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PARTIAL LIQUID VENTILATION: FIRST EXPERIENCE IN CHILDREN WITH ACUTE RESPIRATORY DISTRESS SYNDROME

FEDORA M., NEKVASIL R., ŠEDA M., KLIMOVIČ M., DOMINIK P.

Department of Anesthesiology and Critical Care and ECMO Centre,Mendel Memorial Children's Hospital, Faculty of Medicine, Masaryk University Brno

A b s t r a t

The aim of this prospective, observational study was to verify the possibility of solving potentially reversible respiratory failure in patients in whom extracorporeal life support was contraindicated and extracorporeal membrane oxygenation could not be used, or in patients who had not met the criteria for extracorporeal membrane oxygenation. Partial liquid ventilation was used, in seven applications, in a total of six children with severe hypoxaemic respiratory failure. Preoxygenated perfluorocarbon, Rimar RM 101 (Miteni, Milan, Italy), warmed to 37°C was applied intratracheally at a dose which corresponded to the functional residual capacity of the lungs; this dose of perfluorocarbon was repeatedly administered every hour. The following parameters were recorded before, during and after partial liquid ventilation: pH, blood gases, ventilator setting, alveoloarterial difference for oxygen, dynamic compliance, and indices: oxygenation index and hypoxemia score. The values were compared 1 hour before partial liquid ventilation with the values during partial liquid ventilation; the data before partial liquid ventilation and in the 3rd hour of partial liquid ventilation were evaluated statistically. A statistically significant increase in pH value and hypoxaemia score, and a decrease in fraction of inspired oxygen and oxygenation index occurring during 3 hours of partial liquid ventilation were recorded. Partial liquid ventilation is an effective method for controlling acute respiratory distress syndrome in certain groups of patients with severe lung disease.

K e y w o r d s

respiratory failure, acute respiratory distress syndrome, children, partial liquid ventilation

INTRODUCTION

In spite of the progress in understanding its aetiology and pathophysiology, acute respiratory failure has been a frequent cause of death in pre-term newborns, in children as well as adults. When respiratory failure in pre-term newborns is caused by insufficient surfactant, the disease is called "hyaline membrane disease" or Respiratory Distress Syndrome (RDS); it is a restrictive lung disease. In extremely immature newborns, surfactant deficiency is complicated by insufficient development of alveoli. All these changes lead to decreased lung compliance and poor ventilation-perfusion mismatch with resulting hypoxemia, hypercapnia and increased respiratory effort.

Therapy is effective, not perfect. In the second half of the 1990s, the standard survival of children weighing over 1250g at birth was 93%; nevertheless, the incidence of chronic pulmonary disease in this group of children was 45%.

Although in children and adults the causes of respiratory failure are much more various, these patients commonly show decreased compliance and disturbed ventilation perfusion. The mortality rate ranges between 40 and 70% and the therapy is only symptomatic, as that in pre-term newborns *(11)*.

Most efforts at improving the therapy of respiratory failure have been concentrated on the modernising and improvement of conventional mechanical ventilation. Nowadays, we are probably in the period when detailed knowledge and an understanding of the physiology and pathophysiology of pulmonary functions facilitate the development of new technologies that can help to decrease morbidity and mortality in patients with respiratory failure. One of the unconventional methods, liquid ventilation, was termed a comedy of four acts with a happy end, characterised as follows: terrestrial mammals breathing air, sea mammals breathing liquid, terrestrial mammals breathing liquid and, finally, terrestrial mammals breathing air again. However, at present, the fifth act of the drama begins: human newborns with immature and damaged lungs breathing liquid *(12)* and surviving their respiratory failure.

MATERIALS AND METHODS

During November 1994 to March 1997, partial liquid ventilation (PLV) was used on seven occasions in six children with severe hypoxaemic respiratory failure. Relevant information on the patients are presented in *Table 1*. All the patients were sedated with a combination of benzodiazepine and opiate and, if needed, they were paralysed. Before PLV, pressure controlled ventilation had been used (Siemens Servo 900 C or Siemens Servo 300) or they had been connected to a high-frequency oscillator (SensorMedics 3100A). Ventilation support before, during and after PLV is also shown in *Table 1*.

