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Combination of high frequency oscillatory ventilation and interventional lung assist in severe acute respiratory distress syndrome☆

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Abstract

Background: The combination of high-frequency oscillatory ventilation (HFOV) and extracorporeal carbon dioxide removal with the interventional lung assist (iLA) in severe acute respiratory distress syndrome (ARDS) represents a novel treatment option.

Methods: The study used a retrospective single-center analysis of 21 consecutive adult patients with severe ARDS, ventilated with HFOV/iLA. Efficiency, side effects, and outcome of combined treatment are presented as median (interquartile range).

Measurements and Main Results: The following were used to determine patient characteristics: sequential organ failure assessment score, 14; simplified acute physiology score II, 41; and Murray score, 4. The duration of combined treatment was 6 days. The blood flow through the iLA was 1.9 L/min. The Pa_{O_2}/inspired fraction of oxygen ratio increased from 61 (47-86) to 98 (67-116) within 2 hours and to 106 (70-135) mm Hg at 24 hours. Pa_{CO_2} decreased from 58 (50-76) to 37 (29-47) mm Hg at 2 hours with normalization of pH 7.28 (7.16-7.36) to 7.43 (7.33-7.49) after 2 hours associated with hemodynamic stabilization. In 6 patients, complications due to iLA treatment were observed, and in 3 patients, complications associated with HFOV were seen. Weaning from HFOV/iLA was successful in 10 patients. The 30-day mortality rate was 43%, and hospital mortality rate was 57%.

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Conclusion: The combination of HFOV/iLA is an option in severe pulmonary failure if conventional ventilation fails and pumpdriven extracorporeal membrane oxygenation therapy is not available.

1. Introduction

Acute respiratory distress syndrome (ARDS) is characterized by a rapid onset of respiratory failure with severe hypoxemia refractory to supplemental oxygen; hypercapnia is facultative [1]. Mortality ranges from 31% to 74% [2-5], and severe hypoxemia has been shown to be an independent predictor of unfavorable outcome [6-9]. Mechanical ventilation can perpetuate lung injury. In theory, high-frequency oscillatory ventilation (HFOV) is a very lung protective ventilatory strategy, applying high mean airway pressures with an extremely small tidal volume (1-3 mL/kg) [10], thus, reducing atelectasis and avoiding cyclic alveolar overdistension. Although no randomized clinical study exists demonstrating an improvement in outcome when HFOV is used in patients with ARDS, HFOV has been shown to be safe and effective in improving gas exchange and is increasingly used in patients with severe ARDS with uncontrolled hypoxia under conventional ventilation [11]. The removal of CO_2 can be limited at the expense of hypercapnia and consecutive respiratory acidosis [11].

Recently, a pumpless interventional lung assist device (iLA; Novalung GmbH, Talheim, Germany) has become available, and early clinical results have been published [12-14]. In our own series, we found an elimination capacity of the device of about 50% of the endogenous carbon dioxide production [15]. The iLA may enable a more protective ventilation through its contribution to CO_2 removal [16].

The aim of the current study was to analyze the efficiency of the iLA in combination with HFOV as rescue therapy in patients with severe ARDS and persistent hypoxemia and hypercapnia despite optimization of the conventional mechanical ventilation (CV) according to the ARDSnet protocol [17]. Our hypothesis was that the combination of HFOV with a good oxygenation capacity and iLA with a high carbon dioxide elimination capacity could achieve a reliable and sustained respiratory stabilization and, even in severe pulmonary failure, the continuation of a protective ventilatory strategy.

2. Materials and methods

This is a retrospective single-center investigation using HFOV and iLA as rescue therapy in 21 consecutive adult patients with ARDS. Approval for the publication of the data was given by the University of Regensburg Ethics Committee (Germany).

Patients with severe respiratory failure who had life-threatening hypoxemia and hypercapnia were assigned to HFOV/iLA, if the combined use of optimized conventional therapeutic strategies according to the ARDSnet protocol [17] had failed as shown in Fig. 1 (also see electronic supplemental material). Failure of these strategies was indicated when the Pa_{O_2}/inspired fraction of oxygen (F_{IO_2}) ratio remained lower than 80 mm Hg and/or hypercapnia had induced respiratory acidosis (pH < 7.25) with progressive hemodynamic instability. In 2 patients, the iLA was implanted before interhospital transfer due to severe hypercapnia and hemodynamic instability. According to our algorithm (Fig. 1), 2 subgroups were identified. In the HFOV-first group (n = 7), iLA treatment was added more than 2 hours after beginning HFOV treatment. In the iLA-first group (n = 9), HFOV was initiated more than 2 hours after iLA treatment. In both groups, the effect of the single intervention was analyzed and later the effect of the combined treatment modalities. In 5 patients, HFOV was started shortly after iLA implementation because of rapid respiratory deterioration.

