ORIGINAL ARTICLE

Air Hunger Far Exceeds Dyspnea Sense of Effort during Mechanical Ventilation and a Weaning Trial

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Abstract

Rationale: No systematic investigation into dyspnea in patients receiving prolonged ventilation (>21 d) after recovering from critical illness has been published.

Objectives: We sought to determine the magnitude, nature, and pathophysiological basis of dyspnea during an unassisted-breathing trial in patients receiving prolonged ventilation.

Methods: Dyspnea intensity and descriptor selection were investigated in 27 patients receiving prolonged ventilation during a 60-minute unassisted-breathing trial. Pressure–time product, respiratory mechanics, and Ptc_{CO_2} were also measured.

Measurements and Main Results: Of 10 patients who reported dyspnea during assist-control ventilation, 9 (90.0%) selected "Not getting enough air" to characterize dyspnea. V_T setting was lower in dyspneic than in nondyspneic patients (480.0 vs. 559.4 ml), $P < 0.046$. During the unassisted-breathing trial ($n = 26$), patients developed increases in dyspnea ($P < 0.01$) and Ptc_{CO_2} ($P < 0.01$) but no change in $\dot{V}_E$. Dyspnea score was strongly linked to Ptc_{CO_2} ($P < 0.012$) and airway resistance ($P < 0.013$) but not respiratory work (although pressure–time product was almost three times higher than normal). At 60 minutes into the trial, 83.3% of patients selected "Not getting enough air" on its own or in combination with "Too much effort" to describe discomfort, whereas only 16.7% selected "Too much effort" on its own ($P < 0.001$). Across the dyspnea spectrum, patients chose "Not getting enough air" overwhelmingly over other descriptor options ($P < 0.001$).

Conclusions: Patients developed increases in dyspnea and Ptc_{CO_2} but unchanged $\dot{V}_E$ and work of breathing during an unassisted-breathing trial; patients selected air-hunger descriptors overwhelmingly over excessive effort. The observations support the belief that air hunger results from heightened respiratory center stimulation combined with the incapacity to increase $\dot{V}_E$.

Keywords: mechanical ventilation; dyspnea pathophysiology; ventilator weaning; work of breathing; control of breathing

Critically ill patients who repeatedly fail weaning trials are typically transferred to a facility that specializes in prolonged mechanical ventilation. The main strategy for managing such patients is to undertake repeated trials of unassisted breathing until the ventilator can be removed completely (1, 2). The process is slow and arduous, and patients fail trials recurringly until success is ultimately achieved. The dominant symptom experienced by such patients is dyspnea (3). Investigating dyspnea in ventilated patients is especially taxing, because artificial airways make speech virtually impossible, and investigators must simultaneously gauge patient cognitive capability (4). Although research into dyspnea in ventilated patients is in its infancy, it has already yielded important findings (5–9). Of 10 symptoms documented in ventilated patients, dyspnea is the symptom

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This article has a related editorial.

A data supplement for this article is available via the Supplements tab at the top of the online article.

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At a Glance Commentary

Scientific Knowledge on the Subject: Mechanical ventilation is not only lifesaving but also enhances patient comfort. Indeed, physicians are apt to assume that ventilator assistance eliminates patient dyspnea.

What This Study Adds to the Field: More than a third of patients receiving carefully titrated mechanical ventilation experienced dyspnea, and 90% selected "Not getting enough air" to characterize their discomfort. Patients receiving lower V_T (widely advocated in ventilator guidelines) were more likely to experience dyspnea. During an unassisted-breathing trial, patients experienced intensification of dyspnea and an almost threefold elevation in respiratory work, yet no aspect of dyspnea bore a relationship to any measurement of patient effort. Patients overwhelmingly (83%) selected "Not getting enough air" to describe discomfort, contrasted with only 17% selecting "Too much effort" on its own. These data—obtained in patients confronting a life-or-death situation—provide novel and far-reaching insights into the fundamentals of dyspnea: whereas doctors interpret dyspnea as difficult or laborious breathing, patients perceive it as starvation of air.

that produces the greatest distress (10). Dyspnea is remembered months after successful ventilator discontinuation and is of sufficient severity to induce posttraumatic stress disorder (3). Research on dyspnea in ventilated patients has been confined to the ICU setting and has focused on dyspnea prevalence (5, 6, 9, 11). Detailed investigation into the physiological mechanisms of dyspnea in acutely ill ventilated patients is virtually nonexistent. In particular, no systematic investigation into dyspnea in patients who have recovered from critical illness but are still receiving prolonged ventilation (>21 d) has been published.

