



OPEN ACCESS

Original research

Functional electrical stimulation-assisted cycle ergometry-based progressive mobility programme for mechanically ventilated patients: randomised controlled trial with 6 months follow-up

Petr Waldauf,¹ Natálie Hrušková,² Barbora Blahutová ,¹ Jan Gojda,³ Tomáš Urban,¹ Adéla Krajčová,¹ Michal Fric,¹ Kateřina Jiroutková,¹ Kamila Řasová,² František Duška ¹

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2020-215755>).

For numbered affiliations see end of article.

Correspondence to

Dr František Duška, Fac Med 3, Charles University, PRAGUE, Czech Republic, Czech Republic; frantisek.duska@lf3.cuni.cz

Received 7 July 2020
Revised 15 March 2021
Accepted 6 April 2021
Published Online First
30 April 2021



► <http://dx.doi.org/10.1136/thoraxjnl-2020-215093>
► <http://dx.doi.org/10.1136/thoraxjnl-2021-217009>



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Waldauf P, Hrušková N, Blahutová B, et al. *Thorax* 2021;**76**:664–671.

ABSTRACT

Purpose Functional electrical stimulation-assisted cycle ergometry (FESCE) enables in-bed leg exercise independently of patients' volition. We hypothesised that early use of FESCE-based progressive mobility programme improves physical function in survivors of critical care after 6 months.

Methods We enrolled mechanically ventilated adults estimated to need >7 days of intensive care unit (ICU) stay into an assessor-blinded single centre randomised controlled trial to receive either FESCE-based protocolised or standard rehabilitation that continued up to day 28 or ICU discharge.

Results We randomised in 1:1 ratio 150 patients (age 61±15 years, Acute Physiology and Chronic Health Evaluation II 21±7) at a median of 21 (IQR 19–43) hours after admission to ICU. Mean rehabilitation duration of rehabilitation delivered to intervention versus control group was 82 (IQR 66–97) versus 53 (IQR 50–57) min per treatment day, $p<0.001$. At 6 months 42 (56%) and 46 (61%) patients in interventional and control groups, respectively, were alive and available to follow-up (81.5% of prespecified sample size). Their Physical Component Summary of SF-36 (primary outcome) was not different at 6 months (50 (IQR 21–69) vs 49 (IQR 26–77); $p=0.26$). At ICU discharge, there were no differences in the ICU length of stay, functional performance, rectus femoris cross-sectional diameter or muscle power despite the daily nitrogen balance was being 0.6 (95% CI 0.2 to 1.0; $p=0.004$) gN/m² less negative in the intervention group.

Conclusion Early delivery of FESCE-based protocolised rehabilitation to ICU patients does not improve physical functioning at 6 months in survivors.

Trial registration number NCT02864745.

INTRODUCTION

Preserving independent functioning and acceptable quality of life is as important as survival for most patients in intensive care. Unfortunately, functional disability, a natural consequence of weakness, is a frequent and long-lasting complication in survivors of critical illness.^{1,2} Minimising sedation and a culture of early mobility has potential to reduce long-term sequelae of critical illness.^{3–5}

Key messages

What is the key question?

► Functional-electrical stimulation cycle ergometry allows delivery of exercise to patients who are sedated and unconscious and can enhance progressive mobility programme, but its effects on patients-centred outcomes are unknown.

What is the bottom line?

► Application of very early intensive cycling-based progressive mobility programmes to intensive care unit (ICU)-long stayers did not improve muscle mass and power in ICU or physical function at 6 months.

Why read on?

► This is the first large randomised controlled trial on the use of early cycling-based protocolised rehabilitation in the critically ill.

Protocolised physical therapy has been shown to reduce the duration of mechanical ventilation and intensive care unit (ICU) length of stay,⁶ but these benefits are not consistently translated into improved long-term functional outcomes.^{7–10} The delivery of protocolised physical therapy requires the concomitant presence of a cooperative patient and a trained physiotherapist, often a precious resource in the ICU. In turn, implementation of early mobility strategies may fail in randomised controlled trials and in clinical practice. Only six randomised controlled trials out of 43 published to date in the field reported data of protocol implementation.⁶ Moreover, during acute critical illness no active exercise can be delivered.^{11,12} Yet, immobility-associated muscle loss is evident as early as within 18–48 hours of onset of acute critical illness^{13,14} and during the first week patients lose 10%–20% of rectus femoris muscle cross-sectional diameter¹⁵ and up to 40% of muscle strength.¹⁶

Neuromuscular electrical stimulation (NMES) may mimic active exercise in patients, who lack voluntary muscle activity.^{17–25} During NMES, cutaneous electrodes placed over specific muscle