2.1. Ventilatory strategy on HFOV

High-frequency oscillatory ventilation is used in our center as rescue therapy for patients who remain hypoxemic despite high levels of inspired oxygen during optimized CV according to the ARDSnet protocol [17]. For HFOV in adults, the SensorMedics 3100B (Viasys Healthcare, Yorba Linda, Calif) has been used since 2001. During HFOV, a piston pump oscillates at frequencies between 3 and 15 Hz in a Continuous Positive Air Pressure circuit [18]. The amplitude of the oscillations is manually adjusted, and the inspiratory bias gas flow ranges from 15 to 40 L/min. For initiation of HFOV, we used the following settings: F_{IO_2}, 1.0; mean airway pressure (mPAW), 5 cm H_2O above Pmean on conventional ventilation; inspiration/expiration ratio, 33%; and bias gas flow, 30 $L \cdot min^{-1}$. Because patients had predominantly pulmonary ARDS and were hemodynamically instable, recruitment maneuvers were not routinely done. Frequency was set at 5 to 6 Hz. The amplitude was set between 50 and 100 cm H_2O until the patients wiggled from shoulder to midthigh. Thereafter, settings were adjusted to Pa_{CO_2} in accordance with the MOAT- study [5]. In the case of hypercapnia, the amplitude was increased, and the oscillation frequency could be reduced to 4 Hz; cuff leaks were not allowed due to concern about microaspirations. If oxygenation improved, the first step was to reduce F_{IO_2} less than 0.6. If this was achieved, mPAW was reduced to 1 to 2 cm H_2O every day. At an F_{IO_2} of less than 0.5 and an mPAW

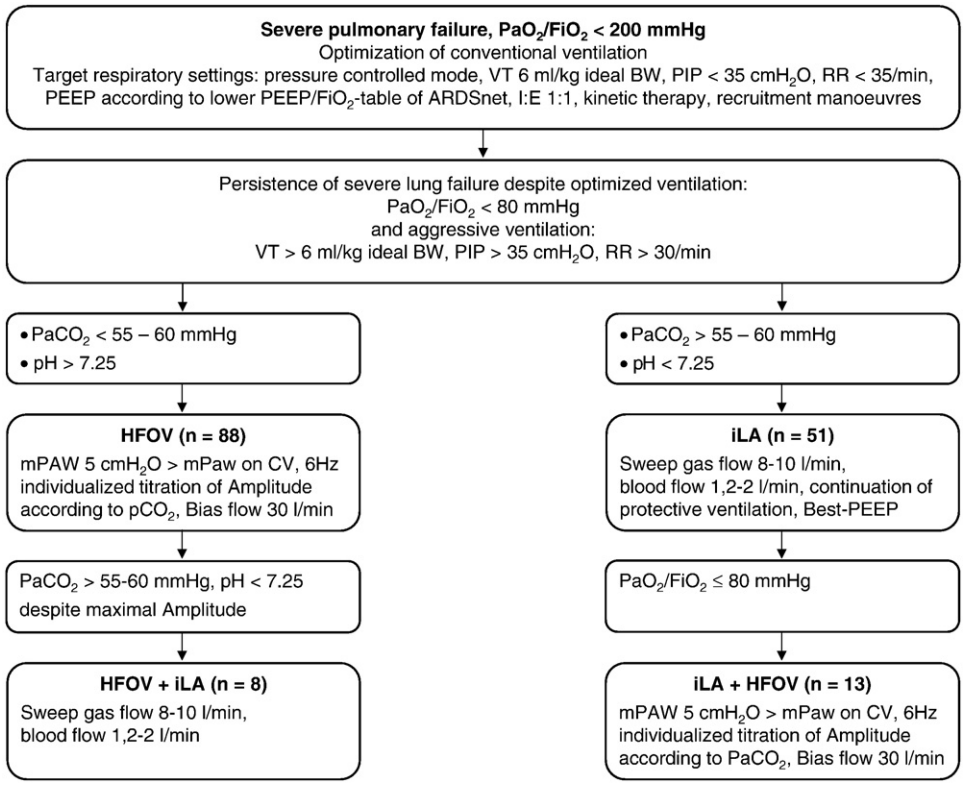

Fig. 1 Algorithm for initiation of HFOV and iLA for patients in severe pulmonary failure if conventional therapy failed. n indicates number of patients treated with each modality during study period.

of less than 24 cm H_2O, the patients were switched to conventional ventilation. Weaning from conventional ventilation was carried out according to our local standard (see electronic supplemental material).

