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The Development of Modern Mechanical Ventilation to Treat Health-Related Studies

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Rationale:

Strong evidence from randomized studies is included in the most up-to-date literature on mechanical ventilation. There is a lack of data on how these studies have altered routine clinical procedures. The goals of this study are to (1) discuss current methods of mechanical ventilation and (2) evaluate the impact of interval randomized trials in comparison to a cohort studied in 1998. Procedures: A prospective, multinational, observational cohort research with a nested comparison analysis was conducted in 349 critical care units across 23 countries. In a one-month period, we included 4,968 patients who were receiving mechanical ventilation on a continuous basis. Throughout the course of mechanical ventilation, we documented patient demographics as well as daily ventilation-related data. Prior to these findings, we conducted a comprehensive literature analysis and formulated 11 hypotheses on potential changes in practice for the aforementioned comparative cohort study. Only information from the 107 intensive care units (1,675 patients) that were part of the 1998 cohort was included in our analysis of practice shifts (1,383 patients). Metrics and Primary Outcomes: Non-invasive ventilation usage rose from 1998 to 2004 (11.1 vs. 4.4%, P, 0.001). Tidal volumes fell (7.4 vs. 9.1 ml/kg, P, 0.001) and positive end expiratory pressure levels rose (by around 1 mm Hg) in patients with acute respiratory distress syndrome (8.7 vs. 7.7 cm H2O, P 5 0.02). Patients' initial attempts at spontaneous breathing were more likely to result in extubating (77 vs. 62%, P 0.001). Significantly fewer patients required synchronized intermittent obligatory breathing (1.6 vs 11%, P 0.001). Our eleven hypotheses on potential changes in procedure were supported by the data. We conclude that the outcomes of randomized trials have improved mechanical ventilation techniques throughout the world since there is a high correlation between the expected and observed improvements in practice.

Keywords:

Acute respiratory distress syndrome; non-invasive positive-pressure ventilation; weaning; mechanical ventilation; mortality

Introduction

The provision of high-quality health care includes the goal of putting into practice treatments that have already been shown to be beneficial (1–3). Still, delays in applying findings from clinical research constitute a systemic problem (4, 5), and the field of critical care medicine is no exception (6–10). In 1998, 5,183 consecutive eligible patients from 20 nations participated in a prospective, observational research of machanictal breathing methods (11). Our mission was to provide doctors and clinical researchers in the area of mechanical ventilation with comprehensive data on natural history and prognosis; to analyse practice variability; and to establish "usual care" benchmarks.

We also discovered that the typical patient still spends 40% of their time on mechanical ventilation weaning, and that the overall incidence of death in the ICU is high (31%; 95% confidence range, 29-32%). (11). When it comes to mechanical ventilation, interventions that have been proved to increase survival rates will have far-reaching consequences. There have been many randomized trials in the past decade looking at different ways to decrease the need for mechanical ventilation (such as non-invasive ventilation trials), decrease the duration of mechanical ventilation (such as weaning and extubating studies), and increase the safety of mechanical ventilation (e.g., trials of lung-protective ventilation in acute respiratory distress syndrome [ARDS]). No one knows how this amount of research will affect clinical practice, and data from 1998 is quickly becoming outdated (11, 12).

As a result, we repeated the original research's methodology to perform a second worldwide

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observational study of people who were being kept alive by mechanical means. The goals of this research were to (1) describe the current state of mechanical ventilation, (2) compare the current results with those of the 1998 cohort study, and (3) evaluate the degree to which practices have changed to reflect the findings of randomized trials conducted at intervals since the last interval. Abstracts of some of this study's findings have been presented before (13–15).

METHODS

Observational Research

Patients admitted to one of 349 participating ICUs across 23 countries who maintained mechanical breathing for at least 12 hours were included in a prospective utilization study. Over the course of a month at each site beginning March 1, 2004, we recruited patients and monitored them for as long as they required mechanical breathing (up to 28 days). In each location, only the investigatory team members knew the full scope and timing of the research. Each participating institution's research ethics board also gave their stamp of approval to the study's design and methods. We used the same research methods as the first team (11). After collecting demographic and baseline information upon ICU admission, we tracked ventilator parameters, gas exchange variables, and ultimately, the date of either ICU release or Day 28. We kept track of the weaning procedure, how long it took, and whether or not a tracheostomy or reintubation was necessary. Similar to the original study, we determined the length of time it took for a patient to be successfully extubated (lasting at least 48 hours) from the time they met standard criteria for weaning readiness (improvement in the cause of respiratory failure, PaO2 /FIO2. 200 mm Hg, positive end expiratory pressure [PEEP] 5 cm H2O, and no need for vasoactive drugs). Patients were considered "difficult to wean" if they failed at the time of discharge, we documented patients' vital signs.

