Patient–Clinician Alliance during Prolonged Mechanical Ventilation

“Never Give Up on a Dream”

Perception is often quite different from reality. This observation fits very well in medicine. In fact, despite extensive experience, many clinicians tend to under- or overestimate the outcomes of their patients (1). The perception of a poor prognosis in patients requiring prolonged mechanical ventilation is a classic example of this phenomenon, which can lead to dramatic ethical dilemmas about the value of continuing the “artificial” support at the expense of the patient’s quality of life, which is often presumed to be miserable (2).

In this issue of the *Journal*, Jubran and colleagues (pp. 1508–1516) challenge this idea in a prospective 1-year study conducted in 315 consecutive patients from a large cohort of subjects enrolled in a previous clinical trial, comparing weaning methods in long-term ventilated patients admitted to a long-term acute care hospital (LTACH) (3, 4).

In line with previous findings from LTACH studies (4, 5), more than 50% of the patients were liberated from mechanical ventilation. However, the most important and novel results were that the majority of subjects at discharge regained the ability to perform daily activities independently, and 85% of survivors indicated a willingness to undergo ventilation again if deemed necessary.

Interestingly, in patients who were still alive at 12 months, respiratory muscle strength was quite well preserved at LTACH admission and did not change during the following year, whereas peripheral strength was very impaired but recovered with time, allowing an overall satisfactory quality of life (3). This was not the case for the patients who died, as they had a severe generalized muscle weakness (in both limb and respiratory muscles) that did not improve during the LTACH stay.

The study by Jubran and colleagues is important because it raises several considerations concerning the weaning process in the ICU, the best location where weaning should be performed in cases of prolonged ventilation, the mechanisms that lead to long-term functional recovery, and lastly, the patient’s perception of this often devastating experience.

First, patients experiencing prolonged ventilation represent a relatively small subset of patients admitted to an ICU, and although many survivors in Jubran and colleagues’s study regained satisfactory autonomy, it should be kept in mind that more than half of the 315 patients died within the 12-month follow-up period (3).

The question that arises is, were these individuals already very sick at ICU admission or did they deteriorate because of prolonged ventilation and the ICU stay? In other words, did these patients receive the best weaning practice, as they did during the LTACH stay?

Little details can make a big difference in the care of mechanically ventilated patients, including the ventilator setting, which can result in under- or overassistance of the diaphragm (6); the judicious use of sedation (7) and medical therapy; the use of care bundles to prevent infections (8); the avoidance of delirium; the prompt recognition of weanibility by means of the appropriate tests (9); and last but not least, early mobilization while patients are on mechanical ventilation (9).

Whatever the medical history of these patients, LTACHs are probably the best settings in which to attempt to liberate them from prolonged ventilation.

On arrival, each patient was evaluated by rehabilitation professionals (occupational therapist, physical therapist, and speech-language therapist) to determine his or her functional status and rehabilitative needs. An exercise-training program was initiated thereafter for a minimum of 30 min/d. In addition, the weaning protocol using pressure support or a tracheostomy collar was strictly supervised (being the procedural part of a randomized controlled trial) (4). Interestingly, 109 of the 315 patients (35%) were not randomized, because they were able to be liberated from the ventilation after the first attempt in the LTACH, suggesting that in the originating ICU the feasibility of weaning was probably not always evaluated at the proper time.

Given the increasing number of patients undergoing prolonged ventilation and tracheotomy, over the last two decades there has been a rapid rise in LTACH use in the United States (10). The main benefits of these units are related to the environment itself, which offers less sleep disturbance, lower light and noise intensity (11), and more liberal visiting hours. In addition, the LTACH enables clinicians to respond to sudden changes in a patient’s clinical condition, allows enough time for a multidisciplinary rehabilitation approach, and serves as a bridge to home-care programs or other forms of continuous assistance (e.g., telemedicine or dedicated long-term units). However, the levels of assistance in LTACHs are not homogeneously distributed, so the conclusions of Jubran and colleagues may not be generalizable.

Upon enrollment the patients who survived at 12 months had a relatively preserved respiratory muscle strength that did not improve between admission and discharge, whereas handgrip strength was very low on arrival and increased during the LTACH stay. The comprehensive rehabilitation program that was continued after LTACH discharge could probably explain this result. In fact, only 11.8% of the patients were sent directly home, and the others were transferred either to a rehabilitation facility or to skilled nursing centers.

As discussed by the authors, physiological studies performed in the ICU showed that diaphragm contractility, assessed using phrenic nerve stimulation, was not different between patients who were successfully weaned and those who failed to wean (12). However, other investigators have demonstrated that the development of diaphragm atrophy during mechanical ventilation strongly impacts clinical outcomes (6). In addition, it was shown that diaphragm dysfunction occurs twice as frequently as limb muscle weakness and has a direct negative impact on weaning outcomes, and that the two types of muscle weakness have only limited overlap (13). It should also be kept in mind that strength itself represents only one side of the so-called load/capacity index (14), i.e., the ratio between the tidal effort that the diaphragm needs to face to overcome the inspiratory load, and the maximal pressure that can be elicited (which unfortunately was not recorded in Jubran and colleagues’s study).

Lastly, the authors reported that 85% of the patients said that they would be willing to undergo the experience of prolonged

The quote in the title is from “Never Give Up on a Dream” by Rod Stewart (November 6, 1981).

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mechanical ventilation again if deemed necessary, and they speculated that the "remembering-self" was probably the leading reason for this affirmation.

