

# Early exercise in critically ill patients enhances short-term functional recovery\*

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**Objectives:** To investigate whether a daily exercise session, using a bedside cycle ergometer, is a safe and effective intervention in preventing or attenuating the decrease in functional exercise capacity, functional status, and quadriceps force that is associated with prolonged intensive care unit stay. A prolonged stay in the intensive care unit is associated with muscle dysfunction, which may contribute to an impaired functional status up to 1 yr after hospital discharge. No evidence is available concerning the effectiveness of an early exercise training intervention to prevent these detrimental complications.

**Design:** Randomized controlled trial.

**Setting:** Medical and surgical intensive care unit at University Hospital Gasthuisberg.

**Patients:** Ninety critically ill patients were included as soon as their cardiorespiratory condition allowed bedside cycling exercise (starting from day 5), given they still had an expected prolonged intensive care unit stay of at least 7 more days.

**Interventions:** Both groups received respiratory physiotherapy and a daily standardized passive or active motion session of upper and lower limbs. In addition, the treatment group performed

a passive or active exercise training session for 20 mins/day, using a bedside ergometer.

**Measurements and Main Results:** All outcome data are reflective for survivors. Quadriceps force and functional status were assessed at intensive care unit discharge and hospital discharge. Six-minute walking distance was measured at hospital discharge. No adverse events were identified during and immediately after the exercise training. At intensive care unit discharge, quadriceps force and functional status were not different between groups. At hospital discharge, 6-min walking distance, isometric quadriceps force, and the subjective feeling of functional well-being (as measured with "Physical Functioning" item of the Short Form 36 Health Survey questionnaire) were significantly higher in the treatment group ( $p < .05$ ).

**Conclusions:** Early exercise training in critically ill intensive care unit survivors enhanced recovery of functional exercise capacity, self-perceived functional status, and muscle force at hospital discharge. (Crit Care Med 2009; 37:2499–2505)

**KEY WORDS:** exercise therapy; physiotherapy; critical illness; intensive care; muscle weakness; bed rest

**M**uscle dysfunction is common in patients in the intensive care unit (ICU) due to inactivity, inflammation, use of pharmacologic agents (corticosteroids, muscle relaxants, neuromuscular

blockers, antibiotics), and the presence of neuromuscular syndromes associated with critical illness (1–6). The onset of respiratory muscle weakness may be an important factor, leading to prolonged ICU stay because of weaning failure (7, 8). The frequency of clinical peripheral muscle weakness has been reported in 25% to 33% of patients mechanically ventilated for 4 to 7 days (9, 10), in 60% of patients with acute respiratory distress syndrome (11), and in 35% to 76% of septic patients (12–14) and has been linked with increased mortality (15). Prolonged ICU stay contributes to impaired functional status and quality of life (16), which may persist even 1 yr after discharge (17). Muscle weakness, but not pulmonary function, is associated with this impaired functional status (17).

Muscle wasting seems to be the highest during the first 2 to 3 wks of ICU stay (18). Hence, it is important to prevent or attenuate muscle deconditioning as early as possible in patients with expected prolonged bed rest. A document of European Respira-

tory Society and European Society of Intensive Care Medicine advises to start early with active and passive exercise in critically ill patients (19). Recent literature suggested that it is possible to conduct early mobility therapy in the ICU (20, 21). However, no evidence is available concerning the effectiveness of a standardized early exercise training intervention in the acute ICU phase when patients are still under sedation (22, 23). Continuous passive motion or passive stretch, provided for at least 9 hrs or 30 mins, respectively, have been shown successful in preventing or attenuating aspects of muscle atrophy (24, 25). A rather new method to train bed-bound patients is the use of a bedside cycle ergometer. This exercise training modality has been shown to be a safe and feasible exercise tool in patients with severe chronic obstructive pulmonary disease confined to bed (26) and during hemodialysis in patients with end-stage renal disease (27).

