Extracorporeal Carbon Dioxide Removal Technique Improves Oxygenation without Causing Overinflation

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Extracorporeal CO_2 removal combined with low frequency positive pressure ventilation ($ECCO_2R$-LFPPV) improves gas exchange and decreases peak pressures, respiratory rates, and tidal volumes in animals and in humans. Recent evidence suggests that pulmonary barotrauma results from lung overinflation rather than from high pressures. This study was to test the hypothesis whether $ECCO_2R$-LFPPV could improve gas exchange without causing lung overinflation, despite the use of higher levels of PEEP, when compared with conventional mechanical ventilation. Eleven patients with severe adult respiratory distress syndrome (ARDS) who failed to respond to different modes of mechanical ventilation were treated with $ECCO_2R$-LFPPV. Risk of pulmonary barotrauma was evaluated by static pressure-volume (P-V) curves and dynamic changes in volumes monitored by respiratory inductive plethysmography (Respitrace). $ECCO_2R$-LFPPV Pa_{O_2}/FI_{O_2} increased from 79 ± 21 to 207 ± 108 ($p = 0.003$). Risk of barotrauma, as shown by the shape of the P-V curve, was present in all patients receiving mechanical ventilation even though most of them were treated with permissive hypoventilation. By contrast, no evidence of persistent lung overinflation could be detected by either static P-V curves or dynamic measurements in nine of 11 patients who were treated by $ECCO_2R$-LFPPV. The two remaining patients had severe airway obstruction because of bleeding, and they remained ventilated with persistent risk of barotrauma. We conclude that $ECCO_2R$-LFPPV improves gas exchange without causing lung overinflation in a majority of patients with ARDS. **Brunet F, Mira J-P, Belghith M, Monchi M, Renaud B, Fierobe L, Hamy I, Dhainaut J-F, Dall'ava-Santucci J. Extracorporeal carbon dioxide removal technique improves oxygenation without causing overinflation. Am J Respir Crit Care Med 1994;149:1557-62.**

High pressure mechanical ventilation is usually required in patients with adult respiratory distress syndrome (ARDS) to achieve adequate gas exchange. Positive end-expiratory pressure (PEEP) was introduced to improve arterial oxygenation and to decrease FI_{O_2}, thereby reducing oxygen toxicity. However, pulmonary barotrauma, as defined by the abnormal presence of air leaks in extraalveolar spaces, often occurs as a result of high pressure mechanical ventilation (1–3). Although experimental studies have demonstrated that high peak pressures were associated with severe pulmonary edema of permeability type (4–6), recent evidence suggests high volumes rather than high pressures actually cause alveolar damage (7, 8). Indeed, increase in airway pressure without concomitant increase in lung volume is not deleterious, but high tidal volume, even obtained with negative pressure, causes permeability edema. In clinical practice, patients are usually treated with positive-pressure ventilation, and one cannot have peak overdistension without increase in peak airway pressure. However, for a given peak pressure, lung distension also depends on airway resistance, lung compliance, and mode of ventilation. Extracorporeal CO_2 removal combined with low frequency positive-pressure ventilation ($ECCO_2R$-LFPPV) improves gas exchange and reduces peak pressures, respiratory rates, and tidal volumes in both animals and humans (9–11). However, high levels of PEEP are necessary during $ECCO_2R$-LFPPV to achieve alveolar recruitment for pseudoapneic oxygenation. Microvascular injury may occur in rats submitted either to very large tidal volume or to "normal" tidal volume superimposed to markedly increased FRC during continuous positive-pressure ventilation (12). Lung overinflation may be due to increased end-expiratory volumes, as assessed by changes in FRC (ΔFRC). There is no evidence in humans that low frequency positive-pressure ventilation could reduce overinflation and hence the risk of "volutrauma" (12). Respiratory inductive plethysmography (Respitrace®; Ambulatory Monitoring, Ardsley, NY) allows measurement of thoracopulmonary volumes, including ΔFRC, in mechanically ventilated patients (13). This technique also allows construction of pressure-volume (P-V) curves corrected for volume losses, including air leak (13). The purpose of this study was to test whether $ECCO_2R$-LFPPV could improve oxygenation without causing lung overinflation as assessed by the shapes of static P-V curves. The upper part of static P-V curves was used to define individual lung overinflation and Respitrace dynamic volume measurements.

