Patients with respiratory failure increase ambulation after transfer to an intensive care unit where early activity is a priority

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Objective: Ambulation of patients with acute respiratory failure may be unnecessarily limited in the acute intensive care setting. We hypothesized that ambulation of patients with acute respiratory failure would increase with transfer to an intensive care unit where activity is a key component of patient care.

Design: Pre-post cohort study of respiratory failure patients.

Setting: Adult intensive care units at LDS Hospital.

Patients: Respiratory failure patients requiring >4 days of mechanical ventilation who were transferred from other LDS Hospital intensive care units to the respiratory intensive care unit.

Interventions: We prospectively applied an early activity protocol to all consecutive respiratory failure patients transferred to the respiratory intensive care unit.

Measurements and Main Results: We studied 104 respiratory failure patients who required mechanical ventilation for >4 days. Transferring a patient to the respiratory intensive care unit substantially increased the probability of ambulation ($p < .0001$). After 2 days in the respiratory intensive care unit, the number of patients ambulating had increased three-fold compared with pre-transfer rates. Female gender ($p = .019$), the absence of sedatives ($p = .009$), and lower Acute Physiology and Chronic Health Evaluation II scores ($p = .017$) also predicted an increased probability of ambulation. Improvements in ambulation with transfer to the respiratory intensive care unit remained significant after adjustment for Acute Physiology and Chronic Health Evaluation II scores and other covariates.

Conclusions: Transfer of acute respiratory failure patients to the respiratory intensive care unit substantially improved ambulation, independent of the underlying pathophysiology. The intensive care environment may contribute unnecessary immobilization throughout the course of acute respiratory failure. Sedatives, even given intermittently, substantially reduce the likelihood of ambulation. Controlled studies are needed to determine whether intensive care unit immobilization contributes to long-term neuromuscular dysfunction or whether early intensive care unit activity improves outcomes. (Crit Care Med 2008; 36:1119–1124)

KEY WORDS: activity; ambulation; critical illness; respiratory failure; intensive care unit

C̲ritically ill patients with respiratory failure who require prolonged mechanical ventilation often have poor physical outcomes, due in part to persistent weakness (1, 2). Prolonged immobilization contributes to neuromuscular abnormalities (1, 2). Physical activity and ambulation may not be started until after acute intensive care unit (ICU) discharge (3). In contrast, we have shown that early activity is feasible and safe while respiratory failure patients are still undergoing acute ICU care (4).

Despite our report showing that early activity in the respiratory ICU (RICU) is feasible, is safe, and leads to desirable functional outcomes (4), we noted that early ambulation did not routinely occur in other medical ICUs in our institution. We wondered whether patients in other medical ICUs were immobilized unnecessarily, despite intrinsic capability for activity. The purpose of this study was to determine whether transfer of respiratory failure patients to the RICU improved ambulation, independent of the underlying pathophysiology.

PATIENTS AND METHODS

From January 1, 2002, through December 31, 2002, we prospectively applied an early activity protocol to all consecutive respiratory failure patients who required mechanical ventilation admitted to an eight-bed RICU at LDS Hospital. We defined respiratory failure patients requiring >4 days of mechanical ventilation as our study population, because these patients are more at risk to develop physical debilitation than are respiratory failure patients with brief or no mechanical ventilation. Patients were excluded if they had a neurologic disease that precluded activity, such as stroke or paralysis; if they were readmitted to the RICU; or if they were terminally ill.

Patients who met the inclusion criteria were also required to be hospitalized for ≥2 days before RICU transfer in another LDS Hospital ICU and to have an RICU stay of ≥2 days, so that we could look at activity levels in the other ICU for 2 days before RICU transfer as compared with activity levels in the 2 days after RICU transfer. Respiratory failure patients are typically admitted to the RICU after initial treatment in another LDS Hospital ICU. We did not capture all patients with respiratory failure requiring >4 days of mechanical ventilation because the RICU has only eight beds, an inadequate capacity for all such patients in our institution.

