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Effect of In-Bed Leg Cycling and Electrical Stimulation of the Quadriceps on Global Muscle Strength in Critically Ill Adults
A Randomized Clinical Trial

Guillaume Fossat, PT; Florian Baudin, PT; Léa Courtes, PT; Sabrine Bobet, PT; Arnaud Dupont, PT; Anne Bretagnol, MD; Dalila Benzekri-Lefèvre, MD; Toufik Kamel, MD; Grégoire Muller, MD; Nicolas Bercault, MD; François Barbier, MD, PhD; Isabelle Runge, MD; Mai-Anh Nay, MD; Marie Skarzynski, MD; Armelle Mathonnet, MD; Thierry Boulain, MD

IMPORTANCE Early in-bed cycling and electrical muscle stimulation may improve the benefits of rehabilitation in patients in the intensive care unit (ICU).

OBJECTIVE To investigate whether early in-bed leg cycling plus electrical stimulation of the quadriceps muscles added to standardized early rehabilitation would result in greater muscle strength at discharge from the ICU.

DESIGN, SETTING, AND PARTICIPANTS Single-center, randomized clinical trial enrolling critically ill adult patients at 1 ICU within an 1100-bed hospital in France. Enrollment lasted from July 2014 to June 2016 and there was a 6-month follow-up, which ended on November 24, 2016.

INTERVENTIONS Patients were randomized to early in-bed leg cycling plus electrical stimulation of the quadriceps muscles added to standardized early rehabilitation (n = 159) or standardized early rehabilitation alone (usual care) (n = 155).

MAIN OUTCOMES AND MEASURES The primary outcome was muscle strength at discharge from the ICU assessed by physiotherapists blinded to treatment group using the Medical Research Council grading system (score range, 0-60 points; a higher score reflects better muscle strength; minimal clinically important difference of 4 points). Secondary outcomes at ICU discharge included the number of ventilator-free days and ICU Mobility Scale score (range, 0-10; a higher score reflects better walking capability). Functional autonomy and health-related quality of life were assessed at 6 months.

RESULTS Among 314 randomized patients, 312 (mean age, 66 years; women, 36%; receiving mechanical ventilation at study inclusion, 78%) completed the study and were included in the analysis. The median global Medical Research Council score at ICU discharge was 48 (interquartile range [IQR], 29 to 58) in the intervention group and 51 (IQR, 37 to 58) in the usual care group (median difference, −3.0 [95% CI, −7.0 to 2.8]; P = .28). The ICU Mobility Scale score at ICU discharge was 6 (IQR, 3 to 9) in both groups (median difference, 0 [95% CI, −1 to 2]; P = .52). The median number of ventilator-free days at day 28 was 21 (IQR, 6 to 25) in the intervention group and 22 (IQR, 10 to 25) in the usual care group (median difference, 1 [95% CI, −2 to 3]; P = .24). Clinically significant events occurred during mobilization sessions in 7 patients (4.4%) in the intervention group and in 9 patients (5.8%) in the usual care group. There were no significant between-group differences in the outcomes assessed at 6 months.

CONCLUSIONS AND RELEVANCE In this single-center randomized clinical trial involving patients admitted to the ICU, adding early in-bed leg cycling exercises and electrical stimulation of the quadriceps muscles to a standardized early rehabilitation program did not improve global muscle strength at discharge from the ICU.

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Visual Abstract

Supplemental content

Author Affiliations: Service de Médecine Intensive Réanimation, Centre Hospitalier Régional d'Orléans, Orléans, France (Fossat, Baudin, Courtes, Bobet, Bretagnol, Benzekri-Lefèvre, Kamel, Muller, Bercault, Barbier, Runge, Nay, Skarzynski, Mathonnet, Boulain); Service de Réanimation Chirurgicale, Centre Hospitalier Régional d'Orléans, Orléans, France (Dupont).

Approximately 50% of patients who receive care in the intensive care unit (ICU) may experience debilitating muscle wasting and its consequence, ICU-acquired weakness, which may prolong duration of mechanical ventilation[1] and may persist for up to 5 years after hospital discharge.[2] The main factors contributing to ICU-acquired weakness are inflammation, metabolic disorders, and forced muscular rest in bedridden or sedated patients, particularly those with sepsis, multiple organ failure, or receiving prolonged mechanical ventilation.[1,3]

Mobilization of the musculoskeletal system has been shown to be safe when applied early in unstable ICU patients[1] and has been shown to prevent ICU-acquired weakness, shorten ICU and hospital stays, decrease the incidence of delirium, and reduce the time until return of functional autonomy.[4,5]

Exercises using a cycle ergometer may improve the strength of the quadriceps muscles and perceived quality of life at hospital discharge.[6] Electrical muscle stimulation may reduce muscle atrophy in ICU patients.[7] Although both cycling exercises and electrical muscle stimulation have no clinically significant adverse effects, these interventions have not been sufficiently studied in ICU patients to know whether they should be incorporated in standardized rehabilitation programs.

The objective of this study was to assess whether the combination of early electrical stimulation of the quadriceps muscles and early in-bed leg cycling on a cycle ergometer added to a standardized early rehabilitation program may improve the effects of early mobilization in ICU patients in terms of global muscle strength assessed at ICU discharge.

Key Points

Question Can the combination of early in-bed leg cycling and electrical stimulation of the quadriceps muscles added to standardized early rehabilitation result in better muscle function in critically ill adult patients at discharge from the intensive care unit?

Findings In this randomized clinical trial that included 314 patients, the addition of in-bed cycling and electrical stimulation of the quadriceps muscles to early rehabilitation compared with early rehabilitation alone did not result in a significant improvement in global muscle strength at discharge from the intensive care unit (48 vs 51 points, respectively, on the 60-point Medical Research Council grading system in which higher values represent better strength).

Meaning Early in-bed cycling and electrical muscle stimulation as used in this study did not improve muscle strength in critically ill patients.

Methods

Study Oversight

The regional ethics committee approved the trial protocol (appears in Supplement 1) and waived the need for written consent. Patients when capable or legal representatives or next of kin when present or reachable by telephone were orally (and in writing as soon as possible) informed of the study and provided oral consent for participation.

