PARTIAL LIQUID VENTILATION IN THE THERAPY OF PEDIATRIC ACUTE RESPIRATORY DISTRESS SYNDROME

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ČÁSTEČNÁ KAPALINOVÁ VENTILACE V LÉČBĚ PEDIATRICKÉHO ACUTE RESPIRATORY DISTRESS SYNDROME

Abstract

Fedora M, Nekvasil R, Seda M, Klimovic M, Dominik P: Partial liquid ventilation in the therapy of pediatric acute respiratory distress syndrome
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Background: **Acute respiratory failure represents life-threatening disease with persistently marked mortality and late morbidity in pre-term newborns (RDS — respiratory distress syndrome), children as well as, adults (ARDS — acute respiratory distress syndrome). We are probably in the period when better understanding of pulmonary pathophysiology enables the development of new technologies that can help in decreasing the morbidity and mortality of patients with respiratory failure. One of these unconvetional methods is partial liquid ventilation (PLV).**
Main purpose: **The main aim of the study was to verify the possibility of treating potentially reversible respiratory failure in patients where extracorporeal life support (ECLS) was contraindicated and extracorporeal membrane oxygenation (ECMO) could not be used, or the patient had not met the criteria for ECMO.**
Methods: **PLV was used in 6 children totally, in 7 applications with severe hypoxemic respiratory failure. Preoxygenated perfluorocarbon Rimar 101 (Miteni, Milan, Italy) warmed to 37 °C was applied intratracheally in the dosis which corresponds with the functional residual capacity of lungs, the dose of perfluorocarbon was repeated every hour. Following parameters were recorded before, during and after PLV: pH, blood gases, ventilator setting, alveoloarterial difference for oxygen, dynamic compliance, and indices — oxygenation index and hypoxemia score (PaO_2/FiO_2). The values obtained 1 hour before PLV were compared with the values during PLV; the data before PLV and in the 3rd hour of PLV were evaluated statistically.**
Results: Statistically significant increase of pH (7.22 vs 7.34, $p<0.05$) and PaO_2/FiO_2 (72 vs 100 Torr, $p<0.01$) and decrease

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Abstrakt

Fedora M., Nekvasil R., Šeda M., Klimovič M., Dominik P.: Částečná kapalinová ventilace v léčbě pediatrického acute respiratory distress syndrome
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Pozadí problému: Akutní respirační selhání je život ohrožující onemocnění se stále značnou mortalitou a pozdní morbiditou u nezralých novorozenců (RDS — respiratory distress syndrome), dětí i dospělých (ARDS — acute respiratory distress syndrome). Jsme pravděpodobně v období, kdy lepší pochopení plicní patofysiologie umožní vývoj nových postupů, které mohou snížit morbiditu a mortalitu pacientů s respiračním selháním. Jednou z těchto nekonvenčních metod je částečná kapalinová ventilace (PLV).
Cíl práce: Cílem práce 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 (ECMO), nebo pacient nesplňoval ECMO kriteria.
Metody: PLV jsme použili u celkem v 7 aplikacích u 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 kapacitě plic, dávku perfluorokarbonu jsme opakovali po hodině. Před, v průběhu a po PLV byly sledovány: pH, krevní plyny, nastavení ventilátoru, alveoloarteriální diference kyslíku, dynamická poddajnost a indexy — oxygenační index a hypoxemia skore (PaO_2/FiO_2). Hodnoty 1 hodinu před a ve 3. hodině PLV byly statisticky srovnány. *Výsledky:* Během 3 hodin PLV jsme zaznamenali statisticky významný vzestup pH (7,22 vs 7,34, $p<0,05$) a PaO_2/FiO_2 (72 vs 100 Torr, $p<0,01$) a pokles FiO_2 (82 % vs 64 %, $p<0,05$) a oxygenačního indexu (23 vs 17, $p<0,05$).
Závěr: Částečná kapalinová ventilace je účinnou metodou léčby ARDS určité skupiny pacientů se závažným plicním postižením. *(Tab. 4, lit. 15.)*

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of FiO_2 (82 % vs 64 %, p<0.05) and oxygenation index (23 vs 17, p<0.05) occurred during 3 hours of PLV.
Conclusion: **Partial liquid ventilation is an effective method for controlling ARDS in certain groups of patients with severe lung disease.** ***(Tab. 4, Ref. 15.)***
Key words: respiratory failure, respiratory distress syndrome, acute respiratory distress syndrome, children, partial liquid ventilation.