To gain a better understanding of the nature of dyspnea, we studied 27 patients who had failed numerous weaning attempts over the course of 29.7 days of mechanical ventilation. Our goal was to quantify the overall magnitude of dyspnea during an unassisted-breathing trial (specifically, a tracheostomy-collar trial) lasting up to 60 minutes and to characterize the nature of dyspnea through the use of descriptors selected by patients. Using an esophageal-balloon catheter, we obtained meticulous measurements of patient work of breathing and respiratory mechanics and monitored P_{CO_2} (with a transcutaneous probe) to determine the pathophysiological basis of dyspnea.

Methods

Setting

This prospective study was conducted in RML Specialty Hospital, Hinsdale, Illinois, a freestanding long-term acute-care hospital (*see* the Supplementary Methods in the online supplement).

Patients

Twenty-seven patients with a tracheostomy who were undergoing ventilator weaning at RML Specialty Hospital were enrolled (Table 1). Patients were eligible for enrollment if they received mechanical ventilation for at least 21 days, were alert and cognitively intact (as assessed by a clinical psychologist), and were able to read and speak English. Patients were excluded if they were unable to tolerate at least 4 hours of an unassisted-breathing trial during the first week of their stay in a long-term acute-care hospital to ensure that patients could tolerate unassisted breathing long enough to obtain physiological measurements. The study was approved by the institutional review board, and informed consent was obtained (*see* online supplement).

Measurements

Intensity and nature of dyspnea were characterized using a questionnaire (4). Patients were asked to rate discomfort on a scale ranging from 0 (comfortable) to 10 (extremely short of breath) in response to the question "How does your breathing feel?" Patients who chose a score of 1 or higher were then asked to select a descriptor "I'm not getting enough air" or "It is too much effort to breathe" to describe their discomfort; patients could select more than one descriptor at a time (4).

Flow, airway pressure, and esophageal pressure were recorded during mechanical ventilation and the unassisted-breathing trial. Oxygen saturation and Ptc_{CO_2} were measured noninvasively (*see* online supplement). Maximum inspiratory pressure was measured before the trial.

Protocol

After placement of the balloon-catheter system, assist-control ventilation was instituted through the tracheostomy tube (*see* online supplement). Physiological variables were recorded for 10 minutes, and dyspnea assessment was performed. Subsequently, ventilator backup rate was increased until all breathing efforts were suppressed and lung and chest-wall mechanics were measured. Maximum inspiratory pressure was then measured, and an unassisted-breathing trial was undertaken. Dyspnea and physiologic data were both measured at 10 and 60 minutes into the trial.

Resistance and static elastance of the total respiratory system, lung, and chest wall

Table 1. Characteristics of Study Population at Enrollment

Variable	Cohort Values (*n* = 27)
Age, yr, median (IQR)	66 (55–75)
Sex, female/male (% female)	11/27 (39)
Postoperative, *n* (%)	4 (15)
Acute lung injury, *n* (%)	15 (56)
Chronic obstructive pulmonary disease, *n* (%)	6 (22)
Neuromuscular, *n* (%)	2 (7)
APACHE II, median (IQR)*	14 (11–15)
Duration of mechanical ventilation at enrollment, d, median (IQR)	25 (21–39)

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; IQR = interquartile range.
*This score has not been validated as an index of disease severity in patients managed at a long-term acute care hospital.

during passive ventilation were quantified using standard formulae (12). Inspiratory resistance of the lung, dynamic lung elastance, intrinsic positive end-expiratory pressure (PEEPi), and pressure–time product (PTP) during the unassisted-breathing trial were computed according to standard formulae (13). V_T, inspiratory time, expiratory time, and respiratory frequency were calculated from flow and esophageal pressure signals (*see* online supplement).

Statistical Analysis

Continuous variables are reported as medians with interquartile range (IQR) and categorical variables as percentages. We performed comparisons between continuous variables using the Wilcoxon rank-sum test, and we performed comparisons between categorical variables using the chi-square test for equal proportions. Effect size was measured in terms of calculated Cohen's *d*. *P* values were two-sided, and $P < 0.05$ was considered significant.

Descriptors chosen by patients were "Not getting enough air," "Too much effort to breathe," or the combination of "Not getting enough air" and "Too much effort to breathe." The relation between dyspnea score and dyspnea type was analyzed using logistic regression and mixed-effects multinomial analyses (*see* online supplement).

The relation between dyspnea score and physiological variables was assessed using mixed-effects linear-regression analyses (*see* online supplement). For each predictor variable identified in the final fixed-effects model, the result is presented as a coefficient (unstandardized and standardized) with 95% confidence interval (95% CI). The unstandardized coefficient of each predictor variable was standardized to compare the relative magnitude of the effect of each variable on dyspnea (14). The greater the standardized coefficient for a physiological variable, the greater the contribution of that variable to the occurrence of dyspnea. The relation between dyspnea type and physiological variables was assessed using mixed-effects multinomial regression analysis (*see* online supplement).