We prospectively collected patient demographic data, reason for ICU admission, comorbid disorders, length of stay, Acute Physiology and Chronic Health Evaluation (APACHE) II scores (5), multiple organ failure scores (6), ventilator data, activity levels, and hospital disposition data. All patients in LDS

Hospital ICUs, including those in the RICU, were managed in collaboration with the LDS Hospital Nutrition Service. Internal feedings were administered to meet standard caloric goals. If the enteral route was unavailable, parenteral nutrition was substituted at the same caloric levels. The LDS Hospital Institutional Review Board approved this study, and individual informed consent was waived.

Early Activity Protocol

We defined the term *early* as the interval starting with initial physiologic stabilization and continuing through the ICU stay. This interval is early compared with activity that begins only after ICU discharge. *A priori* we selected three criteria for initiation of activity, including a neurologic criterion, respiratory criteria, and circulatory criteria. All patients were assessed to determine whether they met early activity criteria within 24 hrs of RICU admission (4). Following is a summary of the early activity protocol.

Initiation of Activity. Patients were assessed daily, based on the following criteria: 1) neurologic criteria were that the patient followed commands and was cooperative (activity was never started in comatose patients); 2) respiratory criteria were $F_{IO_2} \leq 0.6$ and positive end-expiratory pressure ≤ 10; 3) circulatory criteria were no catecholamine drips and no symptomatic orthostasis.

Exception for Activity. Patients fully meeting neurologic criteria but missing a single respiratory or circulatory criterion nonetheless had cautious trials of early activity with close monitoring for adverse events.

Treatment Modifications for Activity. If the patient was intubated, F_{IO_2} was increased by 0.2 before activity.

Monitoring During Ambulation. Oxygen saturation and orthostatic symptoms were monitored.

Activity Events

A priori we defined *activity events* as sit on the edge of the hospital bed without back support, sit in a chair after transfer from the hospital bed, and ambulate using a walker with or without additional support from the RICU staff. During ambulation, a physical therapy technician with a wheelchair followed behind the patient in case of sudden fatigue or any adverse event. We also collected nonactivity events of passive range of motion and no activity, to allow comparisons between the ICUs along a spectrum of activity.

Our primary outcome was ambulation. We choose ambulation due to ease of measurement and because it represents a desired functional outcome. We collected ambulation data for each study patient daily, so that we could determine the percentage of patients ambulating 48 and 24 hrs before RICU transfer com-

pared with the percentage of patients ambulating 24 and 48 hrs after RICU transfer. We recorded daily ambulation data as a categorical variable (ambulate/did not ambulate) and as distance ambulated. We also recorded the distance of ambulation at the time of RICU discharge. For each day that a patient's activity level was categorized as sit on bed, sit in chair, passive range of motion, or no activity, we assigned an ambulation distance of zero feet. The same definitions of activity were used in all ICU environments.

Each patient served as his or her own control, allowing comparison of control (pretransfer) and intervention (posttransfer) activity in the RICU on a patient-by-patient basis. Changes in activity were then compared across RICU transfer.

Statistical Analysis

Descriptive statistics were carried out for demographic, medical, and activity data. Data are presented as mean ± SD and median. To determine the effect of RICU transfer on patient ambulation, we used a multivariable logistic regression model that included the following covariates: APACHE II scores, duration of mechanical ventilation, RICU length of stay, total ICU length of stay, time from hospital admission to RICU transfer, catecholamines, sedatives, gender, age, body mass index at hospital admission, body mass index at RICU admission, and ambulation by ICU location and time with respect to RICU transfer (an ordered categorical variable representing the four time points measured comparing ambulation within each ICU and ambulation between the two ICUs). The response variable was a binary indicator of ambulation vs. no ambulation. A bootstrap procedure was used to adjust the final estimate of the RICU transfer for possible model overfitting due to exploring the effects of the potential confounders (e.g., model uncertainty) (7, 8). The bootstrap method takes a random sample of the original data set with replacement. Sampling with replacement means that every sample is returned to the data set after sampling. So a particular data point from the original data set could appear multiple times in a given bootstrap sample. The model fitting procedure is then applied to this bootstrap sample. The variables found to be important are recorded, and the procedure starting with a new sample is repeated (1,000 times in our analysis). Any variable that is clearly related to the outcome will continue to be selected in the majority of the bootstrap samples, while variables that are not important will only be chosen in a few bootstrap samples. The different bootstrap samples will select different subsets of variables, which provide more information about these variables than the single subset obtained in standard stepwise regression. The data were also ana-

lyzed using a generalized estimating equation model that could take into account any correlation within subjects to see if adjusting for multiple observations on each subject affected the results.