METHODS

Patients

We studied 11 consecutive patients with ARDS (Table 1). Diagnosis was made on clinical, radiologic, and gazometric criteria. Duration of mechanical ventilation preceding onset of $ECCO_2R$-LFPPV was dependent on

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TABLE 1

PATIENT CHARACTERISTICS

Patient No.	Age (yr)	Sex	OSF	Etiology of ARDS	MV	ECMO*	Murray Score*	Barotrauma	Outcome
1	30	F	2	Amniotic embolism	5	Slow	3.6	Yes	S
2	37	M	3	Pulmonary infection	7	Slow	3.1	Yes	D
3	38	F	1	Pulmonary infection	3	Rapid	3	No	S
4	19	F	1	Pulmonary infection	14	Slow	3	Yes	S
5	18	M	1	Acute vasculitis	8	Rapid	3.6	Yes	D
6	25	F	1	Gastric aspiration	15	Slow	4	Yes	S
7	19	F	1	Pulmonary infection	14	Rapid	3	No	S
8	38	M	3	Pulmonary infection	12	Rapid	3.25	No	S
9	15	F	1	Pulmonary infection	8	Rapid	3.6	Yes	S
10	37	M	2	Pulmonary infection	2	Rapid	3.6	No	D
11	20	F	1	Polytraumatism	13	Rapid	3.25	Yes	S
Mean	27		1.5		9		3.4		
± SD	9		0.8		5		0.3		

Definition of abbreviations: OSF = number of organ failures, as defined in reference 10, associated with ARDS (this score was calculated during mechanical ventilation before onset of $ECCO_2R$); MV = total duration of mechanical ventilation, expressed in days, before onset of $ECCO_2R$; barotrauma = recordings of each barotraumatic lesion observed on either standard chest radiograph or CT scan of the lungs during mechanical ventilation.

* ECMO and Murray score were calculated during the initial evaluation of the patient during mechanical ventilation according to definitions in references 14 and 15.

TABLE 2

RESPIRATORY PARAMETERS MEASURED DURING MV AND $ECCO_2R$*

Patient No.	Pa_{O_2}/FI_{O_2}		P_{CO_2} (mm Hg)		PIP ($cm\ H_2O$)		$\overline{Paw}$ ($cm\ H_2O$)		PEEP ($cm\ H_2O$)		VT (ml)		RR	I/E
	MV	$ECCO_2R$	MV	$ECCO_2R$	MV	$ECCO_2R$	MV	$ECCO_2R$	MV	$ECCO_2R$	MV	$ECCO_2R$	MV	MV
1	87	450	42	40	40	32	27	17	14	16	660	250	18	1/2
2	48	142	50	43	68	40	35	22	12	20	900	320	16	1/1
3	79	290	46	36	37	28	19	15	10	14	500	300	20	1/1
4	114	325	57	42	42	32	18	15	6	13	650	250	20	1/1
5	67	92	132	50	55	40	22	18	12	16	560	320	20	1/2
6	58	160	86	48	45	40	28	22	12	20	580	220	24	1/1
7	103	202	55	40	55	40	28	18	6	17	580	230	20	1/1
8	72	152	66	52	56	32	32	21	16	19	790	390	20	1/1
9	84	127	57	42	47	42	21	18	12	17	650	210	20	1/1
10	100	220	59	34	35	34	22	18	13	17	520	320	20	1/1
11	60	120	76	42	45	41	29	20	10	18	450	200	20	1/1
Mean	79	207	66	43	48	37	26	19	11	17	622	274		
SD	21	108	25	6	10	5	6	3	3	2	131	60		
p Values	0.003		0.003		0.003		0.003		0.003		0.003			

Definition of abbreviations: MV = mechanical ventilation; $\overline{Paw}$ = mean airway pressure; PIP = peak inspiratory pressure; VT = tidal volume; RR = respiratory rate; I/E = inspiratory/expiratory time.