This is in keeping with another study that showed that patients would choose to receive aggressive treatment, but only if survival was not associated with severe functional or cognitive impairment (15).

The major factor in a patient–clinician interview is how it is conducted, and this detail is not specified in the article. It has been suggested that "little white lies" in this bidirectional communication are quite common; sometimes in an attempt to "please my doctor who saves my life," a patient may minimize his or her symptoms or bad experiences (16).

In conclusion, this study, besides being well conducted and providing important clinical information, clarifies the issue that perception in medicine may be very misleading. Therefore, the patient and clinician, allied together, should never give up on the dream to liberate the patient from prolonged ventilation and recover a satisfactory quality of life. ■

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Defining the Cell Types That Drive Idiopathic Pulmonary Fibrosis Using Single-Cell RNA Sequencing

Few novel technologies have been welcomed with more excitement by the scientific community than single-cell RNA sequencing (scRNA-seq). The report by Reyfman and colleagues (pp. 1517–1536) in this issue of the *Journal* provides important insight into pathogenic cell types in lung fibrosis on an unprecedented scale (1), making idiopathic pulmonary fibrosis (IPF) the first chronic lung disease to be analyzed using scRNA-seq (#CureIPF).

A single cell is the fundamental unit of life. Dissecting the heterogeneity, dynamics, and interactions of cells will truly unravel how we, as well as diseases we are trying to cure, develop and grow. Until recently, the characterization of specific cell types (of the lung) relied on *ex vivo* labeling or generating large numbers of cells based, at times, on poorly understood isolation techniques, followed by analysis of pooled RNA or proteins for hybridization or sequencing. Although these approaches have revealed robust cell

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ORIGINAL ARTICLE

Long-Term Outcome after Prolonged Mechanical Ventilation
A Long-Term Acute-Care Hospital Study

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Abstract

Rationale: Patients managed at a long-term acute-care hospital (LTACH) for weaning from prolonged mechanical ventilation are at risk for profound muscle weakness and disability.

Objectives: To investigate effects of prolonged ventilation on survival, muscle function, and its impact on quality of life at 6 and 12 months after LTACH discharge.

Methods: This was a prospective, longitudinal study conducted in 315 patients being weaned from prolonged ventilation at an LTACH.

Measurements and Main Results: At discharge, 53.7% of patients were detached from the ventilator and 1-year survival was 66.9%. On enrollment, maximum inspiratory pressure ($P_{I_{max}}$) was 41.3 (95% confidence interval, 39.4–43.2) cm H_2O (53.1% predicted), whereas handgrip strength was 16.4 (95% confidence interval, 14.4–18.7) kPa (21.5% predicted). At discharge, $P_{I_{max}}$ did not change, whereas handgrip strength increased by 34.8% ($P < 0.001$). Between discharge and 6 months, handgrip strength increased 6.2 times more than did $P_{I_{max}}$. Between discharge and 6 months, Katz activities-of-daily-living summary score improved by 64.4%; improvement in Katz summary score was related to improvement in handgrip strength ($r = -0.51$; $P < 0.001$). By 12 months, physical summary score and mental summary score of 36-item Short-Form Survey returned to preillness values. When asked, 84.7% of survivors indicated willingness to undergo mechanical ventilation again.

Conclusions: Among patients receiving prolonged mechanical ventilation at an LTACH, 53.7% were detached from the ventilator at discharge and 1-year survival was 66.9%. Respiratory strength was well maintained, whereas peripheral strength was severely impaired throughout hospitalization. Six months after discharge, improvement in muscle function enabled patients to perform daily activities, and 84.7% indicated willingness to undergo mechanical ventilation again.

Keywords: prolonged mechanical ventilation; survival; respiratory muscles; handgrip strength

Patients requiring prolonged mechanical ventilation are commonly transferred to a long-term acute-care hospital (LTACH) for weaning and rehabilitation (1–5). In 2015, Medicare spent $5.3 billion on care in 426 LTACHs (6). Despite the increasing role of LTACHs in ventilated patients, long-term outcome (survival and quality of life [QOL]) data in such patients are scarce (7, 8).

In a prospective trial conducted at an LTACH comparing methods of weaning from prolonged ventilation, we found that 45% of 500 enrolled patients were alive 1 year after discharge; factors contributing to their survival are poorly understood (1, 2, 9–11). Survivors are expected to have profound muscle weakness (12–15), but its

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At a Glance Commentary

Scientific Knowledge on the Subject: Patients managed at a long-term acute-care hospital for weaning from prolonged mechanical ventilation are at risk for profound muscle weakness and disability, but its impact on functional recovery and quality of life has not been investigated.

What This Study Adds to the Field: This is the first study to provide longitudinal measurements of survival, muscle function, and quality-of-life evaluation in ventilated patients during a long-term acute-care hospital stay and 6 and 12 months after discharge. Half (53.7%) of patients were detached from the ventilator at discharge and their 1-year survival was 66.9%. Respiratory strength was well maintained, whereas peripheral strength was severely impaired. Improvement in muscle function was associated with an increased ability to perform daily activities independently, and 84.7% of survivors indicated willingness to undergo ventilation again if deemed necessary.

impact on functional recovery has not been investigated. Because long-term outcome may be poor and the weaning process daunting to patients (16, 17), some wonder whether it is worthwhile to provide prolonged ventilation (18). Although this negative perception seems to be widespread, direct data on patient QOL and a patient's own assessment of the ordeal are limited.