2.2. Ventilatory strategy on iLA

Interventional lung assist device is used in our center as rescue therapy for patients who remain hypercapnic with marked respiratory acidosis despite aggressive CV (Fig. 1). The iLA was developed and has been optimized since 1996 at the University Hospital Regensburg. In principle, iLA is a pumpless artificial arteriovenous shunt with an interposed low-resistance membrane oxygenator (exchange surface, 1.3 m^2). Technical data and implantation procedures for the iLA have been described [12-14]. After ultrasonographic measurement of the femoral vessels, the median cannula sizes used in this study were 17F (2 × 15F, 13 × 17F, 6 × 19F) for the artery and 19F (5 × 17F, 12 × 19F, 4 × 21F) for the vein. Because the system is coated with heparin, a systemic anticoagulation with heparin and an activated partial thromboplastin time of 1.5 of normal is sufficient. Oxygen is used as sweep gas (flow, 4-12 $L \cdot min^{-1}$). Ventilatory parameters were adjusted according to $PaCO_2$ (normocapnia) and pH. Weaning of the iLA was achieved by gradually decreasing the sweep gas flow to 1.5 $L \cdot min^{-1}$. If there was no respiratory deterioration after 45 minutes of discontinuation of the sweep gas flow, the device was removed. Usually, the device was removed after termination of the HFOV and before weaning from conventional ventilation.

Respiratory, hemodynamic, and metabolic parameters were collected at 5 different times: (1) before first treatment modality (iLA or HFOV), (2) 2 hours after start of first treatment modality, (3) before the implementation of the second treatment modality (HFOV or iLA), (4) 2 hours after combined treatment, and (5) 24 hours after combined treatment. Complications were classified as HFOV or iLA induced. Critical ischemia was defined as the need for intervention (percutaneous transluminal angioplasty, lysis, removal of iLA), uncritical ischemia as reversible clinical signs of limb hypoperfusion, and no need for intervention. Major bleeding was defined as the need for transfusion. Data were collected from the records of all patients with ARDS who were treated at our center with these techniques from the time of introduction until September 2006.

2.3. Statistical analysis

Variables are reported as the median and interquartile range. Categorical variables were compared using the χ^2 test and continuous variables using the Mann-Whitney U test. Data were examined for Gaussian distribution with the Kolmogorov-Smirnov test. Dependent nonparametric variables were analyzed by the nonparametric Wilcoxon test and Friedman test. Independent variables were compared by the Mann-Whitney U test and Kruskal-Wallis H test. A P value

of less than .05 was considered statistically significant. We used SPSS version 15.0 (SPSS Inc, Chicago, Ill).

3. Results

3.1. Patient characteristics

Twenty-one patients with ARDS and critical hypoxemia and hypercapnia were treated with the combination of HFOV/iLA between 2002 and 2006. Patient characteristics are demonstrated in Table 1. Most patients presented with pulmonary ARDS due to pneumonia (n = 17). The diagnosis for patients with extrapulmonary ARDS were sepsis (n = 2), pancreatitis (n = 1), and chemotherapy-associated lung failure (n = 1). Mean duration of iLA treatment was 6.0 (4.0-9.0) days and of HFOV treatment was 6.0 (3.3-9.0) days. Blood flow through the iLA was 1.9 (1.7-2.3) $L \cdot min^{-1}$ after 2 hours and 1.8 (1.6-2.1) $L \cdot min^{-1}$ after 24 hours of treatment.

3.2. Gas exchange and ventilatory parameters

The Pa_{O_2}/F_{IO_2} ratio, Pa_{CO_2}, and pH for the iLA/HFOV treatment of all patients as well as the iLA-first and the HFOV-first subgroup are displayed in Figs. 2 to 4.

Combination treatment with iLA/HFOV led to an increase in Pa_{O_2}/F_{IO_2} ratio, normalization of hypercapnia, and acidosis (each $P < .05$; Fig. 2) resulting in hemodynamic stabilization (Table 2). In the subgroup analysis of the iLA-first group (Fig. 3), iLA-only treatment resulted in an improvement in hypercapnia and acidosis ($P < .05$). The increase in the Pa_{O_2}/F_{IO_2} ratio during iLA-only treatment did not reach significance. In the HFOV-first group (Fig. 4), we observed a trend toward an increase in Pa_{O_2}/F_{IO_2} ratio within 2 hours of HFOV-only treatment ($P < .1$). High-frequency oscillatory ventilation led to a retention of CO_2 with respiratory acidosis ($P < .05$), which was controlled after iLA implementation.

Patients were ventilated with a moderate oscillatory amplitude of 71 (58-87) cm H_2O, which could be decreased after initiation of iLA to 55 (45-68) cm H_2O ($P = .175$). The oscillation frequency remained unchanged with 6 (5.3-6.0) Hz. Initiation of HFOV resulted in a higher mPAW per protocol, which was 28 (23-31) cm H_2O on CV, increased to 33.5 (29-35) cm H_2O after 2 hours of HFOV treatment ($P = .012$), and was 33 (29-34) cm H_2O after 24 hours of HFOV in combination with iLA ($P = .29$).