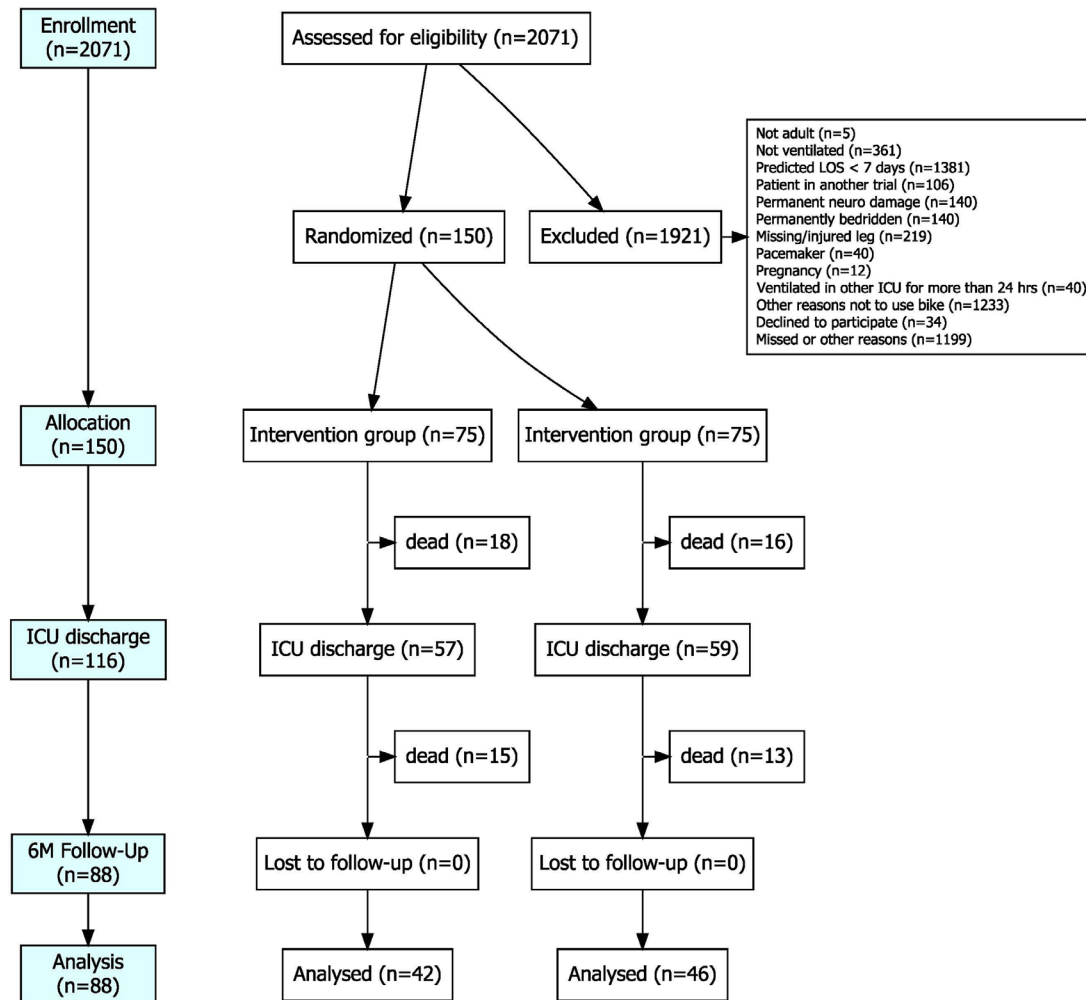


Figure 1 Flowchart of patients enrolled into the trial. Each patient could have one or more reasons not to be included and therefore the sum of reasons exceed the number of patients excluded. Other reasons included missed patients due to logistical reasons or patients who were deemed unlikely to survive; all patients who had been enrolled based on legal representative assent and regained capacity, gave written informed consent by the end of the follow-up period. ICU, intensive care unit; LOS, length of stay

groups electrically trigger muscle contractions. Passive cycling and NMES can be delivered simultaneously and synchronised to produce a coordinated pattern of movements (see online supplemental video 1) and increase whole-body energy expenditure.²⁶ The technique is called functional electrical stimulation-assisted cycle ergometry (FESCE). FESCE is beneficial to patients with stroke and spinal cord injuries (reviewed in Doucet *et al*²⁷) as it prevents the loss of muscle mass²⁸ and improved anabolic resistance and insulin sensitivity in quadriplegic patients.^{29 30} In a pilot study, FESCE seems to be safe and feasible in the critically ill.³¹

In the light of this we aimed to test early FESCE-based protocolised rehabilitation in a randomised controlled trial powered to test treatment effects on patient-centred outcomes. We hypothesised that protocolised progressive mobility programme, which includes FESCE and starts within 72 hours after ICU admission, would improve functional outcomes of ICU survivors at 6 months when compared with the standard of care.

METHODS

This was a single centre, prospective, randomised controlled parallel group trial with a blinded outcome assessor, which had been registered prior to enrolling the first patient at www.clinicaltrials.gov and the full protocol has been published.³²

We used a deferred consent procedure, where patients without capacity were enrolled based on assent gained from legal representatives and asked to provide consent as soon as they regained capacity.

Participants

Participants were recruited in two multidisciplinary ICUs of 11 and 10 level three beds, respectively, at tertiary FNKV University Hospital in Prague, Czech Republic. We included adult (≥ 18 years) patients who received mechanical ventilation for less than 72 hours but were predicted to need ICU for a week or more. We excluded patients bedridden before ICU admission, with missing or injured lower limbs, irreversible paralysis or those with pacemakers (see online supplemental appendix 1 for full list of eligibility criteria).