PLV was used in patients with potentially reversible respiratory failure, in whom extracorporeal life support (ECLS) was contraindicated and extracorporeal membrane oxygenation (ECMO) could not be used, or patients who did not meet the criteria for ECMO. Parents' consent with the use of PLV was obtained in all the patients. The values of selected parameters obtained before PLV are presented in *Table 2*.

Preoxygenated perfluorocarbon, Rimar RM 101 (Miteni, Milan, Italy) warmed to 37°C was administered intratracheally at a dose of about 30 ml/kg, which corresponds to the functional residual capacity (FRC) of the lungs (total dose of perfluorocarbon and its dose per kg body weight are shown in *Table 3*). After filling FRC, pressure-controlled ventilation was applied (Siemens Servo 900 C or Servo 300) or the pressure regulated volume control (PRVC, Siemens Servo 300) regimen was used. This dose of perfluorocarbon was repeated every hour according to the gradual evaporation of perfluorocarbon, which could be seen from the position of the meniscus in the endotracheal tube after short disconnection from the ventilator or according to a "notch" seen on the pressure-volume curve during the monitoring of pulmonary functions (Bicore, Irvine, CA). During PLV, there were no differences in therapy and care of the patients in the periods before and after PLV (sedation, paralysis, etc.); however, during PLV, the patients were without suctioning from the airways.

The following parameters were recorded before, during and after PLV: pH, blood gases, adjustment of a ventilator (fraction of inspired oxygen, FIO_2; peak inspiratory pressure, PIP; mean airway pressure,

Table 1
Demographic data, ventilation before, during and after partial liquid ventilation

Patient	Age (months)	Weight (kg)	Sex	Diagnosis	PRISM	Ventilation before	during PLV	after
1	228	50	M	CF, liver cirrhosis, portal hypertension	13	PCV	PCV	PCV
2	7.5	10	M	Leigh sy, MODS	5	PCV	PCV	PCV
3	72	20	M	Drowning	45	PCV	PCV	PCV
4	6	5.8	F	Pneumonia, ARDS	17	PCV	PCV	PCV
5	1	5	M	Pneumonia, ARDS, st.p. v-a ECMO	13	HFO	PCV	PCV
6	3	4	M	Edwards sy, pneumonia	19	HFO	PRVC	PRVC

PRISM, paediatric risk of mortality score; PLV, partial liquid ventilation; M, male; F, female; CF, cystic fibrosis; PCV, pressure control ventilation; PRVC, pressure regulated volume controlled; HFO, high frequency oscillation; MODS, multiple organ dysfunction syndrome; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation.

Table 2
Selected parameters before partial liquid ventilation

Patient	PaO_2 (kPa)	$PaCO_2$ (kPa)	FiO_2 –	PaO_2/FIO_2 (torr)	$AaDO_2$ (kPa)	Cdyn (ml/cmH_2O/kg)
1	9.3	7.8	0.50	139	27.8	0.56
2	6.2	6.5	0.60	78	42.5	0.26
3	10.7	11.1	1.00	80	70.2	0.33
4	5.2	8.6	1.00	39	78.8	0.45
5	4.5	34.9	0.90	37	37.2	0.38
6	9.8	12.0	1.00	73	70.1	0.23
7	6.5	5.8	0.80	61	62.0	0.66

PaO_2, $PaCO_2$, partial tension of arterial blood gases; FIO_2, fraction of inspired oxygen; $AaDO_2$, alveoloarterial difference for oxygen; Cdyn, dynamic compliance

Table 3
Ventilator setting before partial liquid ventilation and perfluorocarbon administration