3.3. Hemodynamic and metabolic effects

In Table 2, hemodynamic and metabolic parameters are displayed for the iLA-first and the HFOV-first patients. In parallel to reversal of respiratory acidosis by iLA, norepinephrine infusion was reduced. Norepinephrine infusion could be decreased if the mean arterial pressure was above 80 mm Hg. We saw increased lactate levels after 24 hours of iLA treatment ($P = .028$).

Table 1 Patient characteristics

Parameter	All patients	Survivors	Nonsurvivors	*P*
No. of patients	21	9 (43%)	12 (57%)	
Age (y)	51 (42-61)	45.5 (32.1-51.3)	58.4 (44.9-63.7)	.021
Female-male ratio	5/16	2/7	3/9	NS
Body mass index ($kg \cdot m^{-2}$)	27.7 (24.8-30.8)	29.2 (26.2-30.8)	27.1 (24.0-31.4)	NS
SAPS II score	41 (30.5-51.0)	32.0 (27.5-42.5)	47.5 (40.3-52.8)	.028
SOFA score	14 (11.5-15.5)	13.0 (11.5-15.0)	15.0 (10.5-16.0)	NS
Murray lung injury score	4.0 (3.7-4.0)	4.0 (3.7-4.0)	4.0 (3.7-4.0)	NS
Norepinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.31 (0.07-0.53)	0.23 (0.05-0.39)	0.47 (0.06-0.72)	NS
Lactate ($mg \cdot dL^{-1}$)	18.5 (13.5-40.0)	18.0 (13.0-44.0)	19.0 (13.0-36.5)	NS
Renal failure AKIN stage 3, n (%)	16 (76%)	6 (67%)	10 (83%)	.016
Days on ventilator before HFOV/iLA	2.0 (1.0-10.0)	1.0 (1.0-2.0)	6.5 (1.3-14.8)	.037
Peak inspiratory pressure (cm H_2O)	38 (35-41)	40 (33-42)	38 (34-41)	NS
PEEP (cm H_2O)	17 (15-21)	17 (16-21)	18 (13-21)	NS
Mean airway pressure (cm H_2O)	28 (24-31)	28 (24-31)	27 (24-30)	NS
Oxygenation index (cm H_2O mm Hg^{-1})	48 (31-57)	46 (33-51)	50 (27-66)	NS
Pa_{O_2}/Fio_2 ratio (mm Hg)	61 (47-86)	61 (55-85)	56 (45-87)	NS
Pa_{CO_2} (mm Hg)	58 (50-76)	52 (42-65)	67 (56-78)	.032
pH	7.28 (7.16-7.36)	7.34 (7.26-7.39)	7.22 (7.13-7.33)	NS
Days on HFOV/iLA	6.0 (3.3-9.0)	4.5 (3.8-8.0)	6.0 (3.0-9.8)	NS
Days on ventilator after HFOV/iLA	2.8 (0-23.0)	20.5 (8.0-29.8)	0.0 (0.0-0.0) [a]	NS

Patient data and characteristics before initiation of iLA and HFOV; values are presented as median (interquartile range); NS indicates not significant; SAPS II, simplified acute physiology score; SOFA, sequential organ failure assessment; AKIN, Acute Kidney Disease Network category stage 3 = need for renal replacement therapy; PEEP, positive end expiratory pressure.

[a] One patient died 110 days after termination of HFOV/iLA.

