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Improved prognosis of acute respiratory distress syndrome 15 years on

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Abstract *Objective*: Evaluation of the impact of low-volume, pressure-limited ventilation on the recovery rate of acute respiratory distress syndrome (ARDS).
Design: Prospective observational clinical study with historical control.
Setting: University hospital intensive care unit (ICU).
Patients: We studied two groups of, respectively, 33 and 37 ARDS patients separated by 15 years ("historical", June 1978–April 1981, and "recent", October 1993–June1996).
Method: ARDS was defined as the presence of bilateral chest infiltrates and a PaO_2/FIO_2 ratio of less than 200 mmHg under controlled ventilation regardless of PEEP level. Any cardiac participation was excluded by right heart catheterization in the "historical" group and by echo-Doppler examination in the "recent" group. The origin of ARDS was principally pulmonary ($ARDS_p$) in both groups (26/33 and 29/37, respectively), and secondarily extrapulmonary ($ARDS_{exp}$) (7/33 and 8/37, respectively). In the "historical" group, normocapnia was the major goal for respiratory support and was achieved in all patients regardless of airway pressure levels. In contrast, end-inspiratory plateau pressure in the "recent" group was limited to 30 cmH_2O under respiratory support, regardless of $PaCO_2$ level. The "historical" and "recent" ARDS groups were compared with regard to therapeutic procedure and outcome.
Results: Normalization of $PaCO_2$ (36 ± 6 mmHg) in the "historical" group required high airway pressure (end-inspiratory plateau pressure at 39 ± 4 cmH_2O) and high tidal volume (13 ml/kg). Respiratory support used in the "recent" group was less aggressive, with lower airway pressure (end-inspiratory plateau pressure 25 ± 4 cmH_2O) and tidal volume (9 ml/kg) resulting in "permissive" hypercapnia (51 ± 10 mmHg).Mortality rates significantly decreased from 64 % in the "historical" group to 32 % in the "recent" group ($p < 0.01$). This decrease concerned only $ARDS_p$, which was markedly predominant in both groups.
Conclusion: Mortality due to ARDS of pulmonary origin has declined in our unit over the last 15 years. Low-volume, pressure-limited (protective) ventilation seems the most likely reason for improved survival, despite hypercapnia.

Key words Acute respiratory distress syndrome · Protective ventilation · Permissive hypercapnia · Acute cor pulmonale · Mortality rate

Introduction

In recent years the concept of "permissive hypercapnia" [1] has led to major changes in the respiratory support of ARDS patients. Concomitant advances have included nitric oxide (NO) administration [2], tracheal gas insufflation [3], and ventilation in the prone position [4]. A therapeutic optimization strategy including these advances [5] is used daily in our unit and has, we feel, led to some improvement in the survival of ARDS patients.

In October 1993 we started a prospective study of ARDS patients to establish whether or not the survival rate had improved, and to quantify any such improvement. The study included 37 successive patients and was designed as a comparison with a group of ARDS patients we described 15 years ago [6]. This "historical" group was treated with aggressive respiratory support in which normocapnia was an imperative requirement. The present study was completed in May 1996 and the results are discussed in the present report.

Patients and methods

Patients

We studied two groups ("historical" and "recent", separated by 15 years) of ARDS patients requiring respiratory support. Occurring in patients who were in good health 48 h before, ARDS is characterized by acute onset of respiratory failure, bilateral chest infiltrates and a PaO_2/FIO_2 ratio below 200 mmHg under controlled ventilation, regardless of PEEP level [7]. Between June 1978 and April 1981, we had studied 50 successive patients requiring mechanical ventilation for acute respiratory failure, to determine if the initial severity of hypoxemia constitutes a valuable prognosis factor [6]. The physiologic records of these patients are still in our possession. Thirty-three of these patients met ARDS criteria [7] and were selected as the "historical" group. The "recent" group included 37 successive ARDS patients observed between October 1993 and June 1996. Right heart catheterization ("historical" group) or bedside echocardiography ("recent" group) was used to rule out any episode of cardiac edema. In the 'historical' group, a pulmonary artery occlusion pressure higher than 18 mmHg after a rapid fluid challenge was the exclusion criterion. In the 'recent' group, the exclusion criterion was demonstration of chronic cardiopathy by echocardiography associated with a high filling pressure pattern on the Doppler mitral flow velocity.