Accordingly, we prospectively followed patients between arrival at an LTACH to 1 year after discharge (as part of our original clinical trial) to assess the effects of prolonged ventilation on survival, muscle function, and its impact on QOL. We also assessed patient willingness to undergo another episode of prolonged ventilation. To minimize dropouts, postdischarge assessments were performed predominantly at patient residences.

Methods

Setting

The study was conducted between 2003 and 2010 at RML Specialty Hospital, a free-standing LTACH, and the patient's place of residence 6 and 12 months after discharge (*see* the online supplement).

Patients

Of the 500 patients who were enrolled in our clinical trial comparing weaning methods in LTACH patients (*see* online supplement) (1), the last 315 consecutive patients were invited to participate in a 1-year outcome study (*see* Figure E1 in the online supplement). Inclusion/exclusion criteria have been published (1). Patients were considered ventilator-detached if they could breathe without ventilator assistance at LTACH discharge. Patients were considered ventilator-attached if they required ventilator support at LTACH discharge. The study was approved by the institutional review board and informed consent obtained from patients/surrogates.

Measurements

Respiratory muscle strength was assessed by measuring maximum inspiratory pressure ($P_{I_{max}}$) generated against an occluded airway at residual volume (19). In nontracheotomized patients, $P_{I_{max}}$ was measured through the mouth using a nose-clip and flanged mouthpiece (20). In tracheotomized patients, $P_{I_{max}}$ was measured through either the tracheostomy stoma or mouth (*see* online supplement) (19, 21–23).

Handgrip strength was assessed using a dynamometer while patients were seated upright (*see* online supplement) (24). Values are expressed as kilopascals.

Health-related QOL was assessed using the Medical-Outcomes Study 36-item Short-Form General-Health Survey (SF-36) (25). SF-36 measures QOL in eight domains; scores in each domain range from 0 (worst) to 100 (best) (*see* online supplement) (26). Domain scores were combined into two summary (physical/mental) scores, and compared with normative data, standardized to a mean of 50 ± 10 (SD).

Functional status was assessed by patient ability to perform six daily tasks using Katz Activities-of-Daily-Living questionnaire (27). Scores for each task are aggregated to generate a sum score (range, 0 to 18); sum score less than or equal to six indicates independence (*see* online supplement).

Preference about mechanical ventilation. Patients were asked if they remembered having shortness of breath, nightmares, or problems communicating during weaning. Patients were then asked: "If necessary, would you go through the process of being put on a ventilator and everything that happened afterward again, if it was necessary to save your life? In other words, was it all worth it"?

Protocol

Enrollment. $P_{I_{max}}$ and handgrip strength were measured. Using Katz and SF-36 questionnaires, patients were asked to estimate functional status and QOL 2 weeks before hospitalization for critical illness (28, 29); this is considered preillness function (*see* online supplement). When patients were unable to answer, questionnaires were answered by surrogates (44.8% of assessments) (30).

Discharge. $P_{I_{max}}$ and handgrip strength were measured, and patients were asked to complete Katz and SF-36 questionnaires. When patients were unable to answer, questionnaires were answered by surrogates (*see* online supplement).

Follow-up procedure. Patients were contacted at 6 and 12 months after LTACH discharge to determine their status (survival and location). For patients living at home, a face-to-face visit was scheduled. During the visit, $P_{I_{max}}$ and handgrip strength were measured; SF-36, Katz, and preference-about-mechanical-ventilation questionnaires were completed by the patient. For patients who refused a home visit, a telephone interview was conducted and the previously mentioned questionnaires were administered. If successful contact was not achieved after three telephone attempts, questionnaires were mailed (*see* online supplement). For patients at an institution, a family member was contacted and asked if he/she was willing to fill out the questionnaires (*see* online supplement).

Statistical Analysis

Cox proportional hazards regression model adjusted for baseline characteristics was used to obtain hazard ratio (HR) of survival up to 12 months after discharge. Variables included in the model were tested for collinearity and no serious collinearity was identified among the variables (*see* online supplement) (31). The proportional hazards assumption was verified using Schoenfeld residuals. Kaplan-Meier curves were used to assess survival up to 12 months after discharge in ventilator-attached and ventilator-detached patients.

Primary analysis. Change in five primary outcomes (handgrip strength, PI_{max}, Katz summary score, SF-36 physical summary score, SF-36 mental summary score) over time were assessed separately using a mixed-effects model for repeated measures and first-order autoregressive-covariance structure (*see* online supplement) (32). In each model, patients were assigned as random effects; one of the five outcome variables were assigned as the dependent variable, and time was coded as an ordinal independent variable: this constitutes our primary analysis. Further details of analysis are included in the online supplement. Results are presented as estimated-marginal means with 95% confidence interval (CI). *P* values were two-sided: *P* less than 0.05 was considered statistically significant.

Missing data management. Table E2 shows frequency of missing outcomes. The missing-completely-at-random test (33) was significant, indicating that missing data did not occur completely at random (*see* online supplement).

To determine whether missing data compromised interpretation of our results, two sensitivity analyses were performed *post hoc*. First, the relationship between missingness of a covariate and patient characteristics at enrollment was investigated using logistic-regression (*see* online supplement). Then, the primary analysis was repeated with additional variables associated with missingness (*see* Table E3) added as adjusting independent variables. Second, primary analysis was repeated with imputed values to replace missing values (*see* online supplement).