* Reported parameters were measured during mechanical ventilation within 24 h before $ECCO_2R$ and during $ECCO_2R$ after the initial period of instability.

the delay between diagnosis and transfer to our Unit (average, 9 ± 5 d; range, 2 to 15 d). Eight patients already had barotraumatic complications before onset of $ECCO_2R$-LFPPV. All patients had a Murray score (14) at least equal to 3. Seven and four patients met slow and rapid ECMO criteria, respectively (15), which were calculated on optimized mechanical ventilation. Pressure-controlled inverse-ratio ventilation (Pc-IRV) and "permissive hypoventilation" were used (16, 17). PEEP level was defined as the pressure that achieved best Pa_{O_2} for lower FI_{O_2} (18). Individual respiratory data are shown in Table 2. The average of three blood gas measurements, sampled on 100% oxygen at 8-h intervals within the 24 h preceding $ECCO_2R$-LFPPV, was retained for the study.

Patients were fully sedated (barbiturates, benzodiazepines, morphinomimetics) and paralyzed (pancuronium bromide) during both mechanical ventilation and $ECCO_2R$-LFPPV. The study was approved by the Ethics Committee of our institution.

$ECCO_2R$-LFPPV Procedure

We used the protocol described by Gattinoni and colleagues (10). In brief, two cannulae (femoral cannula kit arterial 21fr/venous 21fr; DLP Inc., Grand Rapids, MI) were inserted percutaneously into the two femoral veins. Drainage and return cannulae were located in the lower and upper part (just above right atrium) of the inferior vena cava, respectively. Blood circuit consisted of silicone rubber tubing (diameter: 3/8 inch) with an occlusive pump (Stockäert Shilley, München, Germany) and two silicone artificial membrane lungs 3 m^2 each (Ultrox I; SCI Med, Minneapolis, MN) ventilated with a heated humidified mixture of air and oxygen. Extracorporeal blood flow represented 20% of cardiac output, and it ranged between 1.4 and 2 L/min. The circuit was heated by an external heater, which maintained patient's temperature between 37 and 38° C. Anticoagulation, started just before cannulae insertion, was achieved with a single bolus (100 IU/kg) followed by constant heparin (Léo SA, Montigny, France) infusion to maintain serum heparin concentrations (anti-Xa chromogenic assay by Rotachrom; Diagnostica Stago, Genevilliers, France) between 0.10 and 0.20 IU/ml and activated partial thromboplastin time (APTT reagent; Organon Teknika, Fresnes, France) between 1.5 and 2 times normal values. Platelet counts were maintained above 60,000 cell/mm^3 by infusion of random donor platelets. Fresh frozen plasma was given daily to maintain AT III levels > 70% of the normal. Gas analysis of the circuit venous blood,

blood pressure gradient across the membrane lungs, extracorporeal blood flow, gas flow rates, and systemic temperature were monitored continuously.

Low frequency ventilation was carried out with a Servo 900C (Siemens, Erlangen, Germany) with the following parameters: four cycles per minute, tidal volumes of 300 ± 50 ml, and peak airway pressures limited to 40 to 45 cm H_2O by decreasing working pressures of the ventilator. Tracheal tube sizes ranged from 7.5 to 9 mm, ID. Patient's lungs were continuously inflated with an expiratory positive pressure, obtained by immersion of the end-expiratory circuit of the ventilator in a column of water. The level of PEEP at onset of $ECCO_2R$-LFPPV was set at the mean airway pressure obtained in mechanical ventilation, as previously recommended by Gattinoni and colleagues (10). Then the initial PEEP was decreased if Pa_{O_2} was higher than 100 mm Hg. Moreover, when initial settings did not allow attainment of a tidal volume of 300 ml, PEEP was decreased instead of increasing the working pressure of the ventilator. Data shown in Table 2 on $ECCO_2R$ were sampled at the time of the present study. Oxygen was continuously given through a small catheter (0.7 mm, external diameter) fitted in the tracheal tube, with the tip located just above the carina. Oxygen flow (range, 0.5 to 1.5 L/min) was adjusted to compensate at least oxygen consumption and pleural leak in case of bronchopleural fistula. This was achieved by checking that minimal flow was continuously present from the expiratory output of the ventilator under the column of water, i.e., permanent minimal bubbling. During the study, FI_{O_2} was set to 1.0 on the ventilator, the intratracheal catheter, and the lung membranes. Depending on the evolution of arterial blood gases, FI_{O_2} was then progressively decreased, first on the ventilator and the intratracheal catheter, successively. Changes of FI_{O_2} on the membranes of extracorporeal circuit had little effect on arterial oxygenation.