All patients were studied during the early phase of ARDS, intubation being necessary in all cases on the 1st day in our Intensive Care Unit (ICU). History, clinical presentation, and microbial findings allowed us to divide the patients into pulmonary ARDS ($ARDS_p$) and extrapulmonary ARDS ($ARDS_{exp}$). Extensive bacterial or viral pneumonia, aspiration pneumonia, chest contusion and near-drowning were considered as causes of $ARDS_p$, whereas septic shock of extra-pulmonary origin and peritonitis were considered as causes of $ARDS_{exp}$. Severe extensive bacterial pneumonia may cause secondary circulatory failure. Therefore "septic shock" was defined as circulatory failure produced by extrapulmonary sepsis and resulting in hypotension (systolic arterial pressure < 90 mmHg by invasive monitoring), despite adequate fluid resuscitation, along with the presence of perfusion abnormalities including oliguria, lactic acidosis (blood lactate level > 2.5 mmol/l) and acute alteration of mental status [8].

Severity indices

The PaO_2/FIO_2 ratio was calculated during the first 3 days of respiratory support by averaging three values obtained each day at intervals of 6 h. Total compliance (C_T) was calculated on the 2nd day of respiratory support as inspiratory tidal volume divided by end-inspiratory plateau minus end-expiratory airway pressure. When this value of C_T was recorded, air leak was not present in any patient.

The simplified acute physiology score (SAPS II) was established for each patient during the 1st day of respiratory support in the "recent" group [9]. The logistic organ dysfunction score (LODS)[10] was also calculated retrospectively. The same SAPS II and LODS were calculated retrospectively by re-examining files containing physiologic data recorded during the 1st day of respiratory support for each patient in the "historical" group. We also calculated the probability of hospital mortality using LODS (predicted mortality), and the "Standard Mortality Ratio" (SMR), by dividing the observed by the predicted hospital mortality.

Mechanical ventilation

In the "historical" group, patients were mechanically ventilated in the controlled mode (Bourns Bear I respirator) without limitation in airway pressure. We used a tidal volume of 13 ± 2 ml/kg, an inspiratory flow of 60 l/min, an I/E ratio of 1:2, a respiratory rate of 16 ± 2 cycles/min, an end-inspiratory pause of 0.5 s and a PEEP level of 10 ± 4 cmH_2O. In this "historical" group the PEEP level was titrated to obtain a SaO_2 of 90 % or more, even if a drop in systemic arterial pressure with this PEEP level required supplemental hemodynamic support. Patients were sedated with diazepam and phenoperidine. Controlled ventilation was the only respiratory support used and was maintained until death or weaning.

In the "recent" group, patients were also initially ventilated in the controlled mode (Bennet 7200 respirator) with a limitation of end-inspiratory plateau pressure to 30 cmH_2O, and this mode was replaced by pressure support as soon as some improvement was observed. Initial ventilator settings included a tidal volume of 9 ± 2 ml/kg, an inspiratory flow of 30 l/min, an I/E ratio of 1:1.5, a respiratory rate of 16 ± 2 cycles/min, an end-inspiratory pause of 0.5 s and a PEEP level of 6 ± 4 cmH_2O. In this "recent" group, the PEEP level was selected as producing oxygenation improvement without change in systemic arterial pressure. During ventilation in the controlled mode, patients were sedated with midazolam and sufentanil.