Three time comparisons were modeled to determine the effect of RICU transfer on ambulation. The pretransfer time compared ambulation at 48 hrs with 24 hrs pretransfer to the RICU. The RICU transfer time compared the average of the 48- and 24-hr pretransfer ambulation levels with the average of the 24- and 48-hr posttransfer ambulation levels. The posttransfer time compared ambulation at 24 hrs with 48 hrs posttransfer to the RICU. All *p* values are two-sided.

RESULTS

There were 126 patients who met study inclusion criteria. Twenty-two patients were excluded from the study: seven for stroke or paralysis, six for terminal cancer, six for a second RICU admission, and three for severe traumatic or anoxic brain injury. The remaining 104 patients' mean age was 57.9 ± 18.1 yrs (range 20–89, median 55.9 yrs), and 54% (n = 56) of the patients were female. Reasons for ICU admission are shown in Table 1. Patient medical data are shown in Table 2. The mean duration of mechanical ventilation was 18 days, and mean hospital length of stay was 30 days. Thirteen patients (12%) died while hospitalized. The cause of death and discharge disposition of the survivors are shown in Table 3. On the last full day of RICU admission, the mean distance ambulated by the 91 survivors was 238 ± 191 feet (median 200 feet, range 0–800 feet).

Figure 1 shows the types of patient activity at 24 hrs before RICU transfer compared with 24 hrs after RICU transfer. More intense activities increased after

Table 1. Intensive care unit admission diagnoses

Diagnosis	No.
Sepsis	40
Pneumonia	17
Cardiovascular disease	15
Trauma	10
Gastrointestinal bleed or liver failure	9
Surgery	5
Aspiration	2
Cancer	2
Chronic obstructive pulmonary disease exacerbation	1
Asthma	1
Pulmonary embolism	1
Renal disease	1

Table 2. Patient medical data

Variable	Mean ± SD	Median
Duration mechanical ventilation, days	17.9 ± 11.9	14
Total ICU length of stay, days	25.8 ± 14.3	21
Total RICU length of stay, days	15.0 ± 11.7	10
Hospital length of stay, days	29.6 ± 15.8	24
Days in ICU pre-RICU transfer, days	10.3 ± 7.5	9
LDS Hospital MOF score at hospital admission	4.2 ± 3.2	4

ICU, intensive care unit; RICU, respiratory intensive care unit; MOF, multiple organ failure (6).

Table 3. Patient outcomes

Patient Outcomes	No. (%)
Died in ICU: cause of death	13 (12)
Family requested withdrawal of care	9
Sepsis	3
Cystic fibrosis, declined reintubation	1
Survived: discharge disposition	91 (88)
Rehabilitation unit	33
Home	30
Extended care facility	24
Another hospital	3
Psychiatric unit	1

RICU transfer, whereas the more minimal activities decreased in the RICU. Figure 2 shows the net changes in activity type associated with RICU transfer. A majority of patients increased activity level, compared with only a few patients who decreased their level of activity. The occasional decrease in activity shown in Figure 2 occurred in RICU patients developing new physiologic instability, patients requiring sedatives, and patients undergoing procedures. Ambulation substantially increased after RICU transfer (Fig. 3). Forty-eight hours before RICU transfer, only 6% of the patients ambulated. At 24 hrs before RICU transfer, the percentage of patients ambulating increased only 5% to a total of 11%. In contrast, 28% of patients were ambulating 24 hrs after RICU transfer. There was a further 13% increase in ambulation at 48 hrs after RICU transfer, to a total of 41% of patients ambulating.