$ECCO_2R$-LFPPV is different from ECMO in which the extracorporeal flow rate is close to cardiac output and is the main source of oxygen.

Lung Mechanics and Volume Measurement

Two sets of measurements were made both using Respitrace: (*1*) static P-V curves, and (*2*) dynamic volume including FRC variation measurements. All measurements were made from 12 to 48 h after onset of $ECCO_2R$-LFPPV to exclude initial period of instability.

Static P-V Curves

Static P-V curves were determined by Respitrace for volume (Respisomnograph; NIMS, Miami, FL) and a Validyne transducer for pressure (MP 15, ± 60 cm H_2O; Validyne, Northridge, CA), which were both connected to a time-function recorder (Sefram, Velizy, France). The lungs were inflated with a 2-L syringe using a noncumulative method as previously described (13, 19). In brief, lung inflation was made by independent steps maintained for 15 s, from FRC to a maximal volume that corresponded to a pressure of 40 cm H_2O limit taken for safety purposes according to the literature (20). Volume increase for each step was 100 ml. Before each inflation, FRC was reached by disconnecting the ventilator and interrupting the intratracheal oxygen flow, which allowed full passive relaxation of the lungs at barometric pressure. For each step, a progressive fall in volume and pressure caused by gas exchange and air leak, if any, could be seen during the 15 s of maintained inflation. This error was corrected by backward extrapolation on tracings to obtain actual pressure and volume at each step. Then, computerized plotting of P-V curve was made possible, despite air leak. The volume steps were also used to calibrate the Respitrace (13, 19).

Slope of the static P-V curve (Figure 1) was taken as inflation compliance. The points on the straight part of the curve were selected by two independent observers to allow computerized construction of the slope using Cricket Graph on MacIntosh. The upper point and the lower point of the curve were the inflection and deflection point of the P-V curve, respectively. Although it has the advantage of not being dependent on the observer, maximal errors of ± 50 ml in volume and ± 2.5 cm H_2O in pressure might be seen with this method. The lower inflection point may be considered as the "best PEEP" (20, 21). In most patients, we also observed an upper deflection point on the P-V curve. Further increase in pressure above this point was associated with only small increase in volume. This indicates that maximal inspiratory capacity above FRC, hence maximal stretching, is almost reached (22). This upper deflection point enables us to define individual risk of overinflation. Indeed, overinflation is likely to occur when ventilation actually takes place beyond this point. The patient was considered to breathe above the upper inflection point only if peak inspiratory volume or pressure was more than 100 ml or 4 cm H_2O above this point.