Results

Dyspnea and Physiological Measurements during Mechanical Ventilation

During mechanical ventilation, 10 of 27 patients (37.0%) reported dyspnea at a median score of 3.0 (IQR, 2.0–3.75). Of 10 dyspneic patients, 9 (90.0%) selected the descriptor "Not getting enough air," and 1 (10%) selected "Too much effort to breathe."

Resistance and elastance of the respiratory system, lung, and chest wall were similar in dyspneic and nondyspneic patients (Table 2), but ventilator settings differed. Dyspneic patients had lower set V_T than did nondyspneic patients (median, 500.0 ml [IQR, 500.0–500.0] vs. 550.0 ml [IQR, 487.5–612.5]; $P < 0.046$) and lower set PEEP (median, 5.0 cm H_2O [IQR, 0–5.0] vs. 5.0 cm H_2O [IQR, 5.00-5.00]; $P < 0.028$). (Mean ± SD for set PEEP was 3.0 ± 2.6 cm H_2O in dyspneic patients and 5.0 ± 0.0 cm H_2O in nondyspneic patients.) Maximum inspiratory pressure and Ptc_{CO_2} were similar in dyspneic and nondyspneic patients.

Dyspnea and Physiological Measurements during the Unassisted-Breathing Trial

One patient developed severe discomfort at 5 minutes into the unassisted-breathing trial and was withdrawn from the study. Thus, unassisted-breathing trial data were analyzed in 26 patients.

When ventilator assistance was halted, V_T (275 ml) decreased to 55.0% of that during mechanical ventilation (500.0 ml), and frequency (28.6 breaths/min) increased by 138.3% (over 12.0 breaths/min during mechanical ventilation). V_T and frequency did not change over the 1-hour trial (Table 3). Despite an increase in frequency between mechanical ventilation and 10 minutes into the trial, alveolar ventilation decreased, leading to an increase in Ptc_{CO_2}: 51 mm Hg at 60 minutes versus 47 mm Hg at 10 minutes into the trial ($P < 0.01$) and 42.5 mm Hg during mechanical ventilation. Between 10 minutes and 60 minutes into the unassisted-breathing trial, the dyspnea score increased ($P < 0.01$) and was accompanied by an increase in Ptc_{CO_2} ($P < 0.01$), whereas lung mechanics and patient work (PTP) did not change (Table 3).

Table 2. Ventilator Settings and Physiological Variables during Mechanical Ventilation

Variable	All Patients (*n* = 27)	Dyspnea (*n* = 10)	No Dyspnea (*n* = 17)
Ventilator settings			
V_T, ml	500 (500–550)	500 (500–550)	550 (490–610)*
Frequency, breaths/min	12.0 (10.0–14.0)	12.0 (10.5–14.0)	11.0 (10.0–14.0)
PEEP, cm H_2O	5.0 (5.0–5.0)	5.0 (0.0–5.0)	5.0 (5.0–5.0)*
Physiological variables†			
Rmax,rs, cm H_2O/L/s	13.1 (10.9–17.8)	12.2 (11.2–13.9)	15.4 (10.7–18.0)
Rmax,L, cm H_2O/L/s	12.2 (9.3–17.5)	10.6 (9.9–13.7)	14.3 (9.2–20.9)
Rmax,w, cm H_2O/L/s	1.2 (0.2–1.9)	1.6 (0.5–2.2)	1.2 (0.1–1.4)
Est,rs, cm H_2O/L	26.7 (21.7–32.2)	35.1 (22.1–44.3)	24.8 (22.5–27.3)
Est,L, cm H_2O/L	15.3 (11.3–22.1)	24.2 (10.3–29.7)	14.8 (11.9–19.5)
Est,w, cm H_2O/L	10.2 (6.9–13.0)	11.0 (10.0–14.0)	9.9 (5.6–11.8)
$P_I$max, cm H_2O	35.9 (28.5–50.6)	43.9 (31.1–52.4)	34.3 (20.6–47.8)
Ptc_{CO_2}, mm Hg	42.5 (36.2–49.2)	44.0 (34.0–52.0)	40.0 (37.0–47.0)

Definition of abbreviations: Est,L = elastance of the lung; Est,rs = elastance of the total respiratory system; Est,w = elastance of the chest wall; IQR = interquartile range; PEEP = positive end-expiratory pressure; $P_I$max = maximum inspiratory pressure; Rmax,L = maximum resistance of the lung; Rmax,rs = maximum resistance of total respiratory system; Rmax,w = maximum resistance of the chest wall.
All variables are expressed as median (IQR).
*Dyspneic patients had lower set V_T ($P < 0.046$) and lower set PEEP ($P < 0.028$) than did non-dyspneic patients.
†Respiratory mechanics (resistance, elastance), respiratory muscle strength ($P_I$max), and Ptc_{CO_2} were similar in dyspneic and nondyspneic patients.