Klíčová slova: respirační selhání, respiratory distress syndrome, acute respiratory distress syndrome, děti, částečná kapalinová ventilace.

Introduction

In spite of the progress in understanding its etiology and pathophysiology, acute respiratory failure has been a frequent cause of death in pre-term newborns, children as well as adults. Respiratory failure in pre-term newborns is caused by insufficient surfactant, the disease is called "hyaline membrane disease" or RDS — Respiratory Distress Syndrome, and it is a restrictive lung disease. In extremely immature newborns, the 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 latter half of the 90ies, the standard survival of bigger children (over 1250 g birth weight) is 93 %; nevertheless, the incidence of chronic pulmonary disease in this group of children is 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 of improving the therapy of respiratory failure have been concerned on the modernising and improvement of conventional mechanical ventilation. Nowadays, we are probably in the period when detailed knowledge and understanding physiology and pathophysiology of pulmonary functions enable the development of new technologies that can help in decreasing the morbidity and mortality of patients with respiratory failure. One of unconventional methods — liquid ventilation — was termed a comedy of four acts with a happy end — 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.

Subjects and methods

Within November 1994—March 1997, PLV was used in 6 children totally in 7 applications with severe hypoxemic respiratory failure. Demographic data of patients are given 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 high-frequency oscillation (SensorMedics 3100A). Ventilation support before, during and after PLV is shown in Table 1. The indication for PLV was the effort of solving potentially reversible respiratory failure in patients where extracorporeal life support (ECLS) was contraindicated and extracorporeal membrane oxygenation (ECMO) could not be used, or a patients had not met the criteria for ECMO. Parent's consent with PLV was obtained in all the patients. Selected parameters before PLV are presented in Table 2.

Preoxygenateed perfluorocarbon Rimar RM 101 (Miteni, Milan, Italy) warmed to 37 ˚C was applied intratracheally in the dosis of about 30 ml/kg, which correspondes with the functional residual capacity (FRC) of the lungs (the total dosis of perfluoro-

Tab. 1. Demography of patients, ventilation before, during and after PLV.
Tab. 1. Demografie pacientů, ventilace před, během a po PLV.

Pt Pac	Age Věk months měsíce	Weight Váha kg	Sex Po- hlaví	Diagnosis Diagnóza	PRISM	Ventilation PLV Ventilace PLV before před	 during během	 after po
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 tonutí	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	PRCV	PRCV

Abbreviations/zkratky: PRISM – pediatric risk of mortality score, PLV – partial liquid ventilation, M – male, F – female, CF – cystic fibrosis/cystická fibróza, PCV – pressure control ventilation, PRVC – pressure regulated volume controlled, HFO – high frequency oscillation, MODS – multiple organ dysfunction syndrome, ECMO – extracorporeal membrane oxygenation.

Tab. 2. Selected parameters before PLV.
Tab. 2. Vybrané parametry před PLV.

Pt Pac	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

Abbreviations: 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.
Zkratky: PaO_2, $PaCO_2$ – parciální tlak arteriálních krevních plynů, FiO_2 – frakce inspirovaného kyslíku, $AaDO_2$ – alveoloarteriální diference kyslíku, Cdyn – dynamická compliance.

carbon and the dosis per kg are shown in Table 3). After filling FRC, pressure-controlled ventilation was applied (Siemens Servo 900 C or Servo 300) or Pressure Regulated Volume Conrtol (PRVC, Siemens Servo 300) regimen was used. The dosis of perfluorocarbon was repeated every hour, according to gradual evaporation of perfluorocarbon which could be seen according to the meniscus observable in the endotracheal tube after short disconnection from a ventilator or according to "notch" seen on the pressure-volume curve during monitoring pulmonary functions (Bicore, Irvine, CA). During PLV, there were not differences in the therapy and care of patients with the periods before and after PLV (sedation, paralysis, etc.), however, the patients were without suctioning from the airways during PLV.