In every case, patients were informed about their participation in the study as soon as they regained their mental capacities and the right to refuse participation was emphasized. Data from patients who secondarily refused consent were excluded from the analysis in compliance with French law. Compliance with regulatory requirements, accuracy, and completeness of the study data along with proper application of the assigned interventions was monitored by clinical research assistants and study nurses as mandated by the study sponsor (Centre Hospitalier Régional d'Orléans, Orléans, France).

Study Design, Setting, and Population

The study was conducted in a 20-bed medical-surgical ICU in a regional and 1100-bed teaching hospital in Orléans, France. This single-center, 2-parallel group randomized clinical trial had a 1:1 intervention allocation ratio and assessment of the primary outcome measure by an assessor blinded to the study intervention (**Figure 1**). The period of enrollment was from July 2014 through June 2016 and there was a 6-month follow-up period, which ended on November 24, 2016.

Patients were eligible if they (1) were aged 18 years or older, (2) were admitted to the ICU less than 72 hours before randomization, (3) were deemed to need more than 48 hours of care in the ICU, and (4) had an independent walking ability and a Barthel Index[8] greater than 55 within 15 days before ICU admission as assessed by interview of the patient, his or her family, or caregivers.

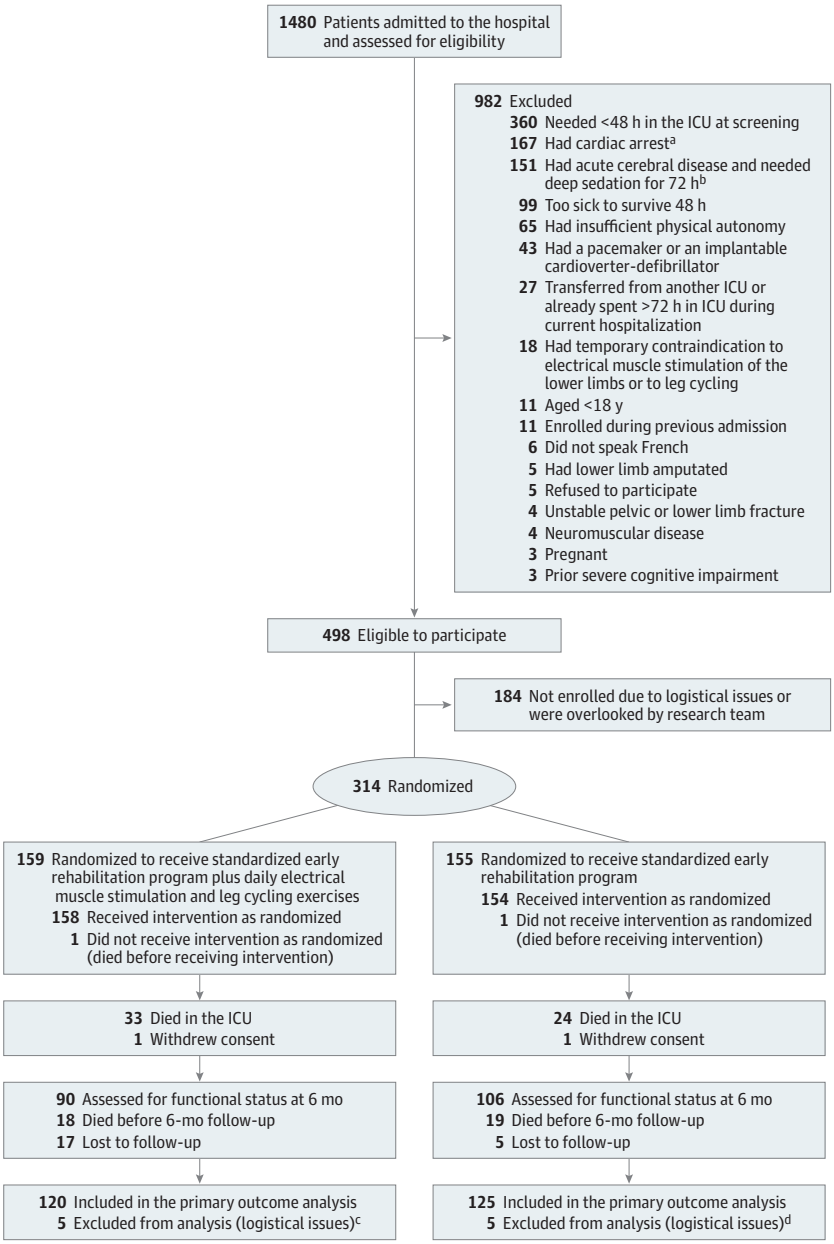
Patients were excluded if (1) pregnant, (2) cardiac arrest was the cause of ICU admission or had cardiac arrest before screening, (3) had a pacemaker or implantable cardioverter-defibrillator, (4) had acute cerebral disease requiring deep sedation for at least 72 hours (due to severe traumatic brain injury, status epilepticus, stroke, or other causes of intracranial hypertension), (5) had acute polyradiculoneuropathy (Guillain-Barré syndrome), (6) had myasthenia, (7) had advanced dementia, (8) had deep venous thrombosis or pulmonary embolism treated for less than 48 hours, (9) had a contraindication to electrical muscle stimulation or leg cycling for musculoskeletal, dermatological, or surgical reasons, (10) had a contraindication to standing or transfer to a chair, (11) had a lower limb that was amputated, or (12) were previously included in the present study.

Randomization and Allocation Concealment

Randomization was stratified by sex (a potential risk factor for ICU-acquired weakness[9]), the respiratory status of patients on the day of enrollment (eg, receiving invasive mechanical ventilation or not), and day of ICU admission (Thursday or Friday vs other days). It was not possible, similar to other studies,[6,10] to apply the different interventions on Saturday and Sunday due to an understaffed physiotherapy team, which is a common in other French ICUs and in other countries. Therefore, for patients enrolled on a Thursday or Friday (expected to represent about 29% of the study population), the difficulty or impossibility to apply early (ie, at least 2 days within the 3 calendar days following ICU admission) mobilization exercises was foreseen.