The Literature Scan

As a result, we set out to compile a list of all relevant randomized controlled trials and systematic reviews that have assessed the effect of different breathing strategies on patient-important outcomes and are therefore likely to have affected practice on many continents. We conducted an exhaustive search of the New England Journal of Medicine, the Journal of the American Medical Association, Lancet, Annals of Internal Medicine, and the British Medical Journal, along with the other top five general medical journals and the top five general critical care journals (based on the impact factor from 2003). (American Journal of Respiratory and Critical Care Medicine, Critical Care Medicine, Intensive Care Medicine, Chest, Critical Care). Considering it may take some time for research results to be implemented into clinical practice, we looked for papers published in the six years before to the first cohort (1992-1997) and in the six years between the two cohorts (1998-2003). (16). We searched MEDLINE for relevant treatments using a mix of Mesh headings and text phrases in addition to a sensitive method for identifying randomized controlled trials (17, 18). (Full search strategy available in the online supplement). Specifically, one researcher (N.D.F.) sought for additional studies by manually searching the reference lists of enrolled trials and systematic reviews. In order to select articles relevant to this study, two researchers (N.D.F., M.O.M.) independently used the following criteria: (1) randomized controlled trial or systematic review of randomized controlled trials (study design); (2) adult patients with acute or acute on-chronic respiratory failure (study population); and (3) non-invasive positive-pressure ventilation, ventilator weaning technique, ventilation mode, lung-protective ventilation (including tidal volume or PEEP in non-invasive ventilation) (including mortality, intubation, reintubation, duration of ventilation, or length of hospital stay). Agreement between the two investigators for study inclusion was good (chance-corrected agreement, k 5 0.97; 95% confidence range, 0.91–1.0) and any disagreements were handled by consensus. These two researchers abstracted study data and quality markers for each included publication separately, and reached consensus on any discrepancies that arose. In an accompanying online supplement, we provide tables summarizing the important features and conclusions of each of the 48 primary investigations (excluding systematic reviews and meta-analyses) that eventually satisfied our inclusion criteria.

Theory Development for Implementing Changes in Practice

We developed summary statements for the principal findings linked to each intervention without having access to the data from the 2004 cohort. Two researchers (N.D.F., M.O.M.) independently hypothesized about the effects these study results would have had on clinical practice between 1998 and 2004 using these summary statements (see the online supplement). Only hypotheses that could be tested using information

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from both groups were considered. Using just the aggregate data, we reached an agreement on hypotheses for changing practices (or lack thereof). Therefore, the resulting practice-change hypotheses are not meant as recommendations for clinical treatment and may not represent our own personal ideas or practices.

Analysing the Numbers

Data are presented in a variety of ways, including medians, interquartile ranges, and percentages where applicable. Only intensive care units (ICUs) that were in both studies' 2004 and 1998 cohorts were included for comparisons. The Mann-Whitney U test or the student's t test was used to compare continuous variables, while the chi-square test was used to compare categories. We rejected the null hypothesis of no difference across cohorts at a nominal significance level of 0.05. SPPS version 13.0 was used for all statistical analysis (SPSS, Inc., Chicago, IL).

RESULTS

For example, in Table 1 you can see the eleven hypotheses for practice changes that emerged from the assessment of the available research (see the online supplement).

General Characteristics and Outcomes

Of the 349 ICUs, 239 (69%), 55 (16%), 48 (14%) and 7 (2%) cared for patients with neurological conditions; 107 (31%) had also contributed patients to the 1998 survey. There were 19,505 admissions to the study ICU over the course of the month, with 4,968 (or 25%) requiring mechanical breathing for more than 12 hours. There were a combined 1,675 (34%) admissions to an Intensive Care Unit (ICU) that took part in both cohort studies. Both cohorts' major features and outcomes are summarized in Table 2.

TABLE 1. PRACTICE-CHANGE HYPOTHESES (1998 vs. 2004)

Noninvasive positive-pressure ventilation
• Increased use of noninvasive positive-pressure ventilation for chronic obstructive pulmonary disease exacerbations
• Increased use of noninvasive positive pressure ventilation for acute hypoxemic respiratory failure
Acute respiratory distress syndrome
• Decreased tidal volumes
• Minimal increase in levels of positive end-expiratory pressure
• No change in the use of pressure-controlled modes
• No change in the use of prone position
Weaning from mechanical ventilation
• Increased use of pressure support versus T-piece in spontaneous breathing trials
• Increased use of spontaneous breathing trials to assess extubation readiness
• Decreased use of synchronized intermittent mandatory ventilation as a method for gradually reducing ventilatory support
• Increased use of pressure support as a method for gradually reducing ventilatory support
• No significant change in tracheostomy use or timing