Table 3. Dyspnea and Physiological Variables during an Unassisted-Breathing Trial

Variable	10 Min into the Trial	60 Min into the Trial	*P* Value*	Effect Size
Dyspnea score	3.0 (0.0–5.5)	3.5 (0.0–7.5)	<0.01	1.20
Ptc_{CO_2}, mm Hg	47.0 (42.8–52.8)	51.0 (42.8–56)	<0.01	0.67
Breath components				
V_T, ml	275 (199–361)	303 (213–374)	0.45	0.31
Frequency, breaths/min	28.6 (21.0–33.2)	31.1 (22.3–34.1)	0.26	0.20
$\dot{V}$ (L/min)	7.28 (6.62–8.64)	7.84 (6.38–9.69)	0.12	0.63
f/V_T, breaths/min/L	107 (63–169)	99 (74–154)	0.83	0.01
T_I, s	0.93 (0.84–1.12)	0.89 (0.80–1.14)	0.26	0.44
T_E, s	1.12 (0.92–1.60)	1.10 (0.89–1.40)	0.28	0.44
V_T/T_I, ml/s	274 (222–342)	300 (247–365)	0.22	0.47
Lung mechanics and patient effort				
Resistance, cm H_2O/L/s	9.7 (8.2–12.4)	9.0 (7.0–13.5)	0.89	0.06
Elastance, cm H_2O/L	27.6 (14.4–36.0	24.1 (16.4–33.5)	0.83	0.09
PEEPi, cm H_2O	1.4 (0.7–2.3)	1.4 (0.9–3.0)	0.30	0.41
PTP/breath, cm H_2O/s	8.2 (5.4–9.8)	8.2 (5.2–9.6)	0.50	0.27
PTP/min, cm H_2O/s/min	203 (163–298)	230 (140–312)	0.37	0.36
PTP/L, cm H_2O/s/L	23.8 (19.0–35.3)	25.4 (18.9–38.7)	0.75	0.13

Definition of abbreviations: f/V_T = index of rapid shallow breathing; IQR = interquartile range; PEEPi = intrinsic positive end-expiratory pressure; PTP = pressure–time product; T_E = expiratory time; T_I = inspiratory time; V_T/T_I = mean inspiratory flow.
Values are presented as median (IQR).
**P* value was calculated using the Wilcoxon rank-sum test.

The dyspnea descriptor that was most commonly selected by patients during the trial was "Not getting enough air." Of 17 patients with dyspnea at 10 minutes into the trial, 11 chose solely "Not getting enough air" and 3 chose the combination of "Not getting enough air" and "Too much effort to breathe." That is, 14 of 17 patients (82.4%) included "Not getting enough air" in their selection, whereas 3 (17.6%) chose "Too much effort to breathe" on its own ($P < 0.0002$).

At 60 minutes into the trial, 10 of 18 dyspneic patients chose solely "Not getting enough air" and 5 chose the combination of "Not getting enough air" and "Too much effort to breathe." That is, 15 of 18 patients (83.3%) included "Not getting enough air" in their selection, whereas 3 (16.7%) chose "Too much effort to breathe" on its own ($P < 0.0001$).

Across the spectrum of dyspnea severity, multinomial regression analysis revealed that patients chose "Not getting enough air" overwhelmingly over other descriptor options ($P < 0.001$). The probability of choosing either "Not getting enough air" on its own or in combination with "Too much effort to breathe" was 1.8–2.8 times greater than the probability of choosing either "Too much effort to breathe" on its own or in combination with "Not getting enough air" ($P < 0.001$) (Figure 1).

Mixed-effects regression analysis revealed that three variables exerted significant effects on dyspnea: Ptc_{CO_2} (unstandardized coefficient, 0.14; 95% CI, 0.04–0.24), resistance (coefficient, 0.19; 95% CI, 0.05–0.33), and $\dot{V}_E$ (coefficient, 0.32; 95% CI, 0.06–0.59). For each increase in Ptc_{CO_2} by 0.14 mm Hg, dyspnea increased by 1 U; for each increase in resistance by 0.19 cm H_2O/L/s, dyspnea increased by 1 U; and for each increase in $\dot{V}_E$ by 0.32 L/min, dyspnea increased by 1 U. When coefficients of the three variables were standardized, analysis revealed that Ptc_{CO_2} (standardized coefficient, 1.24; $P < 0.012$) and resistance (standardized coefficient, 1.19; $P < 0.013$) exerted greater effects on dyspnea, and the contribution from $\dot{V}_E$ was smaller (standardized coefficient, 0.66; $P < 0.024$) (Figure 2).