The present randomized controlled trial was designed to investigate whether

**\*See also p. 2648.**

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Table 1. Exclusion criteria

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| Conditions impairing the cycling movement  |
| Trauma or surgery of leg, pelvis, or lumbar spine  |
| Open abdominal wounds  |
| Extreme obesity (body mass index >35 kg/m <sup>2</sup> )   |
| Serious bedsore or venous ulcers   |
| An anticipated fatal outcome   |
| Body length <1.5 m   |
| Preexisting diagnosis causing neuromuscular weakness, acute stroke, status epilepticus   |
| Coagulation disorders (international normalized ratio >1.5 or concentration of blood platelets <50,000/mm <sup>3</sup> )   |
| Intracranial pressure >20 mm Hg  |
| Psychiatric disorders or severe agitation  |
| Cardiorespiratory instability  |
| Inspiratory oxygen fraction (F <sub>I</sub> O <sub>2</sub> ) >55%  |
| Arterial partial pressure of oxygen (P <sub>a</sub> O <sub>2</sub> ) <65 torr (<8.66 kPa)  |
| Minute ventilation >150 mL/kg body weight  |
| Respiratory rate >30 breaths/min on adequate ventilatory support   |
| Need for significant vasopressive support (noradrenaline >0.2 μg·kg <sup>-1</sup> ·min <sup>-1</sup> , dobutamine >8 μg·kg <sup>-1</sup> ·min <sup>-1</sup> , corotrope >0.25 μg·kg <sup>-1</sup> ·min <sup>-1</sup> ) |

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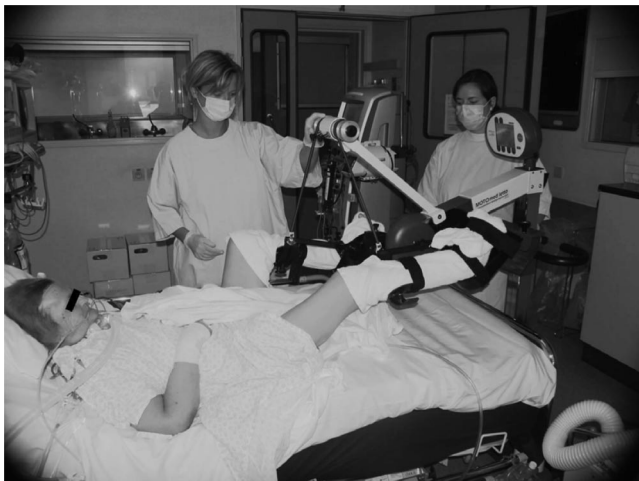


Figure 1. Bedside cycle ergometer (MOTomed Letto 2, RECK, Betzenweiler, Germany).

a daily training session, using a bedside cycle ergometer, started early in stable critically ill patients with an expected prolonged ICU stay could induce a beneficial effect on functional exercise performance, functional status, and quadriceps force compared with a standard physiotherapy program.

## MATERIALS AND METHODS

### Patients

Ninety critically ill patients (age = 59 ± 17 yrs) with an expected prolonged stay in the surgical or medical ICU department of University Hospital Gasthuisberg, Leuven, Belgium, were enrolled in the study between December 2005 and February 2007. Patient eligibility for inclusion in the study was judged on the fifth day of admission to the ICU by the attending intensivist, unrelated to the study. Patients who were expected to have a prolonged ICU stay of at least

7 more days were eligible for inclusion. This prediction was based on the clinical judgment of the attending intensivist. Exclusion criteria are listed in Table 1. Patients showing cardiorespiratory instability on day 5 were screened every subsequent day and inclusion was reconsidered when they became stable (given they still were expected to have a prolonged stay of at least 7 more days). The occurrence of cardiorespiratory instability or other medical conditions impairing the interventions after inclusion led to exclusion of the patient.

Written informed consent was obtained from all patients or from a close relative of sedated patients. Sedated patients signed their informed consent when they regained consciousness. The study protocol was approved by the local ethics committee.

### Study Design

In this randomized controlled trial, patients were allocated to either a treatment

group or a control group by use of sealed opaque envelopes in random block sizes. Patients in both groups were medically treated as prescribed by the responsible physician. All interventions were performed until ICU discharge. All patients received routine physiotherapy during their stay in the ward. Assessments were scheduled on the day of ICU discharge and on the day of hospital discharge. All measurements were taken at both assessment sessions, except for Short Form 36 Health Survey questionnaire (SF-36) and 6-min walking distance (6MWD) which were assessed only at hospital discharge.