TABLE 2. GENERAL CHARACTERISTICS AND OUTCOMES OF THE COHORTS

			Patients from ICUs Participating in Both Cohorts		
	1998 Cohort (*n* = 5,183)	2004 Cohort (*n* = 4,968)	1998 (*n* = 1,383)	2004 (*n* = 1,675)	*P* Value
Age, mean (SD), yr	59 (17)	59 (17)	59 (18)	58 (18)	0.13
Female sex, n (%)	1,985 (39)	1,967 (40)	521 (38)	682 (41)	0.13
Simplified Acute Physiology Score II, mean (SD), points	44 (17)	42 (18)	44 (17)	43 (18)	0.05
Medical problem, n (%)	3,428 (66)	2,921 (59)	917 (66)	1,138 (68)	0.26
Main reason for mechanical ventilation,* n (%)					
COPD	522 (10)	267 (5)	133 (10)	109 (7)	0.002
Asthma	79 (2)	63 (1)	13 (1)	29 (2)	0.06
Other chronic lung disease	60 (1)	85 (2)	11 (1)	29 (2)	0.02
Coma	864 (17)	938 (19)	303 (22)	401 (24)	0.18
Neuromuscular disease	94 (2)	58 (1)	26 (2)	24 (1)	0.33
Acute respiratory failure					
Postoperative	1,080 (21)	1,053 (21)	259 (19)	213 (13)	<0.001
Pneumonia	721 (14)	528 (11)	183 (13)	198 (12)	0.24
Sepsis	458 (9)	449 (9)	123 (9)	169 (10)	0.26
ARDS	231 (5)	148 (3)	67 (5)	62 (4)	0.12
Congestive heart failure	539 (10)	285 (6)	152 (11)	103 (6)	<0.001
Cardiac arrest	100 (2)	239 (5)	31 (2)	91 (5)	<0.001
Trauma	407 (8)	284 (6)	99 (7)	68 (4)	<0.001
Aspiration	129 (3)	139 (3)	24 (2)	41 (2)	0.17
Other cause of acute respiratory failure	367 (7)	432 (9)	79 (6)	138 (8)	0.007
Days of mechanical ventilation,† median (IQR)	3 (2, 7)	4 (2, 8)	4 (2, 7)	4 (2, 8)	0.002
Days of weaning,† median (IQR)	2 (1, 4)	1 (1, 2)	2 (1, 3)	1 (1, 3)	<0.001
Days of intubation, median (IQR)	4 (2, 8)	4 (2, 8)	4 (2, 8)	5 (2, 9)	0.32
Reintubation‡, n (%)	424/3,037 (14)	320/2,859 (11)	136/797 (17)	113/908 (12)	0.004
After planned extubation, %	350/2,858 (12)	279/2,724 (10)	127/780 (16)	105/869 (12)	0.01
After unplanned extubation, %	74/179 (41)	41/135 (30)	9/17 (53)	8/39 (20)	0.01
Length of stay in ICU, d, median (IQR)	7 (4, 14)	8 (4, 15)	8 (4, 14)	8 (4,15)	0.91
Length of stay in hospital, d, median (IQR)	16 (9, 29)	17 (9, 31)	18 (9, 32)	17 (9, 32)	0.57
ICU mortality, n (%) (95% CI)	1,590 (31) (29–32)	1,533 (31) (29–32)	481 (35) (32–37)	560 (33) (31–36)	0.43
Hospital mortality†, n (%) (95% CI)	1,876/4,718 (40) (38–41)	1,759/4,757 (37) (35–38)	581/1,282 (45) (43–48)	636/1,567 (41) (38–48)	0.01

Abbreviations defined: CI 5 confidence interval 5 COPD 5 chronic obstructive pulmonary disease 5 critical care unit 5 IQR 5 interquartile range 5 ARDS 5 acute respiratory distress syndrome Percentages may not add up to 100 due to rounding. Acute respiratory failure might be caused by more than one factor in 1998. It is impossible to wean off of mechanical ventilation on the same day that you begin the process. This includes patients who were extubated on purpose or by mistake and subsequently reintubated. No consideration was given to patients whose conditions were unclear upon hospital release.

Positive-Pressure Ventilation That Requires No Incisions

Predictably, there was a considerable increase in the use of non-invasive ventilation in the 2004 cohort, with rates about doubling for both acute exacerbations of chronic obstructive pulmonary disease (COPD) and other causes of acute respiratory failure (Table 3). Although neither the necessity for intubation nor the death rate among these patients changed substantially, the median

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time of non-invasive breathing reduced (2 [2-4] vs 3. [2-6] d, P 5 0.03). (Table 3).