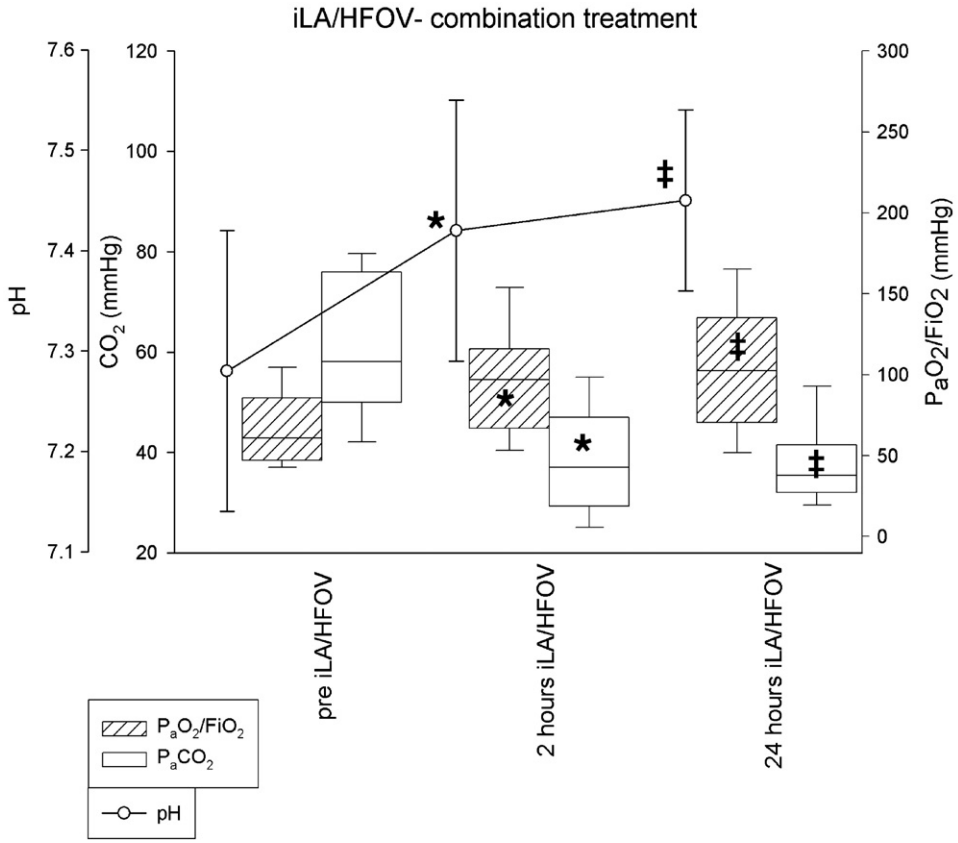

Fig. 2 Interventional lung assist device/HFOV combination treatment. Pao_2/Fio_2 ratio, $Paco_2$, and pH before (pre-iLA/HFOV), after 2 hours, and after 24 hours of combined treatment with iLA and HFOV (2 hours iLA/HFOV and 24 hours iLA/HFOV). Box and whisker plots (95th, 75th, 50th, 25th, and 5th percentiles). Asterisk indicates $P < .05$ to previous value; double dagger, $P < .05$ to first value.

3.4. Complications of iLA and HFOV

During the total support period of 6.0 (4.0-9.0) days on iLA, 3.0 (2.0-5.0) erythrocyte concentrates per patient were transfused. Major bleeding was observed on 2 occasions: in one case due to dislocation of the arterial cannula and in the other case due to loss of a circuit cap, which subsequently resulted in the modification of the iLA circuit. All complications are summarized in Table 3. Severe ischemia of the arterially cannulated leg was observed on 3 occasions. In 1 patient, the femoral arterial cannula had to be removed and surgically implanted into the subclavian artery because the patient still needed iLA support. One patient needed surgical removal of the arterial cannula and a Fogarty maneuver to remove arterial thrombi but no reinsertion because of respiratory stabilization. One patient with arteriosclerosis developed ischemia of the leg after removal of the arterial cannula and needed percutaneous transluminal angioplasty with local thrombolysis. All interventions were successful, and we observed no fatal or disabling (amputation) complications. One patient with severe hypoxemia and septic shock developed profound hypotension after initiation of the iLA, which was inserted as a rescue measure in a referring hospital. Heparin-induced thrombocytopenia was seen in 1 case. The heparinized circuit was left in place, and anticoagulation was switched to argatroban without any clinical sequelae and normalization of platelets. We saw only 3 oxygenator dysfunctions (thrombosis) for the entire support period (3364 hours), which was resolved by an uncomplicated change of the device.

Complications possibly associated with HFOV (Table 3) occurred in 3 patients and were due to air leaks that were treated with chest drains. Three uncritical hypotensive episodes after start of HFOV were observed. All our patients were adequately volume repleted before transition to HFOV.

3.5. Outcome

Ten patients (48%) survived to weaning from HFOV and iLA, of which 9 patients (43%) were discharged from the hospital (hospital mortality rate, 57%). The 30-day mortality rate was 43%; 3 of the long-term survivors were still ventilated at day 30. One patient was weaned but died 110 days after support due to acute liver failure as a result of secondary sclerosing cholangitis and sepsis. Survivors were younger than nonsurvivors, had lower simplified acute physiology score II points, a shorter duration of mechanical ventilation, less often renal failure, and less hypercapnia (each $P < .04$) before initiation of HFOV/iLA (Table 1). The main cause of death was septic shock and multiorgan failure

