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The role of total static lung compliance in the management of severe ARDS unresponsive to conventional treatment

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Abstract. A group of 36 patients with severe adult respiratory distress syndrome (ARDS) meeting previously established blood gas criteria (mortality rate 90%) became candidates for possible extracorporeal respiratory support [low frequency positive pressure ventilation with extracorporeal CO_2 removal (LFPPV-$ECCO_2R$)]. Before connecting the patients to bypass we first switched the patients from conventional mechanical ventilation with positive end expiratory pressure (PEEP) to pressure controlled inverted ratio ventilation (PC-IRV), and then when feasible, to spontaneous breathing with continuous positive airways pressure (CPAP). Forty eight hours after the patients had entered the treatment protocol, only 19 out of the 36 patients in fact required LFPPV-$ECCO_2R$, while 5 were still on PC-IRV, and 12 were on CPAP. The overall mortality rate of the entire population was 23%. The only predictive value of success or failure of a particular treatment mode was total static lung compliance (TSLC). No patients with a TSLC lower than 25 ml (cm H_2O)$^{-1}$ tolerated either PC-IRV or CPAP, while all patients with a TSLC higher than 30 ml (cm H_2O)$^{-1}$ were successfully treated with CPAP. Borderline patients (TSLC between 25 and 30 ml (cm H_2O)$^{-1}$) had to be treated with PC-IRV for more than 48 h, or were then placed on LFPPV-$ECCO_2R$ if $Paco_2$ rose prohibitively. We conclude that TSLC is a most useful measurement in deciding on the best management of patients with severe ARDS, unresponsive to conventional treatment.

Key words: ARDS – Membrane lung – Mechanical ventilation – Lung compliance

We recently introduced low frequency positive pressure ventilation (LFPPV) with extracorporeal CO_2 removal ($ECCO_2R$) to treat severe parenchymal acute respiratory failure (adult respiratory distress syndrome, ARDS), unresponsive to continuous positive pressure ventilation (CPPV) [4]. During LFPPV-$ECCO_2R$ the respiratory functions are dissociated, as the CO_2 is removed extracorporeally through the artificial lung and most of the oxygen is delivered into the natural lungs by apneic diffusion. The natural lungs are kept motionless for most of the time, and gently ventilated with only 3 or 4 breaths per min (sigh) to preserve pulmonary mechanics [2]. The rationale of this therapy is to "rest" the diseased lungs, to assure in static conditions an optimal intrapulmonary distribution of gases and to avoid pressure related complications of CPPV.

Since our preliminary report [3] on the clinical application of LFPPV-$ECCO_2R$, 90 ARDS patients have been referred to our Intensive Care Unit from other hospitals as candidates for extracorporeal support after CPPV had failed to provide an adequate gas exchange. Among these, 36 met established criteria of severity derived from measurement of blood gases under strict ventilatory conditions which defined a life threatening stage of ARDS with an expected mortality of 90% [8] and were judged to be suitable for LFPPV-$ECCO_2R$. Prior to connection to extracorporeal support, however, we first applied in sequence, as a less drastic alternative to CPPV, pressure controlled inverted ratio ventilation (PC-IRV) modified from Lachman et al. [6] and spontaneous breathing with continuous positive airways pressure (CPAP). These two techniques can be expected to provide a better distribution of inspired gases, while reducing the high airways pressures required to ventilate the stiff lungs of ARDS by conventional CPPV.

A protocol of sequential treatments was thus devised in order to find the most effective support for the respiratory function. We wish to report our expe-

Table 1. Etiology of ARDS, duration, and outcome for different modes of treatment. Group A: low frequency positive pressure ventilation with extracorporeal CO_2 removal, Group B: pressure controlled inverted ratio ventilation, Group C: spontaneous breathing with continuous positive airways pressure

Etiology	*n*	Group A			Group B			Group C		
		Days	Recovery		Days	Recovery		Days	Recovery	
			Yes	No		Yes	No		Yes	No
Polytrauma	17	9.2±2.7	1	5	8.3±6.4	4	1	6.7±3.5	6	–
Bacterial pneumonia	3	4.6±1.7	1	1		–	–	2.0	1	–
Viral pneumonia	7	6.3±1.0	3	1		–	–	3.6±2.2	3	–
Septic, toxic shock lung	6	3.6±2.2	5	–		–	–	1.7	1	–
Fat embolism	2	7.3±6.5	2	–		–	–		–	–
Asphyxia	1		–	–		–	–	1	1	–
Total	36		12	7		4	1		12	0
%			63%	37%		80%	20%		100%	

rience with PC-IRV, CPAP and LFPPV-ECCO$_2$R on this selected and defined group of patients, since we feel that it may prove a useful guideline for the appropriate management of ARDS unresponsive to conventional treatment.