## Interventions

Patients in the control group received respiratory physiotherapy adjusted to the individual needs and a standardized mobilization session of the upper and lower extremities on 5 days per week. Passive motion was applied in sedated subjects, whereas awake patients were asked to participate actively. Intensity of the exercises was increased according to the patient's capability. Ambulation was started when considered appropriate by the medical staff.

Patients in the treatment group additionally received a cycling exercise session 5 days a week, using a bedside cycle ergometer (MOTomed Letto 2, RECK-Technik GmbH & Co. KG, Betzenweiler, Germany) (Fig. 1). The device offers the possibility to conduct passive or active cycling at six levels of increasing resistance. The aim of each session was to have the patient cycle for 20 mins at an individually adjusted intensity level. Patients were placed in a comfortable position in between the supine and the semirecumbent position. In sedated patients, cycling was performed in a passive manner for 20 consecutive minutes at a fixed pedaling rate of 20 cycles/min. When patients were able to cycle actively, the cycling session was divided into two bouts of 10 mins or into more intervals when needed. At every session, training intensity was evaluated and an attempt was made to increase the resistance with one level, as tolerated by the patient. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure, transcutaneous oxygen saturation of the blood (Sp<sub>o</sub><sub>2</sub>), and respiratory rate were monitored continuously during exercise. Baseline measurements were taken 2 mins after installing the patients on the cycle ergometer. Exercise was stopped when patients showed an abnormal physiologic response: HR >70% of predicted maximum, >20% decrease in HR, SBP >180 mm Hg, >20% decrease in SBP or diastolic blood pressure, Sp<sub>o</sub><sub>2</sub> <90%, clinical signs and symptoms of cardiorespiratory distress. Malign arrhythmias, symptoms of myocardial ischemia, and respiratory distress leading to

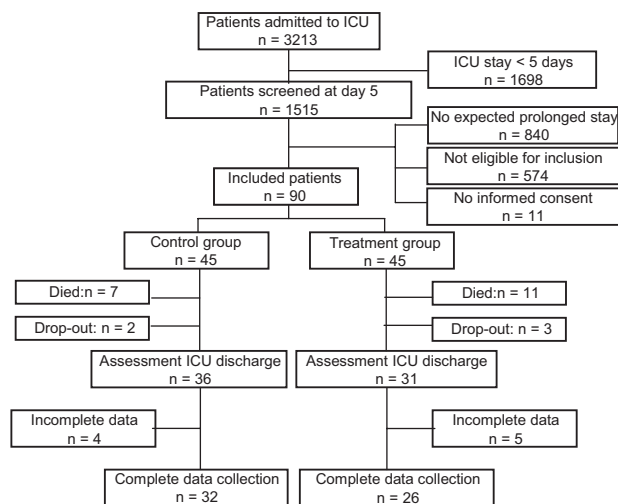


Figure 2. Flow diagram of the patients admitted to the intensive care unit (ICU).

symptoms of intolerable dyspnea were defined as severe adverse events.

## Measurements

**Baseline Characteristics.** Acute Physiology and Chronic Health Evaluation II score was computed at admission to the ICU (28). Length and weight were assessed at hospital discharge.

**Outcomes.** The primary outcome was 6MWD as measured at hospital discharge. Secondary outcomes were isometric quadriceps force and functional status. Weaning time, ICU and hospital stay, and 1-yr mortality were considered to be exploratory outcomes.

**6MWD and Muscle Force.** 6MWD and handgrip force (Jamar, Preston, Jackson, MI) were measured (29, 30). Isometric quadriceps force was quantified, using a handheld dynamometer (Microfet 2, Biometrics, Almere, Netherlands) (31). The patient was placed in supine position with 30° of knee flexion. The dynamometer was placed perpendicular to the leg just above the malleoli. Instruction and encouragement were given to extend their knee maximally over 3 secs. At least three repetitions were performed until results were reproducible.