Patient	RR (breaths/min)	FIO_2	PIP (cmH_2O)	Paw (cmH_2O)	PEEP (cmH_2O)	Vt (ml/kg)	MV (L/min)	Dose of RM 101 /kg weight	total
1	15	0.50	22	12	6	9.0	6.75	18	900
2	30	0.60	40	17	8	6.1	1.83	20	200
3	30	1.00	20	12	8	6.3	1.89	20	200
4	20	1.00	30	13	8	10.0	4.00	22	450
5	25	0.90	28	18	10	6.8	1.02	22	130
6	18	1.00	28	12	6	5.2	0.76	30	150
7	30	0.80	25	15	10	10.0	1.20	30	120

RR, respiratory rate; FIO_2, fraction of inspired oxygen; PIP, peak inspiratory pressure; Paw, mean airway pressure; PEEP, positive end expiratory pressure; Vt, tidal volume; MV, minute ventilation; RM 101, perfluorocarbon

Table 4
Mean values of parameters before and after partial liquid ventilation

Parameter	Before PLV	After PLV	Significance
pH - 7.22 0.21	7.34 0.15	< 0.05	
PaO_2 kPa7.48 2.10	8.55 1.78	n.s.	
$PaCO_2$ kPa12.42 6.42	8.58 2.85	n.s.	
FIO_2 - 0.82 0.16	0.64 0.1	< 0.05	
PIP cmH_2O27.57 4.48	24.04 3.94	n.s.	
Paw cmH_2O14.14 2.16	13.76 1.91	n.s.	
PEEP cmH_2O8.00 1.14	8.00 1.14	n.s.	
$AaDO_2$ kPa	55.57 16.85	44.22 14.47	n.s.
OI -23.76 9.62	17.05 8.10	< 0.05	
PaO_2/FIO_2 torr	72.95 22.92	100.80 29.77	< 0.01
Cdyn ml/cmH_2O/kg	0.41 0.12	0.46 0.15	n.s.

PaO_2, $PaCO_2$, partial tension of arterial blood gases; FIO_2, fraction of inspired oxygen; PIP, peak inspiratory pressure; Paw, mean airway pressure; PEEP, positive end expiratory pressure; $AaDO_2$, alveoloarterial difference for oxygen; OI, oxygenation index; Cdyn, dynamic compliance; PLV, partial liquid ventilation; n.s., non-significant

Paw; positive end expiratory pressure, PEEP), alveoloarterial difference for oxygen ($AaDO_2$), dynamic compliance (Cdyn) and the indices: oxygenation index (OI) and hypoxemia score (PaO_2/FIO_2). The values 1 hour before PLV, were compared, with the values during PLV; the data before PLV and in the 3rd hour of PLV were statistically evaluated. PLV had to be repeated in one patient.

The results were evaluated by Student's *t*-test, with statistical significance of $P<0.05$.

RESULTS

The results are summarised in *Table 4* in which there are the mean values of parameters (SD) in all the patients obtained closely before PLV and in the 3rd hour of PLV. An improvement in pH value (7.22 *vs* 7.34, $P<0.05$) and decreased FIO_2 (82% *vs* 64%, $P<0.05$) are statistically significant. The decrease in the oxygenation index (23 *vs* 17, $P<0.05$) and particularly the increase in PaO_2/FIO_2 (72 *vs* 100 torr, $P<0.01$) are important and statistically significant. Changes in the other parameters are not statistically significant.

