged to yield a representative value for ventilation, hemodynamics and pulmonary gas exchange. Mean values of each period are reported in tables while the 3 distinct observations are detailed in figures.

Measurements

Central venous and systemic arterial pressures were monitored with Hewlett-Packard pressure modules (model 78353B, Hewlett-Packard Company, Andover, MA). Blood gas analysis, corrected for temperature, and calculation of hemoglobin saturation was performed on an ABL 300 (Radiometer, Copenhagen).

Ventilatory volumes, peak, mean and positive end-expiratory pressures were measured using the on line system of the Servo 900C ventilator.

In order to assess roughly changes in lung volumes between conventional ventilation and combined HFJV, total lung area (including the shadow of the heart) was measured planimetrically from antero-posterior chest X-rays taken before and after combined HFJV was started.

The border inside the rib cage and diaphragm were outlined and transferred on to transparent paper and the surface measured using millimetric paper. The difference in area between two corresponding chest X-rays, was then expressed as a percentage of the total lung area during conventional ventilation.

Statistical analysis

Averaged values for each 6-h period of observations were compared through two-way analysis of variance and Neumann-Keuls multiple comparisons procedure [15]. A Friedman non-parametric test was performed when variables were not normally distributed. Differences between groups were assessed by unpaired *t*-test.

Results (see also Table 2)

Data indicated in tables and figures are mean ± SD. The epidemiological characteristics and associated conditions of the 6 children are listed in Table 1. On admission, soon after intubation, mean PaO_2 for the 6 patients was 107±33 mmHg with FiO_2 of 0.83, PEEP of 7.9±4.8 cmH_2O and mean airway pressure of 16.4±6.6 cmH_2O.

Organ failure score was calculated according to the criteria of Wilkinson et al. [16] and varied between 1 and 4 in individual patients.

Effects of instituting combined HFJV

Oxygenation (Fig. 1). From a mean of 48±7 mmHg during “high PEEP” with CMV, PaO_2 rapidly increased to 93±21 mmHg, $p < 0.05$ with combined HFJV while FiO_2 could be progressively reduced to 0.88±0.10 and PEEP to 5.8±4.5 cmH_2O, $p < 0.05$.

Changes in PaO_2 normalized for FiO_2 (PaO_2/FiO_2) [17] during the 5 study periods are illustrated in Fig. 1. As pulmonary gas exchange deteriorated, PaO_2/FiO_2 decreased from 128±40 to 51±9, $p < 0.05$ during conventional ventilation and increased to 106±30, $p < 0.05$ with combined HFJV.

In 4 survivors, when CMV was resumed, PaO_2 slightly decreased from 86±28 to 74±25 mmHg, $p > 0.05$ as did PaO_2/FiO_2 ratio (110±30 vs 91±40, $p > 0.05$ but both PaO_2 and PaO_2/FiO_2 remained significantly higher than before combined HFJV was started (respectively 74±25 vs 48±7 mmHg, $p < 0.05$ and 91±40 vs 51±9, $p < 0.05$).

Ventilation and carbon dioxide elimination. High frequency jet rates ranged from 200–300, mean 225 breaths/min, with a duty cycle of respectively 30 and 40%

Table 1. Epidemiological data for the 6 children treated with combined HFJV for severe ARDS

	Weight kg	Age years	ET tube size	Underlying condition	Triggering event	Combined HFJV (h)	MOF score	Outcome
R.R.	18	6 4/12	6.0	ALL, remission phase	Varicella Pneumonia	74	3	Survived
C.A.	20	7 3/12	5.5	BMT, GVH	pneumonia	276	3	Died
B.Z.	8	6/12	4.5	Subarachnoid hemorrhage	Aspiration pneumonia	45	1	Survived
M.R.	12	21/12	5.0	Healthy	Trauma	94	2	Survived
L.L.	30	10 9/12	5.0	Healthy	Trauma	34	3	Survived
M.M.	14	3 1/12	5.0	Repair of Fallot	Gram-neg. sepsis	89	4	Died