**Functional Status.** The Berg Balance Scale is a measurement of functionality, originally used in stroke patients and healthy elderly (32). The item “from sit to stand” of the Berg Balance Scale, in which the patient’s ability to rise from a chair with armrests was quantified on an ordinal scale of 0 to 4, was used. The Functional Ambulation Categories scale is a 0 to 5 ordinal scale scoring the patient’s autonomy during walking (33). The “Physical Functioning” (PF) item of the SF-36 was used to assess quality of life based on perceived functional status (34). Patients were asked about ten activities that demand different effort levels whether they felt severely, little, or not limited performing the described activities.

## Weaning Time and 1-yr Mortality

Weaning time was considered as the number of days between inclusion and successful weaning (>48 hrs of spontaneous breathing). One-year mortality after hospital discharge was assessed by phone calls to the general practitioners of the patients.

## Statistical Analysis

A sample size of 36 patients was required in each group to demonstrate a difference of 50 m in 6MWD with a statistical power of 80% and an  $\alpha$  level of 0.05. A difference of 50 m has been validated as the minimally clinical important difference among patients with chronic lung disease (35). Anticipating a drop-out rate of 20%, we randomized a total of 90 patients.

All statistical analyses were performed with SAS 9.1.3. Service Pack 4. Continuous variables were expressed as mean  $\pm$  standard deviation (if data were normally distributed) or as medians (interquartile range) (if data were not normally distributed). Categorical variables were summarized as proportions (95% Confidence Interval). Differences between groups were evaluated, using unpaired Student’s *t* tests (comparing normally distributed variables), Wilcoxon, Mann-Whitney *U* tests (comparing variables that were not normally distributed), or Fisher’s exact tests (comparing proportions). Paired observations were analyzed, using paired Student’s *t* tests. Relationships among variables were quantified, using Spearman correlation coefficients (95% Confidence Interval). The type I error was 0.05 for all statistical tests. If baseline imbalances occurred in potentially confounding variables, they were corrected for using analysis of covariance (36).

## RESULTS

### Patient Flow

Figure 2 graphically presents the patient flow. Over the recruitment period, 3213 patients were admitted to the surgical or medical ICU of whom 1515 stayed at least 5 days. One hundred one (15%) of 675 patients with an expected prolonged ICU stay ( $\geq 7$  days) on day 5 were eligible for inclusion in the study. The most frequent reasons for ineligibility in patients with an ICU stay exceeding 5 days were impairment of the cycling movement (26%), an anticipated fatal outcome (23%), and persistent cardiorespiratory instability (17%). Informed consent was unobtainable in 11 patients.

Ninety consecutive patients were randomized into the treatment group ( $n = 45$ ) and the control group ( $n = 45$ ). Seventy-one patients were recruited in the surgical ICU ( $n = 37$  in the treatment group), 19 patients in the medical ICU ( $n = 8$  in the treatment group). The majority of included surgical patients had undergone cardiac surgery (39%), transplant surgery (25%), or thoracic surgery (16%). At inclusion, 4% of the patients received volume-controlled intermittent positive-pressure ventilation, 80% received (assisted) pressure-support ventilation, and 16% were weaned recently from mechanical ventilation and received supplemental oxygen therapy.

Mortality rate during hospital stay was similar in both groups (16% in control group vs. 24% in treatment group;  $p = .29$ ). All deaths were documented by an independent intensivist as unrelated to the interventions in this trial. In the control group, two patients dropped out (one withdrew informed consent and one developed cardiorespiratory instability during the trial) whereas three patients in the treatment group dropped out (one suffered from an Achilles’ tendon rupture and two developed cardiorespiratory instability during the trial). Patients who dropped out were older than patients who completed the trial ( $66 \pm 15$  yrs vs.  $57 \pm 17$  yrs,  $p < .05$ ). Incomplete measurements at hospital discharge were present in four of the remaining 36 patients in the control group and in five of the remaining 31 patients in the treatment group due to an unexpected hospital discharge.