Computer-generated randomization lists were prepared by a clinical research assistant in block sizes of 4 or 6 patients, the

Figure 1. Flow of Patients Through the Study



ICU indicates intensive care unit.

[a] There were 49 patients who had a cardiac arrest during the screening period and it was the reason for hospital admission in 118 patients.

[b] There were 31 patients with severe traumatic brain injury, 51 with status epilepticus, 21 with ischemic stroke, 27 with hemorrhagic stroke, and 21 with other causes.

[c] There were 4 patients who were transferred to another hospital for emergency cardiac surgery. One patient was overlooked by study investigators.

[d] Two patients were transferred to another hospital (one for emergency cardiac surgery and the other for emergency liver transplantation). One patient died within 24 hours after discharge from the ICU before an assessment could be performed. Two patients were overlooked by study investigators.

size of which was not known by the investigators. A clinical research assistant prepared 8 sets of sealed, opaque, and numbered envelopes. When each patient was enrolled in the study, the investigator opened the envelope containing the smallest item number in the appropriate group of stratification.

Interventions

In the usual care group, standardized early rehabilitation was applied each weekday from randomization to ICU discharge. This was a progressive multistep program adapted from the program described and used by Schweickert et al,[4] beginning with 10 passive range of motion exercises with each limb joint applied once every weekday by physiotherapists to comatose or sedated patients, followed by passive or active exercises and then fully active muscle exercises, transfer to the edge of the bed or to a chair, standing, and walking.

In the intervention group, in addition to standardized early rehabilitation as described above, each weekday, the patients underwent a 15-minute session of leg cycling exercise (even in bed) on a cycle ergometer (MOTOmed letto2, RECK-Technik) and, at a different time of the day, a 50-minute electrical stimulation session of the quadriceps muscles delivered by a 4-channel electrical stimulator (Rehab 400, CefarCompex). The cycling exercise intervention was adapted from the study by Burtin et al,[6] in which one 20-minute daily session applied each weekday to ICU patients was shown to improve muscle

strength and self-perceived functional status at hospital discharge. Use of the electrical muscle stimulation intervention was based on the report by Routsi et al,[11] which suggested that such an intervention is safe and may prevent muscle weakness and shorten the duration of mechanical ventilation.

The interventions were delivered by 2 licensed physiotherapists (G.F. and F.B.), who were not blinded to the randomization group, and who each cared for the patients in either group or in both groups with regard to the application of basic mobilization (range of motion, transfer to a chair, standing, or walking). In both groups, the passive aspects, active aspects, or both the passive and active aspects of the interventions and the intensity of the applied interventions were adapted to the patient's cardiorespiratory status, level of wakefulness, cooperation, global muscle strength (assessed each weekday by physiotherapists), and tolerance according to predefined criteria (details appear in Supplement 2).

Primary Outcome

The primary outcome measure was the patient's global muscle strength assessed using the Medical Research Council (MRC) grading system[12] to determine the strength of 6 muscle groups on both sides of the body (overall score range, 0-60; minimal clinically important difference of 4 points[13]) measured on the day of ICU discharge (or on the following day) by a physiotherapist blinded to the randomization group.

Secondary Outcomes

There were several secondary outcome measures. Functional autonomy at ICU discharge (or on the following day) was assessed by a physiotherapist blinded to the randomization group using the ICU Mobility Scale,[14] which grades the patient's self-mobilization capabilities from 0 (no active movements) to 10 (walking without any aid). The proportion of patients who developed delirium in the ICU was defined using the Confusion Assessment Method for the ICU.[15]

The functional independence of patients (measured using the Katz Index of Independence in Activities of Daily Living[16]; range, 0-6 with a score of 6 indicating total independence in bathing, getting dressed, using the toilet, transferring to a chair, continence, and eating) from the period before ICU admission was compared with the level of functioning at ICU discharge and at 6 months (measured using the Barthel Index[8]; range, 0-100 with a higher score indicating greater independence; minimal clinically important difference of 2 points).[17]

The duration of invasive mechanical ventilation and the number of ventilator-free days were measured from study inclusion through day 28. Among patients who received mechanical ventilation, the proportion of patients who needed intubation for a second time during the ICU stay was assessed. The mortality rates were measured during the ICU stay, during the hospital stay, at day 28, and at 6 months.

Functional status and perceived quality of life were assessed using the French version of the 36-Item Short Form Health Survey questionnaire[18] (composed of physical and mental component scores, each ranging from 0-100 with higher scores indicating better quality of life; minimal clinically important difference of 5 points[19]), which was sent via regular mail or administered by telephone interview with the patient, family, caregiver, or treating physician at 6 months after ICU discharge. The telephone interviews were conducted by clinical research assistants blinded to the randomization group.

Safety was evaluated as the proportion of patients who experienced at least 1 clinically significant adverse event (defined as an event that required a therapeutic intervention beyond simple session interruption) during the mobilization sessions.

The final secondary outcome was the change in thickness of the rectus femoris muscle for each thigh, which was measured using ultrasonography (mean measurements for the left and right sides of the body), between study inclusion and ICU discharge. Investigators, who were not blinded to randomization group, were trained to obtain the ultrasound measurements of the thigh muscles using previously described anatomical landmarks[20] and an L12-3 MHz linear array transducer (Philips).

Sample Size

Sample size calculation was based on published data showing a nonsignificant 4-point difference in the median[4] for the MRC score when comparing the rehabilitation intervention with usual care. To show that a difference of 4 points was clinically important[13] and statistically significant, it was estimated that at least 150 patients per group were needed with type I error set at 5% and a power level greater than 90%.[21] This calculation took into account the possibility of a marginally lower risk of death in the intervention group.[22]

Statistical Analysis

Data were analyzed according to randomization group. Patients who died in the ICU were assigned 0 points for the MRC score, the ICU Mobility Scale score, and the Katz Index, and were assigned the worst value observed in the study cohort for the ultrasound measurement of change in the thickness of the rectus femoris muscle.