DISCUSSION

The question is raised as to why it is more beneficial to the patient to use a liquid instead of a gas that fills lungs during RDS. It is generally known that, during RDS, fluid, often large quantity of it, fills better perfused (and, therefore, poorly ventilated) parts of the lungs, which results in a ventilation/perfusion mismatch. This fluid shows a high superficial tension, is full of proteins which make a foam of it, acts as an ideal solvent for surfactant and is probably a perfect medium for free radicals of all types. Moreover, in pre-term neonates with immature lungs or in infants with congenital diaphragmatic hernia, collapsed alveoli are present which are often refractory to PEEP. A prone position, suctioning, prolongation of inspiratory time, an increase in FIO_2, cardiac output or haematocrite, all these methods can be helpful, but the alveoli still retain the unwanted fluid whose effective elimination is difficult; it cannot be aspirated, its rapid restoration cannot be protected, cumulation of intraparenchymal fluid cannot be prevented, and we can do nothing about a micro-obstructive protein and mucopolysaccharide debris that are continuously formed and fill up the alveoli in spite of our effort to fill them with gas during conventional mechanical ventilation. However, if a fluid with density higher than water is available and if this fluid does not form foam, then it may mean an effective tool against RDS. If perfluorocarbon is instilled intratracheally, it then substitutes exudate in the alveoli very quickly and acts as a local PEEP. It transports well both oxygen and carbon dioxide, moreover, it stops the increase of free radicals *(2, 6)*. Perfluorocarbon seems to decrease the release of lysosomal enzymes, to decrease the adherence of granulocytes to endothelial cells, to decrease phagocytosis and chemotaxis and to decrease the formation of superoxid dismutase *(3)*.

It can be concluded that, at RDS *(2,1),* perfluorocarbon (i) re-expands alveoli, (ii) removes exudate from alveoli, (iii) decreases superficial tension within an alveolus,

(iv) improves gas exchange, (v) facilitates more or less continual bronchoalveolar lavage, (vi) enables gas exchange selectively in more consolidated lung areas, (vii) creates alveolar tamponade which prevents alveolar capillary leak, (viii) keeps the alveoli opened and prevents their collapse, (ix) prevents microbial growth and (x) stops an inflammatory response of the lung cells.

Clinical application. The first liquid ventilation in humans was used in 1990; three immature newborns (gestation age 28, 24 and 23 weeks) received an intratracheal dose of Rimar 101 (30 ml/kg) and each patient underwent 2 three-five-minute TLV cycles. A marked improvement in compliance occurred in all three newborns and oxygenation was improved in two of them *(5)*.

At present, PLV has been used in several centres in the U.S.A. It has been reported that the second and third phases of a clinical trial on partial liquid ventilation are under progress; their results are interesting and highly promising.

Perfluorocarbon (PFC) was administered to 10 adult patients, age 19 to 55 years, treated for ARDS by ECLS; their pulmonary shunt dropped from 0.72 to 0.46 and static compliance increased from 0.16 to 0.27 ml/cmH_2O/kg during 72 hours after the application. Five patients have survived *(7)*.

Similarly, six paediatric patients, aged 8 weeks to 5.5 years, were given PFC for 3 to 7 days after their connection to ECLS due to severe respiratory failure. Arterial tension of oxygen (PaO_2) increased from 5.2 to 12.2 kPa during 96 hours after starting PLV, $AaDO_2$ decreased from 84.7 to 66.5 kPa, while static compliance increased from 0.12 to 0.28 ml/cmH_2O/kg. All the patients survived *(4)*.

In a study from Ann Arbor which included adults, children and full-term newborns on ECLS, out of 19 patients, 14 were disconnected uneventfully from the circuit, 11 survived, the mean $AaDO_2$ dropped from 78.5 to 62.7 kPa and static compliance increased from 0.18 to 0.29 ml/cmH_2O/kg *(8)*.

The last study published on this topic has reported a group of 10 immature newborns, gestation age 24 to 34 weeks, birth weight 600 to 2000 g, with severe RDS who were treated conventionally for more than 5 days (high frequency oscillation, surfactant) and in whom ECMO was contraindicated because of their gestation age and body weight. PLV was used for 24 to 72 h. Within one hour of PFC instillation, there was an increase in PaO_2 by 138% (from 60 to 143 mmHg) and in dynamic compliance by more than 60% (from 0.18 to 0.29 ml/cmH_2O/kg). The mean airway pressure dropped by 29% during 24 hours, although tidal volume increased from 5.0 to 7.8 ml/kg. The oxygenation index decreased from 49 to 17 during one hour of PLV and its further reduction to a value of 9 occurred during 24 hours; in that period the mean FIO_2 [24] of 0.6 could be used *(9)*.