Materials and methods

The study group consisted of 19 male and 17 female patients (age 32.2 ± 11.9 years, range 17 – 56) with ARDS of various aetiologies (Table 1) who were admitted, after transfer from other hospitals, to our intensive care unit in a period of 18 months as candidates for extracorporeal support. In all a diagnosis of ARDS was confirmed from the history, the impaired gas exchange, the decreased total static lung compliance, and bilateral X-ray opacification with widespread areas of consolidation. The average number of days on conventional CPPV before transfer had been 7.47 ± 11.8 (range 1 – 56 days).

Monitoring and measurements

The patients were provided with an arterial cannula (pedial or radial) and with a Swan Ganz Thermodilution Catheter – 7 French.

Airways pressures were measured with EMT 35 transducers and recorded on a Mingograf 34.

Blood pressures were measured with Bentley Trantec Model 800 transducers and recorded on a Kontron 128 A monitor. Blood gases were measured with an ABL2 (Radiometer, Copenhagen), and hemoglobin and oxygen hemoglobin saturation with an IL 282 (Instrumentation Laboratory, Inc., Lexington, MA, USA).

Expired gases were measured with an OM 11 O_2 analyser and LB2-CO_2 Beckman analyser and/or Normocap (Datex) gas analyser. Cardiac output was measured by the Edwards 9520 computer. Venous admixture (Q_{VA}/Q) and cardiac index (CI) were computed according to standard formulae.

Assessment of ARDS severity

The severity of respiratory failure was assessed using previously established physiological criteria based on blood gases under defined ventilatory conditions [1]; and these were an arterial blood partial pressure of oxygen (PaO_2) of less than 50 mm Hg for more than 2 h at $F_IO_2 = 1.0$ and positive end expiratory pressure (PEEP) at 5 cm H_2O or more (fast entry criteria for extracorporeal membrane lung oxygenation, (ECMO), or a PaO_2 of 50 mm Hg or less for 12 h with inspired oxygen fraction (F_IO_2) 0.6 and PEEP at 5 cm H_2O or more, or a shunt of more than 30% while breathing 100% oxygen at a PEEP of 5 cm H_2O (slow entry, ECMO criteria).

Assessment of lung mechanics

On admission to our intensive care unit the patients underwent anaesthesia (Althesin) and muscle relaxation (Pancuronium) and a lung volume-pressure curve was measured. At atmospheric pressure, after suction of bronchial secretions and three manual inflations, the lungs were inflated step by step (100 ml at a time) with a 1.5 l syringe, up to a pressure of 40 – 50 cm H_2O, and at each step the inflated volume was held until a plateau was reached. The volume-pressure ratio was then computed from the pressure measured at 8 – 10 ml · kg^{-1} volume inflation on the inflation line of the P-V curve and arbitrarily called the total static lung compliance (TSLC), as an index of the respiratory system elasticity and the opening pressure of the alveoli.

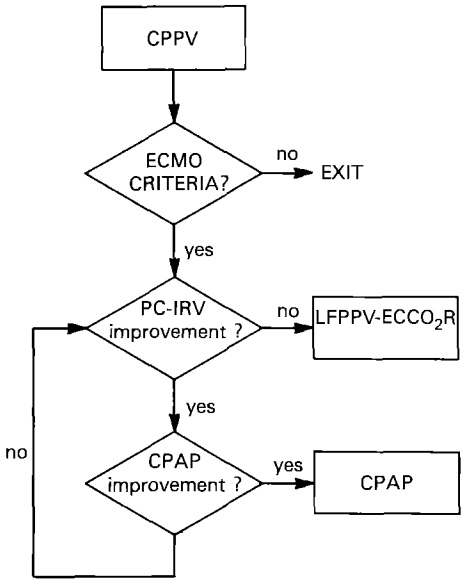

Fig. 1. Protocol of sequential application of respiratory support. See the text for details

Treatment protocol

After basal data collection and severity assessment, those patients that met ECMO entry criteria on conventional continuous positive pressure ventilation (CPPV) were switched from the 1:2 I/E ratio to an I/E ratio of 3:1 or 4:1 and we decreased the PEEP and the working pressure of the ventilator to 30–35 cm H_2O, thus effecting the PC-IRV (see below for further details). If after an average of 4 h on PC-IRV no improvement in gas exchange was observed [no improvement in PaO_2, and/or a rise in arterial blood partial pressure of carbon dioxide ($PaCO_2$)] the patients were scheduled for extracorporeal support on LFPPV-ECCO$_2$R. If PC-IRV improved oxygenation while maintaining a normal $PaCO_2$, an attempt was made to treat the patients with CPAP.