Resistance observed during the unassisted-breathing trial had a significant influence on dyspnea descriptors selected by patients (Figure 3). On multinomial analysis, an increase in resistance from 5 to 25 cm H_2O/L/s decreased the probability of choosing the "Not getting enough air" descriptor on its own from 65.1% to 19.2%, whereas the probability of selecting the combination of "Too much effort to breathe" and "Not getting enough air" increased from 17.8% to 71.9% ($P < 0.02$) (Figure 3). The probability of choosing "Too much effort to breathe" on its own did not change with increasing resistance.

Discussion

While receiving mechanical ventilation, 10 of 27 patients (37.0%) experienced dyspnea, and all but one (90.0%) selected solely "Not enough air" to describe their discomfort. During an unassisted-breathing trial, patients developed an increase in overall dyspnea ($P < 0.01$) and a 4-mm Hg increase in Ptc_{CO_2} ($P < 0.01$), but no change in $\dot{V}_E$ (Table 3). Intensity of dyspnea exhibited a strong mathematical relationship with Ptc_{CO_2} (Figure 2). At 60 minutes into the trial, 83.3% of patients selected "Not getting enough air" on its own or in combination with "Too much effort" to describe their discomfort, whereas only 16.7% selected "Too much effort" on its own ($P < 0.001$). Patient work of breathing, measured with an esophageal-balloon catheter, was almost three times higher than normal, yet neither overall PTP nor its subfractions (PTP per liter or PTP per minute) bore a significant relationship to any aspect of dyspnea.

The major reason why mechanical ventilation is instituted is because clinicians judge a patient's work of breathing to be elevated, and they commonly assume that mechanical ventilation eliminates patient dyspnea (4, 15). However, 37.0% of our patients experienced dyspnea while receiving carefully titrated assist-control ventilation. The proportion of ventilated patients experiencing dyspnea is similar to that of

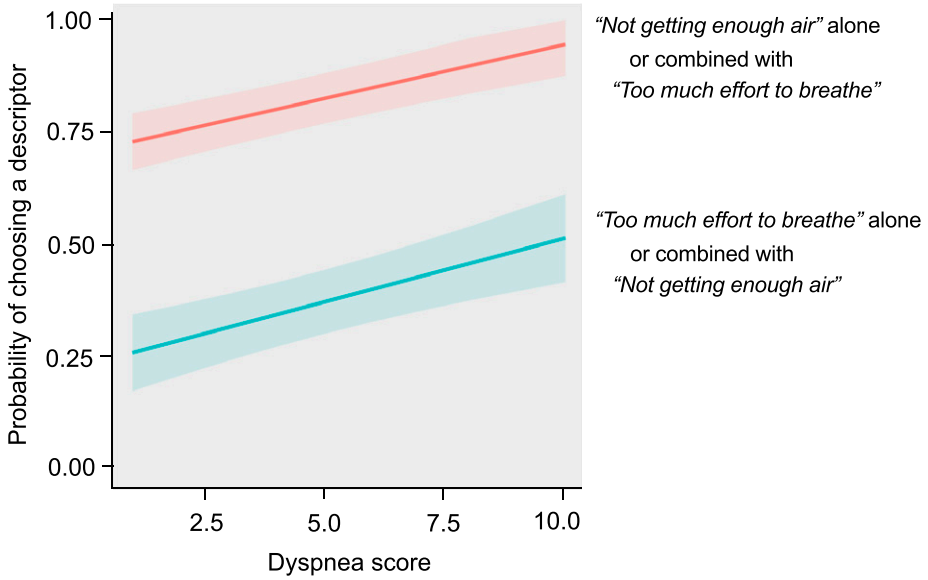

Figure 1. The probability (solid red curve) and 95% confidence interval (CI; shaded red area) of patients choosing the descriptor "Not getting enough air" either on its own or in combination with the descriptor "Too much effort to breathe," compared with the probability (solid blue curve) and 95% CI (shaded blue area) of patients choosing the descriptor "Too much effort to breathe" either on its own or in combination with "Not getting enough air" plotted against dyspnea score during mechanical ventilation and the unassisted-breathing trial. Across all levels of dyspnea severity, the probability of selecting "Not getting enough air" either on its own or in combination with "Too much effort to breathe" was 1.8–2.8 times greater than the probability of selecting "Too much effort to breathe" on its own or in combination with "Not getting enough air" ($P < 0.001$).