Standard care group

Both groups received usual best medical and nursing care in the ICU, which included daily sedation holds when applicable, respiratory physiotherapy and management as usual in the routine practice. Both groups received standard physiotherapy delivered

Table 1 Study subject characteristics

Baseline characteristics		Intervention (n=75)	Control (n=75)	P value
Demographic	Sex male/female (% male)	53/22 (71%)	57/18 (76%)	0.46
	Age (years)	59.9±15.1	62.3±15.4	0.34
	Body mass index (kg/m ²)	29.3±6.3	30.7±8.3	0.24
Pre-admission health and function	Charlson Comorbidity Score	2.8±2.3	3.4±2.4	0.15
	Physical activity (RAPA score)	1 (IQR 1–3)	2 (IQR 1–5)	0.17
	Level of independence (IAPA score)	8 (IQR 7–8)	8 (IQR 7–8)	0.52
Current disease severity	Sepsis on admission (n, %)	19 (25.3%)	18 (24.0%)	0.85
	APACHE II	22.1±5.2	22.2±7.7	0.91
	SOFA score at enrolment	8.8±2.6	8.8±3.2	0.89
Primary reason for admission	Respiratory failure (COPD, pneumonia)	20 (27%)	17 (23%)	0.7
	Isolated TBI	16 (21%)	10 (13%)	0.28
	Multiple trauma with TBI	12 (16%)	9 (12%)	0.64
	Multiple trauma without TBI	2 (3%)	5 (7%)	0.44
	Septic shock (non-respiratory)	8 (11%)	10 (13%)	0.8
	Out-of-hospital cardiac arrest	5 (7%)	6 (8%)	1
	Haemorrhagic stroke (operated)	2 (3%)	6 (8%)	0.28
	Congestive heart failure	2 (3%)	4 (5%)	0.68
	Haemorrhagic shock, non-traumatic	1 (1%)	3 (4%)	0.62
	Meningitis, encephalitis	2 (3%)	2 (3%)	1
	Other diagnoses	5 (7%)	3 (4%)	0.72
	Time from admission to enrolment (hours)*		31.5±19.0	30.8±17.4

CCS³¹; IAPA ranges 0–8 with higher number meaning higher functional independence³²; RAPA score ranges from 1 'I almost never do any physical activities' to 5 'I do 30 min or more per day of moderate physical activity 5 or more days per week'³³.

*Intervention began next calendar day after enrolment.

APACHE, Acute Physiology and Chronic Health Evaluation; CCS, Charlson Comorbidity Score; IAPA, Instrumental Activities Of Daily Living Scale; RAPA, Rapid Assessment of Physical Activity; SOFA, Sequential Organ Failure Assessment; TBI, traumatic brain injury.

two times a day 6 days in a week in a routine way by physiotherapists not involved in the study and adhering to the published safety criteria.³³ Most importantly, a fraction of inspired oxygen less than 0.6 with a percutaneous oxygen saturation more than 90% and a respiratory rate less than 30 breaths/min and normal and stable intracranial pressure (ICP) were required for in-bed and out-of-bed mobilisation. In the control group the therapy was initiated on request of the treating physician and was documented, but not protocolised. It included passive and active range of motion, application of stretch reflex to upper and lower extremities and activation of global motor response according to Vojta reflex locomotion, positioning in bed, sitting, mobility activities progressing from activity in-bed to out-of-bed activities such as up to chair or ambulation, multi-component intervention (eg, combination with respiratory physiotherapy) and education.

Intervention group

The intervention began the calendar day after randomisation and consisted of a progressive mobility programme tailored to patients' condition and supplemented by the use of FESCE (online supplemental table 1). The goal was to deliver a total of 90 min of active exercise a day until ICU discharge or day 28 whichever occurred earlier. Early in the course of the disease the intervention included FESCE (RT300 System, Restorative Therapies 2005-2016. LB100108 V.37).³¹ See online supplemental appendix 1—online supplemental table 1 for details. In brief, after warm-up phase (5 min of passive cycling), patients received therapy consisting of functional electrical stimulation or active cycling with duration adjusted per protocol and patient's

tolerance) followed by relaxation phase (5 min of passive cycling). FES impulses had pulse width 250 μ s, pulse frequency 40 Hz and the lowest output per channel (in a range 0–60 mA) that allowed locomotive movement of lower extremities. Once the patient was more alert and able to participate, they were encouraged to engage in therapy. To increase the intervention workload, both resistance (3–10 Nm) and cycling cadence were increased incrementally. Face-to-face individual therapy was delivered two times a day by a certified physical therapist (MSc) specially trained in FESCE application in ICU.

Measures to ensure protocol implementation

Study physiotherapists (NH, KR) were appointed as 1.8 full working time equivalent specifically for this study and delivered the intervention 7 days/week. Throughout the study, 20 randomly selected exercise sessions were monitored by a hidden observer to ensure reliability and consistency of protocol implementation data reported by physiotherapists. Rehabilitation after discharge from ICU was not altered nor monitored in either group. Data on safety outcomes (ICP elevation, dialysis interruptions) were collected from clinical information system Metavision V.5, iMDsoft, Israel. A multi-step approach was used to minimise number of patients lost to follow-up (see online supplemental appendix 1 for more details).