The following parameters were recorded before, during and after PLV: pH, blood gases, adjustment of a ventilator: FiO_2, Peak Inspiratory Pressure — PIP, Mean Airway Pressure — Paw, Positive End Expiratory Pressure — PEEP), alveoloarterial differfence for oxygen ($AaDO_2$), dynamic compliance (Cdyn), and indices — oxygenation index (OI) and hypoxemia score (PaO_2/FiO_2). The values were compared 1 hour before PLV with the values during PLV; the data before PLV and in the 3rd hour of PLV were evaluated statistically. PLV had to be repeated in one patient.

The results were evaluated statistically by Student's t-test with statistical significance $p<0.05$.

Results

The total results are presented in Table 4 — there are given mean values of parameters (with standard deviation) of all the patients closely before PLV and in the 3rd hour of PLV. The improvement of pH (7.22 vs 7.34, $p<0.05$), decreased FiO_2 that had to be applied (82 % vs 64 %, $p<0.05$) are statistically significant. The decrease of oxygenation index (23 vs 17, $p<0.05$) and particularly the increase of PaO_2/FiO_2 (72 vs 100 Torr, $p<0.01$) are important and statistically significant. The changes of other parameters are not statistically significant.

Discussion

The question is why, in fact, advantagenous to use a liquid instead of a gas that fills lungs during RDS. It is generally well-known that during RDS a fluid, often a large quantity of fluid, fills in better perfused (and, of course, worse ventilated) parts of the lungs, it resuls in the V/Q mismatch. This fluid has 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 those with congenital diaphragmatic hernia, there are present collapsed alveoli, often refractory to PEEP. Prone position, suctioning,prolongation of inspiratory time, increase of FiO_2, of cardiac output and hematocrite — all these methods can be helpful, nevertheless, the alveoli contain an unwanted fluid that cannot be eliminated effectively — it cannot be aspirated, its rapid restoration cannot be protected, the cumulation of intraparenchymal fluid cannot be prevented, and we can make

Tab. 3. Ventilator setting before PLV and the dose of perfluorocarbon.
Tab. 3. Nastavení ventilátoru před PLV a dávka perfluorocarbonu.

Pt Pac	RR (breaths /min)	FiO_2	PIP (cmH_2O)	Paw (cmH_2O)	PEEP (cmH_2O)	Vt (ml/kg)	MV (L/min)	Dosis of RM /kg weight	101 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

Abbreviations: 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
Zkratky: RR – počet dechů, FiO_2 – frakce inspirovaného kyslíku, PIP – vrcholový tlak v dýchacích cestách, Paw – střední tlak v dýchacích cestách, PEEP – positivní tlak na konci výdechu, Vt – dechový obejm, MV – minutová ventilace

Tab. 4. Mean values of studied parameters before and after PLV.
Tab. 4. Průměrné hodnoty sledovaných parametrů před a po PLV.

Parameter Parametr		Before PLV Před PLV	After PLV Po PLV	Significance Významnost
pH		7.22±0.21	7.34±0.15	0.02
PaO_2	kPa	7.48±2.10	8.55±1.78	0.31
$PaCO_2$	kPa	12.42±6.42	8.58±2.85	0.15
FiO_2		0.82±0.16	0.64±0.14	0.05
PIP	cmH_2O	27.57±4.48	24.04±3.94	0.25
Paw	cmH_2O	14.14±2.16	13.76±1.91	0.26
PEEP	cmH_2O	8.00±1.14	8.00±1.14	1.00
$AaDO_2$	kPa	55.57±16.85	44.22±14.47	0.25
OI		23.76±9.62	17.05±8.10	0.02
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	0.35

nothing of microobstructive protein and mucopolysaccharide debris that is continuously formed and fills in the alveoli, although we try to fill in them with a gas during conventional mechanical ventilation. However, if we have a fluid, which is of higher density that water and if this fluid is unable to form foam, then an effective tool against RDS can be considered. If perfluorocarbon is instilled intratracheally, then it substitutes the 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, to decrease the formation of SOD (3).

Generally: Perfluorocarbon at RDS (1, 2):

— re-expands the aleveoli,
— removes exudate from the alveoli,
— decreases superficial tension within an alveolus,
— improves gas exchange,
— performs more or less continual bronchoalveolar lavage,
— enables gas exchange selectively in more consolidated lung areas,
— creates alveolar tamponade which prevents alveolar capillary leak,
— keeps the alveoli opened, prevents their collapse,
— prevent microbial growth,
— stops an inflammatory response of the lung cells.