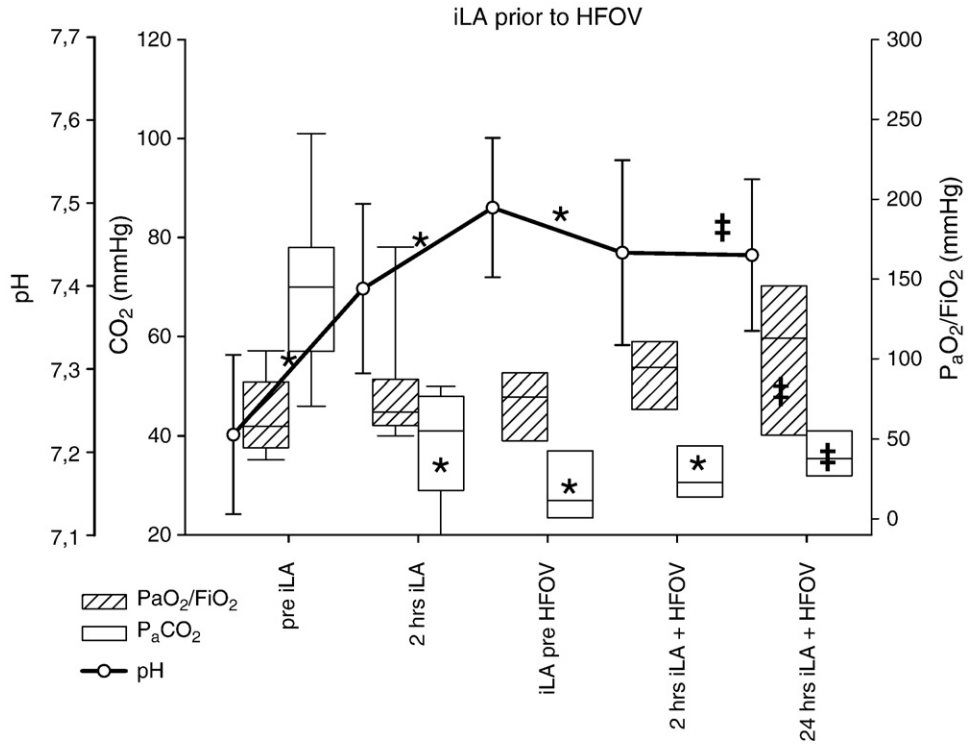

Fig. 3 The iLA-first group. Subgroup of patients with iLA-only treatment for 2 hours or more before initiation of HFOV (n = 9). Pa_{O_2}/Fi_{O_2} ratio, Pa_{CO_2}, and pH before initiation of pre-iLA, on iLA (after 2 hours iLA and pre-iLA + HFOV), and on combined treatment (after 2 hours iLA + HFOV and 24 hours iLA + HFOV). Box and whisker plots (95th, 75th, 50th, 25th, and 5th percentiles). Asterisk indicates $P < .05$ to previous value; double dagger, $P < .05$ to first value.

(6 patients). One patient developed fatal cerebral bleeding due to disseminated intravascular coagulopathy; 1 patient had hypoxic brain damage due to severe pretreatment hypoxia. Two patients died of intractable respiratory failure, and 1 patient developed right heart failure due to progressive pulmonary fibrosis.

4. Discussion

The current study is the first of its kind to analyze the efficacy of combined treatment with HFOV and iLA in a cohort of adult patients with severe ARDS [19,20]. It demonstrates that the combination of HFOV and iLA as rescue therapy in severe respiratory failure improved oxygenation, hypercapnia, and respiratory acidosis and allowed for continuation of a less aggressive ventilatory strategy.

4.1. Effects on oxygenation

The presented patients had severe respiratory failure before the initiation of HFOV and iLA. If hypoxemia without severe respiratory acidosis was the predominant problem, patients were started on HFOV (Fig. 1). The trend toward an increase in the Pa_{O_2}/Fi_{O_2} ratio observed was less than that reported in the literature [18,21-23]. An explanation is that most of our patients had pulmonary ARDS, which responds to a lesser degree to an increase in positive end expiratory pressure [24,25] or mPAW in HFOV. Because infiltrated parenchyma of the lung cannot be recruited, a further increase in airway pressure can lead to overdistension of healthy lung areas and was therefore avoided.

The initiation of iLA resulted in a small improvement in arterial oxygenation as well. Interventional lung assist device is not suited for transferring large amounts of oxygen because it is perfused with arterial blood, and the blood flow is too small [15]. Its leading indication is removal of CO_2. The combination of iLA and HFOV led to a significant increase in the Pa_{O_2}/Fi_{O_2} ratio.

4.2. Effects on hypercapnia

If respiratory acidosis was the primary problem, patients were started on iLA first to augment CO_2 removal. After implementation of iLA, we observed a rapid and sustained reduction in CO_2, allowing a more protective ventilatory mode. Ventilation in HFOV is directly related to the pressure amplitude of oscillation and inversely related to the frequency of oscillation. With increasing amplitude and decreasing frequency, the aggressiveness of ventilation rises, in part due to larger tidal volumes. Generally, in HFOV of adults, an amplitude between 60 and 90 cm H_2O [5,26] is necessary to achieve sufficient CO_2 elimination. We saw an increase in Pa_{CO_2} after 2 hours of HFOV treatment with a median amplitude of 71 cm H_2O. After implementation of