If the attempt was successful (no decrease in oxygenation with normal $PaCO_2$) the patients were maintained on CPAP, otherwise PC-IRV was resumed until sufficient improvement (PaO_2 70 mm Hg or higher at F_IO_2 0.4 while on PC-IRV) allowed CPAP to be tried again. The schema of this protocol is summarized in Figure 1. It is evident that the final treatment is represented by LFPPV-ECCO$_2$R or CPAP, while PC-IRV is a form of "temporary" support.

Three groups of patients could be identified within 48 h after application of the protocol. Group A, patients on or scheduled for LFPPV-ECCO$_2$R; Group B, patients on PC-IRV; and Group C, patients on CPAP.

Techniques of respiratory support

Pressure controlled inverted ratio ventilation. The patients were ventilated (Servo Ventilator 900 B Siemens Elema) with the pressure of the ventilator set at 30–35 cm H_2O (pressure control) and "decelerated" inspiratory flow. PEEP levels ranged from 4 to 8 cm H_2O. The inspiratory time was set at 50% of the respiratory cycle and the inspiratory pause at 20%–30%. The respiratory rate ranged between 16 and 22 bpm. F_IO_2 was initially the same as in the CPPV period and was then modified according to the clinical course. Minute ventilation during PC-IRV was obviously dependent on the respiratory system compliance. During the procedure the patients were anesthetized (Althesin) and paralyzed (Pancuronium) while end tidal CO_2 and arterial gases were carefully monitored.

Continuous positive airways pressures. The equipment for CPAP consisted of two rotameters which provided a gas flow of between 20 and 30 l min^{-1} through a plastic tube of large bore (ID 2 cm) connected through a Bennet cascade humidifier and T piece to a 25 liter latex reservoir (reservoir compliance 330 ml cm H_2O^{-1}), and then to the patient. The expiratory limb of the T piece was placed under water to provide the selected PEEP. No valves were inserted into the circuit and, due to the mechanical characteristic of the reservoir, no drop in pressure of more than 1 to 2 cm H_2O was observed even at peak inspiratory flow.

Low frequency positive pressure ventilation with extracorporeal CO_2 removal. The LFPPV technique has already been described [7] and will only be summarized. The patients underwent vein to vein bypass from the inferior vena cava via an internal jugular vein. In the last seven perfusions we used a single double lumen catheter introduced through the common femoral vein and the bypass was successfully performed entirely through the inferior vena cava. Blood was pumped by a Sarns roller pump through two Sci Med 3.5 m^2 membrane lungs (ML) connected in series and the minute CO_2 production was thus removed extracorporeally. The oxygen supplied extracorporeally was limited by the low extracorporeal blood flow and accounted approximately for 20%–30% of total O_2 consumption. The blood flow averaged 1.5 l · min^{-1}. Temperature, ML blood flow and gas flow, blood pressure across the ML and oxygen saturation of input venous blood were continuously monitored.

The patients, while on anesthesia and paralysis, were ventilated at 3–4 breaths per min, with pressure limited to 30–35 cm H_2O. The inspiratory time lasted 1.5–2 s with an inspiratory pause of 1–1.2 s and the

Table 2. Baseline respiratory and hemodynamic parameters (mean ± 1 SD). The QVA/Q and hemodynamic parameters of Group C patients refer to 5 patients out of 12 (in the remaining 7 patients the Swan Ganz catheter was placed later during the alternative treatment). Significant differences were observed only in TSLC, PAP and QVA/Q of Group C patients. [a] $p < 0.05$