Table 2. Baseline characteristics of patients at inclusion in the control and treatment group

|   | Control Group<br>(n = 36) | Treatment Group<br>(n = 31) |
|---|---------------------------|-----------------------------|
| Gender, male/female                     | 26/10                     | 22/9                        |
| Age, yrs                                | 57 ± 17                   | 56 ± 16                     |
| BMI, kg/m <sup>2</sup>                  | 24 ± 4                    | 24 ± 5                      |
| PaO <sub>2</sub> on oxygen, torr [kPa]  | 110 ± 29 [14.7 ± 3.9]     | 100 ± 27 [13.3 ± 3.6]       |
| PaCO <sub>2</sub> on oxygen, torr [kPa] | 40 ± 6 [5.3 ± 0.8]        | 39 ± 9 [5.2 ± 1.2]          |
| pH                                      | 7.42 ± 0.04               | 7.44 ± 0.05                 |
| Hemoglobin, g/dL                        | 8.8 ± 1.2                 | 9.7 ± 1.7                   |
| CRP, mg/L                               | 118 ± 76                  | 108 ± 90                    |
| White blood cells, ×10 <sup>9</sup> /L  | 11 ± 5                    | 13 ± 14                     |
| Creatinine, mmol/L                      | 1.4 ± 1.0                 | 1.3 ± 1.7                   |
| APACHE II score on ICU admission, 0–71  | 25 ± 4                    | 26 ± 6                      |
| History of cardiac disease, n (%)       | 14 (39)                   | 10 (32)                     |
| History of respiratory disease, n (%)   | 12 (33)                   | 13 (42)                     |
| Surgical patients, n (%)                | 29 (81)                   | 28 (90)                     |
| ICU stay before inclusion, days         | 10 ± 8                    | 14 ± 10 <sup>a</sup>        |

BMI, body mass index; CRP, C-reactive protein (<5 mg/L, normal); APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.

<sup>a</sup>*p* < .05 compared with control group. Data are presented as mean ± standard deviation or number (%). All measurements were taken at inclusion time except for APACHE II score.

Table 3. Use of medication during ICU stay

|   | Control Group<br>(n = 36) | Treatment Group<br>(n = 31) |
|---|---------------------------|-----------------------------|
| Intravenous sedation days, median and IQR                                 | 8 [3.5–13.5]              | 11 [8.5–16] <sup>a</sup>    |
| Patients receiving vasopressors, n (%)                                    | 33 (92)                   | 24 (77)                     |
| Patients receiving CS, n (%)  | 16 (45)                   | 15 (48)                     |
| Average daily dose (in mg) of CS, median and IQR in patients receiving CS | 27 [14–37]                | 23 [15–33]                  |
| Patients receiving NMBAs, n (%)   | 8 (22)                    | 11 (35)                     |
| Total dose (in mg) of NMBAs, median and IQR in patients receiving NMBAs   | 75 [50–100]               | 150 [100–300] <sup>a</sup>  |

ICU, intensive care unit; IQR, interquartile range; CS, corticosteroids (hydrocortisone equivalent); NMBA, neuromuscular blocking agent (esmeron).

<sup>a</sup>*p* < .05 compared with control group.

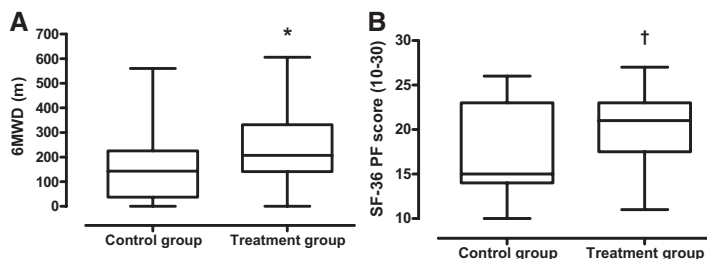


Figure 3. A, Boxplot of 6MWD at hospital discharge. 6MWD, 6-min walking distance. \**p* < .05 compared with control group. B, Boxplot of SF-36 PF score at hospital discharge. SF-36 PF, “Physical Function” item of Short Form 36 Health Survey Questionnaire. †*p* < .01 compared with control group.