Additional respiratory therapy

Additional respiratory therapy was used in some patients of both the "historical" and "recent" groups. Except for *differential lung ventilation*, which was used in three patients during 36–48 h, no other additional respiratory therapy was used with the "historical" ARDS patients, for whom mechanical ventilation was the only respiratory support. In contrast, several additional therapeutic modalities were used in the "recent" ARDS group. *NO inhalation* was used during the first days of respiratory support in eight patients who remained severely hypoxemic ($PaO_2/FIO_2 < 100$). NO was directly delivered by the tracheal tube to 2–8 ppm, according

to the dose-response curves reported by Puybasset et al. [11]. *Direct administration of low-flow oxygen in the tracheal tube* was used in five patients to reduce hypercapnia. *Ventilation in the prone position* was used in four patients, in whom computed tomography revealed extensive posterior areas of consolidation.

Hemodynamic monitoring and hemodynamic support

All patients had invasive radial artery monitoring via a small Teflon catheter, permitting continuous arterial pressure recording and repeated arterial samples for blood gas analysis. In the "historical" group, pulmonary artery occlusion pressure and right heart pressures were monitored through a Swan-Ganz catheter. Bedside echocardiography was performed in 23 patients as reported elsewhere [12]. The echographic pattern of acute cor pulmonale (ACP) has been extensively described in a recent review [13]. Using an apical four-chamber view, ACP was ruled out when the right/left ventricular area ratio at end-diastole was less than 0.6, graded as moderate when it ranged from 0.6 to 1, and severe when more than 1.0 [13]. In the "recent" group, right heart catheterization was no longer performed, the hemodynamic status being daily assessed by bedside two-dimensional echocardiography.

Hemodynamic support by infusion of a vasoactive agent for more than 24 h was required in 18 patients of the "historical" group (55 %) and in 25 patients of the "recent" group (68 %).

Fluid balance

To avoid fluid overload, careful adjustment in fluid balance was deemed imperative in both groups [14], so that fluid intake exactly compensated fluid loss. Extracorporeal fluid removal was required in 18 patients, by means of repeated hemodialysis in 9 patients of the "historical" group, and by prolonged hemodiafiltration in 9 patients of the "recent" group.

Statistical analysis

Statistical calculations were performed using the Statistical Analysis System software package (SAS version 5, SAS Institute, Cary, N. C.). The data are expressed as means ± 1 standard deviation. Inter-group comparisons of physiologic data were performed using a Mann-Whitney U test. A p value less than 0.05 was considered as statistically significant. Cumulative survival curves in both "historical" and "recent" ARDS groups were computed by the Kaplan-Meier method and were compared by the log-rank test.

Results

Mean age, physiologic data and mortality rates are presented in Table 1. Patients were older in the "recent" group, but general severity indices revealed no inter-group differences. With regard to respiratory status, PaO_2/FIO_2 on days 1, 2 and 3 were similar. A major and significant reduction in hospital mortality was observed in the "recent" group compared to the "historical" group (32 % versus 64 %) resulting in a highly significant change in SMR from 1.42 to 0.66.

The etiologic features of ARDS are presented in Table 2. Both groups contained a majority of patients with $ARDS_p$. No major change of etiologic characteristics was noted between the two study periods. The two main causes of $ARDS_p$ were aspiration pneumonia (in almost all cases as complication of a suicide attempt by drug overdose), and extensive bacterial or viral pneumonia. The main cause of $ARDS_{exp}$ was severe sepsis of extrapulmonary origin, including peritonitis. In the "recent" group, extensive pneumonia (5 cases) or septic shock (2 cases) complicated AIDS, an illness unknown at the time of the "historical" study. A reduction in mortality only concerned $ARDS_p$. The hospital mortality rate of $ARDS_{exp}$ was unchanged, but the limited number of patients in this subgroup precludes any conclusion. Fourteen of the 23 patients studied by two-dimensional echocardiography in the "historical" group had ACP (61 %), which was moderate in 9 patients and severe in 5. This prevalence was significantly lower in the "recent" group where only three patients had an echocardiographic pattern of moderate ACP (8 %).