	Group A $n = 19$	Group B $n = 5$	Group C $n = 12$
TSLC ml cm H_2O^{-1}	21.3 ± 7.00	27.4 ± 2.70	38.00[a,b] ± 8.50
F_IO_2	0.81 ± 0.14	0.74 ± 0.09	0.7 ± 0.09
PEEP, cm H_2O	12.20 ± 5.30	7.60 ± 2.3	8.30 ± 4.10
$\dot{V}e$, ml min^{-1} kg^{-1}	252.00 ± 67.00	231.00 ± 95.00	220.00 ± 59.00
TV, ml kg^{-1}	11.6 ± 2.30	10.70 ± 4.80	11.10 ± 3.10
PaO_2, mmHg	49.50 ± 12.00	52.70 ± 10.60	49.10 ± 7.20
$PaCO_2$, mmHg	45.20 ± 8.50	47.30 ± 8.70	41.40 ± 8.60
pHa	7.38 ± 0.06	7.38 ± 0.08	7.42 ± 0.09
QVA/Q	0.56 ± 0.10	0.40[a] ± 0.03	0.35[a] ± 0.06
CI, l min^{-1} m^{-2}	4.14 ± 1.01	4.42 ± 0.12	4.09 ± 1.01
PAP, mmHg	32.80 ± 10.80	23.70 ± 7.80	23.20[a] ± 7.10
CVP mmHg	7.60 ± 5.50	6.20 ± 7.10	9.50 ± 6.20
WP, mmHg	9.50 ± 5.20	7.00 ± 5.80	10.50 ± 5.50
mAP mmHg	87.60 ± 18.80	80.40 ± 20.80	90.00 ± 11.10
PVR dyne s cm^{-5}	280.00 ± 107.00	164.00 ± 16.00	140.00 ± 67.00

$\dot{V}e$ = minute ventilation; TV = tidal volume; pHa = arterial blood pH; CVP = central venous pressure; WP = pulmonary artery wedge pressure; mAP = mean arterial blood pressure, PVR = pulmonary vascular resistance. [a] Significant differences ($p < 0.05$) compared to group A; [b] significant differences ($p < 0.05$) compared to group B. For remaining abbreviations see text

end expiratory pause was 12 – 16 s. PEEP, F_IO_2 in the ventilator and F_IO_2 in the ML were set according to the clinical course.

A continuous 100% oxygen flow (550 – 1000 ml min^{-1}) was introduced through a small catheter advanced to the level of the carina to maintain the selected PEEP during the end expiratory pause and to provide oxygenation of the patient by diffusion. Any oxygen in excess of that consumed was vented through the expiratory port of the ventilator.

Results

Every patient met either the slow (32 patients) or fast (4 patients) ECMO entry criteria while in our intensive care unit and while on conventional CPPV. The mean time we kept the patients on conventional CPPV averaged 40 h following which the sequence of alternative treatment outlined in the protocol was applied.

The starting point for this protocol is taken from the time of inversion of the I/E ratio and the decrease of working pressure of the ventilator (PC-IRV).

Forty-eight hours after PC-IRV began, the patients fell into three groups: Group A: LFPPV-$ECCO_2R$, 19 patients; Group B: PC-IRV, 5 patients; and Group C: CPAP, 12 patients.

Table 1 summarizes the ARDS etiology, the duration of treatment and the final outcome of the three groups. Twenty five out of 36 patients (77%) fully recovered their lung function, with PaO_2 over 70 mm Hg and $PaCO_2$ less than 45 mm Hg, while spontaneously breathing room air 1 month after extubation.

The respiratory and haemodynamic parameters collected during the basal period on CPPV are listed in Table 2. Although the three groups were homogeneous with respect to blood gases, the Group A patients had a QVA/Q and mean pulmonary artery pressure (PAP) significantly higher than Group C patients. However, any one measurement alone did not suggest the appropriate mode of treatment, as considerable overlap existed among the 3 groups.

TSLC was the most helpful in broadly suggesting success or failure of a particular treatment (Fig. 2). Patients with TSLC lower than 25 ml · cm H_2O^{-1} could not be maintained on PC-IRV or CPAP, while all the patients (but one) with TSLC higher than 30 ml · cm H_2O^{-1} were successfully treated with CPAP. The borderline patients with TSLC between 25 and 30 ml · cm H_2O^{-1} had to be treated with prolonged PC-IRV, or with LFPPV-$ECCO_2R$ if PC-IRV resulted in a significant rise in $PaCO_2$.

The effectiveness of our treatment, 48 h after the application of the protocol, is shown in Table 3. Of great importance is the rapid improvement in Group C patients with relatively high compliance when conventional CPPV was suspended and the patients were placed on CPAP (Fig. 3).