ALL, Acute lymphocytic leukemia; BMT, Bone marrow transplant; GVH, Graft vs host disease; MOF, Multiple organ failure [16]

Table 2. Ventilatory and gas exchange variables during the 5 periods of observation in children treated with combined HFJV

	Conventional ventilation		Combined HFJV		Conventional ventilation Resumed
	Initial	High PEEP	Early	Late	
	All patients ($n = 6$)			Survivors ($n = 4$)	
FiO_2	0.83 ± 0.10	0.95 ± 0.08*	0.88 ± 0.10	0.73 ± 0.22**	0.83 ± 0.18**
PaO_2 (mmHg)	107 ± 33	48 ± 7*	93 ± 21**	86 ± 28**	74 ± 25**
PEEP (cmH_2O)	7.9 ± 4.8	14.7 ± 1.5*	5.8 ± 4.5**	5.6 ± 4.4**	9.0 ± 3.4** ***
Mean AWP (cmH_2O)	16.4 ± 6.6	25.3 ± 3.5*	14.8 ± 3.2**	12.4 ± 4.1**	16.9 ± 2.4**
Peak AWP (cmH_2O)	41.7 ± 9.7	46.7 ± 8.0	35.1 ± 5.6**	28.8 ± 1.7**	37.1 ± 4.1*****
Conventional tidal volume (ml/kg)	12.4 ± 3.2	10.9 ± 1.8	4.4 ± 2.7**	4.0 ± 0.4**	9 ± 1***
Estimated HFJV tidal volume (ml/kg)			1.8 ± 0.7	1.7 ± 0.5	
Total minute ventilation (l/min)	6.8 ± 1.9	6.8 ± 2.2	10.1 ± 2.6**	8.3 ± 2.3**	6.7 ± 2.1***

Values are average of three determinations during a 6 h period (mean ± SD). AWP = airway pressure. * = $p<0.05$ vs "initial" conventional ventilation. ** = $p<0.05$ vs "high PEEP" conventional ventilation. *** = $p<0.05$ vs "late" combined HFJV