Comparisons between respiratory management of "historical" and "recent" ARDS patients are given in Table 3. The duration of mechanical ventilation was similar in the two groups. Tidal volume was smaller in the "recent" group, resulting in a higher $PaCO_2$. The PEEP level used in the "recent" group was significantly lower.

The significant improvement in recovery in the "recent" ARDS group is also illustrated by survival curves

Table 1 Mean age, physiological data, and mortality rate of "historical" and "recent" ARDS. * $p < 0.05$

	"historical" ARDS (n = 33)	"recent" ARDS (n = 37)
Mean age (years)	44 ± 15	52 ± 16*
SAPS II	52.4 ± 12	53.4 ± 15.2
LODS	7.7 ± 3.3	8.1 ± 3.9
PaO_2/FIO_2 day 1	113 ± 39	121 ± 40
PaO_2/FIO_2 day 2	163 ± 100	134 ± 54
PaO_2/FIO_2 day 3	190 ± 113	168 ± 80
Mortality rate	64 %	32 %*

Table 2 Etiologic features of ARDS and respective mortality rates in subgroups. * $p < 0.05$

	"historical ARDS"	"recent" ARDS
$ARDS_p$	26	29
Extensive pneumonia	10	15
Aspiration	14	13
Chest contusion	2	
Near-drowning		1
Mortality rate	65 %	21 %*
$ARDS_{exp}$	7	8
Septic shock	3	6
Peritonitis	4	2
Mortality rate	60 %	75 %

Table 3 Respiratory management of "historical" and "recent" ARDS. MV: mechanical ventilation, TV: tidal volume, RR: respiratory rate, EIP: end-inspiratory plateau pressure, EEP: end-expiratory pressure. C_T: total compliance. Blood gas values are the averages for the first day on respiratory support. * $p < 0.05$

	"historical" ARDS (n = 33)	"recent" ARDS (n = 37)
Days on MV	14 ± 12	17 ± 14
TV (ml/kg)	13 ± 2	9 ± 2*
RR	16 ± 2	16 ± 2
FIO_2	0.59 ± 0.11	0.63 ± 0.13
EIP ($cm H_2O$)	39 ± 4	25 ± 4*
EEP ($cm H_2O$)	10 ± 4	6 ± 4*
PaO_2 (mm Hg)	66 ± 19	77 ± 22*
$PaCO_2$ (mm Hg)	36 ± 6	51 ± 10*
C_T (ml/cm H_2O)	31.4 ± 9.9	33.2 ± 12.6

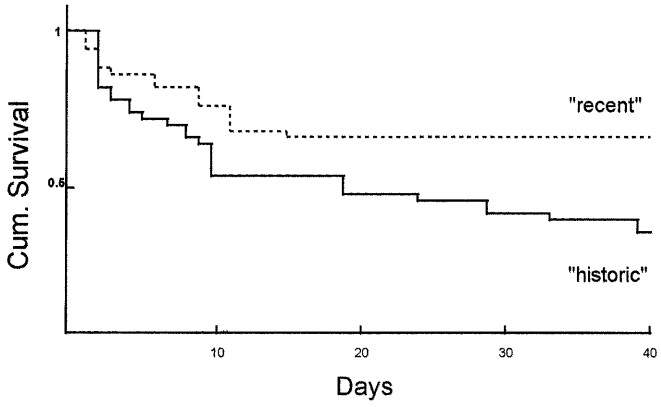

Fig. 1 Cumulative survival curve in "historical" and "recent" ARDS patients, showing better outcome in the "recent" group ($p < 0.01$; log-rank test of the lifetest procedure, SAS)