Results

Of 315 patients included in the study (original cohort), 52 (16.5%) patients died between enrollment and discharge; 253 of 260 eligible patients (97.3%) were evaluated at discharge (*see* Figure E1). Between discharge and 6 months, an additional 115 patients died, and 118 of 139 eligible patients were evaluated at 6-month follow-up. Another 13 patients died before 12-month follow-up (cumulative mortality, 57.1%), and 108 of 126 eligible patients (34.3% of original cohort) were evaluated at 12 months (*see* Figure E1). Of 315 patients, 169 (53.7%) were detached from the ventilator and 94 (29.8%) were still attached to the ventilator at LTACH discharge (*see* Table E4); the remaining 16.5% died during the LTACH stay.

Long-Term Survival

Table 1 shows the baseline characteristics of 12-month survivors versus nonsurvivors. Using a Cox proportional hazards model to adjust for baseline covariates, four variables were associated with 1-year survival: Simplified Acute Physiology Score II (HR, 1.03; 95% CI, 1.01–1.05; $P = 0.0002$), body

Table 1. Characteristics of Study Population at Enrollment according to Whether Patients Survived to 1 Year after Discharge from an LTACH

Variable	12-mo Survivors (*n = 132*)	Nonsurvivors (*n = 183*)*	*P* Value†
Age, yr, median (IQR)	64 (56–71)	74 (67–79)	<0.001
Sex, F/M (% F)	52/80 (39)	69/114 (38)	0.76
Postoperative, *n* (%)	62 (47)	73 (40)	0.21
Acute lung injury,‡ *n* (%)	47 (36)	64 (35)	0.91
Chronic obstructive pulmonary disease, *n* (%)	7 (5)	19 (10)	0.11
Neuromuscular, *n* (%)	16 (12)	27 (15)	0.50
SAPS II, median (IQR)	23 (18–31)	35 (27–42)	<0.001
APACHE II, median (IQR)	14 (10–16)	17 (14–20)	<0.001
Body mass index, kg/m^2, median (IQR)	30.3 (24.5–36.9)	27.4 (23.1–32.8)	0.007
Albumin, mg/dl	2.3 (2.0–2.5)	2.1 (1.8–2.4)	0.001
Variables measured at enrollment			
PI_{max}, cm H_2O, median (IQR)	42 (36–54)	38 (24–44)	0.003
Handgrip strength, kPa, median (IQR)	18 (0–30)	14 (0–25)	0.01
Preillness status			
Katz summary score, mean (95% CI)	2.2 (1.5–3.0)	3.2 (2.5–4.0)	0.07
SF-36 physical summary score, median (IQR)	39 (31–47)	34 (26–41)	<0.001
SF-36 mental summary score, median (IQR)	50 (45–57)	50.5 (41–57)	0.56
Duration of mechanical ventilation			
At randomization,§ d, median (IQR)	26 (21–35)	29 (21–40)	0.15
At LTACH, ‖ d, median (IQR)	12 (5–27)	32 (12–51)	<0.001
Length of stay at LTACH,¶ d, median (IQR)	33 (23.8–47)	40 (27–55)	0.006

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; IQR = interquartile range; LTACH = long-term acute-care hospital; PI_{max} = maximum inspiratory pressure; SAPS = Simplified Acute Physiology Score; SF-36 = Medical-Outcomes Study 36-item Short-Form General-Health Survey.
*Three of the patients who withdrew at 6 months died before 12 months.
†The Wilcoxon rank sum test was used for continuous variables, and the chi-square test was used for categorical variables.
‡Patients were categorized as having acute lung injury if they had pneumonia or pulmonary edema as the precipitating cause of respiratory failure.
§Duration of ventilation at randomization was calculated from the day of intubation at the ICU to the day the patient was randomized at the LTACH.
‖Duration of ventilation at the LTACH was calculated from the day of admission to the LTACH to the last day that the patient was attached to the ventilator at the LTACH.
¶Length of stay at LTACH was calculated from the day of admission to the LTACH to the day the patient was discharged from the LTACH.

mass index (HR, 0.97; 95% CI, 0.96–0.99; $P = 0.004$), Acute Physiology and Chronic Health Evaluation II (HR, 1.04; 95% CI, 1.00–1.09; $P = 0.03$), and being detached from the ventilator at discharge (HR, 0.31; 95% CI, 0.22–0.44; $P < 0.0001$) (*see* Table E5). Figure 1 shows a Kaplan-Meier plot of proportion alive in ventilator-detached patients and ventilator-attached patients up to 1 year after discharge. The 1-year survival was 66.9% for ventilator-detached patients and 16.4% for ventilator-attached patients.

Muscle Strength

Respiratory muscle strength. Between admission and discharge, PI_{max} did not change, 41.3 (95% CI, 39.4–43.2; 53.1% predicted [34]) versus 42.9 (95% CI, 40.9–44.9) cm H_2O (55.9% predicted). PI_{max} increased to 54.4 (95% CI, 51.2–57.6) cm H_2O (67.5% predicted) at 6 months ($P < 0.001$) and did not change at 12 months, 58.0 (95% CI, 54.5–61.6) cm H_2O (70.1% predicted) (Table 2).

Handgrip strength. Between admission and discharge, handgrip strength increased from 16.4 (95% CI, 14.1–18.7) kPa (21.5% predicted [35]) to 22.1 (95% CI, 19.7–24.5) kPa (29.1% predicted) ($P < 0.001$). Handgrip strength increased to 58.6 (95% CI, 55.0–62.1) kPa (81.0% predicted) at 6 months ($P < 0.001$) and did not change at 12 months, 62.5 (95% CI, 58.4–66.5) kPa (85.9% predicted) (Table 2).