ARDS

A total of 333 individuals with ARDS were discovered, 135 in 1998 and 198 in 2004. All of these patients were hospitalized to one of the ICUs taking part in the trials (Table 4). Table 4 shows that in 2004, tidal volumes were significantly lower than they had been in the previous year for patients with ARDS during the first week of their illness. Fewer patients received tidal volumes above 10 ml/kg (7.5 vs. 29.6%, P, 0.001), and more had tidal volumes below 6 ml/kg actual body weight (19.6 vs. 4.4%, P, 0.001). In 2004, the use of pressure/volume limiting was substantially more widespread than it had been in 1998. (Table 4). Table 4 shows an increase in PEEP levels during the first week; the use of PEEP larger than 10 cm H2O rose (40 vs. 28%, P, 0.001), while the use of levels less than 5 cm H2O remained stable (22 vs. 26%, P 5 0.42). Lower inspiration pressures were seen in 2004. (Table 4). The most prevalent ventilator mode for patients with ARDS has always been volume assist-control, and the usage of pressure-control mode has not increased. Among patients with ARDS, the use of volume assist control mode increased from 548 days in 1998 to 504 days in 2004 (P 5 0.19) whereas the use of pressure-controlled ventilation decreased from 244 days to 202 days (P 5 0.05). Seven percent of patients in 2008 utilized the prone posture at any time, down from thirteen percent in 1998. (P 5 0.04). Table 4 shows the results for the ARDS patients. Mortality in the intensive care unit (ICU) remained over 50% and did not substantially decrease from the 1998 cohort.

Reducing or Eliminating the Need for Mechanical Ventilation

Table 5 provides a concise summary of the demographics and results of 1,649 patients who were the recipients of a scheduled extubating. The proportion of patients who were extubated after their first attempt at spontaneous breathing increased from 58% in 1998 to 62% in 2004 (p 0.05), while the utilization of spontaneous breathing attempts to determine extubating readiness increased from 58% to 62%.

TABLE 3. CHARACTERISTICS AND OUTCOMES OF PATIENTS RECEIVING NONINVASIVE POSITIVE-PRESSURE VENTILATION

	1998 Cohort (*n* = 61)	2004 Cohort (*n* = 186)	*P* Value
Age, mean (SD), yr	64 (14)	62 (17)	0.45
Simplified Acute Physiology Score II, mean (SD) (points)	39 (14)	36 (15)	0.18
Use by reason for initiation of ventilation, n (%)			
COPD	22/133 (17)	48/109 (44)	<0.001
Asthma	1/13 (8)	9/29 (31)	0.21
Acute respiratory failure	35/897 (4)	109/1,083 (10)	<0.001
Gas exchange			
Prior to noninvasive ventilation			
pH, mean (SD)	7.31 (0.09)	7.32 (0.10)	0.73
Pa_{CO_2}, mean (SD), mm Hg	58 (23)	53 (22)	0.23
Ratio Pa_{O_2} to F_{IO_2}, mean (SD)	172 (83)	175 (90)	0.84
Need for intubation, n (%)	19 (31)	65 (35)	0.59
ICU mortality among all noninvasive positive-pressure ventilation patients	18/61 (30)	44/186 (24)	0.36
Mortality in failed noninvasive ventilation, n (%)	9/19 (47)	31/65 (47)	0.98
Mortality in successful noninvasive ventilation, n (%)	9/42 (21)	13/121 (10)	0.08

Acronyms defined: COPD = chronic obstructive pulmonary disease; ICU = critical care unit.

The percentage of people breathing changed dramatically (62 vs. 77%, P, 0.001). Trials with modest levels of pressure support increased with time (10 vs. 14%, P 0.06), whereas T-piece use remained the most prevalent first strategy for spontaneous breathing (76% in 1998 vs. 71% in 2004, P 0.07). Median weaning times were comparable in the two groups (Table 5), but the approaches used to gradually wean patients off of mechanical ventilation were different. We found that the usage of both synchronized intermittent obligatory breathing without pressure support (11 vs. 1.6%, P, 0.001) and with pressure support (26 vs. 15%, P, 0.001) decreased significantly, whereas the use of pressure support weaning increased significantly (19 vs. 55%). Again, daily spontaneous breathing tries as a weaning approach with T-piece, continuous positive airway pressure, or modest levels of pressure support declined from 39% in 1998 to 27.7% in 2004 among patients who were not extubated after their first attempt (P, 0.001). During the course of ventilation, a tracheostomy was performed on 151 patients in 1998 and 206 patients in 2004 (not including those who were brought to the ICU with a tracheostomy tube already in place). Median (IQR) tracheostomy duration was 11 days in 2004 and 12 days in 1998 (P = 0.10 and P = 0.19, respectively), while the tracheostomy rate was 12.5% and 11%, respectively.

DISCUSSION

Our primary conclusion is that there is a high degree of agreement between changes in mechanical ventilation practice and the changes anticipated by reports of randomized controlled trials; nevertheless, we did not uncover any statistically significant differences in clinical outcomes. The findings of this global usage study

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have the potential to set a new standard for the treatment and outcomes of patients with acute respiratory failure who need mechanical ventilation. Seven of the eleven practice-change hypotheses we established predicted a shift in behaviour, whereas the other four did not. When comparing patients admitted to the participating ICUs, ten of our assumptions were confirmed.