Outcomes

The primary outcome of this trial was the Physical Component Summary (PCS) score of the SF-36 quality of life questionnaire

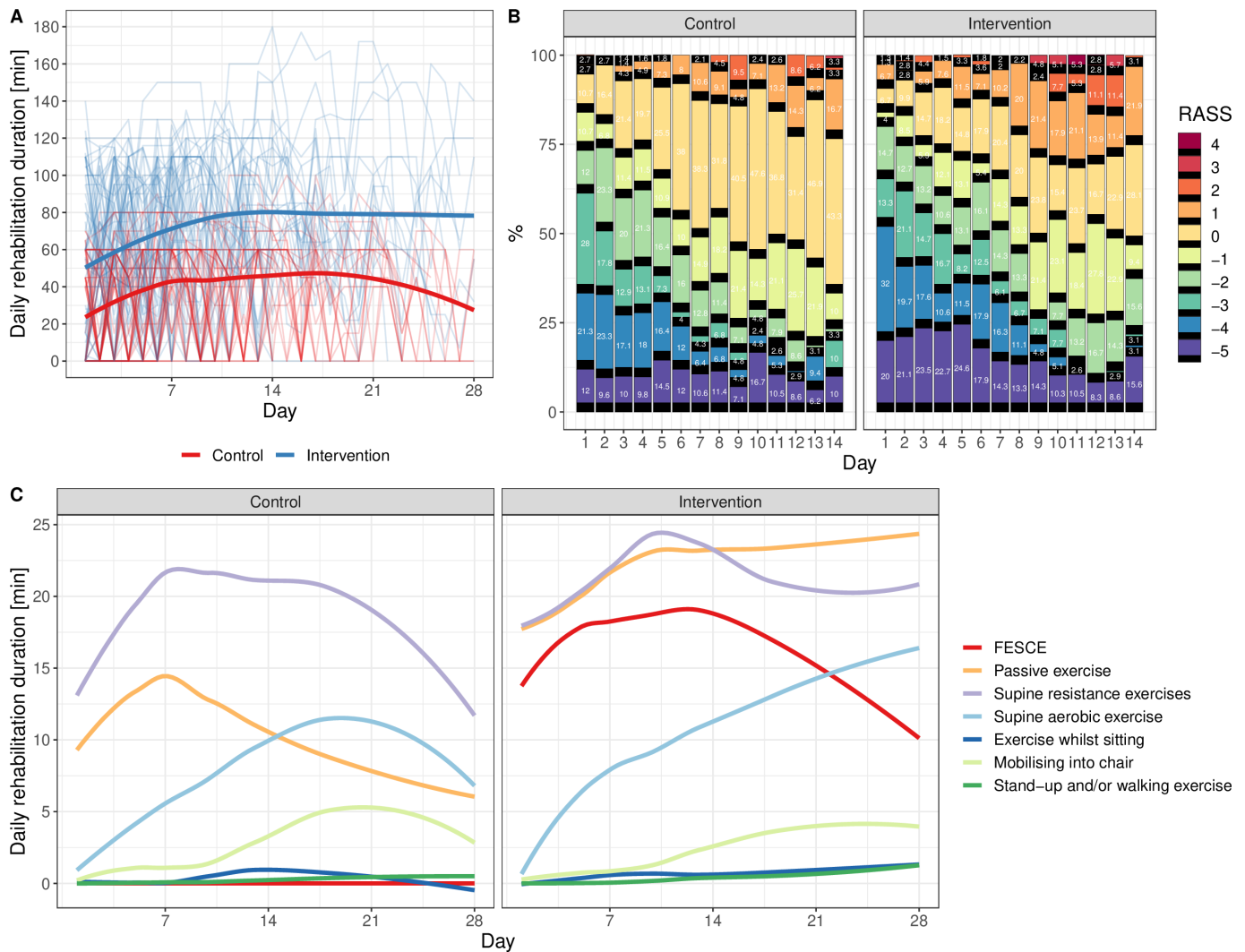


Figure 2 Protocol implementation indices. (A) Average duration of rehabilitation in intervention (blue line) and control (red line) groups in all days of all patients (ie, including days without rehabilitation). Thin lines are individual patients (one outlier received up to 180 min of rehabilitation a day due to protocol violation). (B) Sedation level heatmap. (C) Average types of exercise delivered daily. FESCE, functional electrical stimulation-assisted cycle ergometry; RASS, Richmond Agitation-Sedation Scale, where 0 (alert and calm) or -1 (drowsy) were target levels of sedation management.

measured in ICU survivors at 6 months and calculated as per RAND methodology, V.1.³⁴ Because there was no study in similar population reporting on PCS, we calculated the power of the study based on an important determinant of PCS, which is physical function. Based on the study by Kayambu *et al*,³⁵ where physical function score was 60.0 ± 29.4 points in the control group, 108 patients are required in order to have 80% chance to detect a difference (at $p < 0.05$) a change by 15.8 points or more, which is within the limits determined as clinically important for patients with COPD, asthma and myocardial infarction.³⁶ To compensate for 28% mortality, we aimed to randomise 150 patients. More details on power analysis are in online supplemental appendix 1.

Secondary outcomes were Four-item Physical Fitness in Intensive Care Test (PFIT-s),³⁷ rectus muscle cross-sectional diameter on B-mode ultrasound, mean daily nitrogen balance, muscle power as per the Medical Research Council score, number of ventilator-free days and ICU length of stay, all measured at discharge from ICU or day 28, whichever occurred earlier. Prespecified secondary safety outcomes were the number of episodes of elevated ICP and dialysis interruptions. Detailed

description of secondary outcome assessment is in online supplemental appendix 1.