Functional Status and QOL

Functional status. Before critical illness, Katz summary score for entire cohort was 2.8 (95% CI, 2.3–3.3). At discharge, the score was 14.6 (95% CI, 13.9–15.2) (requiring full assistance). Katz summary score at 6 months decreased to 5.2 (95% CI, 4.3–6.0; independent or requiring special equipment; $P < 0.001$) and remained unchanged at 12-months, 4.7 (95% CI, 3.8–5.6) (Table 2). Katz summary score correlated with handgrip strength at 6 (Spearman $r = -0.51$; $P < 0.001$) and 12 months ($r = -0.52$; $P < 0.001$), indicating that patients with objective muscle weakness were less capable of performing daily activities. A weaker correlation was observed between Katz summary score and PI_{max} at 6 ($r = -0.27$; $P = 0.02$) and 12 months ($r = -0.22$; $P = 0.06$). Percentage of patients needing assistance in performing daily activities (Katz summary score >6) was 16.7% at preillness, 95.6% at discharge, 22.0% at 6 months, and 25.9% at 6 months (Table 3).

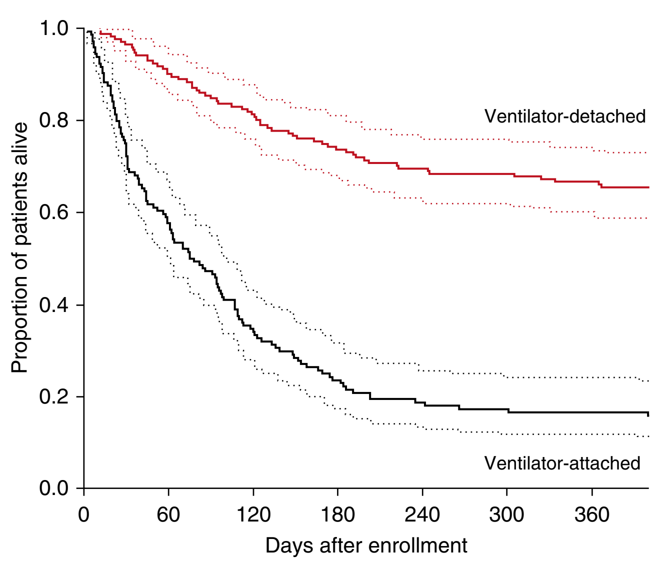

Figure 1. Proportion of patients alive in the ventilator-detached group and ventilator-attached group. Dotted lines represent 95% confidence intervals.

Quality-of-life. Figure 2 shows scores of domains of SF-36 questionnaire at preillness and 6 and 12 months after discharge. Before critical illness, physical summary score was 36.1 (95% CI, 35.0–37.3; normal, 50). At discharge, score was 24.0 (95% CI, 22.7–25.3). Between discharge and 6 months, score increased to 33.2 (95% CI, 31.4–35.0; $P < 0.001$) and remained unchanged at 12 months (36.5; 95% CI, 34.6–38.5) (Table 2). Physical summary score correlated with handgrip strength at 6 ($r = 0.46$; $P < 0.001$) and 12 months ($r = 0.47$; $P < 0.001$). Physical summary score correlated with PI_{max} at 6 ($r = 0.45$; $P < 0.001$) and 12 months ($r = 0.34$; $P = 0.002$).

Before critical illness, mental summary score was 49.1 (95% CI, 47.9–50.3; normal, 50). At discharge, score was 46.8 (95% CI, 45.5–48.2). Between discharge and 6 months, score increased to 52.5 (95% CI, 50.6–54.3; $P < 0.001$) and remained unchanged at 12 months (51.9; 95% CI, 49.9–53.9) (Table 2).

Preference about Mechanical Ventilation

Patients were asked about their weaning experience 6 and 12 months after discharge. Because responses were equivalent at both times, only 6-month data are presented. Of 118 patients (79.7% of survivors; 37% of original cohort) interviewed, 34.5% recalled shortness of breath, 38.8% reported problems communicating with staff/family, and 8.6% recalled nightmares.

When asked (6 mo after discharge) whether they would go through the process of mechanical ventilation again, 100 (84.7%) answered yes, 10 answered no, and eight were unsure. Compared with patients who would be willing to undergo ventilation again, patients not willing had lower SF-36 physical (28.2 ± 8.3 vs. 34.4 ± 11.2; $P = 0.04$) and mental (47.8 ± 13.7 vs. 53.3 ± 10.1; $P = 0.06$) summary scores at 6-month follow-up.

Sensitivity and Subgroup Analysis

Reanalyzing data to include variables associated with missingness in mixed-effects models did not change main findings (*see* Table E6). Reanalyzing data with imputed values substituted for missing values yielded results similar to the primary analysis (*see* Table E7). To ensure that data loss consequent to death did not influence

Table 2. Mixed-Effects Model (Primary Analysis)