After 3 hours of PLV, our patients showed the restoration of acid-base balance, an increase in PaO_2 and a decrease in arterial tension of carbon dioxide ($PaCO_2$). The changes in blood gases were statistically insignificant; however, the decrease

in FIO_2 and the resulting increase in hypoxaemia score (PaO_2/FIO_2) indicating severe pulmonary affection were significant. The drop in PIP (after filling FRC with the liquid) was surprising, other airway pressures remained at the same level before as well as during PLV. The changes in $AaDO_2$ and dynamic compliance were not statistically significant, which is rather surprising. This may be due to the fact that the sample of our patients was not sufficiently large so that the deviations in individual patients could not influence the mean results.

Other possibilities. Although the use of perfluorocarbons to influence the course of pulmonary disease may seem to be a top therapeutic approach, the opposite is true, because endogenous production of surfactants increases during PLV both in healthy and surfactant-deficient lungs *(13).* A question remains whether surfactant application by means of PFC only can be a suitable method *(10).* Techniques of administrating vasoactive drugs dissolved in PFC (tolazoline) have been described; they have a directed action and, therefore, are without undesirable systemic effects *(14).* Similarly, it has been found that antibiotics locally applied during PLV appear in serum at the same levels as when administrated intravenously, but they are present at much higher levels in the lung tissue *(15).*

The inertness and insolubility of PFC in other fluids have already been mentioned. Nitric oxide, on the other hand, is soluble. Furthermore, as much as 15% of oxygen consumption can be secured by intraperitoneal application of preoxygenated PFC: a 3% “fluorocrite“ emulsion can supply as much as 50% oxygen delivery *(6)*.

Another possibility is a model of congenital diaphragmatic hernia where PFC was applied selectively to the hypoplastic lungs. Conspicuously faster maturation and growth of the lung tissue occurred and exchange of blood gases remained almost unaffected.

Recently, PLV has started to be used in intensive care practice, first by neonatologists and later also by paediatricians and clinicians in adult intensive care. PLV can assist in controlling respiratory failure in a certain group of patients with severe lung disease. The issues still to be resolved are: indications for PLV, the duration of PLV, some technical details and also the principal problem of an optimal dose of perfluorocarbons. We believe that, after these issues have been resolved, the method of PLV support will have a very promising future.

Fedora M., Nekvasil R., Šeda M., Klimovič M., Dominik P.

ČÁSTEČNÁ KAPALINOVÁ VENTILACE – PRVNÍ ZKUŠENOSTI U DĚTÍ SE SYNDROMEM AKUTNÍ DECHOVÉ TÍSNĚ

S o u h r n

Cílem prospektivní observační studie bylo ověřit možnost řešení potencionálně reversibilního respiračního selhání u pacientů, u kterých byla kontraindikována mimotělní podpora životních funkcí a kde nebylo možné použít extrakorporální membránovou oxygenaci nebo pacient nesplňoval kriteria pro extrakorporální membránovou oxygenaci. PLV jsme použili u celkem v 7 aplikacích 6 pacientů se závažným hypoxemickým respiračním selháním. Preoxygenovaný perfluorokarbon Rimar RM 101 (Miteni, Milano, Itálie) ohřátý na 37°C jsme aplikovali intratracheálně v dávce odpovídající funkční residuální kapacitě plic, dávku perfluorokarbonu jsme opakovali po hodině. Před, v průběhu a po částečné kapalinové ventilaci byly sledovány: pH, krevní plyny, nastavení ventilátoru, alveoloarteriální diference kyslíku, dynamická poddajnost a indexy – oxygenační index a hypoxemia skore. Hodnoty 1 hodinu před a ve 3. hodině částečné kapalinové ventilace byly statisticky srovnány. Během 3 hodin částečné kapalinové ventilace jsme zaznamenali statisticky významný vzestup pH a hypoxemia skore a pokles frakce vdechovaného kyslíku a oxygenačního indexu. Částečná kapalinová ventilace je účinnou metodou léčby syndromu akutní dechové tísně určité skupiny pacientů se závažným plicním postižením.

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