Missing values for the outcomes at ICU discharge were replaced using multivariable imputation by chained equations (MICE package; R Foundation for Statistical Computing). One hundred imputed data sets were generated and analyzed. The primary outcome measure and all other semicontinuous or nonnormally distributed continuous variables were compared between groups using the Mann-Whitney test, which was adjusted for stratification[23] (Sanon package, R Foundation for Statistical Computing).

The median differences and 95% CIs were obtained using bootstrapping (2000 bootstrapped samples). For the variables that needed multiple imputation because of missing values, the median differences, 95% CIs, and *P* values were pooled. The estimates were calculated for each of the 100 imputed data sets and the median of the 100 median differences is reported. The lower and upper bounds of the 95% CI are reported as the 2.5% and 97.5%, respectively, of the lower and upper bounds of 95% CIs calculated on each of the 100 imputed data sets. The *P* values reflect the 2.5 percentile of the 100 pooled *P* values.

Table 1. Baseline Characteristics

	Intervention Group (n = 158)	Usual Care Group (n = 154)
Age, mean (SD), y	65 (13)	66 (15)
Male patients, No. (%)	103 (65)	98 (64)
Simplified Acute Physiology Score II, mean (SD)[25,a]	47 (19)	46 (17)
Sequential Organ Failure Assessment score, median (IQR)[26,b]	9 (6-12)	8.5 (6-12)
Barthel Index, median (IQR)[c]	100 (95-100)	100 (95-100)
Weight, median (IQR), kg	74 (62-87)	76 (67-91)
Height, median (IQR), cm	170 (163-175)	169 (162-173)
Body mass index, median (IQR)[d]	26.1 (21.9-30.1)	27.1 (24.0-31.5)
Type of Comorbidity, No. (%)[e]		
Chronic arterial hypertension	71 (45)	64 (42)
Type 2 diabetes	41 (26)	43 (28)
Alcoholism	42 (27)	40 (26)
Chronic respiratory failure	39 (25)	33 (21)
Chronic obstructive pulmonary disease	37 (23)	32 (21)
Type of immunocompromising condition[f]	31 (20)	28 (18)
Solid organ with active cancer	12 (8)	9 (6)
Malignant hemopathy	10 (6)	6 (4)
Chemotherapy or radiotherapy within 6 mo	13 (8)	10 (6)
Neutropenia	6 (4)	2 (1)
Transplant recipient	3 (2)	0
Treatment with corticosteroids	9 (6)	12 (8)
Other cause of immunosuppression	6 (4)	7 (4)
Chronic congestive heart failure	20 (13)	25 (16)
History of atrial fibrillation or flutter	17 (11)	25 (16)
History of myocardial infarction	18 (11)	21 (14)
Home oxygen therapy	17 (11)	11 (7)
Home noninvasive mechanical ventilation	16 (10)	12 (8)
Cirrhosis	11 (7)	14 (9)
Dialysis	4 (3)	3 (2)
Admission Diagnosis, No. (%)		
Acute respiratory failure	89 (56)	92 (60)
Exacerbation of chronic respiratory failure	33 (21)	29 (19)
Acute respiratory distress syndrome	27 (17)	22 (14)
Type of infection		
Pulmonary pleura	71 (45)	69 (45)
Abdomen	12 (8)	17 (11)
Urinary tract	6 (4)	4 (3)
Other	11 (7)	11 (7)
Positive blood culture at ICU admission	76 (48)	74 (48)
Severe sepsis	65 (41)	52 (34)
Septic shock	44 (28)	37 (24)
Hemorrhagic shock	12 (8)	9 (6)
Cardiogenic shock	10 (6)	14 (9)
Acute renal failure	39 (25)	29 (19)
Acute liver failure	16 (10)	16 (10)
Coma	40 (25)	35 (23)
Trauma	2 (1)	2 (1)
Drug overdose	5 (3)	1 (1)

(continued)

Table 1. Baseline Characteristics (continued)

	Intervention Group (n = 158)	Usual Care Group (n = 154)
Type of Therapy Provided Before Study Enrollment, No. (%)[g]		
Surgery within 2 d before ICU admission	13 (8)	15 (10)
Urgent surgery between ICU admission and enrollment	11 (7)	9 (6)
Noninvasive ventilation	40 (25)	37 (24)
Invasive mechanical ventilation[h]	121 (77)	121 (79)
Continuous intravenous sedation	119 (75)	118 (77)
Continuous intravenous muscle relaxant	35 (22)	26 (17)
Renal replacement therapy	16 (10)	11 (7)
Time elapsed between admission and receipt of first study intervention, median (IQR), h	31 (19-46)	30 (19-45)

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

[a] Range, 0 to 163 points; a higher score indicates an increased risk of mortality (eg, a score of 46 predicts a hospital mortality rate of 37%).

[b] Grades the number and severity of organ failure from a score of 0 (no organ failure) to a score of 24 (highest severity of organ or system failure among respiratory, hematologic, renal, liver, cardiovascular, and neurological systems).

[c] Evaluates the patient's functional status[8] and is composed of 10 variables describing activities of daily living and mobility. Range, 0 to 100; a higher score indicates greater independence.

[d] Calculated as weight in kilograms divided by height in meters squared.

[e] Ascertained through interviews with the patient, his or her family, by family practitioner interview, and by reviewing the patient's hospital health record.

[f] A patient may have had more than 1 immunocompromising condition.

[g] Unless otherwise indicated.

[h] Ongoing at the time of enrollment for the 121 patients in each group.

Missing values for the outcomes assessed at 6 months were not imputed. Binary end points were compared using the Mantel-Haenszel χ^2 test, which was adjusted for stratification. The absolute risk reduction values were calculated using Mantel-Haenszel risk differences, which were adjusted for stratification, and appear with Wald 95% CIs. The homogeneity across strata was assessed using the Breslow-Day test.