Outcome Variables	Estimated Marginal Means (95% Confidence Interval)*						
	Enrollment	Discharge	*P* Value†	6 mo	*P* Value‡	12 mo	*P* Value§
PI_{max}, cm H_2O	41.3 (39.4–43.2) (*n* = 306)	42.9 (40.9–44.9) (*n* = 249)	0.61	54.4 (51.2–57.6) (*n* = 80)	<0.001	58.0 (54.5–61.6) (*n* = 77)	<0.001
Handgrip strength, kPa	16.4 (14.1–18.7) (*n* = 308)	22.1 (19.7–24.5) (*n* = 251)	<0.001	58.6 (55.0–62.1) (*n* = 84)	<0.001	62.5 (58.4–66.5) (*n* = 79)	<0.001
Katz summary score	2.8 (2.2–3.3)‖ (*n* = 301)	14.6 (13.9–15.2) (*n* = 227)	<0.001	5.2 (4.3–6.0) (*n* = 118)	<0.001	4.7 (3.8–5.6) (*n* = 108)	0.002
SF-36 physical summary score	36.1 (35.0–37.3)‖ (*n* = 299)	24.0 (22.7–25.3) (*n* = 225)	<0.001	33.2 (31.4–35.0) (*n* = 117)	<0.001	36.5 (34.6–38.5) (*n* = 108)	0.99
SF-36 mental summary score	49.1 (47.9–50.3)‖ (*n* = 299)	46.8 (45.5–48.2) (*n* = 225)	0.02	52.5 (50.6–54.3) (*n* = 117)	<0.001	51.9 (49.9–53.9) (*n* = 108)	0.11

Definition of abbreviations: PI_{max} = maximum inspiratory pressure; SF-36 = Medical-Outcomes Study 36-item Short-Form General-Health Survey.
*Estimated marginal means derived from the mixed-effects model for repeated measures.
†Comparison between enrollment and discharge.
‡Comparison between discharge and 6 months.
§Comparison between enrollment and 12 months.
‖Preillness value.

the results, pairwise comparison of the raw data was performed using paired Student's *t* tests. Differences obtained with Student's *t* tests (which include only alive patients with paired data) and differences obtained with the mixed-model analysis at the specified time-point for the five outcomes were similar (*see* Table E8).

Potential confounders that could have influenced the results were randomization status and weaning method (*see* online supplement). Reanalyzing data to include potential confounders in mixed-effects models showed that interpretation of the main findings remained the same regardless of randomization status and weaning method (*see* online supplement).

Table 3. Independence in Daily Activities before Illness, at Discharge, and 6 and 12 Months after Discharge from an LTACH

	Preillness (*n* = *301*)	Discharge (*n* = *227*)	6 mo (*n* = *118*)	12 mo (*n* =*108*)
Bathing, *n* (%)				
No help	208 (69)	6 (3)	64 (54)	60 (55)
Special equipment	35 (12)	4 (2)	22 (19)	17 (16)
Partly assisted	24 (8)	19 (8)	6 (5)	12 (11)
Assisted	34 (11)	198 (87)	26 (22)	19 (18)
Dressing, *n* (%)				
No help	231 (77)	9 (4)	82 (70)	75 (69)
Special clothes	5 (2)	6 (3)	5 (4)	3 (3)
Assistance in tying shoes	24 (8)	11 (5)	5 (4)	3 (3)
Other assistance	41 (13)	201 (88)	26 (22)	27 (25)
Toileting, *n* (%)				
Normal	217 (72)	5 (2)	68 (58)	61 (57)
Special equipment	45 (15)	17 (8)	25 (21)	26 (24)
Assistance	27 (9)	35 (15)	5 (4)	9 (8)
Not possible to go to bathroom	12 (4)	170 (75)	20 (17)	12 (11)
Transfer, *n* (%)				
Normal	225 (75)	8 (4)	71 (60)	69 (64)
Special equipment	37 (12)	17 (7)	20 (17)	13 (12)
Help	29 (10)	146 (65)	14 (12)	19 (18)
Does not get out of bed	10 (3)	55 (24)	13 (11)	7 (6)
Continence, *n* (%)				
Normal	251 (83)	30 (13)	83 (70)	79 (73)
Special medications	5 (2)	7 (3)	4 (4)	2 (2)
Occasional accidents	28 (9)	10 (5)	11 (9)	15 (14)
Help	17 (6)	180 (79)	20 (17)	12 (11)
Feeding, *n* (%)				
Normal	258 (86)	44 (19)	95 (80)	89 (82)
Special equipment	7 (2)	19 (8)	5 (4)	2 (2)
Little help with cutting and buttering	14 (5)	88 (39)	4 (4)	5 (5)
Help	22 (7)	76 (34)	14 (12)	12 (11)

Definition of abbreviation: LTACH = long-term acute-care hospital.