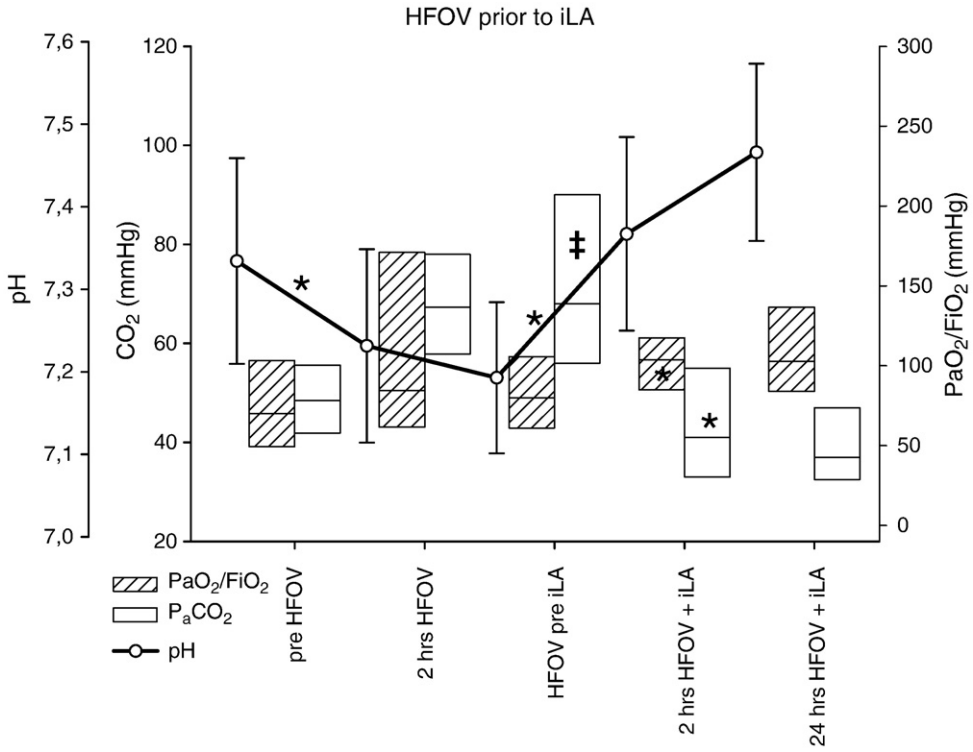

Fig. 4 The HFOV-first group. Subgroup of patients with HFOV-only treatment for 2 hours or more before initiation of iLA (n = 7). PaO_2/FIO_2 ratio, $PaCO_2$, and pH before initiation of HFOV (pre-HFOV), on HFOV (after 2 hours HFOV and pre-HFOV + iLA), and on combined treatment (after 2 hours HFOV + iLA and 24 hours HFOV + iLA). Box and whisker plots (95th, 75th, 50th, 25th, and 5th percentiles). Asterisk indicates $P < .05$ to previous value; double dagger, $P < .05$ to first value.

iLA, the oscillation amplitude could be reduced to 55 cm H_2O because the $PaCO_2$ decreased. With stable oscillatory frequency, this is expected to generate lower tidal volumes as well as reduced shear stress and therefore promote a better protection of the injured lung.

In a recent feasibility trial of very high-frequency ventilation in 30 patients failing conventional lung protective ventilation, an acceptable gas exchange could be established with oscillatory frequencies above 6 Hz and an oscillatory amplitude of 81 ± 11 cm H_2O [27]. Compared to our study population, patients had a higher proportion of extrapulmonary ARDS and less severe pulmonary failure (PaO_2/FIO_2 ratio, 78 ± 28 mm Hg; FIO_2, 0.93 ± 0.11; positive end expiratory pressure, 13 ± 4 cm H_2O). It can be assumed that these patients had a higher potential for lung recruitment resulting in better gas exchange. In theory, a very high oscillation frequency should bring about a more protective ventilation, but this must be investigated in future trials. We

Table 2 Hemodynamic parameters

		Pre-iLA	2 h iLA	24 h iLA
"iLA-first" patients	MAP (mm Hg)	75.0 (63.5-79.8)	84.0 (72.3-95.5) *	80.5 (74.5-86.3) **
	Norepinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.31 (0.07-0.53)	0.19 (0.07-0.48)	0.09 (0.02-0.29)
	Lactate ($mg \cdot dL^{-1}$)	19.0 (13.5-47.5)	20.0 (17.0-66.0)	30.0 (14.0-35.3) ***
	Hb level ($g \cdot dL^{-1}$)	9.9 (8.6-12.8)	9.6 (8.4-11.4)	10.3 (9.2-11.8)
	CO ($L \cdot min^{-1}$)	9.7 (7.4-10.1)	9.9 (7.6-10.8)	8.8 (7.3-11.0)
		Pre-HFOV	2 h HFOV	24 h HFOV
"HFOV-first" patients	MAP (mm Hg)	83.3 (73.3-94.2)	83.3 (70.3-96.2)	83.3 (75.0-89.3)
	Norepinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.3 (0.03-0.58)	0.39 (0.04-0.65)	0.13 (0.01-0.38)
	Lactate ($mg \cdot dL^{-1}$)	26.0 (17.3-43.5)	25.5 (17.8-40.0)	26.0 (17.0-46.0)

Values are depicted as median (interquartile range). MAP indicates mean arterial blood pressure; CO, cardiac output (thermodilution/pulmonary artery catheter [n = 11]); Hb, hemoglobin.