### Baseline Characteristics

Baseline characteristics of all patients completing assessments at ICU discharge are summarized in Table 2. The treatment group had a longer ICU stay at inclusion in the study (*p* < .05) (Table 2) and a longer period of intravenous sedation in the ICU (*p* < .05) (Table 3). There

were no differences between groups concerning the proportion of patients receiving corticosteroids, neuromuscular blocking agents, or vasopressive support (Table 3). The cumulative dose in patients who received neuromuscular blockers was higher (*p* < .05) in the treatment group (n = 11) compared with

the control group (n = 8). All patients were on intensive insulin treatment. Four patients in both groups were diagnosed with critical illness polyneuropathy post electrophysiological testing.

Length of ICU stay at inclusion was identified as a strong confounder of treatment effects in the present study, so the results were statistically corrected for this variable. All descriptive data in the document are the unadjusted data.

### Practicality and Safety

The median number of cycling sessions between inclusion and ICU discharge was seven sessions (interquartile range = 4–11 sessions). Median cycling frequency was four sessions/wk (interquartile range = 4–5 sessions/wk). In general, no changes in HR, SBP, diastolic blood pressure, or respiratory rate were observed whereas SpO<sub>2</sub> decreased during cycling (−1.3 ± 1.7% on day 8 and −1.7 ± 3.0% during the final session, *p* < .05). During a total of 425 sessions of cycling, no severe adverse events were identified. Exercise was terminated early in 16 individual sessions because of SpO<sub>2</sub> <90% (n = 8), SBP >180 mm Hg (n = 6), or a >20% decrease of diastolic blood pressure (n = 2). In the first cycling session, 45% of patients in the treatment group participated actively and this proportion increased to 87% during the final training session before ICU discharge. Mean resistance in the active cycle group increased from 0.7 ± 1.2 watt during the first session to 3.2 ± 1.5 watt during the final session.

### Outcome Measurements in Survivors

6MWD at hospital discharge was higher in the treatment group compared with the control group (196 m [126–329 m] vs. 143 m [37–226 m]; 29 [19–43] vs. 25 [8–36] %pred., *p* < .05; Fig. 3A). In line with this finding, SF-36 PF score was higher in the treatment group (21 points [18–23 points] vs. 15 points [14–23 points], *p* < .01) (Fig. 3B). Figure 4 shows that quadriceps force improved more between ICU discharge and hospital discharge in the treatment group (1.83 ± 0.91 N·kg<sup>−1</sup> vs. 2.37 ± 0.62 N·kg<sup>−1</sup>, *p* < .01) than in the control group (1.86 ± 0.78 N·kg<sup>−1</sup> vs. 2.03 ± 0.75 N·kg<sup>−1</sup>, *p* = .11). Handgrip force was not different between treatment and control group at ICU discharge (46 ± 20%pred. vs. 47 ± 11%pred., *p* = .83)

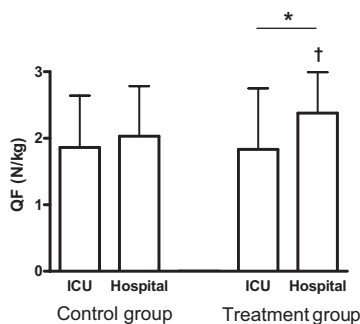


Figure 4. Isometric quadriceps force at intensive care unit (ICU) discharge and at hospital discharge. Data are presented as mean and standard deviation. QF, quadriceps force; hospital, day of hospital discharge. \* $p < .01$  between ICU and hospital discharge; † $p < .05$  compared with control group.

and at hospital discharge ( $51 \pm 16\%$  pred. vs.  $59 \pm 25\%$  pred.  $p = .15$ ). At hospital discharge, 6MWD was correlated with quadriceps force ( $r = .40, p = .002$ ) and SF-36 PF score ( $r = .55, p < .001$ ). Quadriceps force and SF-36 PF were also correlated ( $r = .46, p < .001$ ). Handgrip force was not correlated with the other outcome measures.

