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Niall D. Ferguson
Robert M. Kacmarek
Jean-Daniel Chiche
Jeffrey M. Singh
David C. Hallett
Sangeeta Mehta
Thomas E. Stewart

Screening of ARDS patients using standardized ventilator settings: influence on enrollment in a clinical trial

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N. D. Ferguson (✉) · J. M. Singh · D. C. Hallett · S. Mehta · T. E. Stewart
Division of Respirology,
Department of Medicine,
and the Interdepartmental Division of Critical Care Medicine,
University Health Network
and Mount Sinai Hospital,
University of Toronto,
Toronto, Canada
e-mail: n.ferguson@utoronto.ca
Tel.: +1-416-6036203
Fax: +1-416-6035375

R. M. Kacmarek
Department of Anesthesia
and Critical Care,
Harvard Medical School,
Boston, Massachusetts, USA

J.-D. Chiche
Paris V University,
Paris, France

Present address:
N. D. FergusonToronto Western Hospital,
399 Bathurst Street, EC2–024,
Toronto, Ontario, M5T 2S8, Canada

Abstract *Objectives:* The American–European consensus conference (AECC) definition for acute respiratory distress syndrome (ARDS) requires a $PaO_2/F_IO_2 \leq 200$ mmHg, regardless of ventilator settings. We report the results of using standardized ventilator settings to screen and enroll ARDS patients in a clinical trial of high-frequency oscillatory ventilation (HFOV), including the impact on study enrollment, and potential effects on study outcome. *Design:* Prospective cohort study. *Setting:* Intensive care units in two teaching hospitals. *Participants:* A consecutive sample of 41 patients with early ARDS by AECC criteria (baseline $PaO_2/F_IO_2 \leq 200$) who met all other inclusion/exclusion criteria for the HFOV trial. *Interventions:* Patients were placed on standardized ventilator settings (tidal volume 7–8 ml/kg, PEEP 10 cmH_2O, F_IO_2 1.0), and the PaO_2/F_IO_2 was reassessed after 30 min. *Results:* Seventeen patients (41.5%) had PaO_2/F_IO_2 ratios that remained $\leq$200 mmHg [Persistent ARDS; PaO_2/F_IO_2=94±36 (mean±SD)] and went on to inclusion in the HFOV study; however, in 24 patients (58.5%) the PaO_2/F_IO_2 was >200 mmHg [Transient ARDS; PaO_2/F_IO_2=310±74] and these patients were ineligible for the HFOV study. The ICU mortality was significantly greater (52.9 vs 12.5%; p=0.01) in the Persistent ARDS patients. *Conclusions:* The use of these standardized ventilatory significantly impacted the PaO_2/F_IO_2 ratio and therefore the ARDS prevalence and trial enrollment. These results have effects on the evaluation of the current ARDS literature and conduct of clinical trials in ARDS and hence consideration should be given to the use of standardized ventilatory settings in future ARDS trials.

Keywords Adult respiratory distress syndrome · Artificial respiration · Mechanical ventilation · Anoxemia · Diagnosis

Introduction

Because there remains no available gold standard for the presence of acute respiratory distress syndrome (ARDS), this clinical entity is commonly diagnosed using the American–European consensus conference (AECC) definition [1, 2]. This definition, developed to lend clarity and uniformity to the diagnosis of ARDS, was designed

for use in many settings including research, epidemiology, and individual patient care [1]. The AECC defined ARDS as a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiologic, and physiologic abnormalities. Specifically, it stated that ARDS should be diagnosed when there is the acute onset of hypoxemia with bilateral infiltrates on frontal chest radiograph in the absence of left atrial hypertension. The hypoxemia criterion for ARDS is a $PaO_2/F_IO_2 \leq 200$ mmHg, regardless of positive-end expiratory pressure (PEEP) or other ventilator parameters [1].

The PaO_2/F_IO_2 ratio, however, may be affected by other ventilator settings [3, 4, 5, 6]. Alterations in PEEP and F_IO_2 can dramatically change the PaO_2/F_IO_2 ratio, and it is well established that total shunt fraction is altered by changes in F_IO_2. At an F_IO_2 of 1.0 the effects of ventilation/perfusion mismatch are eliminated and true shunt is measured [5, 6]. Ventilation with 100% oxygen can, however, induce absorption atelectasis and increase true shunt unless PEEP is applied [7, 8]. Recognition of these physiologic phenomena prompted the use of standardized procedures, such as an F_IO_2 of 1.0 and ≥ 5 cmH_2O PEEP, for measuring hypoxemia and defining severe ARDS in the 1970s [9].