The first per-protocol analysis was planned for patients who received the allocated intervention at least 2 days within the 3 calendar days following ICU admission. The second per-protocol analysis was planned for patients who received the allocated intervention at least 80% of the weekdays spent in the ICU. Subgroup analyses were planned (1) among patients who received invasive mechanical ventilation and those who did not, (2) among male and female patients separately, and (3) among patients admitted on a Thursday or Friday and those admitted on another day separately. The interactions between the variables used for stratification and the studied intervention were checked using the aligned rank transform test[24] (ART package, R Foundation for Statistical Computing) for outcomes compared using the Mann-Whitney test and the Breslow-Day test for homogeneity for categorical outcomes.

No adjustment for multiple testing was planned; therefore, the secondary analyses should be considered exploratory. A 2-tailed $P<.05$ was considered statistically significant. The analyses were performed using R software version 3.3.1 (R Foundation for Statistical Computing).

Results

Among 498 eligible patients, 314 were randomized. There were 159 patients randomized to the intervention group (standardized early rehabilitation program plus daily electrical stimulation of the quadriceps muscles and leg cycling exercises) and 155 patients were randomized to the usual care group (standardized early rehabilitation program).

Among the 314 randomized patients, 71 (22.6%) gave consent in person before randomization. There were 58 patients (18.5%) for whom next-of-kin gave consent during a telephone interview and there were 94 patients (29.9%) for whom a face-to-face interview was conducted with a family member. In addition, 91 patients (29.0%) were included based on the opinion of the investigators because (1) the patients were unable to understand the study-related information and give informed consent or (2) a family member was neither present nor reachable by telephone within the first 12 hours. In the latter case, the patients and their family were informed as soon as possible and were asked for their consent.

One patient in each group died before they could receive the intervention. All the remaining randomized patients received the intervention. One patient in each group withdrew consent; therefore, 312 patients (mean [SD] age, 66 [15] years; 111 [36%] women; mean [SD] Simplified Acute Physiology Score II, 46.2 [18.1]) completed the study and were included in the analysis. Most patients (64%) had an infection at ICU admission and received mechanical ventilation (78%) at study inclusion. The baseline characteristics of the patients were similar between the groups (**Table 1**).

Mobilization sessions were provided during 1387 patient-days (median, 5.5 [interquartile range {IQR}, 3-11] days per patient) in the intervention group and during 1190 patient-days (median, 5.0 [IQR, 3-10] days per patient) in the usual care group. There were no significant between-group differences in the amount of time elapsed until the first transfer to the edge of the bed or to a chair, until the first standing positioning, or until the first walking try (Supplement 2).

Fifty-seven patients (18.7%) died in the ICU and 10 ICU survivors (5 in each group) could not be assessed for the primary

Table 2. Primary and Secondary Outcome Measures Assessed at Discharge From the Intensive Care Unit (ICU)

	Median (IQR)[a]			
	Intervention Group (n = 158)	Usual Care Group (n = 154)	Between-Group Difference (95% CI)[b]	*P* Value
Primary Outcome				
Global MRC score at ICU discharge among ICU survivors[12,c]	48 (29 to 58)	51 (37 to 58)	MD, −3.0 (−7.0 to 2.8)	.28[d]
Secondary Outcomes				
ICU Mobility Scale score at ICU discharge among ICU survivors[14,e]	6 (3 to 9)	6 (3 to 9)	MD, 0 (−1.0 to 2.0)	.52[d]
Frequency of delirium, No. (%) [95% CI][f]	39 (24.7) [18.6 to 32.0]	39 (25.3) [19.1 to 32.7]	ARR, 0.3 (−9.4 to 10.0)	.94[g]
Invasive mechanical ventilation, d				
Intention-to-treat population	5 (2 to 10)	5 (2 to 11)	MD, 0 (−2.0 to 1.5)	.69[h]
ICU survivors				
No. of patients	103	109		
Mechanical ventilation for ≥1 d	6 (4.0 to 10.0)	6 (3.0 to 12.3)	MD, 0 (−2.0 to 2.0)	.91[h]
ICU decedents				
No. of patients	28	24		
Mechanical ventilation for ≥1 d	12.5 (5.0 to 18.5)	7.5 (3.0 to 15.5)	MD, −5.0 (−11.0 to 3.5)	.41[h]
No. of invasive mechanical ventilation-free days at day 28				
Intention-to-treat population	21 (6 to 25)	22 (10 to 25)	MD, 1.0 (−2.0 to 3.0)	.24[h]
ICU survivors with mechanical ventilation for ≥1 d	22 (18 to 24)	22 (16 to 25)	MD, 0 (−2.0 to 2.0)	.93[h]
ICU decedents with mechanical ventilation for ≥1 d	0 (0 to 0)	0 (0 to 0)	MD, 0 (0 to 0)	>.99[h]
Frequency of reintubation within 48 h after first extubation, No./total (%) [95% CI]	12/131 (9.2)[5.3 to 15.3]	13/133 (9.8)[5.8 to 16.0]	ARR, 0.7 (−6.7 to 7.9)	>.99[g]
Change from study inclusion to ICU discharge				
Rectus femoris muscle thickness, mm	−1.9 (−8.0 to 0.2)	−2.4 (−7.1 to −0.3)	MD, −0.5 (−1.0 to 2.4)	.17[d]
Katz Index of Independence in Activities of Daily Living[16,i]	−3.3 (−5.5 to −1.5)	−3.5 (−5.5 to −1.6)	MD, 0.3 (−1.0 to 1.3)	.57[d]
ICU mortality, No. (%) [95% CI]	33 (20.9) [15.3 to 27.9]	24 (15.6) [10.7 to 22.1]	ARR, 5.4 (−3.3 to 14.0)	.27[g]

Abbreviations: ARR, absolute risk reduction; IQR, interquartile range; MRC, Medical Research Council.

[a] Data are expressed as median (IQR) unless otherwise indicated.

[b] The median differences (MDs) were obtained using bootstrapping. For the outcome measures that had missing values, the MDs are pooled estimates obtained from the analysis of 100 imputed data sets (additional details appear in the Methods section). The median of 100 MDs is provided. The ARRs were obtained using the Mantel-Haenszel test and were adjusted for stratification and appear with Wald 95% CIs.