(Fig. 1). Furthermore, in the "historical" ARDS group, a significant proportion of deaths occurred late, after the 10th day of respiratory support, from refractory respiratory failure or multiple organ failure, while late deaths were uncommon in the "recent" ARDS group. NO inhalation was used during the first days of respiratory support in eight "recent" ARDS patients. In this subgroup, PaO_2 significantly increased from 53 ± 15 mmHg before, to 79 ± 33 mmHg during, NO inhalation. This additional therapy was maintained for 2.2 ± 1.4 days. Ventilation in the prone position was used during an average 5 days in four patients of the 'recent' group in whom respiratory failure had not improved after 48 h of respiratory support. Two patients who underwent this type of ventilation recovered.

Seven "historical" ARDS patients developed tension pneumothorax during mechanical ventilation (21%) which led to a sudden worsening of respiratory failure. Pneumothorax was corroborated by chest X-rays and required emergency chest tube placement. This complication occurred during the 2nd or 3rd week of mechanical ventilation, and air leak worsened progressively until death, despite drainage. Tension pneumothorax was observed only once in the "recent" ARDS patients (3%), and was successfully treated by drainage.

Discussion

In recent years the concept of "permissive hypercapnia" has led to changes in the respiratory support of ARDS patients. In ARDS, tidal delivery is impaired by alveolar flooding or parenchymal consolidation. Applying a large tidal volume may normalize $PaCO_2$, but requires a high airway pressure and runs the theoretical risk of barotrauma [15]. Barotrauma-related worsening of lung disease may partly account for the very poor outcome of ARDS in the past. More recent clinical studies have suggested a better prognosis in recent series of ARDS [16], emphasizing the impact of low tidal volume and reduced airway pressure in one instance [17]. However, a longitudinal retrospective study did not confirm this feeling [18] and two recent randomized studies were unable to demonstrate the protective effect of reduced tidal delivery [19, 20]. However, neither of these studies used a tidal volume as large as that required to control hypercapnia in our "historical" group, and the plateau pressure was not high in the control group in either study.

Protective ventilation, designed to avoid superimposing barotrauma on already severely damaged lungs, has progressively been introduced in our unit and tidal volume has been reduced by approximately 30% (from 13 ml/kg to 9 ml/kg on average) when compared with the normocapnic respiratory support used 15 years ago [6]. The ARDS patients in our "historical" and "recent" groups had similar causes and severity of illness, and their management was very similar except for the respiratory support strategy. The mean age was significantly higher in the "recent" group, but there was no other difference: $ARDS_p$/ $ARDS_{exp}$ ratio was similar, the severity of respiratory failure (judged on PaO_2/FIO_2 ratio) was similar and general severity indices (SAPS II and LODS) were in the same range. However, less severe respiratory failure in the 'recent' group may not be totally excluded because a similar PaO_2/FIO_2 ratio was obtained with a significantly lower average PEEP level. As expected, the marked reduction in tidal volume allowed for the persistence of hypercapnia in the "recent" group. Despite this, a marked improvement was observed with protective ventilation, resulting in a drop in mortality rate from 64% in the "historical" normocapnic group to 32% in the "recent" hypercapnic group. This beneficial effect may have occurred only in the group with $ARDS_p$; in the small number with $ARDS_{exp}$,

the mortality rate was similar in the two groups. However, there were more patients with septic shock in the recent group (6/8 versus 3/7).

The respiratory data reported here strongly suggest that the better outcome in the "recent" ARDS group mainly resulted from the reduction of airway pressure and tidal volume, which, in other respects, was the major change in respiratory support introduced during the period separating the two groups. Both groups were initially ventilated with the same controlled mode, for approximately the same duration, with similar FIO_2 and with the same respiratory rate. We never used high PEEP levels because of their adverse hemodynamic consequences [21], or an inverse I/E ratio since an excessively reduced expiration does not allow sufficient time for spontaneous damping of right ventricular afterloading by lung inflation [22, 23]. The potential effect of NO inhalation, used in some patients of the "recent" group, was associated with a clear improvement in arterial oxygenation. Hence, we could not totally exclude that NO inhalation might have contributed to some improvement in mortality rate by correcting refractory hypoxemia during the first days of respiratory support. But a recent report has denied any effect of NO inhalation on ARDS mortality [24].