In the context of a clinical trial evaluating the safety and efficacy of high-frequency oscillatory ventilation (HFOV) [10], we prospectively placed consecutive patients meeting the AECC ARDS definition on standardized ventilator settings, including an F_IO_2 of 1.0. This was performed both to serve as the final inclusion criterion of the HFOV study, gauging the severity of hypoxemia, and to provide a uniform baseline on conventional ventilation prior to transitioning to HFOV. In this article we describe the results of this screening process, its impact on study enrollment, and its potential effects on study outcome.

Methods

The protocol for the HFOV study was approved by the research ethics boards of both participating institutions. The boards waived the need for informed consent for screening with standardized conventional ventilatory settings. Informed consent was obtained from patients (or their surrogates) who remained eligible for the HFOV trial prior to transitioning to HFOV. For this report, we obtained permission from the research ethics boards to publish non-identifying data on patients who were screened but who were not included in the HFOV study.

Patient selection

Patients in the intensive care units of two quaternary teaching hospitals (Mount Sinai Hospital, Toronto, and Cochin Hospital, Paris) who met the following criteria were prospectively screened. Inclusion criteria were: (a) age >18 years; (b) endotracheal intubation and mechanical ventilation; (c) respiratory failure as a result of one or more risk factors for ARDS; (d) bilateral infiltrates on frontal chest X-ray; and (e) hypoxemia defined as a $PaO_2/F_IO_2 \leq 200$ mmHg. Notable exclusion criteria included: (a) anticipated duration of ventilation <48 h; (b) >48 h since all inclusion criteria were met; (c) minimal chance of ICU survival; (d) significant heart disease; and (e) significant chronic lung disease.

Standardized conventional ventilation

During the standardized screening period all patients were ventilated with pressure control ventilation set to achieve a tidal volume of 7–8 ml/kg predicted body weight [11], ensuring peak inspiratory pressures remained <35 cmH_2O. F_IO_2 was set at 1.0 and PEEP at 10 cmH_2O or the level required to establish a SpO_2 >88%, whichever was higher. The inspiratory:expiratory ratio was set at 1:2 and the respiratory rate adjusted to 15–30 breaths/minute to match previous minute ventilation.

Data gathering and statistics

Baseline data were collected after meeting initial inclusion and exclusion criteria. Physiologic, laboratory, and ventilator data were then collected after 30 min of standardized ventilator settings. All patients were eligible or excluded from the HFOV study based on their PaO_2/F_IO_2 response to the standardized ventilator settings (using a threshold of 200 mmHg).

Student *t* tests were used for continuous variables and dichotomous outcomes were compared with Fisher's exact test. All analyses were performed using standard software (Excel 2000, Microsoft, Redmond, Wash.; and SAS version 8.1, The SAS Institute, Cary N.C.). An expanded Methods section with further details on patient selection and data handling is available online in the electronic supplementary material.

Results

From March through August 2000 (Toronto center; n=20) and from March 2001 to June 2002 (Paris center; n=21), 41 consecutive patients were identified who met the inclusion and exclusion criteria in the two participating ICUs. All of these patients were screened using standardized conventional ventilation settings. In 17 patients (41%), hypoxemia was persistent (PaO_2/F_IO_2<200 mmHg, the Persistent ARDS group) and all consented to continue into the HFOV trial; however, in 24 patients (59%; the Transient ARDS group), the PaO_2/F_IO_2 was >200 mmHg after 30 min of standardized ventilator settings and they were thus excluded from the HFOV study.

Table 1 lists the baseline demographic data, which did not differ significantly between Persistent and Transient ARDS patients.

Ventilator, hemodynamic, and gas exchange data for both the Persistent and Transient groups at baseline and after 30 min of standardized ventilator settings are presented in Fig. 1 and Table 2. Baseline differences between the two groups included a higher F_IO_2, mean airway pressure, respiratory rate, and PEEP in the Persistent group. By design, however, all patients in both groups initially met the AECC criteria for ARDS.