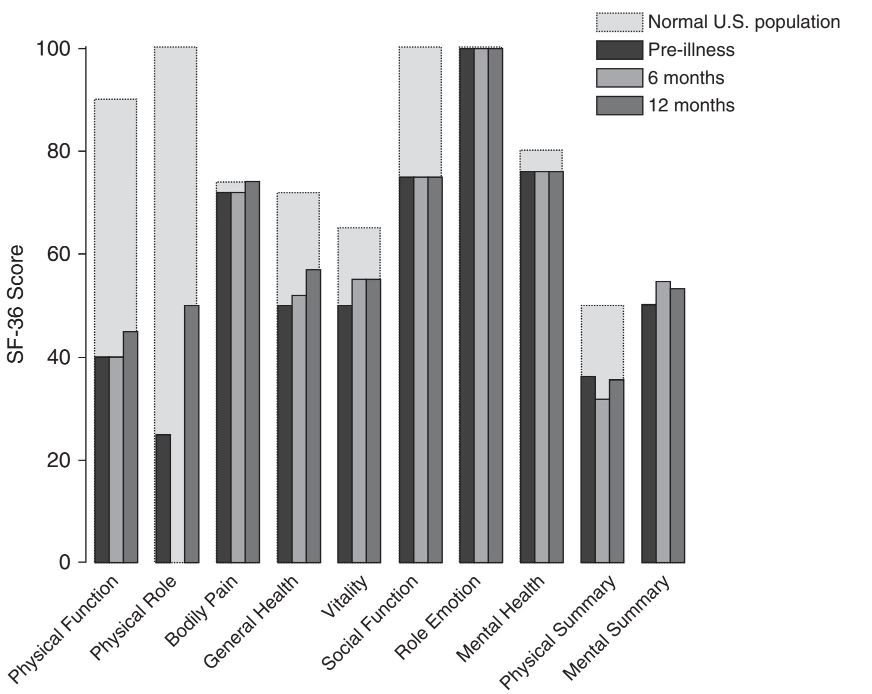

Figure 2. Medical-Outcomes Study 36-item Short-Form General-Health Survey (SF-36) at preillness (*n* = 299), 6 months (*n* = 117), and 12 months (*n* = 108) after discharge in long-term acute-care hospital patients compared with U.S. general population. Preillness score for all domains of the SF-36 questionnaire were below those of age- and sex-matched U.S. population except for emotional role, which was similar to published norms (25). At 6 months, all domains returned to preillness values except for physical role, which was zero at 6 months. Bars represent median value.

Discussion

Studies on impact of short-term (median, 9-d) ventilation on outcome in ICU survivors have been conducted (15, 36–42), but one cannot extrapolate from short-term ventilated patients to LTACH patients who require prolonged ventilation (median, 53-d): the clinical picture and experience of the two groups differ substantially (13). This is the first study to provide longitudinal measurements of survival, muscle function, and QOL evaluation in LTACH patients. At discharge, 53.7% of patients were detached from the ventilator and their 1-year survival was 66.9%. Between admission and discharge from LTACH, PI_{max} did not change, whereas handgrip strength increased. Between discharge and 6-month follow-up, handgrip strength increased by 165.2% and PI_{max} increased by 26.8%. At 6-month follow-up, 78.0% of patients were able to perform daily activities without assistance (Katz summary score ≤6); improvement in Katz summary score was related to improvement in handgrip strength. When LTACH survivors were asked if they would be willing to undergo prolonged ventilation again if deemed necessary, 84.7% said they would be willing.

Some clinicians perceive that prognosis of patients requiring prolonged mechanical ventilation is poor. That perception is accurate regarding patients who remain attached to a ventilator after repeated weaning attempts in an LTACH: only 16.4% of ventilator-attached patients were alive 1 year after study enrollment. Conversely, survival of patients detached from the ventilator during their LTACH stay was 66.9%, similar to survival of patients who receive short-term ventilation in an ICU (64.6%) (36, 38, 40, 43). Particularly striking was the high proportion of patients admitted to our LTACH who were successfully detached from the ventilator: 53.7%. The better-than-expected outcome among patients (albeit patients enrolled in a clinical trial) underscores the need for clinicians to alter their mindset about the management of patients receiving prolonged ventilation. Instead of limiting (or abandoning) weaning efforts based on perceived poor prognosis, clinicians should adopt a more aggressive approach and evaluate patient performance in the complete absence of ventilator assistance (trach-collar trials or T-tube trials), which facilitates earlier ventilator discontinuation (1). Such an approach minimizes the risk of failing to identify patients who can be detached from the ventilator (44).

The possibility that mechanical ventilation induces respiratory muscle atrophy and injury is arousing much interest (45–48). If any group of patients is at risk for this disorder, it should be patients requiring prolonged ventilation (47). Our ventilator-attached patients received mechanical ventilation for 46.2 days at the LTACH, yet PI_{max} did not decrease between admission and discharge (36.2 ± 1.0 vs. 35.2 ± 1.3 cm H_2O). These novel data signify that ventilator-induced diaphragmatic dysfunction did not ensue during the LTACH stay. Moreover, if respiratory muscle strength was an important factor for ventilator detachment, one would have expected PI_{max} to increase over time in ventilator-detached patients. In reality, PI_{max} did not change between admission and discharge (45.4 ± 1.3 vs. 48.1 ± 1.3 cm H_2O), indicating that an increase in respiratory muscle strength was not an important determinant of ventilator detachment (47). The latter observation is in accordance with our findings in ventilated patients in an ICU setting; PI_{max} was not higher in weaning-success versus weaning-failure patients (46.3 ± 3.1 vs. 41.6 ± 5.3 cm H_2O) (19). In another experimental study, we showed that direct neurophysiologic measurement of diaphragmatic contractility (achieved by invasive measurements of transdiaphragmatic pressure in response to phrenic-nerve stimulation) was equivalent in weaning-failure and weaning-success patients: 8.9 ± 2.2 and 10.3 ± 1.5 cm H_2O (49). That PI_{max} was lower in the ventilator-attached patients than in the ventilator-detached patients suggests that respiratory muscle weakness may have been a factor in why some patients remained attached to the ventilator.

When patients arrived at the LTACH, PI_{max} was considerably higher than handgrip strength: 53.1% versus 21.5% predicted. The better preservation of respiratory versus limb-muscle strength probably arose because respiratory muscles were contracting around-the-clock (for ventilator triggering) from the time ventilation had been instituted in the home ICU (50). In contrast, limb muscles were almost completely inactive throughout this period and predisposed to development of atrophy and weakness (51).