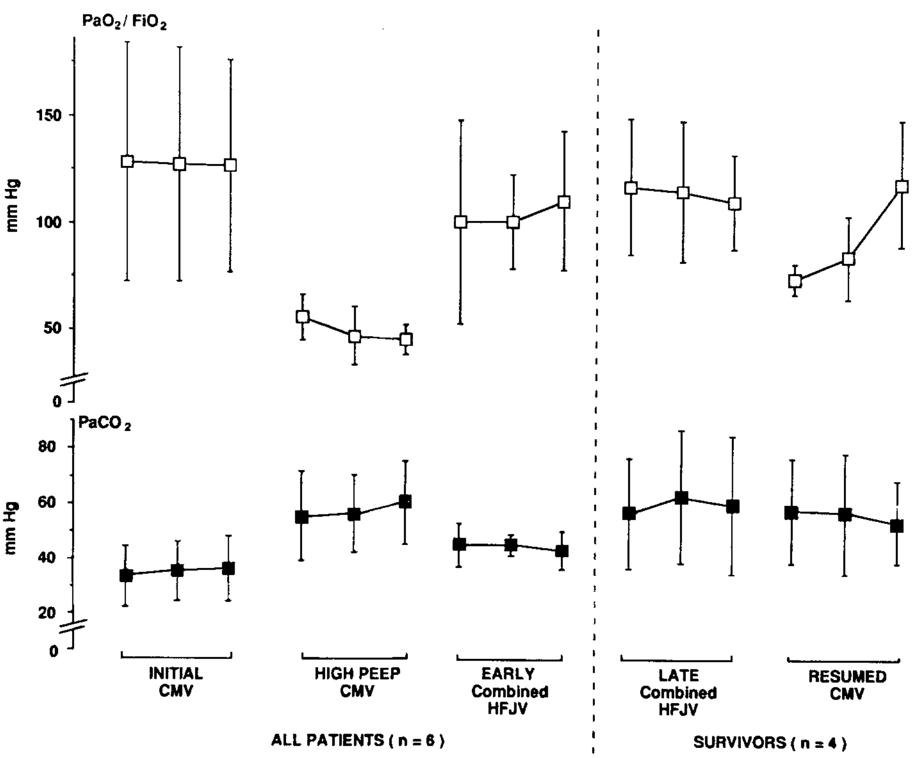

Fig. 1. Mean ± SD of PaO_2 normalized for FiO_2 and $PaCO_2$ are illustrated by the 3 separate measurements made during each of the 5 successive 6-h periods of observation. Statistically significant differences are indicated in the result section. *CMV*, Conventional mechanical ventilation

for each half of the children. Driving pressure ranged from 0.5 to 1.5 bar corresponding to mean jet pulses of 1.8 ml/kg.

The frequency of the conventional ventilator was 31±10 and 35±14 breaths/min during CMV and 40±18 and 41±15 breaths/min, during the 2 periods of combined HFJV. During CMV, $PaCO_2$ increased from 34±11 on admission to 57±14 mmHg, $p<0.05$ at "high-PEEP" (Fig. 1) while conventional tidal volume (12.4±3.2 vs 10.9±1.8 ml/kg, $p>0.05$) and respiratory rate (32±11 vs 35±15 breaths/min, $p>0.05$) were unchanged.

With combined HFJV, $PaCO_2$ decreased to 44±6 mmHg, $p<0.05$ while conventional tidal volume was reduced from 10.9±1.8 to 4.4±2.7 ml/kg, $p<0.05$ and an estimated mean pulse of 1.8 ml/kg was delivered by HFJV. This corresponded to an increase in minute ventilation from 6.8±2.2 to 10.1±2.6 l/min, $p<0.05$.

When CMV was resumed in the 4 survivors, $PaCO_2$ slightly decreased from 60±23 to 56±18 mmHg, $p>0.05$, while conventional tidal volume was increased from 4.0±0.4 to 9±1 ml/kg, $p<0.05$, conventional ventilatory rate was unchanged and minute ventilation decreased from 8.3±2.3 to 6.7±2.1 l/min, $p>0.05$.

Airway pressures. Mean airway pressure increased as pulmonary gas exchange deteriorated on CMV from 16.4±6.6 on admission to 25.3±3.5 cmH_2O, $p<0.05$ while PEEP was increased from 7.9±4.8 to 14.7±1.5 cmH_2O, $p<0.05$ and peak inspiratory pressure passed from 41.7±9.7 to 46.7±8 cmH_2O, $p>0.05$.

With combined HFJV, PEEP was reduced from 14.7±1.5 to 5.8±4.5 cmH_2O, $p<0.05$. Proximal mean airway pressure decreased from 25.3±3.5 to 14.8±3.2 cmH_2O, $p<0.05$ and peak inspiratory pressure from 46.7±8 to 35.1±5.6 cmH_2O, $p<0.05$.

One patient (L.L.) intubated with a 6.0 Hi-Lo jet (Mallincrodt) endotracheal tube had airway pressures measured simultaneously proximally (Siemens 900C) and distally (through the Hi Lo jet line). During the whole course of combined HFJV, mean proximal airway pressure readings were always 2–3 cmH_2O higher than were distal readings.

In the 4 survivors, CMV could be resumed at lower PEEP (9±3.4 vs 14.7±1.5, $p<0.05$), mean (16.9±2.4 cm H_2O vs 25.9±4, $p<0.05$) and peak airway pressure (37.1 vs 46.5±9.7 cmH_2O, $p<0.05$) compared to values before combined HFJV was started, but at higher peak and PEEP compared to the late combined HFJV.

Hemodynamics (Fig. 2). From admission to "high PEEP", central venous pressure increased slightly from 6±4 to 10±6 mmHg, $p<0.05$, whereas heart rate, mean arterial pressure and diuresis did not change significantly.