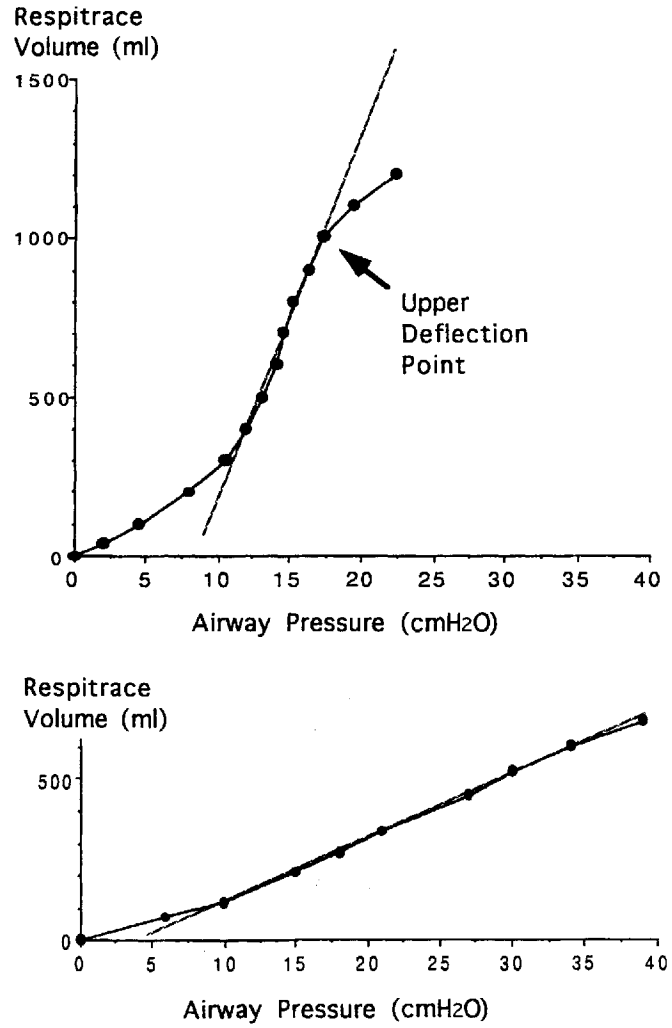

Figure 1. Static inflation pressure-volume curves used to define the risk of lung overdistention, i.e., ventilation above the upper deflection point, in two typical patients. In Patient 10 (*upper panel*), the upper deflection point was reached at a pressure far less than 40 cm H_2O. In Patient 7 (*lower panel*), there was no observable upper deflection point, and this point is likely to be reached at a pressure > 40 cm H_2O. This figure shows that the pressure and the volume for which a patient is at risk of overdistension can only be determined patient by patient. For complete evaluation, dynamic measurements of volumes with Respitrace are required to determine at which level of this curve the patient actually breathes for a given pattern of ventilator settings.

Dynamic Volumes Measurements

Respitrace dynamic volume measurements allowed determination of volume above FRC and V_T during the ventilation with actual settings of the ventilator. ΔFRC and time constant of the respiratory system were measured during full relaxation of the lung at atmospheric pressure (23). Total volumes shown in Table 3 represent the sum of ΔFRC and V_T measured in $ECCO_2R$-LFPPV. Expiratory airway resistance was calculated from the following relationship: Time constant = Resistance × Compliance.

Statistical Analysis

Comparisons between respiratory parameters obtained during mechani-

TABLE 3

STATIC P-V CURVES AND DYNAMIC VOLUME TRACINGS IN $ECCO_2R$

	Static Pressure-Volume Curves				Dynamic Volume Tracings				
			Upper Deflection Point						
Patient No.	Total Compliance (ml/cm H_2O)	Lower Inflection Point (cm H_2O)	Volume (ml)	Pressure (cm H_2O)	ΔFRC (ml)	VT (ml)	Total Volume (ml)	Time Constant (s)	Resistance (cm $H_2O \cdot L^{-1} \cdot s$)
1	25	6	650	28	700	250	950	1.0	40
2	37	16	800	40	430	370	800	0.7	19
3	40	6	1,000	30	740	300	1,040	1.0	25
4	18	No*	500	30	150	350	500	0.8	44
5	20	No*	400	40	400	320	600	4.0	200
6	18	No*	700	40	350	350	700	0.9	50
7	20	10	> 600	> 40†	450	400	850	0.8	40
8	81	12	2,000	31	1,700	350	2,050	1.5	19
9	35	17	400	27	270	220	490	0.5	14
10	65	12	1,000	17	1,500	400	1,900	8.5	131
11	15	No*	> 400	> 40†	230	260	490	0.7	47
Mean	34				629	325	943	1.9	57
± SEM	21				514	61	544	2.4	57

* No lower inflection point observed on P-V curve.
† No upper deflection point observed in the range of pressures tested.

cal ventilation and $ECCO_2R$-LFPPV were performed using Wilcoxon's nonparametric test. Results were expressed as mean ± standard deviation, and $p < 0.05$ was taken as significant.

RESULTS

The 11 patients were treated by $ECCO_2R$-LFPPV without technical problems. Extracorporeal support was maintained for a mean duration of 14 d (range, 6 to 65 d).