Table 1 Baseline characteristics

	Persistent ARDS	Transient ARDS	*p* value[b]
No. of patients	17	24	
Age (years)	50.2 (15.7)	51.0 (16.8)	NS
Gender (percent female)	46.7	50.0	NS
APACHE II	25.7 (7.3)	21.8 (4.9)	0.08
ARDS risk factor(s)[a]			
Pneumonia	12 (70.6%)	10 (41.7%)	NS
Aspiration of gastric contents	3 (17.6%)	5 (20.8%)	NS
Sepsis	6 (35.3%)	8 (33.3%)	NS
Shock	3 (17.6%)	0 (0%)	NS
Multiple transfusions	1 (5.9%)	2 (8.3%)	NS
Pancreatitis	0 (0%)	2 (8.3%)	NS
Inhalation injury	3 (17.6%)	0 (0%)	NS

Mean values (standard deviation in parentheses) or number are presented
[a] Patients could have more than one risk factor
[b] *NS* not significant with a *p* value >0.10

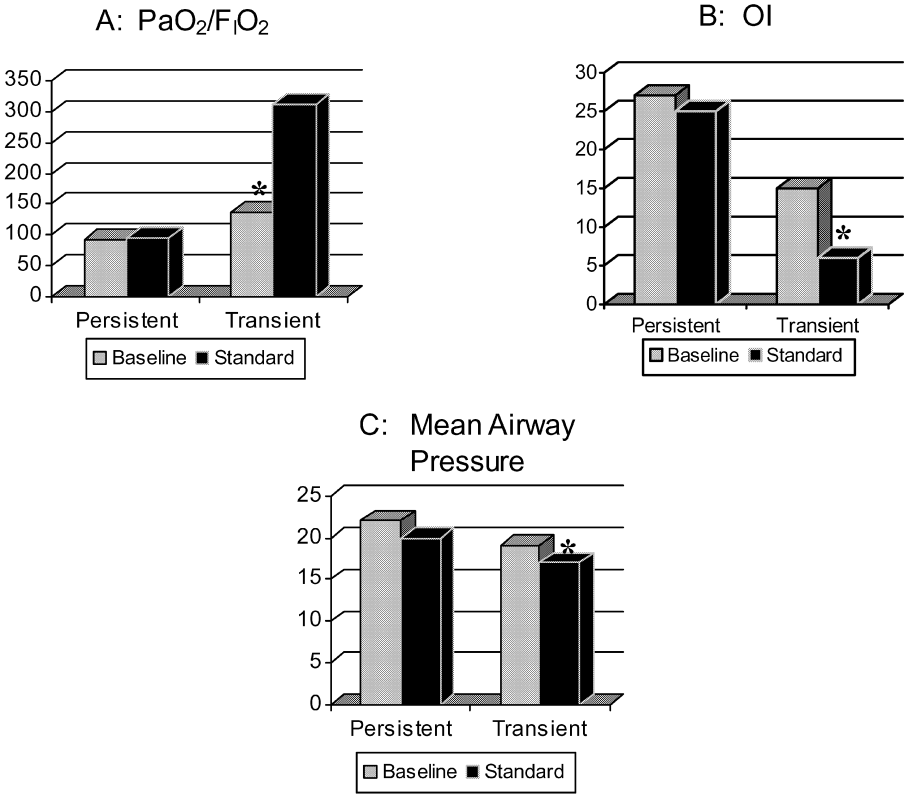

Fig. 1A–C Baseline and standardized oxygenation and airway pressures. **A–C** Mean values for PaO_2/F_IO_2, oxygenation index (*OI*), and mean airway pressure for each group (Persistent vs Transient ARDS) at baseline and after 30 min of standardized ventilator settings (standard). All comparisons made between Persistent and Transient ARDS groups (baseline vs baseline and standard vs standard) have *p* value <0.05. *p* value <0.05 for comparisons between baseline and standard settings values

Because of the usual practices employed in both study ICUs, tidal volumes and PEEP levels changed only a small amount with the application of the screening settings (Table 2). The major ventilator change due to standardized settings was the use of 100% oxygen.