With combined HFJV heart rate decreased from 164±14 to 150±14 beats/min, $p<0.05$ while CVP (10±6 vs 11±5 mmHg, $p>0.05$), MAP (68±12 vs 64±11 mmHg, $p>0.05$) and diuresis (2.8±1.5 vs 1.7±1.6 ml/kg/min, $p>0.05$) showed no significant difference. During the same periods, one patient (R.R.) monitored with a thermodilution Swan-Ganz catheter had a cardiac index of 2.75 and 2.85 $l/min/m^2$ associated with a small decrease in pulmonary (5.1–4.2 $mmHg/l/min/m^2$) and systemic vascular resistance (18.9–15.4 $mmHg/l/min/m^2$).

When CMV was resumed in 4 survivors, mean arterial pressure (74±7 vs 79±6 mmHg, $p>0.05$) and heart rate (155±22 vs 153±23 beats/min) did not change. Central venous pressure decreased from 12±1 to 8±1 mmHg, $p<0.05$ and diuresis increased from 1.9±0.8 to 3.8±1.75 ml/kg/h, $p<0.05$.

Planimetric measurements of thoracic X-rays. Mean total cardiopulmonary area determined on comparative chest X-rays obtained at end-inspiration increased 1% (range −6 to +6%) from conventional to combined HFJV. This was not statistically significant.

Discussion

This report suggests a place for combined HFJV and low PEEP levels to ventilate children with ARDS and severe

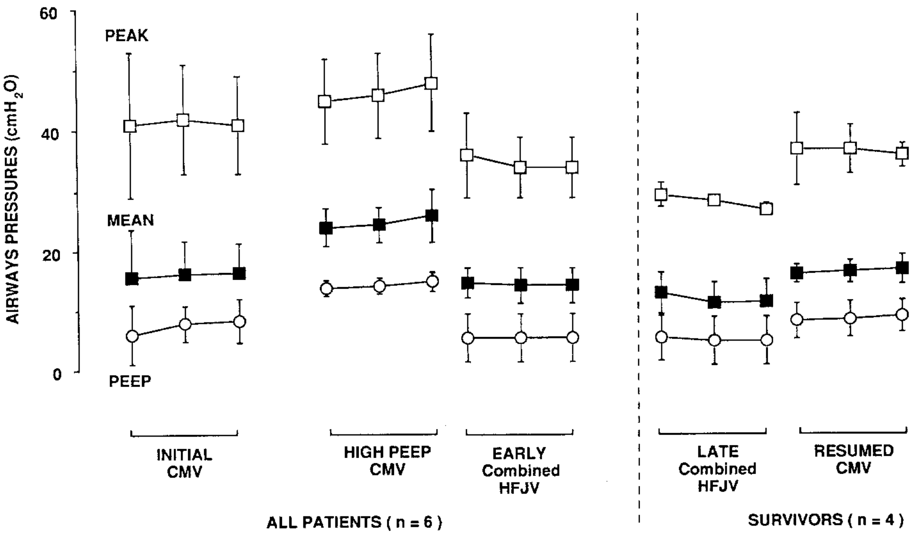

Fig. 2. Airway pressures (peak □, mean ■ and PEEP ○) indicated by the 3 separate measurements made during each of the 5 successive 6-h periods of the study. Statistically significant differences are indicated in Table 2

hypoxemia as an alternative to the use of very high levels of PEEP and conventional ventilation. It is in agreement with the results reported recently by Borg [10] in adults.

In 6 children with marked hypoxemia persisting at a mean PEEP level of 15 cmH_2O, combined HFJV resulted in a rapid increase in PaO_2. This immediate effect was followed by a more sustained improvement in pulmonary function as documented by the lower airway pressure and FiO_2 required to resume conventional ventilation in 4 survivors a mean of 3 days later.