In contrast, the patients' physiologic state, as measured by APACHE II score, showed a slow decline during the study. Mean APACHE II scores corresponding to the four time intervals, starting with 48 hrs before RICU transfer, were 18.0, 17.3, 16.4, and 15.9, respectively. Average values for F_{IO_2} (0.46 vs. 0.43), positive end-expiratory pressure (7 vs. 6 cm H_2O), and PaO_2 (71 vs. 75 mm Hg) were similar 24 hrs before vs. 24 hrs after RICU transfer.

Mechanical ventilation for the patients who ambulated were as follows: 48 hrs before RICU transfer (n = 6), 67% (four of six) had an endotracheal tube and 33% (two of six) had a tracheotomy; 24 hrs before RICU transfer (n = 10), 60% (six of ten) had an endotracheal tube, 20% (two of ten) had a tracheotomy, and 20% (two of ten) were not mechanically ventilated; 24 hrs after RICU transfer (n = 29), 62% (18 of 29) had an endotracheal tube, 7% (two of 29) had a tracheotomy, and 31% (nine of 29) were not mechanically ventilated; and 48 hrs after RICU transfer (n = 40), 60% (24 of 40) had an endotracheal tube, 33% (13 of 40) had a tracheotomy, and 8% (three of 40) were not mechanically ventilated.

A multivariable logistic regression model, after adjustment for covariates, found four significant predictors of increased ambulation: RICU transfer (odds ratio [OR] 2.47; 95% confidence interval [CI] 1.85–3.4, or 1.67–3.48 after bootstrap adjustment, $p < .0001$), absence of sedatives (OR 1.90; 95% CI 1.19–3.15; $p = .009$), female gender (OR 1.88; 95% CI 1.11–3.22; $p = 0.019$), and lower APACHE II scores (OR 1.06; 95% CI 1.01–1.12; $p = .017$). Figure 4 shows regression model predictions for ambulation in four hypothetical patients before and after RICU transfer: a man without sedative use, a man with intermittent sedative use, a woman without sedative use, and a woman with intermittent sedative use. The generalized estimating equation model results did not significantly differ from the logistic regression model and are not reported here. RICU transfer remained a statistically significant predictor of ambulation after adjustment for model uncertainty using the bootstrap method. The individual 95% bootstrap confidence intervals for sedative use, gender, and APACHE II scores include a score of 1, meaning there is a possibility that there was no effect. However, only 0.6% of the bootstrap samples did not include any of the three covariates and

>96% of the bootstrap samples included at least two covariates, indicating that some of the covariates influence ambulation. There was no significant change in ambulation in the pre-RICU transfer time comparison (OR 1.37; 95% CI 0.83–2.40; $p = .228$). However, there was a significant increase in ambulation in the post-RICU transfer time comparison (OR 1.35; 95% CI 1.01–1.83; $p = .047$).

DISCUSSION

The RICU environmental effect was the strongest single predictor of ambulation in our respiratory failure patients. Transferring a patient to the RICU, a setting where activity is a key component of patient care, resulted in a statistically and clinically significant increase in ambulation. After 2 days in the RICU environment, the number of patients ambulating had increased almost three-fold compared with the pretransfer rates, whereas there had been no significant increase in ambulation in the time intervals before RICU transfer. RICU transfer remained a significant predictor of ambulation after adjusting for model uncertainty.

Our patients had an increase in activity with RICU transfer that is not explained by improvement in physiology. Indeed, one would not expect physiology to change just because a patient is moved to a different hospital room. Our patients showed the capability to improve their activity level substantially when provided the opportunity to do so. Stated differently, our patients seemed to have the capability for more activity before their transfer to the RICU but did not achieve their activity potential due to a lack of opportunity.