The proportion of patients with a Berg Balance Scale score of  $\geq 2$ , indicating the ability to stand up independently, was not different between the treatment group and the control group at ICU and hospital discharge (34% vs. 23%,  $p = .40$  and 85% vs. 79%,  $p = .74$ , respectively). The proportion of patients with a Functional Ambulation Categories score of  $\geq 4$ , indicating the ability to walk independently, was also not different at ICU and hospital discharge (10% vs. 14%,  $p = .72$  and 73% vs. 55%,  $p = .18$ ).

Weaning time (6 days [3–13 days] vs. 6 days [3–16 days],  $p = .40$ ), length of ICU stay (25 days [15–37 days] vs. 24 days [17–34 days],  $p = .14$ ), length of ICU stay after inclusion (11 days [5–21 days] vs. 14 days [8–26 days],  $p = .13$ ), and hospital stay (36 days [28–47 days] vs. 40 days [28–49 days],  $p = .15$ ) were not different between treatment and control groups, respectively. All patients in both groups succeeded to be liberated from mechanical ventilation at ICU discharge. In the control group, 24 patients (66%) were discharged home, six patients (17%) to another hospital, and six patients (17%) to a rehabilitation center. In the treatment group, 23 patients (74%) were discharged home, five patients (16%) to another hospital, and three patients (10%) to a rehabilitation center. One-year mor-

tality was three (8%) of 36 in the control group and three (10%) of 31 in the treatment group.

## DISCUSSION

This randomized controlled trial is the first to examine the practicality and effectiveness of early exercise training in a selection of acute critically ill patients with an expected prolonged ICU stay. We showed that a daily cycle session with a bedside ergometer is feasible and safe early during ICU stay. The intervention improved functional exercise capacity, muscle force, and perceived functional status at hospital discharge in ICU survivors.

### Practicality and Safety

A bedside cycle ergometer was used because this device can perform a prolonged continuous mobilization at the same time the training intensity can be adjusted continuously to the patient's health status and the physiologic responses to exercise. The median cycling frequency of four sessions/wk (exercise adherence of 80%) indicates that about one session/wk was canceled for medical reasons. Still published useful comprehensive guidelines for ICU physiotherapists to assess the safety of mobilization in critically ill patients based on physiologic data and clinical experience (37). To assure safety in our trial, patients were monitored closely to identify abnormal physiologic responses during exercise training. This resulted in early exercise cessation during 16 individual training sessions (4% of all training sessions), but the physiologic parameters normalized within the first 2 mins of recovery in all cases. In general, the achieved absolute workload during cycling exercise was very low and HR, blood pressure, and respiratory rate did not change. The decrease in oxygen saturation was statistically significant but not clinically relevant.

The performance of a single training session (including installing, uninstalling, and cleaning) takes 30 to 40 mins, depending on the patient's cooperation and the number of attachments. In total, it would take 3 to 4 hrs to provide the intervention in the median patient (number of sessions  $\times$  time to perform one session) in our study population.

### Early Exercise Training

Most published trials involving exercise training in mechanically ventilated patients are performed in a respiratory intermediate care unit (38–40), often including patients 3 to 6 wks after the initial hospital admission (39, 40). However, recent literature demonstrated that muscle wasting is the highest during the first 3 wks of ICU stay (18). This indicates that exercise training as a strategy to prevent muscle atrophy should probably start as early as possible. A cohort trial reported that the intensive care environment may contribute to unnecessary immobilization (41). Bailey et al started (on average) with an early ambulation protocol on day 6 from ICU admission and reported adverse events in  $<1\%$  of the activity sessions (20). Morris et al (21) showed significant reductions of intensive care and hospital length of stay after an early physical therapy program in patients with acute respiratory failure with a relative short ICU (about 6 days) and hospital stay (about 14 days). We aimed at inclusion of patients with an expected protracted critical illness with a minimal stay of 12 days in the ICU. Most of our patients were cardiorespiratory unstable, resulting in a delayed inclusion (on average 10 days after ICU admission for the control group and 14 days for the treatment group).