In ARDS, PaO_2 largely depends on alveolar recruitment and lung volume which can probably be restored similarly by combined high-frequency jet, oscillatory or conventional ventilation [18, 19]. Thus, oxygenation might have been improved by setting a much higher PEEP level. However, using PEEP above 15 cmH_2O, has been associated, in children, with a questionable increase in oxygen delivery [4], a high incidence of barotrauma [5] and often persisting poor outcome [11] motivating the search for alternative therapies.

In our patients, combined HFJV allowed to decrease "external" PEEP and conventional tidal volume to about half their value during CMV. However, assessment of alveolar pressure to determine the degree of "intrinsic" PEEP possibly created by HFJV was not feasible because of the location of the jet canula inside the conventional endotracheal tube [20]. Thus, we can only speculate that, in this acute stage, better oxygenation was obtained at similar or lower airway pressures. We cannot exclude that higher alveolar pressures were responsible for this improvement; this seems less likely considering first the decrease in proximal airway pressure, second the absence of change in CVP and third, the similarity of planimetric estimations of lung volume on chest X-ray.

Decreased airway pressures during HFJV have been reported from several animal models mainly for peak airway pressure [21, 22] and during combined HFJV in adults for mean airway pressure [10]. Starting combined HFJV did not induce clinically relevant cardiovascular depression as judged by the absence of changes in central venous and mean arterial pressures nor decrease in urine output compared to conventional ventilation.

However, after lung function had improved, switching back from combined HFJV to conventional ventilation in 4 survivors resulted in a decrease in central venous pressure and an increase in urine output. Thus, the effects of combined HFJV on cardiovascular function probably depend on the actual severity of lung consolidation and compliance.

In adults, HFJV is proposed to treat bronchopleural fistula [23, 24]. In our group, 3 children developed air leaks during conventional ventilation before the transition to combined HFJV while no barotrauma was observed to progress or develop during combined HFJV.

Combined HFJV allowed to control CO_2 elimination. The individual contribution of conventional and jet tidal volumes to CO_2 elimination is difficult to assess. Carbon dioxide elimination during HFJV alone is directly related to the tidal volume over a wide range of frequencies [25] and is limited by the increasing level of intrinsic PEEP produced by HFJV which, in turn, depends on the time left for passive expiration to be complete [26]. Intrinsic PEEP on the other hand is probably one of the essential mechanisms by which HFJV improves oxygenation [18, 19, 27]. In our study, the additional small conventional breaths probably facilitated CO_2 elimination. CO_2 retention consistently occurred when conventional ventilation was reduced below one third of the total minute ventilation.

In addition to the beneficial effect of periodic lung inflation to prevent alveolar collapse [28], there are practical reasons to favour combined HFJV over HFJV alone in children. With the combined mode, HFJV can be introduced gradually on CMV while decreasing PEEP simultaneously to avoid excessive peak airway pressures. This brings up a smooth and progressive transition phase, easily monitored by using a pulse oximeter. Switching back to the prior settings of CMV is realized without difficulty. Also, combined HFJV allows the use of the alarm and security system of the conventional ventilator for both volumes and pressures. To minimize the risk of tracheal injury [29], humidification can be ensured partly by the conventional ventilator system. The danger of direct mucosal injury by the jet stream can be decreased possibly by placing the jet above the end of the endotracheal tube. We did not observe tracheal lesions in the 4 of the 6 children where this was examined: 2 children who had tracheoscopy after resolution of their disease, and, at autopsy, in the 2 children who died after 4 and 12 days respectively of combined HFJV.

We used this combined mode of ventilation as a temporary rescue measure. A trial back to conventional ventilation was attempted as soon as a sustained improvement in gas exchange was observed together with an important reduction in ventilatory pressures. The 2 children who eventually died maintained acceptable gas exchange for 4 and 12 days on combined HFJV but developed multiple organ system failure.

In conclusion, the results presented here suggest that combined HFJV is a valuable "rescue" mode of ventilation which can improve pulmonary gas exchange in children with catastrophic pulmonary failure. This ventilatory mode could be an interesting alternative to the use of high PEEP levels in children with severe hypoxemia and might decrease the risk of complications such as cardiovascular compromise and barotrauma.

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