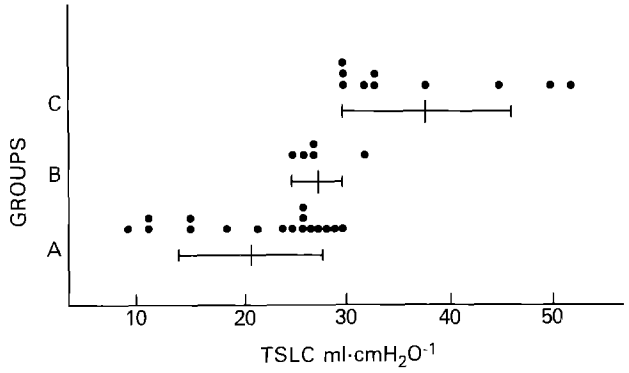

Fig. 2. Baseline total static lung compliance in Groups A, B, and C during conventional continuous positive pressure ventilation

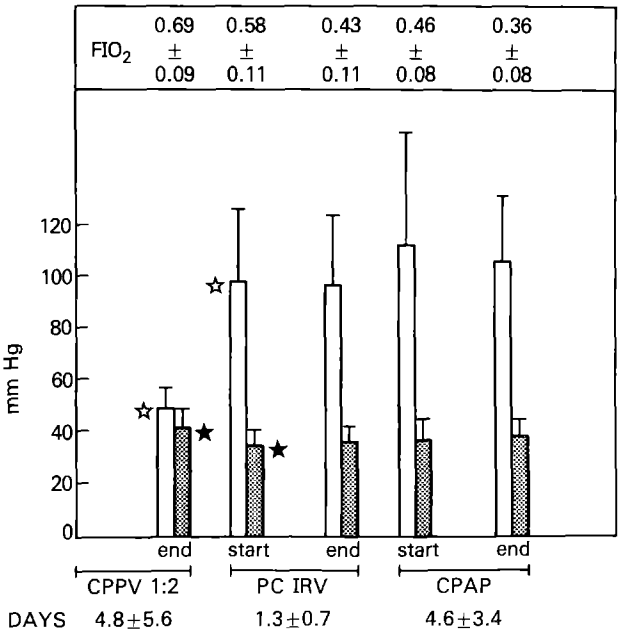

Fig. 3. Arterial PO_2 (□) and PCO_2 (▨) of Group C patients in transition from CPPV to PC-IRV to CPAP. Significant changes ($p < 0.05$) are indicated by open (PO_2) and closed (PCO_2) stars. The "start" measurements were taken within 2 h after the beginning of the new mode of ventilation. The "end" measurements were taken immediately before the change. Mean values ±1 SD

Discussion

Severe hypoxemia is the most characteristic feature of acute parenchymal respiratory failure. Primary determinants of hypoxemia are a possible diffusion impairment, a true right to left shunt (Qs/Qt), and a ventilation-perfusion (VA/Q) mismatch. While improvement of the first two components is associated with anatomical resolution of the underlying pathology, the VA/Q mismatch can partially be corrected by the mode of ventilation. After several days of CPPV treatment, all those patients had severely impaired gas exchange, irrespective of TSLC. The change from CPPV treatment to one outlined in this protocol allowed a rapid and striking improvement in arterial blood gases, even though in most instances the lung pathology had probably remained unchanged.

The lungs in ARDS are likely characterized by alveolar units having different time constants, secondary to variations in compliance and airways resistance. High volume and high pressure CPPV can result in hypoventilation of the stiffer zones and hyperventilation of the less stiff zones, encouraging diversion of the blood flow. In contrast, apneic diffusion in static conditions of inflation as during LFPPV-ECCO$_2$R allows even distribution of alveolar PO_2 unaffected by differences in time constants: VA/Q impairment, if any, is in this case completely reversed, and allows for the best possible oxygen uptake at any given course of the patient's illness [5].

A similar mechanism may play a role in PC-IRV, where oxygenation is improved through perhaps a

Table 3. Respiratory and hemodynamic parameters of Group A, B, and C during the differential treatment. Data in Group B and C were taken 48 h after start of PC-IRV. In Group A data refer to values obtained at 25% (average 36 h) of total time of the extracorporeal support. Mean ±1 SD