[c] The score reflects the strength of the muscle groups used to mobilize joints on both body sides from 0 (no visible contraction) to 5 (normal strength). The joint motions examined were shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion. The overall score range is from 0 to 60.

[d] Reflects the 2.5% percentile of the 100 *P* values yielded by the Mann-Whitney test. The *P* value was adjusted for stratification performed on each of the 100 imputed data sets (additional details appear in the Methods section) and missing values were replaced by multiple imputation.

[e] Grades the patient's self-mobilization capabilities from 0 (no active movements) to 10 (walking without any aid).

[f] Recorded by study nurses every day and describes whether the patient was diagnosed as being confused or agitated. When the patient was not diagnosed as being confused or agitated, the study nurses further assessed the existence of delirium using the Confusion Assessment Method for the ICU.[15] Once the patient had been diagnosed as having delirium, the patient was no longer assessed for delirium during the remaining days spent in the ICU.

[g] Assessed using the Mantel-Haenszel χ^2 test, which was adjusted for stratification after the Breslow-Day test for homogeneity yielded no significant difference across strata.

[h] Assessed using the Mann-Whitney test, which was adjusted for stratification.

[i] Evaluates the functional independence of patients. The score range is from 0 to 6; a score of 6 indicates total independence in bathing, getting dressed, using the toilet, transferring to a chair, continence, and eating.

outcome measure for logistical reasons, mainly because they had to be transferred to another hospital while still sedated, intubated, or both for emergency cardiac surgery or liver transplantation (Figure 1). For the MRC score and the ICU Mobility Scale score, there were 5 missing values (3.2%) in each group. There were missing values for the ultrasound measurement of muscle thickness for 4 patients in the intervention group and 3 patients in the usual care group. For the Katz Index, there were missing values for 12 patients in the intervention group and 6 patients in the usual care group.

Primary Outcome: Global Muscle Strength at Discharge From the ICU

The median MRC score at ICU discharge did not differ between groups (48 [IQR, 29 to 58] in the intervention group and 51 [IQR, 37 to 58] in the usual care group; median difference, −3.0 [95% CI, −7.0 to 2.8], *P* = .28).

Secondary Outcomes

The median ICU Mobility Scale score at ICU discharge was 6 (IQR, 3 to 9) in both the intervention group and the usual

Table 3. Secondary Outcome Measures Assessed at 6 Months

	Median (IQR)[a]			
	Intervention Group (n = 158)	Usual Care Group (n = 154)	Between-Group Difference (95% CI)[b]	*P* Value
Barthel Index[8,c]				
No. of patients	90	106		
At 6 mo	100 (90 to 100)	100 (85 to 100)	MD, 0 (−5 to 5)	.90[d]
Change in score at 6 mo	0 (−5 to 0)	0 (−10 to 0)	MD, 0 (0 to 0)	.46[d]
36-Item Short Form Health Survey score[18,e]				
No. of patients	86	96		
Physical functioning	55 (25 to 80)	45 (25 to 75)	MD, 10 (−10 to 25)	.22[d]
Role physical	50 (0 to 100)	50 (0 to 100)	MD, 0 (−38 to 25)	.96[d]
Bodily pain	68 (45 to 90)	57 (45 to 80)	MD, 12 (0 to 24)	.12[d]
General health	48 (38 to 58)	50 (31 to 61)	MD, −2 (−8 to 6)	.86[d]
Vitality	50 (38 to 63)	44 (31 to 56)	MD, 6 (−6 to 12)	.34[d]
Social functioning	75 (50 to 100)	63 (50 to 88)	MD, 12 (−12 to 25)	.64[d]
Emotional role	67 (0 to 100)	67 (0 to 100)	MD, 0 (−34 to 67)	.82[d]
Mental health	63 (50 to 80)	60 (41 to 75)	MD, 3 (−5 to 10)	.20[d]
Physical component	51 (36 to 76)	50 (33 to 66)	MD, 1 (−11 to 16)	.38[d]
Mental component	61 (42 to 78)	57 (39 to 75)	MD, −4 (−16 to 9)	.46[d]
Mortality, No. (%) [95% CI]				
In the hospital	42 (26.6) [20.3 to 34.0]	32 (20.8) [15.1 to 27.9]	ARR, 4.8 (−5.1 to 14.7)	.35[f]
At 28 d	34 (21.5) [15.8 to 28.6]	24 (15.6) [10.7 to 22.1]	ARR, 5.9 (−3.4 to 14.8)	.24[f]
At 6 mo	51 (32.3) [25.5 to 39.9]	43 (27.9) [21.4 to 35.5]	ARR, 4.4 (−6.1 to 14.8)	.48[f]

Abbreviations: ARR, absolute risk reduction; IQR, interquartile range; MD, median difference.

[a] Data are expressed as median (IQR) unless otherwise indicated. Only the complete cases were analyzed. Missing values were not imputed.

[b] The MDs were obtained using bootstrapping. The ARRs were obtained using the Mantel-Haenszel test and were adjusted for stratification.

[c] Evaluates functional status and is composed of 10 variables describing activities of daily living and mobility. The score range is 0 to 100 and a higher score indicates greater independence.

[d] Assessed using the Mann-Whitney test, which was adjusted for stratification.

[e] Evaluates health-related quality of life. Each item has a score range from 0 to 100; a higher score indicates better self-reported health.

[f] Assessed using the Mantel-Haenszel χ^2 test, which was adjusted for stratification. The Breslow-Day test was used to assess homogeneity across strata.

care group (median difference, 0 [95% CI, −1 to 2], *P* = .52). None of the secondary outcome measures assessed at ICU discharge yielded significant between-group differences (**Table 2**). Similarly, there were no significant between-group differences in the secondary outcome measures assessed at 6 months (**Table 3**).