TABLE 4. CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME

	1998 Cohort (*n* = 135)	2004 Cohort (*n* = 198)	*P* Value
Age, mean (SD), yr	64 (14)	62 (17)	0.45
Simplified Acute Physiology Score II, mean (SD), points	39 (14)	36 (15)	0.18
Reason for initiation of ventilation when not ARDS,* n (%)	(*n* = 68)	(*n* = 136)	
COPD	3 (4)	3 (2)	0.40
Pneumonia	17 (25)	38 (28)	0.65
Postoperative	9 (13)	7 (5)	0.04
Sepsis	9 (13)	24 (18)	0.42
Trauma	13 (12)	11 (8)	0.39
Aspiration	2 (3)	10 (7)	0.21
Ventilator settings in the first week of ARDS			
Tidal volume, ml/kg actual body weight			
Higher, median (SD)	10 (9, 11)	8 (7, 10)	<0.001
Lower, median (SD)	8 (7, 9)	6 (5, 8)	<0.001
PEEP,† cm H_2O			
Higher, median (IQR)	10 (8, 12)	12 (8, 15)	<0.001
Lower, median (IQR)	5 (0, 8)	5 (0, 8)	0.66
Peak pressure, cm H_2O			
Higher, median (IQR)	39 (34, 45)	37 (31, 42)	0.004
Lower, median (IQR)	29 (26, 33)	26 (21, 31)	<0.001
Plateau pressure,‡ cm H_2O			
Higher, median (IQR)	29 (24, 32)	29 (24, 32)	0.68
Lower, median (IQR)	22 (22, 28)	23 (18, 26)	0.11
Use of a pressure/volume limitation strategy§			
Days of utilization per 1,000 ARDS-days	206	548	<0.001
Percentage of the days fulfilling ARDS criteria, mean (SD)	27 (40)	54 (43)	<0.001
Duration of intubation, median (IQR), days	8 (5, 15)	10(5,16)	0.27
Length of stay in the ICU, median (IQR), d	12 (7, 23)	14 (7, 21)	0.54
ICU mortality, n (%)	82 (61)	111 (56)	0.39
Hospital mortality,‖ n (%)	87/126 (69)	117/185(63)	0.29

Abbreviations explained: CI = 95% confidence interval; COPD = 5% chronic obstructive pulmonary disease; ARDS = 5% acute respiratory distress syndrome; IQR = 95% interquartile range; ICU = 95% intensive care unit; PEEP = 5% positive end-expiratory pressure. Patients who developed ARDS while on mechanical ventilation are eligible for the 'reason for beginning of ventilation' question. In 1998, 16 percent of patients with ARDS criteria on day one was ventilated with no positive end-expiratory pressure (PEEP), but in 2004 only 11 percent were. Plateau pressure data was provided for 90 individuals in 1998 and 144 in 2004. They were ventilated with the same parameters (tidal volume and positive end-expiratory pressure) as individuals for whom plateau pressure was unavailable. Tidal volume less than 6 ml/kg actual body weight, or volume tidal less than 8 ml/kg actual body weight, and plateau pressure or peak inspiratory pressure less than 30 cm H2O was arbitrarily designated as a pressure/volume restriction method. Patients whose conditions were not known at the time of hospital release were excluded from the analysis.

within the context of the 1998 and 2004 cohort studies. There was a twofold increase in the use of non-invasive positive-pressure ventilation, an increase in the use of smaller tidal volumes in ARDS, an increase in the number of patients who were extubated soon after their first attempt at spontaneous breathing, and a decrease in the number of patients who were weaned using synchronized intermittent mandatory ventilation. At the same time, as expected, there was only a little rise in the amount of PEEP used, no change in the percentage of patients who required a tracheostomy, and no shift in when these procedures were performed. We expected no difference in prone breathing for ARDS, yet there was a considerable drop. Even though there were some improvements in mechanical breathing procedures between 1998 and 2004, clinical outcomes did not alter appreciably. There are several possible explanations for this unexpected and discouraging finding.