In contrast to $P_{I_{max}}$, limb-muscle strength increased during LTACH stay. One explanation for the increase was very low handgrip strength on arrival, which afforded greater opportunity for improvement as compared with $P_{I_{max}}$. Another contributor was the nature of rehabilitation. Professional therapists performed whole-body exercises (3–5 times/wk) specifically designed toward strengthening limb muscles. In contrast, rehabilitation specifically targeting inspiratory muscles was not provided (20).

At 6 months, handgrip strength increased by 165.2%, reaching near-normal values (81.0% predicted). The increase in muscle strength may reflect the action of rehabilitation therapy received in acute or subacute rehabilitation facilities following discharge. In addition to increase in size of muscle fibers and enhanced contractility, increases in recruitment of muscle units and motor neuron firing rate may also have contributed to the increase in handgrip strength (52, 53). Psychological factors modulate muscle recruitment during voluntary contractions (54, 55). Patient mental well-being (SF-36 mental summary score) increased significantly between discharge and 6-month follow-up, suggesting a link between enhanced voluntary activation and increase in handgrip strength.

$P_{I_{max}}$ increased by 26.8% at 6 months, reaching 67.5% predicted, well above the threshold (35% predicted) shown to induce dyspnea or impede physical performance (56). When patients were asked at 6 months whether health impeded walking, climbing stairs, or carrying groceries, more than 70% said they were not limited (or only a little). Near maximum recovery of global muscle function by 6 months left little opportunity for further increase over ensuing follow-up, as reflected by lack of change in $P_{I_{max}}$ and handgrip strength between 6 and 12 months.

Functional status improved considerably after discharge. At 6 months, 78% of patients were functionally independent (Katz summary score ⩽6) and SF-36 physical summary score was 92.0% of score before illness. Improvement in functional status likely resulted from improvements in skeletal-muscle function, as reflected by corresponding increases in handgrip strength. Support that muscle strength mediated functional recovery is the close correlations between handgrip strength and Katz summary score ($r = -0.51$) and SF-36 physical summary score ($r = 0.46$) at 6 months. Functional recovery in our patients was better than that reported in patients requiring prolonged ventilation (duration, 27 d) who were managed in an ICU (57); whole-body rehabilitation and the focus on weaning at the LTACH most likely attributed to the more favorable outcome.

The physical summary score at 1-year follow-up was similar to the score in acute-lung-injury survivors (37, 58). Given longer duration of ventilation and bed rest in our patients than in ICU-ventilated patients, one might expect our patients to exhibit lesser recovery at 1 year (15, 59, 60). Our patients were physically limited before acute illness (physical summary score, 36.1 at baseline) consequent to age and comorbidities (61). Investigators have assumed normal physical function at baseline in ICU-survivor studies (score, 50) (62). Accordingly, return to baseline required smaller improvement in functional status in our patients than in ICU survivors.

An early criticism of LTACHs was the existential objection that patient misery related to prolonged ventilation (16, 43, 63) (repeated experiences of severe dyspnea consequent to unremitting failed-weaning attempts) (64) entailed that patients would not volunteer for the ordeal if they fully understood what it involved. In reality, 84.7% of our patients said they would be willing to undergo the experience again if deemed necessary.

Nobelist Kahneman (65) notes that humans have two types of self: an experiencing-self, which addresses "Is it uncomfortable now?" and a remembering-self, which addresses "How was the overall experience?" Kahneman (65) concludes that "Memories are all we get to keep from our experience of living, and the only perspective that we can adopt as we think about our lives." It is the remembering-self that makes decisions. Contrary to presupposition of caregivers, patients are poor at remembering duration of an unpleasant experience. Indeed, two-thirds of patients did not have unpleasant memories of time on the ventilator, explaining why 84.7% would be willing to undergo a further episode of prolonged ventilation.

This study has limitations. Assessment of muscle strength before illness was impossible because critical illness is unpredictable. Almost half (45%) of preillness QOL was estimated from surrogates because patients were too ill to fill out the questionnaires themselves. To determine if using surrogates influenced study outcome, the mixed-effect model was recomputed to include the source of the responder (patient or surrogate) as an additional independent variable (*see* online supplement). The use of surrogates had a significant effect on Katz summary score: preillness score was higher (lower function) in the surrogate-responder group than in the patient-responder group (*see* Table E9). The surrogate-responder group were sicker than the patient-responder group, which could account for higher Katz scores; an overestimation of patient functional dependence by the surrogate, however, cannot be excluded (*see* online supplement) (66). Muscle-strength assessments after discharge were completed in 60% of survivors. The main reason for missing measurements was inability to achieve face-to-face encounters. Sensitivity analyses revealed that missing data did not bias our results (*see* Tables E6 and E7). The study took 10 years to complete, which may have influenced the results. The study was conducted in a single LTACH as part of a clinical trial; thus, it is possible that our findings may not be generalizable to patients requiring prolonged ventilation at other settings. A prerequisite for generalizability (external validity) is sound internal validity (67). The major obstacle to internal validity is systematic error, which can be more carefully controlled in a single center where selection and patient care is uniform. That the ventilator-detachment rate at our LTACH was virtually identical to that reported in a study conducted in 23 LTACHs (54.1%) (7) supports the likelihood that our results are generalizable to other LTACHs.

In conclusion, two-thirds of patients who were detached from the ventilator at discharge from the LTACH were alive 1 year later. Respiratory muscle strength was well maintained in patients being weaned from prolonged ventilation at a LTACH, whereas peripheral strength was severely impaired. Six months after discharge, improvement in peripheral muscle function was associated with an increased ability to perform daily activities independently, and 84.7% indicated willingness to undergo ventilation again if deemed necessary. ■

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