### Outcome Measurements

At ICU discharge, the majority of patients in both groups were unable to stand up or walk independently, which is a result from the observed low quadriceps force. Patients were discharged to the ward as soon as their medical (cardiorespiratory) condition was sufficiently stable, regardless of their functional status. The intervention did not seem to prevent the acute effects of prolonged ICU stay on muscle function and functional status of the patients. However, possibly effort-dependent handheld dynamometry was not a sufficiently sensitive measure to detect subtle differences in muscle function in weak bed-bound patients with often suboptimal cooperation. Muscle biopsies (42) or ultrasound assessment of muscle bulk (18) may have given us better insight into the effect of the intervention at the muscular level.

We speculate that patients in the training group consistently started their rehabilitation on the ward with an advantage. This could possibly be a conse-

quence of a partial prevention of muscle atrophy (24), a better muscle coordination (43), or an enhanced psychological status (44). Hence, they showed an enhanced recovery of their functionality, associated with a larger increase of their quadriceps force during their stay on the ward. Functional exercise capacity (reflected by the 6MWD), quadriceps force, and self-perceived functional status (reflected by the SF-36 PF) at hospital discharge were higher in the training group. The likelihood that this is explained by chance is very low. The positive correlation between these variables indicates that quadriceps force contributes to walking performance and subjective feeling of functional well-being. Along the same lines, the proportion of patients who could walk independently at hospital discharge tended to be higher in the training group (73% vs. 55%). Sample size calculation revealed that 125 patients would have to finish the trial in each group to find a significant difference. Hence, our study was not powered to show a statistically significant difference. Interestingly, no difference in handgrip force was found between groups, which we expected because the intervention focused on the lower limbs.

In addition to a small, but not significant, difference in length of hospital stay in favor of the treatment group, a higher proportion of patients in the control group (17%) were referred to a rehabilitation center at hospital discharge compared with the treatment group (10%). The study was not powered to show a statistically significant difference, but from a clinical and an economic point of view, every single patient who can be referred to home instead of a rehabilitation center is important.

## Limitations

When interpreting these promising results, some limitations of this trial should be taken into account. First, the treatment group received an additional 20 mins of daily physical activity compared with the control group. We cannot rule out whether an additional 20-min standard physical therapy mobilization session in the control group would yield the same beneficial effects, especially if this intervention would include more opportunity to be upright. However, cycling was chosen because it provides a well-controlled and targeted training stimulus in bedridden patients. Second, exercise

intensity during cycling therapy was mainly based on the patient's or the physiotherapist's subjective perception on the exercise tolerability. Only a small proportion of the patients were sufficiently adequate to rate their perceived training intensity with a Borg scale. Intensity was not high enough to induce clinically relevant changes in cardiorespiratory parameters that could be used to adjust training load. It is possible that the provided exercise intensity was not the maximal cardiorespiratory tolerable intensity, but in these critically ill patients, it was felt inappropriate to force these patients to high training intensity because of ethical and safety issues (37). Furthermore, other limitations at the level of pulmonary gas exchange (indicated by the decrease in  $SpO_2$ ), neuromuscular level, or psychological (fear or anxiety to perform exercise) level could have been responsible for early onset of exercise intolerance. Third, rehabilitation during the ward stay was not strictly standardized. However, the distribution of the patients toward the different wards (cardiac surgery, pulmonology, thoracic surgery, abdominal surgery, etc.) was the same in both groups. Furthermore, physiotherapists on the ward were naive for the aims and treatment allocation of the present study and received standard instructions to provide all patients with the usual care. Lastly, a prospective screening for the presence of critical illness neuromuscular abnormalities in all patients was not performed. Electrophysiological testing was only executed in a proportion of patients with an extremely long ward stay. Hence, the incidence of critical illness polyneuropathy in our study population is likely underestimated.

## CONCLUSIONS

In conclusion, this adequately powered, randomized controlled trial showed that an individually tailored exercise training protocol can be initiated during the acute ICU stay in critically ill patients. When instituted early in ICU survivors with prolonged ICU stay, exercise training may enhance recovery of functional exercise capacity, self-perceived functional status, and quadriceps force at discharge from hospital.

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