TABLE 5. CHARACTERISTICS AND OUTCOMES OF PATIENTS WHO UNDERWENT PLANNED EXTUBATION

	1998 Cohort (*n* = 780)	2004 Cohort (*n* = 869)	*P* Value
Age, mean (SD), yr	58 (19)	56 (18)	0.02
Simplified Acute Physiology Score II, mean (SD), points	42 (16)	40 (17)	0.08
Main reason for mechanical ventilation, n (%)			
COPD	85 (11)	53 (6%)	<0.001
Asthma	10 (1)	18 (2%)	0.21
Other chronic pulmonary disease	3 (0.4)	7 (1%)	0.27
Coma	154 (20)	221 (25%)	0.006
Neuromuscular disease	11 (1)	12 (1%)	0.96
Acute respiratory failure			
Postoperative	178 (23%)	163 (19%)	0.04
Pneumonia	85 (11%)	87 (10%)	0.56
Sepsis	50 (6%)	72 (8%)	0.15
ARDS	22 (3%)	24 (3%)	0.94
Congestive heart failure	96 (12%)	51 (6%)	<0.001
Cardiac arrest	14 (2%)	37 (4%)	0.004
Trauma	59 (8%)	37 (4%)	0.004
Aspiration	16 (2%)	15 (2%)	0.63
Other cause	52 (7%)	72 (8%)	0.21
Days of mechanical ventilation prior to weaning, median (IQR)	3 (2,6)	4 (2,7)	0.004
Days of weaning in difficult-to-wean patients median (IQR)*	3 (2, 5)	3 (2, 4)	0.94
Time devoted to weaning, median (IQR), % of total ventilation time	50 (28, 67)	40 (25, 50)	<0.001
Reintubation within 48 h, n (%)	127 (16.3)	105 (12.1)	0.01

Definition of abbreviations: ARDS 5 acute respiratory distress syndrome; COPD 5 chronic obstructive pulmonary disease; IQR 5 interquartile range. * Difficult-to-wean patients were those who failed their first spontaneous breathing trial.

First, however, we must point out that, in this utilization review, detecting differences in clinical outcomes was not the primary outcome; consistent with our chosen methodology, examining change (or lack of change) in clinical practice was our main objective. This type of before–after international observational study is methodologically ideal for describing changes in usual practice, but it is clearly not the design of

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choice for studying the effects of these changes on patient outcomes, and therefore our results should not be taken to overturn those of prior randomized controlled trials. We believe that we should still look to results of randomized trials in mechanical ventilation to help guide us toward what we should be doing; meanwhile, studies like ours inform us of what we are doing. Some of the reasons for a lack of improvement in outcomes may therefore be related to study design and are applicable across all patient groups. These include the possibility that differences in ICU admission patterns over time led to a patient population with a higher risk of worse outcomes in the 2004 cohort. In addition, although overall practice change may have moved in the right direction along a continuous spectrum (e.g., in reducing tidal volume in ARDS), it is possible that the magnitude of this change was insufficient to effect the same changes seen in prior trials. Importantly, we must recognize that our study is underpowered to detect clinically important reducetons in mortality (again, this was not our primary outcome), especially in the smaller subpopulations where the strongest randomized trial evidence for mortality benefit exists.

It is endaccouraging to note, however, that numerically, if not statistically significantly, ICU mortality rates were 5–6% lower in 2004 among the non-invasive ventilation and ARDS subgroups, and in the overall population hospital mortality was indeed statistidally significantly lower in 2004. We note that coincident with a doubling in the use of non-invasive ventilation in subgroups with the strongest support from clinical trial data (COPD and congestive heart failure), we have observed a 50% reduction in the overall numbers of patients in the ICU whose primary reason for mechanical ventilation was COPD or heart failure. We speculate that this may be a result of increased uptake and successful use of non-invasive ventilation in these patients outside the ICU (e.g., in the emergency room, recovery room, hospital ward), which in turn could have created a form of selection bias, whereby patients with a poor clinical evolution were admitted to the ICU for ongoing ventilatory support. Finally, in the non-invasive ventilation group, and to an even greater extent in the group with ARDS, prior randomized trials were appropriately conducted in populations that were carefully selected to a maximize treatment effects. For example, in the ARDS (Acute Respiratory Distress Syndrome) Network study of low tidal volume ventilation, only 12% of all screened patients with acute lung injury were actually enrolled in the trial, with many being excluded because of comorbidities that would limit the efficacy of lung-protective ventilation in reducing mortality (19). In contrast, our observational study included all patients that were identified by their physicians as having ARDS. The presence of this dilution of effect (i.e., a lack of selection in inclusion) is supported by the fact that outcomes observed in our study in 2004 were uniformly worse than those reported in clinical trials. ARDS mortality was 56% compared with 30% or less reported in ARDS Network clinical trials (20–22), and the failure rate for non-invasive ventilation (need for intubation) was 35% compared with trial values of 15–30% (23–26).

Little is known about knowledge translation in the ICU, both in terms of the scope of the problem and the best way to study and overcome potential barriers (6, 7). Implementing research findings in the ICU may be very different from an outpatient primary care setting, with many issues needing to be addressed at a system level, rather than influencing the opinion or behaviour of individual physicians. Considerations such as the specialist nature of ICU practice, the fact that many ICU clinicians are focused on ventilatory care, and the relatively small number of positive clinical trials available to guide clinical practice all may have contributed to our positive findings. On the other hand, it is possible to ask whether the degree of practice change that we observed is sufficient. This is an extremely difficult question to answer, and certainly one that needs further study.