34.0%, reported by Demoule and colleagues (6), and 46.9%, reported by Schmidt and colleagues (5). Air hunger was the dominant form of dyspnea experienced by our patients, and all but 1 of the 10 dyspneic ventilated patients selected solely "Not enough air" to describe their discomfort. The frequency with which our dyspneic patients selected "Not enough air," 90%, was 2.7-fold greater than the 33.3% frequency of air hunger reported by Schmidt and colleagues in dyspneic ventilated patients (5) and even higher than the 71.0% frequency of air hunger in dyspneic ventilated patients reported by Demoule and colleagues (6). Sound scientific justification exists for the use of lower V_T in patients with acute respiratory distress syndrome (ARDS) (16), but low V_T are now used increasingly during mechanical ventilation for all disorders (17). That 90% of ventilated patients experiencing dyspnea selected the descriptor "Not enough air" is one more reason to doubt the wisdom of using low V_T in patients who do not have ARDS. This apprehension is heightened by the significantly lower V_T setting in dyspneic patients, 480.0 ml, than in nondyspneic patients: 559.4 ml ($P < 0.046$).

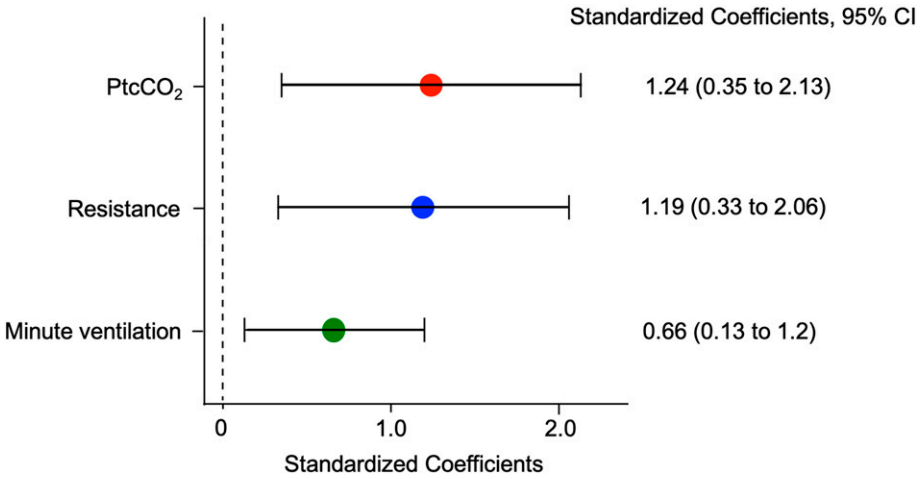

Figure 2. Forest plot (obtained with a mixed-effects linear regression model) of standardized coefficients (closed circles) and 95% confidence intervals (horizontal lines) of the linkage between three variables—Ptc_{CO_2}, resistance, and $\dot{V}_E$—and dyspnea during the unassisted-breathing trial. Standardized coefficients revealed that Ptc_{CO_2} ($P < 0.012$) and resistance ($P < 0.013$) exerted the greatest effects on dyspnea, with a small contribution from $\dot{V}_E$ ($P < 0.024$). CI = confidence interval.

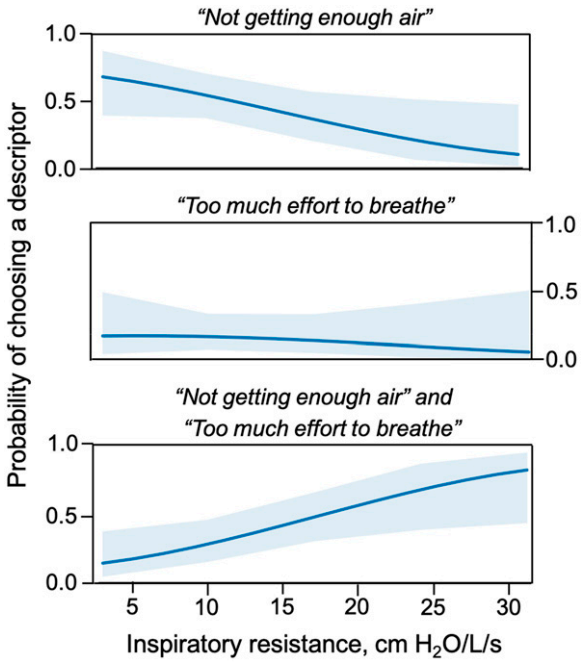

Figure 3. The probability (solid curve) and 95% confidence interval (shaded blue area) of choosing dyspnea descriptor "Not getting enough air" (top), the descriptor "Too much effort to breathe" (middle), and the combination of "Not getting enough air" and "Too much effort to breathe" (bottom) plotted against inspiratory resistance during the unassisted-breathing trial. As airway resistance increased, the probability of choosing the "Not getting enough air" descriptor on its own decreased, whereas the probability of selecting the combination of "Too much effort to breathe" and "Not getting enough air" increased.