Randomisation

Eligible patients were randomly assigned (1:1) to receive either standard care or the intervention using offsite independent randomisation protocol embedded in the electronic case report form. Randomisation was stratified according to the presence or absence of sepsis and whether a specific consent was given to be involved in a nested metabolic substudy that included serial muscle biopsies.^{32,38} There were permuted blocks of four in each stratum. Both the study team and clinical personnel were aware of subject treatment allocation. The outcome assessors (JG, BB) were not involved in patient care and remained blinded to treatment allocations.

Statistical methods

The primary outcome and all secondary outcomes were reported as medians (IQR) in an intention-to-treat population and compared between the intervention and standard of care

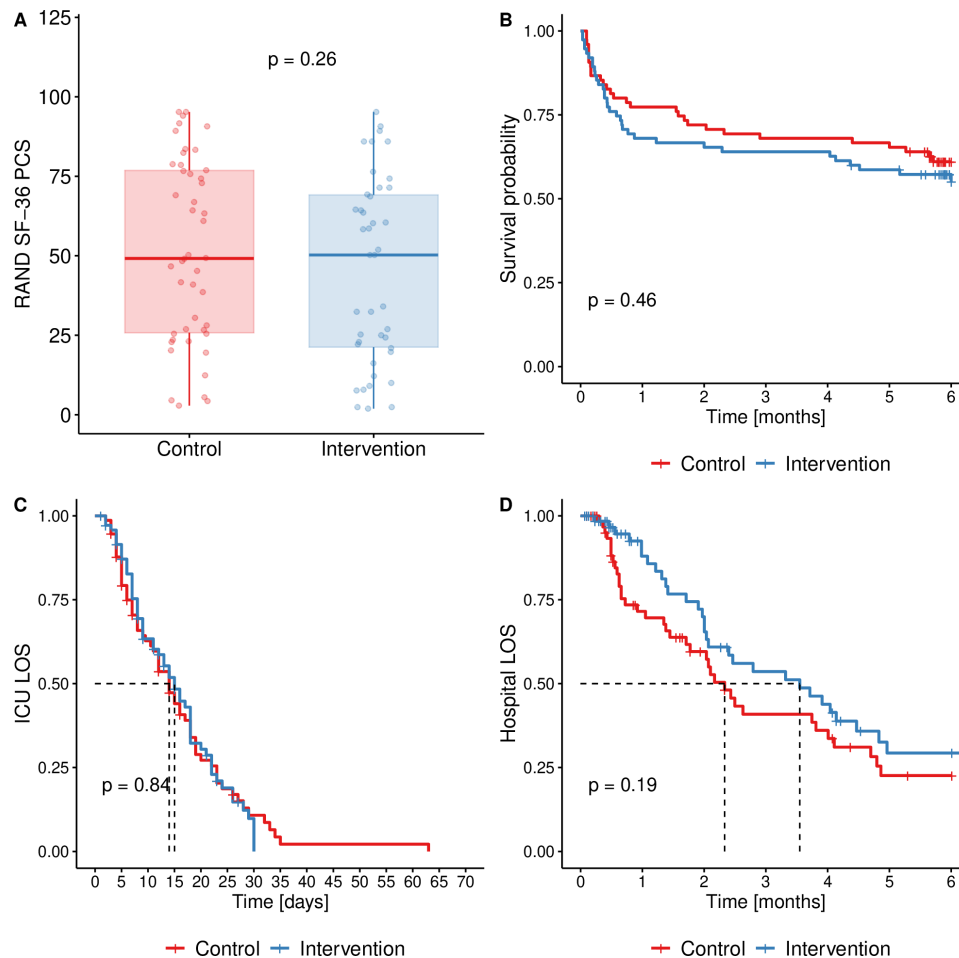


Figure 3 (A) Physical component summary of SF-36 score (primary outcome); (B) Kaplan-Meier curve of survival in the study; (C) Kaplan-Meier curve of patients in the ICU (censored for non-survivors); (D) Kaplan-Meier curve of patients at hospital (censored for non-survivors). P values are from Wilcoxon in (A) and log-rank test in (B), (C) and (D). ICU, intensive care unit; LOS, length of stay; PCS, Physical Component Summary.

groups, with all tests two-sided using the level of significance set at $p < 0.05$. Normality of data distribution was tested by Shapiro-Wilks' test and data are reported as means \pm SD or median (IQR), as appropriate. We used log-rank test for time-to-event analyses, t-test or Wilcoxon test for continuous variables (depending on normality of distribution), and χ^2 for frequency of event comparisons. No imputation of missing data was used. All calculations were performed in R, V.4.0.3 (updated on 10 October 2020) and ggplot2 package was used to create figures.

RESULTS

Between October 2016 and November 2019 (see online supplemental figure 3), 2071 patients were screened in order to enrol the prespecified number of 150 (7.2%) participants into the trial. Participant flow is shown in figure 1 and baseline characteristics of randomised patients in table 1.