	Group A	Group B	Group C
F_IO_2	0.48± 0.10	0.44 ± 0.05	0.44 ± 0.08
PEEP, cm H_2O	17.90± 3.40	9.50[a]± 1.00	7.91[a]± 4.53
PaO_2 mmHg	100.90± 44.53	109.05 ±30.92	108.71 ±45.14
$PaCO_2$ mmHg	35.76± 6.00	36.50 ± 3.98	40.68 ±10.94
pHa	7.30± 0.72	7.44 ± 0.05	7.42 ± 0.04
QVA/Q	0.39± 0.16	0.18 ± 0.12	0.21[a]± 0.11
CI l min^{-1} m^{-2}	3.53± 1.12	3.16 ± 0.13	4.33 ± 0.57
PAP mmHg	28.84± 7.11	24.00 ± 6.08	16.78[a]± 6.63
CVP mmHg	7.63± 2.90	9.33[a]± 1.15	2.18[a]± 2.09
WP mmHg	12.07± 8.03	8.00 ± 2.65	5.67 ± 4.06
mAP, mmHg	94.32± 15.20	94.25 ±24.06	92.90 ± 9.80
PVR dyne s cm^{-5}	276.00±120.00	246.00 ± 1.41	128.80[a]±56.40

For abbreviations see Table 2 and text

more even gas distribution due to a prolonged inspiration phase, also partially overcoming the scattered time constants of different lung units.

It is more difficult to speculate on the mechanism through which CPAP may improve oxygenation compared to CPPV. A redistribution of pulmonary blood flow due to lower mean airways pressure and/or changes in intrapleural pressure in spontaneous breathing is possibly involved. However, our patients were not transferred directly to CPAP from CPPV, but after a transition period while on PC-IRV. A short period of PC-IRV may even be mandatory to provide safe transition from CPPV to CPAP.

Whatever the process involved in the improved oxygenation, carbon dioxide elimination follows different mechanisms and in our study conditions, was mainly dependent on TSLC. Conventional CPPV failed in our patients to assure adequate oxygenation, but provided an adequate CO_2 elimination though at the cost of high tidal and minute volumes. Each of the forms of ventilation we used as an alternative to CPPV succeeded in improving oxygenation, but the choice and applicability was governed by the ability of the technique to ensure CO_2 removal and was thus TSLC dependent. When the TSLC was higher than 30 ml · cm H_2O^{-1}, we did not find any difficulty in using PC-IRV, and later CPAP treatment, as the resulting ventilation was adequate to clear to CO_2. But when TSLC was between 25 and 30 ml · cm H_2O, only 5 out of 14 patients could tolerate pressure controlled ventilation and the remaining patients with the TSLC in this range (25 – 30) had to be submitted to LFPPV-$ECCO_2R$ because CO_2 removal was inadequate. The patients whose TSLC was below 25 ml · cm H_2O^{-1} could not be treated with any chance of success save by LFPPV-$ECCO_2R$.

When considering the overall study, the place for conventional CPPV in such severe ARDS appears to be quite restricted. The patients with adequate compliance do not in fact require CPPV as positive pressure breathing can be spontaneously sustained with excellent gas exchange, while in the patients with very low compliance CPPV is not of itself enough if it cannot ensure adequate CO_2 elimination as well as proper oxygenation without excessive pressures or volumes. Extracorporeal support in these cases is mandatory.

This study was not designed to compare the merits of different forms of ventilation in patients with severe ARDS, all of whom met ECMO entry criteria and a projected mortality in excess of 90%. For ethical reasons we could not randomize those patients who tolerated spontaneous breathing and who were in fact improving, into the highly invasive LFPPV-$ECCO_2R$. Similarly, we could not withhold LFPPV-$ECCO_2R$ from those patients who did not tolerate spontaneous breathing, or were deteriorating during CPPV, and PC-IRV. Hence, by design of our protocol we are unable to draw conclusions regarding the superiority of one form of ventilator management over another form of ventilator management, using control groups. However, our results suggest that each of the forms of ventilation may play a specific role in the management of patients with ARDS. Our results also suggest that TSLC (Fig. 4) may be the most useful guide to the proper choice of optimal treatment in severe ARDS.

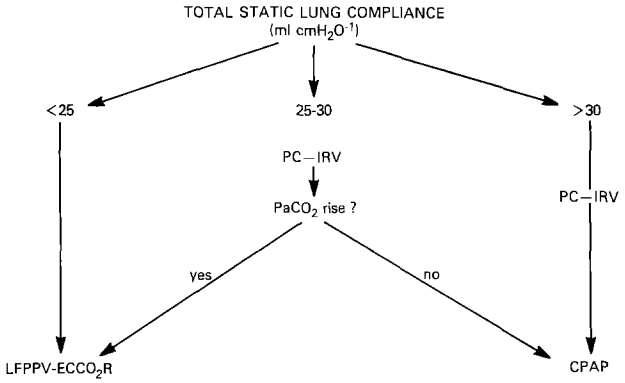

Fig. 4. Compliance oriented pulmonary management in severe ARDS

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