If a patient were able to increase activity substantially just by transfer to an ICU environment where early activity was a focus of care, then the previous ICU environment, rather than just the patient's underlying illness, is contributing to unnecessary immobilization. Our data suggest that this is the case, even in an institution where there has been considerable interest in achieving early mobilization. Since immobilization contributes to physical dysfunction, and ICU care may contribute to unnecessary immobilization, our data raise the possibility that the unnecessary immobilization during ICU care contributes to long-term physical dysfunction. Controlled trials are now needed to clarify this relationship.
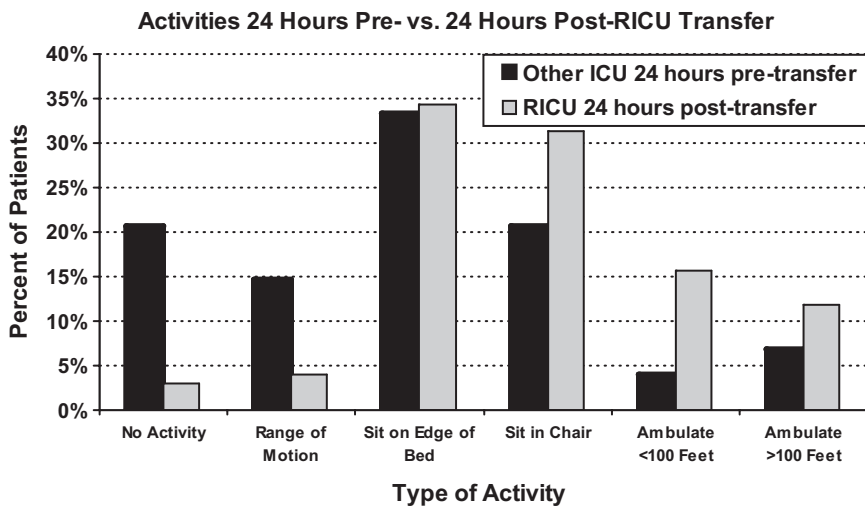
Activities 24 Hours Pre- vs. 24 Hours Post-RICU Transfer

Figure 1. Types of activity before and after respiratory intensive care unit (*RICU*) transfer. *ICU*, intensive care unit.

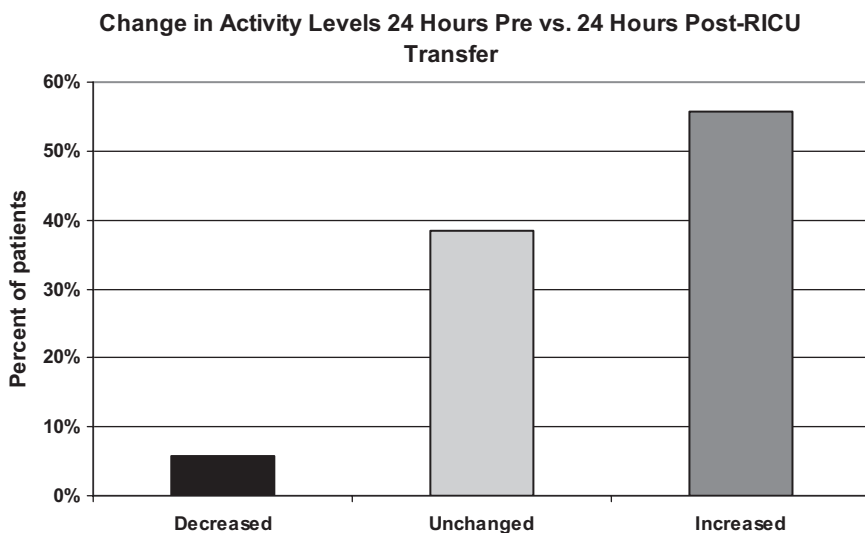## Change in Activity Levels 24 Hours Pre vs. 24 Hours Post-RICU Transfer