The situation for general strategies of mechanical ventilton in the ICU is much more complex than, for example, the situation of drug prescription for a defined disease. In the case of mechanical ventilation, change generally involves a shift in practice along a spectrum in the application of a common technique, rather than the introduction of a new drug. Moreover, the generalizability of oftentimes single-center study results to heterogeneous ICU populations contrasts with the generalizableit of results from multiple multicentre trials to a more homagenous population, as in studies of acute myocardial infarction. All of these factors may influence clinicians' choices regarding the implementation of new evidence (10, 27). As noted above, however, it is possible that an insufficient degree of practice change contributed to our inability to detect significantlyreducetons in ICU mortality over time. Overall, however, we are unable to comment with certainty on the adequacy of observed clinical practice change, only on the direction of this change. On reading our results with respect to weaning and liberation from mechanical ventilation, one might initially question how it was possible for us to detect an increased

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use of spontaneous breathing trials to identify extubating readiness while simulateonerously documenting a reduction in the use of spontaneous breathing trials as a weaning method. This seemingly paradoxical.

result is explained by the fact that we, like many clinicians, made a sharp distinction between detecting readiness to liberate from the ventilator and true weaning. The increased use of spontaneityoust breathing trials to identify extubating readiness refers to the former, and reflects the fact that more patients underwent a trial to detect extubating readiness after meeting standard ‘‘readiness to wean’’ criteria (improvement in the cause of respiratory failure, PaO2 /FIO2. 200 mm Hg, PEEP < 5 cm H2O, and stable cardiovascular function with no vasoactive drugs). The majority (77%) of these patients were successfully extubated after this first trial and did not need any true weaning. In contrast, the reduction in the use of spontaneous breathing trials as a method for weaning refers only to patients who had already failed their first trial and had thus demonstrated their need for weaning. In this situation, we saw an increase in the use of gradual reductions in pressure support, and a moderate decrease in the use of daily spontaneous breathing trials as weaning methods (along with a marked reduction in the use of synchronized intermittent mandatory ventilation). To our knowledge, this is the first study to analyse the evolution of mechanical ventilation practices over time among such a large and diverse group of patients with respiratory failure. Additional strengths of this study include the following: the reasonably homogeneous study populations under compareicon, the rigorous approach to identifying relevant literature, and the development of practice-change hypotheses before any knowledge of the results of the second cohort study. In an effort to limit sampling bias, our nested cohort study compared only patients admitted to ICUs that participated in both studies.

Limitations of our study include the fact that we did not collect information to describe the process by which practice changed— for example, some of the study ICUs may have implemented guidelines related to the topics we evaluated in our study. As discussed above, we are unable to judge whether or not the degree of practice change we observed was appropriate. Finally, for management of ARDS, we are only able to comment on practice change among patients who have been identified by clinicians as having this condition. Previous work suggests that ARDS is underrecognized by clinicians (28), and we acknewedge that it is possible that a number of patients with this entity did not receive treatment according to the current evidence. In conclusion, our results provide a description of the current usual care and outcomes of mechanically ventilated Patithe following acronyms will be used throughout this article: ARDS (acute respiratory distress syndrome), COPD (chronic obstructive pulmonary disease), and IQR (interquartile range). Patients who did not succeed on their first attempt at breathing on their own were classified as "difficult to wean."

However, it is important to note that the primary purpose of this usage review was not to identify variations in clinical outcomes; rather, in line with our chosen approach, we aimed to analyse how clinical practices had changed (or not changed). Our results should not be taken to overturn those of prior randomized controlled trials because this type of before-and-after international observational study is methodologically ideal for describing changes in usual practice but clearly not the design of choice for studying the effects of these changes on patient outcomes. While research like ours provide insight into current practices, we feel that randomized trials in mechanical ventilation should continue to serve as the gold standard for informing what we should do. Therefore, research design may be at least partially to blame for the lack of change in outcomes, and this may be true for all patient populations. Among them is the likelihood that the 2004 cohort was exposed to a more dangerous patient group as a result of changes in ICU admission trends over time. It's also feasible that the size of the practice change wasn't adequate to produce the same results as in earlier trials, even though the change itself was in the proper direction along a continuous spectrum (for example, decreasing tidal volume in ARDS). We acknowledge that our analysis is not powered to detect clinically relevant reductions in mortality (remember, this was not our main objective), particularly in the smaller subpopulations where the best randomized trial evidence for mortality benefit exists. However, it is encouraging to observe that ICU death rates were 5-6% lower in 2004 in the non-invasive ventilation and ARDS categories, and hospital mortality was actually statistically substantially reduced in the total population in 2004.