Protocol implementation

Patients in intervention and control arms stayed for a median of 12 (IQR 7–21) and 12 (IQR 6–19) days in ICU ($p = 0.76$ log-rank test). Six and eleven patients randomised to intervention and control group, respectively, received no rehabilitation. At least one physiotherapy session was delivered in 817 out of 932 (88%) versus 615 out of 895 (69%) ICU days ($p < 0.001$, χ^2 test) and the first rehabilitation occurred 63 (IQR 45–84) versus 68 (48–95) hours after ICU admission ($p = 0.14$ Wilcoxon) in the

intervention versus control groups, respectively. During the days where rehabilitation was delivered, the median daily duration of it was 82.2 (IQR 65.6–96.6) versus 53.3 (IQR 50.1–57.1) min in the intervention and control group, respectively (median difference 29 min, $p < 0.001$, Wilcoxon test). This included in the intervention group 33 (IQR 22–39) min per treatment day of FESCE (figure 2). Further details on rehabilitation in both groups can be found in online supplemental appendix 1 (online supplemental tables 2A, 2B and 3).

Outcomes

Forty-two (56%) and forty-six (61%) patients were alive and all available to follow-up at 6 months in intervention and control groups, respectively ($p = 0.51$, χ^2 test). This represents 81.5% (88/108) of prespecified sample size. Median physical component score of SF-36 in survivors (primary outcome) was 50 (IQR 21–69) in the intervention group and 49 (IQR 26–77) in controls ($p = 0.261$, Wilcoxon test, see also online supplemental figures 4–6 and Table S5 in online supplemental data file). Patients' in the intervention group had by 0.6 (95% CI 0.2 to 1.0) g/m^2 of body surface area less negative mean daily nitrogen balance ($p = 0.004$, t-test) as compared with control group, in the small subgroup with ICP monitoring in place ($n = 4$ vs 3) more ICP elevations in the interventional (23 elevations/15 ICP days vs 0/15; $p = 0.018$, Wilcoxon test), none of which occur during or immediately after FESCE exercise (see online supplemental

Table 2 Secondary outcomes

Secondary outcomes	Intervention	Standard of care	P value
PFIT-s at ICU discharge	9.4 (8.0 to 10.8) n=37	9.6 (8.3 to 10.9) n=42	0.77*
Rectus muscle diameter at ICU discharge (mean difference from baseline (cm))	-11 (-17 to -6) % n=57	-13 (-19 to -7) % n=54	0.64
MRC score at ICU discharge	42.4 (39.2 to 45.6)	39.4 (36.5 to 42.4)	0.13
Nitrogen balance (gN/m ² /day)	-2.7 (-3.1 to -2.4) n=852 days of 75 patients	-3.4 (-3.7 to -3.0) n (days)=759 days of 75 patients	0.004
Ventilator-free days at D28	9.3 (6.5 to 12.0) n=75	11.0 (8.2 to 13.8) n=75	0.33
Number of untoward dialysis interruptions/days of rehabilitation during dialysis	0/17	0/41	N/A
Numbers of ICP elevations/days with ICP measured	1.5 (0.2 to 2.9) (n=4 patients, 15 ICP days)	0 (n=3 patients, 15 ICP days)	0.018*

Unless stated otherwise, data presented as means (95% CIs) and p values are from t-test.

PFIT-s ranging from 0 to 12 points with lower scores meaning higher degree of disability, see also online supplemental figure 1 and online supplemental table 4 in online supplemental appendix 1.

MRC score ranging from 0 to 60 points with higher scores meaning increasing muscle power.

Bold values indicate statistical significance.

*Wilcoxon test.

ICP, intracranial pressure; ICU, intensive care unit; MRC, Medical Research Council; PFIT-s, Four-item Physical Fitness in Intensive Care Test.

appendix 1). There were no significant differences in any of seven other prespecified secondary outcomes (see figure 3 and table 2).

Ancillary analyses

Of note, although not a prespecified outcome, in the intervention group there was worse mental component summary score of SF-36 at 6 months 54.8 (IQR 37.1–69.6) versus 70.2 (IQR 51.5–81.3), $p=0.009$, Wilcoxon test (see online supplemental figures 5 and 7 in online supplemental appendix 1). Despite neither number of ICU days on pharmacological treatment for delirium (36% vs 37%, $p=0.86$, χ^2 test) nor doses of sedatives (see online supplemental figure 8 in online supplemental appendix 1) were different, patients in the intervention group spent more time in the ICU either agitated or deeply sedated as seen on the heatmap in online supplemental figure 2B and online supplemental table 10 in online supplemental appendix 1.

DISCUSSION

The main finding of this study is that in mechanically ventilated patients with anticipated long ICU length of stay, progressive mobility programme started very early and containing FESCE did not improve physical disability 6 months after surviving critical illness. The intervention led to 0.6 gN/m²/day improvement in nitrogen balance, which during a median of 11 days equals to sparing of approximately 380 g of lean body mass. This did not translate into measurable preservation into leg muscle mass, muscle power, physical fitness at ICU discharge or shortening of mechanical ventilation or ICU stay.