Outcome varied greatly between the Persistent and Transient ARDS groups (Table 3). There was a large difference in mortality, duration of ventilation, and ventilator-free days, favoring the Transient ARDS group ($p<0.05$). No adverse effects of the standardized conventional mechanical ventilation settings were noted.

Discussion

The primary finding of this paper is that many patients meeting the American–European Consensus Conference (AECC) criteria for ARDS had a substantial alteration in their PaO_2/F_IO_2 ratio following the early application of standardized ventilator settings using 100% oxygen and PEEP of at least 10 cmH_2O. The magnitude of this change was sufficient in more than half of the cases to prevent patients from continuing to satisfy the AECC ARDS definition. The observation that ventilator settings not

Table 2 Ventilatory, hemodynamic, and arterial blood gas variables

	Persistent ARDS			Transient ARDS			Baseline vs baseline[a]	Standard vs standard[a]
	Baseline	Standard	*p* value[b]	Baseline	Standard	*p* value[†]	*p* value	*p* value
Ventilator								
Rate	27 (7.3)	25 (5.1)	0.08	19 (3.7)	19 (3.4)	NS	<0.001	0.001
V_T	526 (120)	550 (110)	NS	502 (107)	481 (92)	NS	NS	0.04
F_IO_2	0.9 (0.15)	1.0 (0)	0.004	0.6 (0.14)	1.0 (0)	<0.001	<0.001	NS
PEEP	13 (2.9)	12 (2.5)	0.01	11 (2.3)	10.0 (0)	0.005	0.02	0.02
PIP	32 (5.6)	32 (3.5)	NS	28 (3.9)	28 (4.4)	NS	0.01	0.001
P_{AW}	22 (3.3)	20 (2.5)	0.09	19 (2.9)	17 (1.9)	0.006	0.005	0.001
Hemodynamics								
HR	123 (23)	118 (25)	0.10	105 (21)	100 (18)	0.01	0.02	0.01
MAP	83 (18)	77 (8)	NS	75 (9)	75 (9)	NS	0.08	NS
ABGs								
pH	7.32 (0.06)	7.28 (0.11)	NS	7.33 (0.05)	7.35 (0.05)	0.009	NS	0.02
$PaCO_2$	40 (9.1)	43 (9.9)	NS	42 (8.4)	39 (6.9)	0.002	NS	NS
PaO_2	79 (29.9)	94 (36.1)	0.03	80 (16.5)	310 (76.4)	<0.001	NS	<0.001
HCO_3	21 (6.2)	20 (5.9)	NS	22 (4.0)	22 (4.1)	NS	NS	NS
SaO_2	91 (5.6)	93 (8.1)	NS	95 (2.2)	99 (1.0)	<0.001	<0.001	0.009
PaO_2/F_IO_2	92 (34.2)	94 (36.1)	NS	136 (35.6)	310 (74.1)	<0.001	<0.001	<0.001
OI	27 (12.8)	25 (11.4)	NS	15 (4.2)	6 (1.4)	0.007	0.001	<0.001

Mean values (standard deviation in parentheses)
[a] Comparisons made between persistent and transient ARDS groups
[b] Comparisons made within persistent and transient ARDS groups
NS not significant with a *p* value >0.1
Abbreviations and units of measure: tidal volume (V_T, ml); fractional concentration of inspired oxygen (F_IO_2); positive end-expiratory pressure (PEEP, cm H_2O); peak inspiratory pressure (PIP, cm H_2O); mean airway pressure (P_{AW}, cm H_2O); heart rate (HR, bpm); mean arterial pressure (MAP, mm Hg); partial pressure of arterial carbon dioxide ($PaCO_2$, mm Hg); partial pressure of arterial oxygen (PaO_2, mm Hg); arterial bicarbonate concentration (HCO_3, mmol/l); percent oxygen saturation (SaO_2); oxygenation index (OI; $OI=P_{AW}\times F_IO_2\times 100/PaO_2$)

Table 3 Outcomes

	Persistent ARDS	Transient ARDS	*p* value
Mortality	9 (52.9%)	3 (12.5%)	0.01
Duration of ventilation (d)	14 (11.0)	6 (6.4)	0.02
Ventilator-free days[a]	7 (8.8)	20 (9.4)	<0.001