Figure 2. Changes in activity levels with respiratory intensive care unit (*RICU*) transfer.
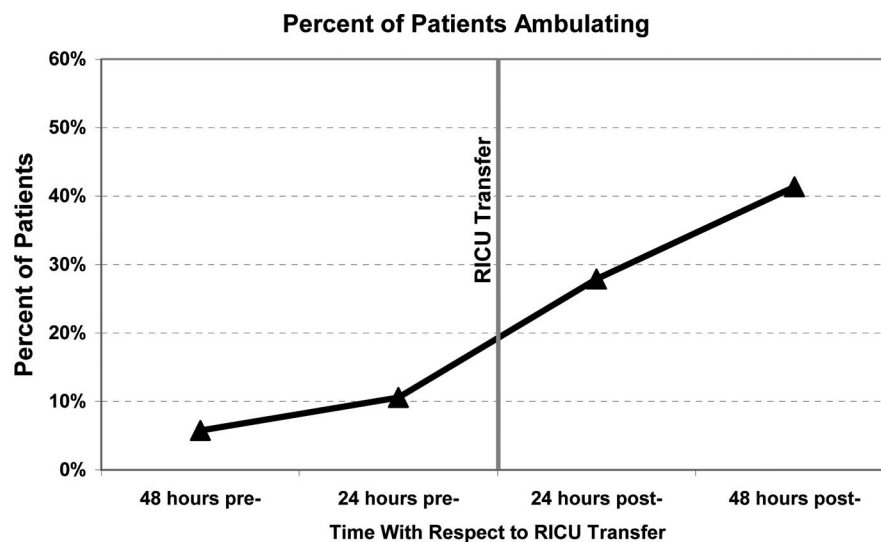
Percent of Patients Ambulating

Figure 3. Percent of patients ambulating before and after transfer to the respiratory intensive care unit (*RICU*).

The likelihood of ambulation in our patients decreased almost two-fold when sedatives were used, even though sedative administration was only intermittent. While sedative use is sometimes unavoidable in critically ill patients, we document here another significant adverse sedative effect. Adverse effects of sedatives have been reported in mechanically ventilated patients, such that a daily interruption of sedative infusions reduces the duration of mechanical ventilation and the length of ICU stay (9) and also decreases the incidence of complications of critical illness associated with prolonged intubation and mechanical ventilation (10). Newer sedative agents or regimens that do not prolong ICU stay or reduce ambulation potential are needed.

Decreasing APACHE II scores correlated with increased ambulation, as would be expected. Our patients had small improvements in physiology during the study interval, as measured by declining APACHE II scores. For every point decrease in the APACHE II score, likelihood of ambulation increased by about 6%. This effect, while statistically significant, was much smaller than the effect of transferring a patient to the RICU.

Our female patients were almost twice as likely to ambulate as our male patients after we accounted for covariates (e.g., APACHE II scores, duration of mechanical ventilation, RICU length of stay, total ICU length of stay, time from hospital admission to RICU transfer, catecholamines, sedatives, gender, age, body mass index, and ambulation by ICU location and time with respect to RICU transfer). It is unclear why we found differences in ambulation between men and women in our study. Previous data indicate that muscle wasting (11), weakness, and physical disability occur following ICU discharge (1). Furthermore, 14 days of bed rest results in a 4.1% decrease in lean thigh mass (12), 6 wks of bed rest results in a 15% to 30% decrease in quadriceps strength (13), and there is a positive association between lower extremity muscle strength and ambulation (14, 15). While we did not assess muscle mass in our respiratory failure patients, one potential explanation for the two-fold decrease in ambulation in men may be greater lower extremity lean muscle loss after critical illness. For example, following total knee arthroplasty, men had a significant decrease in thigh muscle volume that was associated with physical functional deficits, including ambulation (16). Muscle strength is important for functional performance in
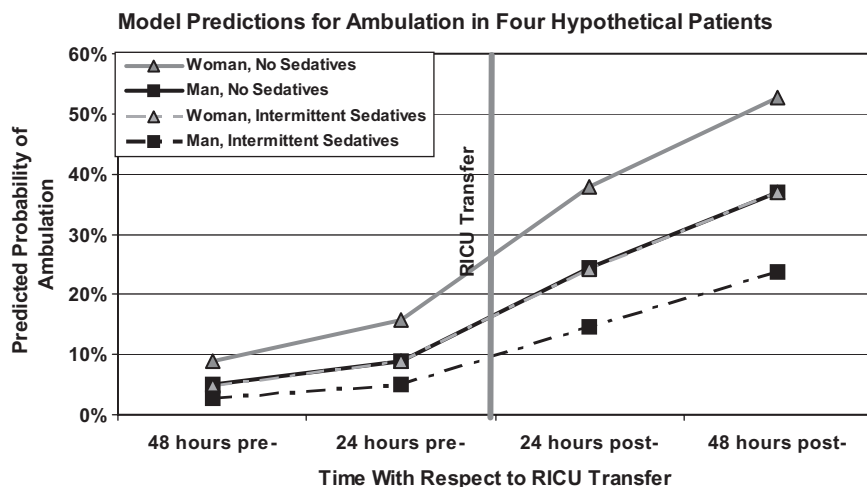
Model Predictions for Ambulation in Four Hypothetical Patients