Effects of $ECCO_2R$-LFPPV on gas exchange are shown in Table 2, comparing mean values obtained during optimal mechanical ventilation and $ECCO_2R$-LFPPV. Improvement of gas exchange was observed in all patients: Pa_{O_2}/FI_{O_2} increased from 79 ± 21 to 207 ± 108 ($p < 0.01$). Carbon dioxide elimination was effective in all patients: P_{CO_2} fell from 66 ± 25 to 43 ± 6 mm Hg ($p < 0.01$). These beneficial effects on gas exchange were obtained even though ventilator settings were reduced: peak inspiratory pressure (PIP) decreased from 48 ± 10 to 37 ± 5 cm H_2O ($p < 0.01$); mean airway pressure decreased from 26 ± 6 to 19 ± 3 cm H_2O ($p < 0.01$); VT decreased from 622 ± 131 to 274 ± 60 ml ($p < 0.01$). Hemodynamic tolerance was satisfactory and allowed reduction of inotropic support in most cases. Only two patients (Patients 5 and 10) had severe hemorrhagic complications related to acute vasculitis responsible for alveolar hemorrhage (Patient 5) and diffuse bleeding (Patient 10) and finally died. Eight patients recovered from the acute respiratory failure and were finally discharged from the hospital.

Static P-V Curves

In nine patients, as shown in Table 3, an upper deflection point was present at a pressure ≤ 40 cm H_2O (range, 17 to 40 cm H_2O). Comparison between ventilator settings and static P-V curves showed that all patients were at risk for overinflation, considering PIP and total volume during mechanical ventilation.

In the two others (Patients 7 and 11), the upper deflection point was not reached because the curve was interrupted for all patients at 40 cm H_2O for safety reasons, according to the literature (20). However, these two patients had such low compliances (20 and 15 cm H_2O, respectively) that a high risk of barovolutrauma was likely to be present during conventional ventilation with PEEP and normal tidal volumes in such very stiff lungs.

Dynamic Volumes

In $ECCO_2R$-LFPPV, ΔFRC and total volume averaged 629 ± 514 and 943 ± 544 ml, respectively, as shown in Table 3. Total volume represents the actual thoracopulmonary volume above FRC in LFPPV. Seven patients had total volumes below the upper deflection point at the time of the study. In two other patients (Patients 1 and 7), ventilator settings could be modified to be below upper deflection point volume without worsening of oxygenation. This change was made immediately at the end of the protocol according to the results of the mechanical testing (data not reported in Tables). This was not possible in the two remaining patients (Patients 5 and 10) who remained ventilated with total volumes greater than the upper deflection point volumes of 300 and 900 ml, respectively.

Time constants and calculated resistances averaged 1.9 ± 2.4 s and 57 ± 57 cm $H_2O \cdot L^{-1} \cdot s$, respectively. Patients 5 and 10 had very high time constant values (4 and 8.5 s, respectively) and resistances (200 and 131 cm $H_2O \cdot L^{-1} \cdot s$, respectively).

DISCUSSION

This study confirms that $ECCO_2R$-LFPPV improves arterial oxygenation and allows significant reduction in peak inspiratory pressure and tidal volume when compared with mechanical ventilation, as previously reported (10, 11). The main results show that this improvement could be achieved with no overinflation in nine of the 11 patients treated by $ECCO_2R$-LFPPV. The two other patients with severe airway obstruction due to bleeding remained overinflated during $ECCO_2R$-LFPPV.

The risk of overinflation was defined in this study by determinations made on static P-V curves of the upper deflection point. Above this critical P-V point some normal or diseased alveoli likely began to be overdistended in these inhomogenous lungs. Indeed, thoracic CT-scan analysis of patients with ARDS has clearly demonstrated that the lung injury is not homogeneous (24). P-V curves represent the characteristics of the whole lungs and cannot, therefore, discriminate between normal and diseased areas. Another limitation of this method is that absolute values of FRC were not measured. The changes in the shape of P-V curves, usually drawn from FRC in patients with ARDS (13, 19,

20, 21), is likely to be dependent on the overall reduction of total lung volume and not on the inspiratory capacity only. However, for the purpose of the study, the most important part of the total lung volume is the inspiratory capacity where overinflation may occur only with mechanical ventilation.