Number or mean values (standard deviation in parentheses)
[a] Number of days alive and not requiring mechanical ventilation in a 28-day period starting on the day of enrollment

only affect PaO_2/F_IO_2, but do so sufficiently to alter patient enrollment into clinical trials carries substantial implications for the study of ARDS. The possible impact of this finding is highlighted by the fact that recently published clinical trials have employed a wide range of mechanical ventilator settings during the time of enrollment and screening for the presence of ARDS [11, 12, 13, 14, 15]. Our report clearly demonstrates that an individual patient's eligibility for an ARDS clinical trial may be affected by changes in ventilator settings, which has obvious implications in study validity and generalizability.

The PEEP and mean airway pressure levels decreased by 1 and 2 cmH_2O, respectively, in both groups upon switching to standardized settings. This suggests that the improved oxygenation in the Transient ARDS group was not due to improved lung opening but rather to the elimination of the effects of ventilation/perfusion mismatching by breathing 100% oxygen [5, 6, 16]. This probable greater proportion of ventilation/perfusion mismatch relative to shunt seen in the Transient ARDS group may suggest that these patients had less severe lung pathology compared with Persistent ARDS patients.

Wide splits in mortality have been reported both by Villar et al. [17] (68 vs 23%) and the European collaborative study (61 vs 29%) when they divided patients with ARDS by AECC criteria into two groups according to their PaO_2/F_IO_2 ratio ($\leq$150 vs >150 mmHg) on PEEP of 5 cmH_2O and an F_IO_2 of 0.5 [18]. The fact that these investigators studied patients 24 h after ARDS diagnosis (rather than immediately as in our study) implies, however, that their mortality differences were due not only to the findings on standardized settings, but also were related to the patients initial response to treatment.

In addition, many ARDS clinical trials require recruitment to take place within a few hours of ARDS diagnosis, and thus this 24-h measurement is less helpful. Nevertheless, the findings of these studies are consistent with our data, demonstrating that patients can be divided into high- and low-risk groups for mortality based on their oxygenation response to standardized ventilator settings [17, 18].

One major concern in examining the outcomes of patients described in this report is the fact that the two groups of patients were treated differently. By design, patients in the Persistent ARDS group were treated with high frequency oscillatory ventilation (HFOV), whereas the others received conventional mechanical ventilation throughout their stay in the ICU. It is possible that HFOV contributed to the increased mortality in the Persistent patients; however, a recently completed randomized trial did not demonstrate increased mortality with HFOV compared with conventional ventilation and suggested, instead, that mortality might be lower with HFOV. In addition, it is important to recognize that the Persistent group had other baseline differences in key prognostic variables compared with the Transient patients (Tables 1, 2); these included a higher APACHE II score, an increased number with pneumonia, a lower PaO_2/F_IO_2 ratio, and a higher oxygenation index, all of which have been independently associated with worse outcome in ARDS patients [19, 20, 21, 22].

The AECC definition was designed for use in many settings including research, epidemiology and individual patient care [1]. While laudable in terms of simplicity and generalizability, this broad set of objectives may put the AECC definition at a disadvantage in certain situations. For example, as a screening tool it would ideally be highly sensitive, but specificity and reliability are demanded in clinical trials. Similarly, ease of use and broad applicability are necessary for routine use in clinical practice, but in clinical trials researchers may need to forgo these properties in exchange for improved operating characteristics. Given the findings and concerns outlined above, the introduction of standardized ventilatory settings into an ARDS definition designed specifically for the use in clinical trials may be desirable.

Conclusion

In conclusion, increases in PaO_2/F_IO_2 of a magnitude great enough to disqualify the diagnosis of ARDS by AECC criteria were seen in more than half of patients studied on standardized ventilatory settings. The importance of this finding to clinical trial design is potentially increased because of observed differences in outcome. Although they were treated differently (one group receiving HFOV), and it is therefore impossible to draw firm conclusions, patients whose PaO_2/F_IO_2 exceeded 200 mmHg after standardized ventilatory settings had lower mortality, a shorter duration of mechanical ventilation, and more ventilator-free days. We propose that uniform standardized ventilator settings for patient enrollment be incorporated into future trials studying ARDS.

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