Ultimately, ventilation in the prone position, an adjunctive therapy effective on arterial oxygenation [4], might also improve final recovery, but, for practical reasons, it has seldom been brought into play, although its institution might have been warranted more often. However, associated with a 50% recovery rate in the four patients of the 'recent' group in whom it was used, it may not have significantly reduced the mortality rate of this group. Thus, the different respiratory management seems to be the most likely reason for improved survival. However, with 15 years between the two studies, it is difficult to be sure that other aspects of management, such as the use of antibiotics and nursing therapy etc., have not changed. In addition, change in renal support might have some impact on recovery: conventional hemodialysis, which usually carries a bad hemodynamic tolerance, was used in nine patients in the 'historical' group, whereas extracorporeal fluid removal was obtained in the same number of patients in the 'recent' group by prolonged hemodiafiltration, a hemodynamically better tolerated method. In addition, antibiotics were probably more rationally used in the 'recent' group as a result of general medical progress. We should also underscore that the significant reduction in PEEP level in our "recent" group" (6 ± 4 cmH_2O versus 10 ± 4 cmH_2O in the "historical" group") is thought to facilitate airway pressure limitation. Whereas increased therapeutic levels of PEEP have recently been advocated [25], our study suggests that low PEEP levels are not incompatible with lung healing and a good outcome in patients with $ARDS_P$

In a recent study, Gattinoni et al. demonstrated that increased elastance of the total respiratory system, the hallmark of ARDS, primarily resulted from increased lung elastance in $ARDS_p$, whereas the participation of increased chest wall elastance was substantial in $ARDS_{exp}$ [26]. In addition, a different response to PEEP suggested that lung consolidation was prevalent in $ARDS_p$, whereas edema and alveolar collapse were prevalent in $ARDS_{exp}$ [26]. With these mechanical characteristics differentiating the two syndromes, it is possible to hypothesize that lung inflation might cause harmful distension in $ARDS_p$, in which there is little recruitable lung. In contrast, patients with $ARDS_{exp}$, in whom substantial recruitable lung regions are present, were not at risk of excessive distension by lung inflation. Data reported in the present study were recorded in two ("historical" and "recent") ARDS groups, where $ARDS_p$ was largely predominant (70% and 78%, respectively) and are concordant with Gattinoni's concept.

Another interesting difference between our two groups concerned the hemodynamic impact of ARDS. Whereas the "historical" group had a 61% prevalence of ACP, this hemodynamic complication was only present in 8% of patients in the "recent" group. Pulmonary arterial hypertension complicating ARDS was first reported by Zapol et al. [28], and subsequently confirmed by our group [29]. It is generally considered to result from diffuse and irreversible microvascular obstructions [30]. However, these historical findings were obtained at a time when normocapnic aggressive respiratory support was the general rule. ARDS patients were ventilated with high inspiratory pressure, large tidal volumes and high PEEP levels. In previous studies we underlined that this kind of respiratory support might afterload the right ventricle [22, 24]. One might therefore hypothesize that aggressive respiratory support in the past may in part have been responsible for the development, in ARDS patients, of pulmonary hypertension, which is described as the vascular component of the disease [30]. In an experimental study, ventilator-induced lung injury caused pulmonary hypertension [31].

In conclusion, our study confirms that ARDS mortality is declining, particularly when the syndrome is of pulmonary origin. Changes in respiratory support, with the use of a low-volume, pressure-limited ventilation, seem to be the most likely reason for improved survival. Normocapnia at any price, our guiding principle 15 years ago, may well have deleterious consequences.

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