Clinical application

The first liquid ventilation in humans was applied in 1990 — three immature newborns (gestation age 28, 24 and 23 weeks) were given intratracheal application of Rimar 101 in the dosis 30 ml/kg, each patient underwent 2 three-five-minutes cycles of Total Liquid Ventilation. Conspicious improvement of compliance occurred in all the three newborns, oxygenation was improved in two of them (5).

At present, PLV has been dealt with at several centres in the U.S.A. Nowadays, phase II/III of clinical trial of partial liquid ventilation is being performed, present results are interesting and highly promising.

10 adults patients, age 19—55 years, treated for ARDS by ECLS, were administered PFC — by 72 hours after the application pulmonary shunt dropped from 0.72 to 0.46 and static compliance increased from 0.16 to 0.27 $ml/cmH_2O/kg$. 5 patients have survived (7).

Similarly, 6 pediatric patients, aged 8 weeks—5.5 years, were given PFC for 3—7 days after their connection to ECLS due to severe respiratory failure. 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 have survived (4).

Summarised data about the group from Ann Arbor in adults, children and full-term newborns with 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 published study has given a set of 10 immature newborns, gestation age 24—34 weeks, birth weight 600—2000 g, with severe RDS who were treated conventionally for more than 5 days (HFO, surfactant) in whom ECMO was contraindicated because of their gestation age and body weight. The PLV duration was 24—72 hours in these newborns, during one hour after PFC instillation, there occurred the increase of PaO_2 by 138 % (from 60 to 143 mmHg) and that of dynamic compliancce by more than 60 % (from 0.18 to 0.29 $ml/cmH_2O/kg$), mean airway pressure dropped by 29 % during 24 hours, although tidal volume increased from 5 to 7.8 ml/kg. Oxygenation index decreased from 49 to 17 during one hour of PLV and then to 9 during 24 hours, in that period the mean FiO_2 0.6 could be used (9)!

After 3 hours of PLV, our patients showed the restoration of acid-base balance, increase of PaO_2 and decrease of $PaCO_2$. The changes in blood gases are statistically insignificant, however, the decrease of FiO_2 and resulting increase of hypoxemia score (PaO_2/FiO_2) showing severe pulmonary affection of our patients are significant. The drop of PIP — after filling the FRC with a liquid — was surprising, other airway pressures were on the same level before as well as during PLV. The changes of $AaDO_2$ and Cdyn were not statistically significant, which is rather surprising, however, the set of patients is not sufficiently large so that the deviations in individual patients could not influence the mean results.

Other possibilities

We seem to be on the top of therapeutical possibilities or influencing the course of a pulmonary affection by perfluorocarbons, but the opposite is true — endogenous production of surfactant increases during PLV both in healthy and surfactant-deficient lungs (13), the question remains whether the surfactant application just by means of PFC can be the suitable method (10). There have been described techniques of administrating vasoactive drugs dissolved in PFC (tolazoline) that have directed action and, therefore, are without undesirable systemic effects (14), as well as local applications of antibiotics during PLV where serum levels reach the same values as those at i.v. application, but substantially higher levels in the lung tissue (15).

Inertness and insolubility of PFC in other fluids have been already mentioned, on the other hand, what is soluble is NO! The combination of PLV with NO in solving pulmonary hypertension? Furthermore: as much as 15 % of VO_2 can be secured by intraperitoneal application of preoxygenated PFC and also: 3 % "fluorocrite" emulsion can supply as much as 50 % DO_2 (6).

Or: in a model of congenital diaphragmatic hernia where PFC was applied selectively in the hypoplastic lungs, there occurred conspiciously faster maturation and growth of the lung tissue and nearly unaffected exchange of blood gases.

Summary

PLV has started to get into clinical practice of intensive care — first of neonatologists but now, even pediatrics and adult intensivists. It can represent the control of respiratory failure for a certain group of patients with severe lung disease. The question of these days is the indications of PLV, lenght of PLV, some technical details, but even such important and principal problems as an optimal dose of perfluorocarbons. In spite of some of these still unclear problems, this fascinating ventilation support has been facing its promising future.*

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