Adverse Events

The frequency of clinically significant events (≥1 event) that occurred during mobilization sessions and needed therapeutic interventions (beyond simple session interruption) was numerically similar between groups (7 patients [4.4%] in the intervention group and 9 patients [5.8%] in the usual care group). Among patients in the intervention group, 2 experienced adverse events that were directly attributable to the mobilization sessions (1 skin allergy to electrode pads used for electrical muscle stimulation and 1 unplanned extubation during an in-bed passive cycling session that needed immediate reintubation) compared with none in the usual care group (Supplement 2).

Planned Per-Protocol and Subgroup Analyses

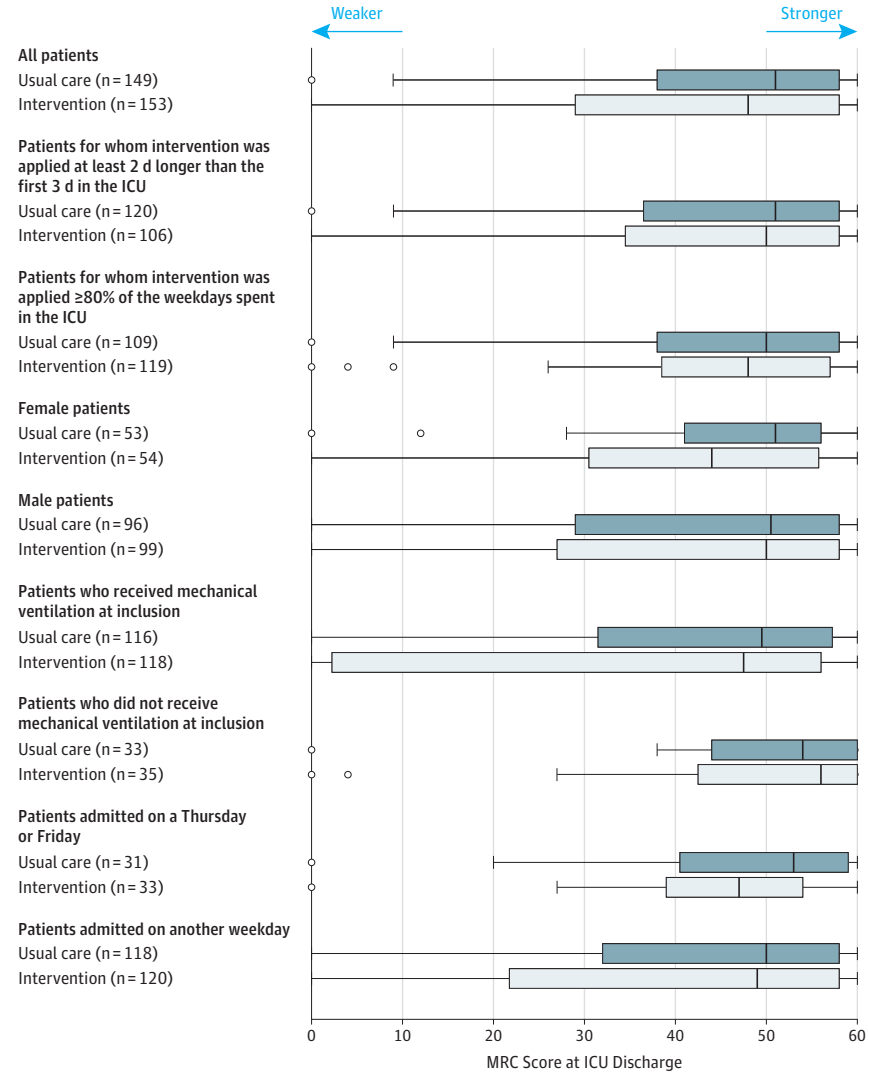
None of the interaction tests was significant between the interventions and for any of the patient characteristics used for stratification or defining patient subsets for the per-protocol analyses (eTable 3 in Supplement 2). These interaction tests may have been underpowered. The results of the subgroup analyses appear in **Figure 2** and should be considered exploratory regarding the primary outcome measure (eTable 4 in Supplement 2). The complete results for the secondary outcome measures appear in eTables 5 through 12 in Supplement 2.

Discussion

The main finding of this single-center clinical trial was that among patients admitted to the ICU, early in-bed cycling and electrical stimulation of the quadriceps muscles added to early rehabilitation compared with early rehabilitation alone did not result in improved global muscle strength as assessed by the MRC score at ICU discharge. The study also showed no significant differences in important secondary outcomes such as the number of ventilator-free days or self-reported quality of life at 6 months as reflected by the physical and mental components of the 36-Item Short Form Health Survey questionnaire.

There are not many large randomized clinical trials that have examined the effects of in-bed leg cycling or electrical stimulation of the quadriceps muscles applied early during the ICU stay, and none have studied the combination of

Figure 2. Box Plots of Medical Research Council Muscle Strength Score by Randomization Group



ICU indicates intensive care unit.

In these box-and-whisker plots, the middle vertical line represents the median; the horizontal lines extend from the minimum to the maximum value, excluding outside values, which are displayed as separate open circle points. The outside values are smaller than the lower quartile minus 1.5 times the interquartile range or are larger than the upper quartile plus 1.5 times the interquartile range. The Medical Research Council (MRC) score[12] reflects the strength of the muscle groups used to mobilize joints on both sides of the body from 0 (no visible contraction) to 5 (normal strength). The joint motions examined were shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion. The overall score range is from 0 to 60. This graph excludes 5 surviving patients in each group in whom the primary outcome could not be assessed. The patients who died in the ICU were assigned a value of 0 for the MRC score. The randomized intervention group × subgroup interaction was tested using the aligned rank transform test and no plausible interactions were found. The results of the comparisons between the intervention group and the usual care group within each subgroup appear in eTable 4 in Supplement 2.

both interventions. Burtin et al[6] showed that when applied each weekday to stable patients starting on the fifth day in the ICU, a 20-minute cycling exercise was able to improve the 6-minute walking distance, the quadriceps force, and the patient-reported functional status at hospital discharge; however, longer-term functional status was not reported. The single-center study findings[6] were obtained in 58 patients and should be investigated further.