The choice of dyspnea descriptors by patients undergoing ventilator weaning has not been previously investigated. While our patients were experiencing an unassisted-breathing trial, air hunger was the dominant form of dyspnea throughout its course. At 60 minutes into the trial, for example, five times more dyspneic patients, 83.3% (15/18), selected either "Not getting enough air" on its own or "Not getting enough air" in combination with "Too much effort" as contrasted with only 16.7% (3/18) of dyspneic patients who selected solely "Too much effort" ($P < 0.001$). Across all levels of dyspnea severity, patients chose overwhelmingly "Not getting enough air" over other descriptor options ($P < 0.001$).

In the largest study of dyspnea in hospitalized patients, Stevens and colleagues (18) documented 47 patients with moderate dyspnea (scores for overall dyspnea ranged from 4.0 to 7.9 on a scale ranging from 0 to 10) who had a virtually identical mean score for air hunger and respiratory muscle work (approximately 4.0 for each). Among 82 patients with severe dyspnea (scores for overall dyspnea were 8–10), the mean rating for air hunger was approximately 8.1, and the mean rating for respiratory muscle work was approximately 7.2; the investigators did not state whether these ratings differed statistically. The investigators did not allow patients to select more than a single descriptor (at a time) to best communicate their discomfort: 27.8% of our patients at 60 minutes into the unassisted-breathing trial, for example, did not select either "Not getting enough air" on its own or "Too much effort" on its own but rather the two descriptors in combination. To enumerate our data solely in terms of the number of patients selecting "Not getting enough air" on its own would underestimate the extent of air hunger experienced by patients, which is the preeminent finding of the study. To communicate the true magnitude of air hunger, it is necessary to meld patients selecting "Not getting enough air" on its own and patients who selected it in combination with "Too much effort." Stevens and colleagues (18) did not attempt to quantify respiratory muscle work, and their patients were admitted to a general medical–surgical floor. Our patients were in a much more precarious position and were expected to die if not reconnected to the ventilator after the unassisted-breathing trial. Our patients included "Not getting enough air" far more frequently than "Too much effort" in their selection ($P < 0.001$) (Figure 1), in contrast with the much smaller disparity in relative ratings of these two descriptors in the hospitalized patients of Stevens and colleagues (18).

Dyspnea is the dominant symptom among patients attending a pulmonary clinic. When a new patient is first seen, a physician's opening question is usually "Do you have difficulty with breathing?" The word "dyspnea" has been used by medical authors for centuries and appears in the writings of René Laennec (19), William Stokes (20), Austin Flint (21), and William Osler (22). Etymologically, the word stems from the Greek, δύσπνοιᾰ, *dús* (difficult) *pnoia* (breathing) (23). Despite "difficulty" being the essential attribute contained in the word "dyspnea," only 16.7% of our patients chose "Too much effort to breathe" to describe their discomfort, whereas 83.3% selected "Not getting enough air" either alone or in combination with "Too much effort" (at 60 min into the trial).

Using an esophageal-balloon catheter, we obtained meticulous measurements of work of breathing throughout the unassisted-breathing trial. Patient work, quantified in terms of PTP, was almost three times greater than the normal value (94.1 cm H_2O/s/min) (24). Neither severity of dyspnea nor type of dyspnea bore a significant relationship to overall PTP or its subfractions (PTP per liter or PTP per minute). That only 16.7% of patients selected "Too much effort" to describe their breathing discomfort signifies that patients recognize what the detailed esophageal-catheter measurements revealed: Respiratory work is not the dominant sensation being communicated by a complaint of breathing discomfort. The orientation of physicians toward the dictionary understanding of dyspnea as difficult breathing (23) needs to be redirected toward air hunger.