There are only limited number of other randomised controlled trials looking at long term effects on functional outcomes of a rehabilitation intervention delivered in ICU. Randomised controlled trials investigating in-bed cycling only^{39 40} and most studies on progressive mobility programmes^{7–10 41 42} demonstrated no difference in physical health after 6 months. The lack of effect in these trials could have been caused by problems with protocol implementation⁶ as in the only study reporting on duration of rehabilitation that was delivered,⁷ it was only 24% of prescribed duration (22 min vs 90 min per protocol). Largest

trial so far by Morris *et al*⁹ randomised 300 ICU patients very similar to ours to receive up to three sessions of resistance exercise delivered 7 days/week or a standard rehabilitation. There was no effect on the duration of hospital stay (primary outcome) and physical function was identical at hospital discharge; interestingly, patients in the intervention group improved faster after discharge and reached significantly better physical function scores after 6 months.⁹ Kayambu *et al*³⁵ also demonstrated better physical function at 6 months in ICU patients with sepsis exposed to protocolled rehabilitation, but this study is criticised due to small sample size and 40% loss of follow-up. Therefore, when designing our trial, we put emphasis on achieving protocol implementation and minimising loss of follow-up. Indeed, rigorously monitored delivery of exercise and successful protocol implementation is the main strength of this trial. Intervention group received exercise on 88% ICU days (as compared with 66% in the control group, see also online supplemental figure 9) with median duration per treatment day of 82 min with clear and significant separation of the rehabilitation duration from the control group. Despite successful implementation, we failed to demonstrate short-term or long-term effects, with the exception of the slight improvement of nitrogen economy. Preservation of lean body mass could be clinically meaningful, but in our study, it occurred unaccompanied by any signal of improvement of muscle function and its significance is therefore questionable. Indeed, the difference could have also occurred by chance due to multiple testing.

The lack of effect of the intervention could have been caused by multiple factors. First, median rehabilitation duration in our control group of 53 min per treatment day was far longer than expected and rare among rehabilitation trials.⁴³ Our patients were discharged from ICU in better functional status (higher PFIT-s scores) than in other trials,^{44 45} which could mean that our discharge policy is conservative or reflect the fact that the rehabilitation in the control group was effective and FESCE-based intervention added no further benefit. On the same note, if rehabilitation delivered to the control group was close to the tolerable maximum, the intervention could have overstretched physiological reserves of some patients and offset potential

benefits. In a study on healthy volunteers²⁶ we have found that unloaded FESCE as used in our study can lead to aerobic lactate production and increase whole-body energy to $138\pm 29\%$ and leg blood flow to $160\pm 30\%$ of baseline, analogously to 25 W aerobic exercise. In contrast, physical therapy in the critically ill is known to cause very little increase in energy expenditure only analogous to 6 W exercise.⁴⁶ Second, as shown in figure 2, in the intervention group there were more patients who were either agitated or unresponsive, possibly due to unequal distribution of patients with traumatic brain injury at baseline (37% vs 25%, in the intervention vs control groups, respectively $p=0.11$). Therefore, the increment in the duration of rehabilitation in the interventional group mostly consisted of passive elements of therapy (for details see online supplemental appendix 1) while out of bed mobilisation therapy duration was very similar to control group.

With regards of safety of the intervention, during 1000 FESCE sessions delivered to ICU patients, we have not observed any immediate impairment of cardiorespiratory function nor dialysis malfunction. We aimed to specifically look at safety of FESCE in patients with neurological injuries and allowed the intervention in patients with ICP monitoring in place, provided that ICP was normal and stable and the patient had not been receiving any second-tier therapy. The subgroup of enrolled patients with ICP monitoring in place was small ($n=7$) and we have not observed any immediate effect of FESCE or control rehabilitation on ICP. In line, none of the sessions had to be interrupted due to ICP elevation. Nonetheless, delayed ICP elevations only occurred in the intervention group and after 6 months mental health as well as emotional and social functions were worse in interventional compared with control group. The use of sedatives and antipsychotics was not different between groups offering no explanation for these phenomena. It should be stressed that mental function after 6 months was measured as a part of SF-36 score, but on its own it was not a prespecified secondary outcome and the difference may have occurred by chance. Nonetheless, we cannot rule out that the use of FESCE itself was responsible for the impairment of central nervous system function, as progressive mobility programme alone was safe in neuro patients⁴⁷ or led to improvement of mental functions in unselected ICU patients.³⁹ In the most recent multicentre RCT of Berney *et al*³⁴ randomised 162 patients with sepsis or systemic inflammation to receive 60 min/day of FESCE in addition to usual rehabilitation or usual rehabilitation alone (median of 15 min of active exercise per day). FESCE was delivered for a median of 53 min per day for a median of 5 days in the intervention group, there was no difference in muscle strength at hospital discharge and no major adverse events. Patients with neurological injuries at baseline had been excluded from Berney *et al*'s study. Although underpowered, this trial also did not demonstrate any influence of the intervention on the incidence of cognitive impairment at 6 months, in keeping with our results.

Indeed, although our study adds important knowledge to the field, its limitations are to be recognised, too. Due to higher-than-expected mortality (in fact, 41% of enrolled patients were not alive after 6 months) the study only achieved 81.5% of the prespecified sample size evaluated for primary outcome (88 out of 108) and it is therefore underpowered. In addition, our sample size was based on surrogate physical function in the control group of 16 patients in the study of Kayambu.³⁵ Based on data in our study ($PCS=51.7\pm 28.8$ in the control group), 133 patients would be needed to demonstrate 15 points difference in PCS at $\alpha=0.8$ and $p<0.05$. The generalisability of our results is limited by single-centre design and relatively very intensive exercise in the control group. It is possible and likely

that in different clinical environment with less intense rehabilitation in the control group, results would be different. In addition, we have not controlled nor monitored patient recovery pathway between ICU discharge and collection of the primary outcome.