Inconsistent results have been reported regarding muscle mass preservation with electrical muscle stimulation in ICU patients.[7,27,28] The most recent randomized trials with assessor-blinded ultrasound measurement of the thickness layers of the quadriceps seemed to confirm that electrical muscle stimulation could minimize critical illness-induced muscle mass loss.[7,28]

In parallel with this effect on muscle mass, a positive effect on functional outcomes like muscle strength might be expected. However, the available trials reported contradictory results. Trials without blinded assessment showed that electrical muscle stimulation had a positive effect on muscle strength measured either during the ICU stay or at ICU or hospital discharge.[11,27] In contrast, trials in which muscle strength was assessed by investigators blinded to treatment allocation did not show such an effect.[29,30]

One of these studies, which was performed in 128 patients,[30] showed encouraging but nonsignificant findings suggesting better outcomes with electrical muscle stimulation, however, this study may have been underpowered. Based on these observations, the hypothesis of the current study was that combining both interventions of in-bed cycling and electrical stimulation of the lower limbs could potentially lead to better preservation of muscle strength than observed in the above-cited studies. The study findings did not confirm this hypothesis.

It is possible that among the most fragile patients with severe inflammation-induced muscle protein breakdown, early additional muscle exercises are unlikely to improve muscle function. The results of recent clinical trials published since the current study was launched in 2014 have called

into question the efficacy of standardized early rehabilitation programs similar to the one used in the present study, which was based on the program of Schweickert et al[4] and was recommended by French national guidelines.[31]

In the study by Moss et al,[32] an intensive physical therapy program, which closely resembled the approach used for usual care in the present study except it was applied later (on the eighth day), failed to improve functional status at 1, 3, and 6 months. In the study by Morris et al,[33] such intensive physical therapy, which additionally comprised resistance exercises as early as on the fourth day, also failed to improve muscle strength and functional status at hospital discharge.

However, conflicting results[34] were found among ICU patients who underwent surgery and were receiving mechanical ventilation. The early, goal-directed mobilization program was tailored to each patient and it improved functional mobility at hospital discharge. In addition, a meta-analysis[5] showed that active mobilization may at least improve muscle strength at ICU discharge as assessed using the MRC score.

Regarding the observation in the current study of no significant difference in long-term outcomes such as functional status and perceived quality of life at 6 months, another possible explanation could be that the combination of interventions was applied only during the ICU stay. A positive effect on muscle function was not apparent at ICU discharge. However, because muscle function assessment through the MRC score may have been affected by a ceiling effect,[35] a positive effect may still have existed and may have been attenuated during the days spent in the hospital without intensive rehabilitation.

Data have suggested that ICU survivors may derive benefit from systematic rehabilitation while receiving treatment during stays in the general hospital ward.[33,36] However, these findings were contradicted by other randomized trials.[32,37]

In the present study, because the ethical committee allowed proxy consent in accordance with French law for low-risk studies, the very early application of interventions was made possible, resulting in a median time between ICU admission and first intervention of approximately 30 hours in both groups. This could explain why the encouraging results from the study by Burtin et al,[6] in which cycling exercises began only from the fifth day after admission, were not confirmed. It is possible that repeatedly attempting to stimulate muscles that still were in a catabolic phase may have been ineffective or even deleterious. Recent observational data suggesting that electrical stimulation may be beneficial only when applied from the seventh day[7] could indirectly support this view.

Therefore, a wide range of questions remains unanswered regarding the timing, safety, efficacy, and modalities of physical rehabilitation for ICU patients. Potential long-term benefits that ICU patients may derive from daily basic rehabilitation as described by Schweickert et al[4] and used as standard care in the present study should be further investigated. Physiological studies should aim at identifying patients most likely to derive benefit from resistance muscle exercises beyond those necessary to achieve basic needs during the ICU stay.

Limitations

This study has several limitations. First, this was a single-center study and the findings may not be generalizable to other settings. However, the single-center setting also might be seen as a strength because the sedation and ventilator weaning protocols were similar in both groups.

Second, the MRC score may not have been the ideal tool to assess physical status. Twenty-five percent of the patients had an MRC score higher than 58 at ICU discharge. The highest possible score is 60 points so this suggests that a ceiling effect[35] could have prevented detection of between-group differences among patients with high MRC scores. However, such a hypothetical difference did not result in better self-perceived health status at 6-month follow-up.

Third, because the study population was mostly composed of nonsurgical patients with sepsis, the findings may not be generalizable to other patient categories. Fourth, the insufficient sample size prevented any meaningful interpretation of the subgroups analyses.

Fifth, to account for informative missingness, the recommended method used in this study consisted of assigning the worst rank of MRC score[22] (the primary outcome measure) to the patients who died in the ICU and whose death precluded the assessment of the MRC score at ICU discharge. This required assumptions to be made regarding the direction and size of the effect of the intervention on the risk of death in the ICU. The assumption made (ie, a marginally favorable effect of the tested intervention on survival in the ICU) may have been incorrect and have led to an overestimation in the power of the study.

Sixth, a weak point in the study design was the lack of longitudinal assessment of the MRC score during the ICU stay, which would have allowed the joint analyses[38] of the MRC score trajectory and the cumulative incidence of death in the ICU.

Conclusions

In this single-center randomized clinical trial involving patients admitted to the ICU, adding early in-bed leg cycling exercises and electrical stimulation of the quadriceps muscles to a standardized early rehabilitation program did not improve global muscle strength at discharge from the ICU.

ARTICLE INFORMATION

Corresponding Author: Thierry Boulain, MD, Service de Médecine Intensive Réanimation, Centre Hospitalier Régional d'Orléans, 14 Boulevard de l'Hôpital, F-45100 Orléans, France (thierry.boulain@chr-orleans.fr).

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Author Contributions: Dr Boulain had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Fossat, Baudin, Boulain.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Fossat, Baudin, Boulain.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Boulain.
Administrative, technical, or material support: Fossat, Baudin, Bretagnol, Benzekri-Lefèvre, Bercault, Barbier, Nay, Mathonnet, Boulain.
Supervision: Kamel, Boulain.

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