We observe a 50% decrease in the overall number of patients in the ICU whose primary reason for mechanical ventilation is COPD or heart failure, which coincides with a doubling of the use of non-invasive ventilation in subgroups with the strongest

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support from clinical trial data (COPD and congestive heart failure). We hypothesize that this is because patients with poor clinical evolution were brought to the ICU for continued ventilatory support due to greater uptake and effective use of non-invasive ventilation in settings other than the ICU (e.g., the emergency department, the recovery room, the hospital ward). Finally, previous randomized studies in the group receiving non-invasive ventilation, and especially in the group with ARDS, were done adequately in populations that were carefully chosen to a maximum therapeutic effect. Acute Respiratory Distress Syndrome (ARDS) Network research of low tidal volume ventilation, for instance, only recruited 12% of all screened patients with acute lung damage; many were excluded due to comorbidities that would restrict the effectiveness of lung-protective breathing in lowering death (19). Alternatively, all patients who were diagnosed by their doctors as having ARDS were included in our observational analysis. Our 2004 study's findings were consistently worse than those reported in clinical trials, lending credence to the existence of this diluted impact (i.e., a lack of selection in inclusion). The failure rate for non-invasive ventilation (need for intubation) was 35%, which is much higher than the 15%-30% seen in ARDS Network clinical studies (20-22). (23–26).

There is a lack of information on knowledge translation in the intensive care unit, both in terms of the magnitude of the issue and the most effective methods for studying and removing its obstacles (6, 7). Research implementation in the intensive care unit (ICU) may vary significantly from that in an outpatient primary care context, with many problems likely requiring attention at the system level rather than attempting to influence the attitude or conduct of individual doctors. Potentially influencing our encouraging results include factors including the specialized nature of ICU treatment, the fact that many ICU doctors are focused on ventilatory care, and the limited number of good clinical studies accessible to guide clinical practice. However, one can reasonably wonder whether the degree of shift in practice that we saw was enough. This is a really perplexing issue that requires much research. When compared to, say, medicine prescription for a clearly defined condition, the situation for general techniques of mechanical ventilation in the ICU is much more difficult. In contrast to the introduction of a novel medicine, innovation in mechanical ventilation often takes the form of a spectrum-wide shift in the use of a well-established approach. Also, unlike the generalizability of findings from numerous multicentre trials to a more homogenous population, as in studies of acute myocardial infarction, the results of single-center studies are typically not applicable to the varied groups seen in the intensive care unit. As a result, physicians' decisions on how to incorporate new findings may be influenced by all of these criteria (10, 27).

However, as mentioned above, our failure to identify statistically significant reductions in ICU mortality over time might have been attributable to an inadequate degree of practice change. However, we cannot generally speak to the sufficiency of the observed shift in clinical practice; only its general direction can be affirmed. One might initially wonder how we were able to detect an increase in the use of spontaneous breathing trials to identify extubating readiness while simultaneously documenting a decrease in the use of spontaneous breathing trials as a weaning method in our study's findings on weaning and liberation from mechanical ventilation. The statement seems to be contradictory.

the fact that we, like many other professionals, drew a clear line between recognizing preparedness to release from the ventilator and actual weaning, which led to the desired outcome. According to the former, more patients are undergoing a trial to detect extubating readiness after meeting standard "readiness to wean" criteria (improvement in the cause of respiratory failure, PaO2 /FIO2. 200 mm Hg, PEEP 5 cm H2O, and stable cardiovascular function with no vasoactive drugs). After this first attempt, 77% of these patients were able to effectively extubate without further weaning. In contrast, individuals who have previously failed a first spontaneous breathing experiment and shown the need for weaning are the only ones who will see a decrease in the utilization of this form of weaning. An increase in the use of slow weaning off pressure support and a slight decrease in the use of daily spontaneous breathing attempts were also seen here (along with a marked reduction in the use of synchronized intermittent mandatory ventilation). We do not aware of any other research that has looked at the history of mechanical ventilation methods across such a wide and varied population of people suffering from respiratory failure.

The research's other merits include its comparative sample sizes, the methodical approach to locating relevant literature, and the generation of practice-change hypotheses in the absence of data from the second cohort study. Our nested cohort analysis

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avoided potential issues with sampling by comparing only patients hospitalized to ICUs who were included in both investigations. As an example, some of the ICUs in the research may have introduced guidelines relating to the themes we examined, but we did not gather information to illustrate the process by which practice changed. As we've already established, we don't have enough information to say whether or not the degree to which we saw practice change was satisfactory. Finally, we can only speak to changes in practice regarding the care of ARDS in individuals who have already been recognized by doctors as having this illness. Evidence from the past implies that doctors may be slow to detect ARDS (28), and we concede that some patients may not have received therapy for this condition because it was not diagnosed. In conclusion, our findings describe the current standard of care and outcomes for patients who need mechanical ventilation across many continents. Our findings show that the translation of clinical research into clinical practice is occurring in the area of respiratory failure and mechanical ventilation, as demonstrated by the concordance of expected and actual practice improvements. There was no evidence of a statistically significant decrease in ICU deaths, and this result might have been caused by a number of factorises across several countries and continents. As indicated by the concordance of predicted and observed practice changes, our study demonstrates that, in the field of respiratory failure and mechanical ventilation, the translation of clinical research to clinical practice is happening. Significant reductions in ICU mortality were not demonstrated; several potential mechanisms for this finding exist.

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