* $P = .001$.

** $P = .021$.

*** $P = .028$ to first value; otherwise not significant.

Table 3 Frequency of complications and side effects

Complications/side effects iLA	n
Circulatory failure	1
Major bleeding	2
Critical ischemia	3
Uncritical ischemia	4
Oxygenator dysfunction	3
Heparin-induced thrombocytopenia type II	1
Complications/side effects HFOV	n
Pneumothorax bilateral	1
Tension pneumothorax	1
Subcutaneous emphysema	1
Chest drains (total)	4

did not increase the oscillatory frequency according to our protocol at the time but decreased the oscillatory amplitude. Accepting permissive hypercapnia, we could have decreased the oscillation amplitude further and/or increased the oscillation frequency to decrease ventilatory aggressiveness allowing an even more protective ventilation.

4.3. Effects on hemodynamics

An explanation for the hemodynamic stabilization with decreasing doses of catecholamines is an improved action of vasopressors due to a normalization of pH. Cardiac output increased from 8.4 $L \cdot min^{-1}$ to 9.2 $L \cdot min^{-1}$ after start of iLA, which may be a result of improved cardiac contractility or due to the implanted arteriovenous shunt of the iLA device. Increased lactate levels after 24 hours could be a sign of peripheral ischemia and a locally reduced oxygen delivery or a sign of progressive sepsis.

4.4. Complications of HFOV/iLA

In all patients, support could be continued until the patients can be weaned from the systems or died already. Serious complications were seen in 6 cases in association with the iLA and were in the range of published experience with iLA treatment (24%) [16]. Three patients had peripheral ischemia, which made surgical intervention necessary but caused no persistent damage to the patient. That we used larger arterial cannulas in the past (17F-19F) may have contributed to this complication rate, despite ultrasonographic measurement of the femoral vessels before choosing the cannula size. These bigger cannulas were used for higher blood flow rates through the iLA due to the fear of oxygenator thrombosis and insufficient gas exchange. With the more recent application of smaller cannulas, we saw a reduced rate of complications (12%) [28].

In comparison to venovenous extracorporeal membrane oxygenation (ECMO) therapy, the iLA device needs less systemic anticoagulation because the extracorporeal circuit is smaller, has a low resistance oxygenator with sufficient blood flow rates, and the system is coated with heparin. The average transfusion requirement of 3 U of packed red blood cells during the total support period reflects this improvement, which is much less compared to previous reports on ECMO therapy [29,30]. Furthermore, only 3 oxygenator dysfunctions due to slowly progressive thrombosis for a total of 3364 hours of extracorporeal support occurred. This was resolved by an uncomplicated exchange of the oxygenator.

Complications possibly associated with HFOV is in the range of published experience (9%-25%). Several trials comparing CV and HFOV found no difference in the incidence of barotraumas [5,31,32].

4.5. Outcome

Ten (48%) of our patients survived to weaning from HFOV/iLA, and the hospital mortality rate was 57%. Mortality in very severe ARDS remains high and is not comparable to less severe forms that are generally included in clinical trials [17]. Our patients had very severe ARDS (Murray lung injury score, 4.0; Pa_{O_2}/F_{IO_2} ratio, 61 mm Hg; oxygenation index, 48 cm $H_2O \cdot mm\ Hg^{-1}$; initial pH 7.28). According to published data, expected mortality of the present patients could reach to more than 80% [4,33]. Because of the limited number of patients and the retrospective design, the current study is not suited for clarifying whether combined treatment with HFOV and iLA improves survival in severe ARDS. The presented data can help to understand the efficacy of combined HFOV/iLA treatment with respect to oxygenation and hemodynamic stabilization. Larger prospective trials are needed to elucidate the effect on mortality in severe ARDS.

5. Conclusion

The combination of HFOV and iLA is an option for selected patients as rescue therapy in severe pulmonary failure. The techniques possibly complement one another; HFOV as a potentially very protective mode of ventilation can achieve a sustained improvement in oxygenation, and iLA can support extracorporeal CO_2 elimination with rapid correction of respiratory acidosis associated with hemodynamic stabilization. This can implicate a less injurious ventilatory setting, which is crucial for long-term outcome. High-frequency oscillatory ventilation and iLA using smaller cannulae may also be an alternative to venovenous ECMO in the treatment of adult patients with severe ARDS.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jcrc.2009.11.004.

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