Figure 4. Regression model predictions for ambulation in four hypothetical patients before and after respiratory intensive care unit (*RICU*) transfer.

men (living in long-term care facilities) but not women (17). It is also possible that personality or cultural factors related to gender either on the part of the patient or during interaction with their caregivers may account for the observed gender differences. Research is needed both to determine possible contributors for the gender differences in ambulation that we observed and to replicate our findings.

The effects of gender, sedative use, and APACHE II scores are less clear after adjustment for model uncertainty (the adjusted 95% CIs on each OR include a score of 1, meaning there is a possibility that there was no effect). However, the same bootstrap adjustment procedure shows that it is very unlikely that none of the covariates affected ambulation. Only 0.6% of the bootstrap samples did not include any of the three covariates, and >96% of the bootstrap samples included at least two covariates, indicating that some of these covariates influence ambulation. More research needs to be carried out using a new independent data set and *a priori* hypotheses to fully understand the impact of gender, sedative use, and APACHE II scores on ambulation.

Strengths of our study include a prospective consecutive inclusive cohort of patients with mechanical ventilation of >4 days admitted to the RICU. We tried to be as inclusive as possible, excluding primarily patients not reasonably able to achieve meaningful ambulation in any environment.

We did not randomize our patients to the activity intervention. Achievement of early activity in complex and difficult to mobilize patients requires prolonged ICU cultural change (18), making it difficult to turn an activity intervention on or off in a randomized fashion. The achievement of ambulation by the majority of patients at acute ICU discharge, without significant safety problems (4), supports the utility of the intervention. Nonetheless, randomized studies of activity and ambulation are needed, now that initial feasibility and safety studies have been completed (4, 18).

Our study enrolled patients primarily with respiratory failure due to medical illness or after general surgical or trauma events (Table 1). For example, we had only one patient suffering exacerbation of chronic obstructive pulmonary disease without radiographic pneumonia. Our results may not be applicable to other patient groups. We were unable to capture all respiratory failure patients requiring >4 days of mechanical ventilation in the RICU due to space and patient flow limitations. It is possible that we selected patients for transfer who were more likely to increase ambulation than those who were not transferred. However, even if this bias were true, the patients who actually were transferred to the RICU appeared to have unnecessary immobilization before arrival.

Ambulation of critically ill patients is difficult and potentially dangerous. Tubes and catheters may become dislodged, and both staff and patients are at risk of injuries. However, with a dedicated and trained team, early ICU activity can be feasible and safe (4). Development of the culture necessary to accomplish this task has been discussed elsewhere (18).

CONCLUSIONS

Transfer of patients with respiratory failure to the RICU where activity was a key priority substantially improved ambulation, independent of the underlying pathophysiology. The ICU environment may contribute unnecessary immobilization to the course of acute respiratory failure. Sedatives, even given intermittently, substantially reduce the likelihood of ambulation. Female gender and decreasing APACHE II scores also predicted increased ambulation. Despite severe illness and mechanical ventilation >4 days, our patients achieved an average of 238 feet of ambulation by the time of acute ICU discharge. Controlled studies are needed to determine whether ICU immobilization contributes to the long-term neuromuscular dysfunction that follows critical illness or whether early ICU activity improves outcomes.

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