The risk of barotrauma is usually discussed in terms of pressures. Marini and Kelsen (25) pointed out the difficulty in determining a safe level of PIP. A threshold of PIP of 40 cm H_2O is considered safe, and it is used as the maximum in permissive hypoventilation and in mechanical studies (17, 20). In the present study, the "safe" PIP was closely dependent on the mechanical characteristics of each patient. In nine of them, the "safe" value of PIP ranged from 17 to 40 cm H_2O. These results may explain why barotrauma could occur with low PIP as was recently reported in animals (26). Our study suggests that in clinical practice the "safe" level of PIP has to be determined individually from mechanical data. PIP decreased significantly in our patients receiving $ECCO_2R$-LFPPV. However, improvement in oxygenation may be due to higher levels of PEEP in our patients receiving $ECCO_2R$-LFPPV as compared with that during mechanical ventilation. Indeed, high levels of PEEP may be responsible for the persisting risk of barotrauma even though small tidal volumes are given, as recently reported in animals (12). The lung overdistension, which could be the true source of barotraumatic lesions (7, 8, 12, 27), was assessed by comparing total lung volumes measured during LFPPV to the volume of the upper deflection point of the P-V curve. Total volumes measured by this method during $ECCO_2R$-LFPPV represent the sum of the ΔFRC caused by PEEP and the small tidal volumes given four times per minute. Nine of the 11 patients had no evidence of risk of overdistention. Only in Patients 5 and 10 did $ECCO_2R$-LFPPV fail to allow such a reduction. This is likely due to unusually high airway resistances responsible for dynamic hyperinflation (28).

Determination of expiratory resistance by Respitrace deserves some comment. The resistance is calculated from time-constant measured during passive expiration by disconnecting the ventilator. Normal values of resistances and time-constants obtained with this method in previous study in mechanically ventilated patients was 8.0 $\pm$ 2.3 cm $H_2O \cdot L^{-1} \cdot s$ and 0.7 $\pm$ 0.3 s, respectively (23, 29). The expiratory resistance measured with this method includes tracheal tube resistances. During $ECCO_2R$-LFPPV the resistance caused by the intratracheal catheter is added and may contribute to high values observed in this study. However, the very high values of expiratory resistances in Patients 5 and 10 cannot be explained by these effects only, and they could be reasonably related to airway obstruction caused by bleeding. Even though $ECCO_2R$-LFPPV provides a long expiratory time, the increased time constants of these two patients may cause dynamic hyperinflation. Another potential cause of increased lung inflation is continuous flow of oxygen given through the intratracheal catheter. Optimal final adjustment of this flow in the present study was made using Respitrace tracings to limit this phenomenon, as previously described (11). Tidal volume measured by Respitrace was only 50 ml higher than that measured by ventilator in the present study (325 $\pm$ 61 versus 274 $\pm$ 60, $p = 0.02$).

There is another advantage to using Respitrace with the actual settings of the ventilator in addition to P-V curves to evaluate the risk of overinflation. P-V curves are static, and therefore if volume above FRC at PIP is only determined on these curves, dynamic overinflation is not detected, and inflation may be underestimated.

Clinical benefit of reduction of lung overinflation by $ECCO_2R$-LFPPV is difficult to analyze in this short-term study. Most patients already had severe barotraumatic complications before onset of $ECCO_2R$-LFPPV. Borelli and colleagues (31) reported the role of the duration of prior mechanical ventilation on barotraumatic lesions. In only one patient with dramatically increased airway resistances (Patient 10) did pneumothorax occur during $ECCO_2R$-LFPPV. Moreover, the underlying lung disease may play an important role in the development of barotraumatic lesions, as shown in animals (30). Similarly, this uncontrolled study does not allow conclusions on the effect of reduction of lung overinflation on final outcome, which might be related because of other events in patients with ARDS.

In conclusion, this study confirms that $ECCO_2R$-LFPPV allows improvement of arterial oxygenation in patients with severe ARDS who do not respond favorably to mechanical ventilation. The "safe" level of PIP depends on lung mechanical properties, and it must be defined individually in ARDS. During mechanical ventilation all of the patients were at risk of barotrauma. By contrast, during $ECCO_2R$-LFPPV only two of them with extremely high airway resistances because of bronchoalveolar bleeding had persistent risk. $ECCO_2R$-LFPPV improves oxygenation without lung overinflation in a majority of patients with ARDS.

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