In a series of elegant experiments, Banzett and colleagues have demonstrated that the defining experimental design for evoking air hunger is induction of an increase in the drive to breathe (with hypercapnia) while mechanically restricting a person's ability to increase ventilation (25). Through stimulation of the brainstem respiratory centers, an increase in P_{CO_2} usually elicits an increase in $\dot{V}_E$. While our patients were experiencing an increase in dyspnea during

the unassisted-breathing trial ($P < 0.01$), their Ptc_{CO_2} increased from 47 mm Hg at 10 minutes into the trial to 51 mm Hg at 60 minutes ($P < 0.01$; Table 3). On the basis of the normal ventilatory response to hypercapnia (2.7 ± 0.31 L/min/mm Hg) (26), one would expect a 4-mm Hg increase in Ptc_{CO_2} to arouse an increment in $\dot{V}_E$ of 10.8 L/min. $\dot{V}_E$, however, did not change over the course of the unassisted-breathing trial (Table 3). The concurrence of dyspnea, increase in Ptc_{CO_2} during the trial, lack of increase in $\dot{V}_E$, and preponderant selection of the "Not getting enough air" descriptor is consistent with the physiological mechanism for air hunger proposed by Banzett and colleagues (25).

Airway resistance was a major determinant of dyspnea during the unassisted-breathing trial. A mixed-effects regression model revealed that the standard coefficient for airway resistance was as strong a contributor to dyspnea intensity as was Ptc_{CO_2} (Figure 2). Moreover, multinomial analysis revealed that an increase in airway resistance was linked with the dyspnea descriptor selected by patients ($P < 0.02$). As airway resistance increased from 5 to 25 cm H_2O/L/s, the probability of choosing the "Not getting enough air" descriptor on its own decreased from 65.1% to 19.2%, whereas the probability of selecting the combination of "Too much effort to breathe" together with "Not getting enough air" increased from 17.8% to 71.9% (Figure 3). The observed pattern is consistent with physiological understanding: An increase in resistance is expected to incur an increase in respiratory effort, whereas induction of air hunger by means of imposed resistance occurs with extremely elevated resistance, 260–280 cm H_2O/L/s (27); airway resistance averaged 11.6 cm H_2O/L/s in our patients, and the highest individual reading was 31.0 cm H_2O/L/s.

Contemporary understanding of the pathophysiology of dyspnea has been constructed largely from scientific experiments involving CO_2 rebreathing, imposed elastic or resistive loads, bicycling to the point of exhaustion, and other challenges (28). By their nature, such laboratory provocations do not replicate the quotidian plight experienced by patients, and the generated data are open to criticism that findings do not apply to *bona fide* clinical settings (29, 30). In contrast, we simply witnessed (albeit with the aid of meticulously calibrated instrumentation) an activity performed by doctors every day in hospitals around the world: an attempt to remove ventilator support in patients receiving prolonged ventilation. The ultimate outcome of this experiment of nature carries the direst danger faced by a patient: death if the status quo ante is not reinstituted. Our real-life observations, devoid of all artifice, furnish concrete data that support robustly the prevailing theoretical framework for exploring mechanisms of air hunger (25).

Limitations of our study include its modest size. Recruitment was constrained by necessitating patient cognitive proficiency and willingness to tolerate invasive measurements. Small sample size is sometimes seen as hampering generalizability (external validity), but the bedrock of generalizability is robust internal validity, which is best ensured by eschewing systematic error through scrupulous measurements in a controlled patient sample (31, 32). We did not validate the rating scale used to quantify dyspnea. Such scales, however, evince sound test–retest reliability in ventilated patients in the ICU (33). Dyspnea descriptors were confined to two attributes; "chest tightness" was not included because of the rarity of asthma among patients receiving prolonged ventilation. Patients were unable to speak freely because of tracheal tubes. This problem was mitigated by using a simple intensity scale and a restricted listing of descriptors.

In summary, 37.0% of patients who received prolonged mechanical ventilation (29.7 d) experienced dyspnea while receiving standard assist-control ventilation. Among dyspneic ventilated patients, 90.0% selected "Not getting enough air." This, combined with the significantly lower V_T setting in dyspneic patients (480.0 ml), compared with that in nondyspneic patients (559.4 ml), raises disconcerting questions about the use of low V_T in patients without ARDS (17). During an unassisted-breathing trial, patients developed dyspnea, an increase in Ptc_{CO_2}, no change in $\dot{V}_E$, and 83.3% of dyspneic patients selected "Not getting enough air" alone or in combination as opposed to only 16.7% selecting "Too much effort" on its own. The conjunction of these physiological observations is consistent with the thesis that air hunger is the consequence of heightened sensory stimulation of the respiratory centers combined with an incapacity to actuate an increase in $\dot{V}_E$.

In conclusion, contrary to the dictionary definition of dyspnea as difficult breathing, patients who experienced dyspnea in a life-threatening situation overwhelmingly choose air-hunger descriptors, rather than excessive respiratory effort, to communicate their discomfort. ■

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