Future outcome-based trials should certainly put emphasis on delivering progressive mobility element in the interventional group, enrol more homogeneous and specific patients' populations.³⁷ So far, the safety of FESCE-based is uncertain in patients with neurological injuries and needs investigation. There is also a burning need for studies focused on understanding physiology of FES-triggered contraction of healthy muscle versus muscle altered by underlying critical illness.³ In the meantime, protocolised physical therapy delivered by appropriately trained personnel remains the only evidence-based intervention to shorten duration of ICU stay and possibly improve long-term outcomes.

In conclusion, early FESCE-based protocolised physiotherapy delivered to mechanically ventilated patients does not change PCS score 6 months after discharge, nor duration of mechanical ventilation or any parameters of skeletal muscle mass, power and function at ICU discharge, apart from borderline improvement of nitrogen balance. These results must be interpreted in the context of very high dose and early start of rehabilitation in the control group, and relatively good physical functional status achieved by patients in the control group compared with other studies of long-stay ICU patients.

Author affiliations

¹Department of Anaesthesiology and Intensive Care Medicine, 3rd Faculty of Medicine and FNKV University Hospital, Charles University, Prague, Czech Republic

²Department of Rehabilitation, 3rd Faculty of Medicine and FNKV University Hospital, Charles University, Prague, Czech Republic

³Department of Internal Medicine, 3rd Faculty of Medicine and FNKV University Hospital, Charles University, Prague, Czech Republic

Twitter František Duška @FrantaDuska

Acknowledgements We thank the team of physiotherapists and research nurses, namely Marie Hejnová, Irena Kozáková, Jana Kukulová, Šárka Gregorová, Šárka Vosalová and Kateřina Topková. The study was funded exclusively from Agentura pro zdravotnický výzkum (grant agency of Czech Ministry of Health) AZV number 16-28663A.

Contributors PW and FD are the authors of the main idea and overlooked the conduct of the study. PW, KJ and MF were responsible for consenting and recruiting patients and performing clinical procedures. PW is data analyst and biostatistician. NH and KR are the study physiotherapists. JG and BB were blinded outcome assessors. All authors have access to record-level data and have seen and approved the final version of the manuscript.

Funding Grant Agency for Research in Healthcare AZV 16-28663A, email info@azvcr.cz ISDS: f7eike4, Phone: +420 271 019 257 For updated contact details, see <http://www.azvcr.cz/kontakt>.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The trial design is in accordance with Declaration of Helsinki and the protocol, care report form and informed consent formularies were reviewed and approved by FNKV University Hospital Research Ethics Board ('Ethical Committee') on 24 June 2015 (decision number EK-VP-27-0-2015). All patients or their legal representatives gave their prospective written informed consent to participate in the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. We will sent de-identified patient-level data upon reasonable request to the corresponding author.

Author note FD, KAR FNKV, Charles University, Fac Med 3, Srobarova 50, 10034 Prague, Czech Republic. Phone: +420267162451, Email: frantisek.duska@lf3.cuni.cz.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which

permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Barbora Blahutova <http://orcid.org/0000-0003-1617-0656>
František Duška <http://orcid.org/0000-0003-1559-4078>

REFERENCES

- Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364:1293–304.
- Herridge MS, Moss M, Hough CL, et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. *Intensive Care Med* 2016;42:725–38.
- Herridge MS, Mobile HMS. Mobile, awake and critically ill. *CMAJ* 2008;178:725–6.
- Needham DM. Mobilizing patients in the intensive care unit: improving neuromuscular weakness and physical function. *JAMA* 2008;300:1685–90.
- Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. *N Engl J Med* 2014;370:1626–35.
- Waldauf P, Jiroutková K, Krajčová A, et al. Effects of rehabilitation interventions on clinical outcomes in critically ill patients: systematic review and meta-analysis of randomized controlled trials. *Crit Care Med* 2020;48:1055–65.
- Wright SE, Thomas K, Watson G, et al. Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial. *Thorax* 2018;73:213–21.
- Hodgson CL, Bailey M, Bellomo R, et al. A binational multicenter pilot feasibility randomized controlled trial of early goal-directed mobilization in the ICU. *Crit Care Med* 2016;44:1145–52.
- Morris PE, Berry MJ, Files DC, et al. Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: a randomized clinical trial. *JAMA* 2016;315:2694.
- Moss M, Nordon-Craft A, Malone D, et al. A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. *Am J Respir Crit Care Med* 2016;193:1101–10.
- Bailey P, Thomsen GE, Spuhler VJ, et al. Early activity is feasible and safe in respiratory failure patients. *Crit Care Med* 2007;35:139–45.
- Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009;373:1874–82.
- Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* 2008;358:1327–35.
- Hermans G, De Jonghe B, Bruyninckx F, et al. Clinical review: critical illness polyneuropathy and myopathy. *Crit Care* 2008;12:238.
- Puthucherry ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. *JAMA* 2013;310:1591–600.
- Topp R, Ditmyer M, King K, et al. The effect of bed rest and potential of prehabilitation on patients in the intensive care unit. *AACN Clin Issues* 2002;13:263–76.
- Zanotti E, Felicetti G, Maini M, et al. Peripheral muscle strength training in bed-bound patients with COPD receiving mechanical ventilation: effect of electrical stimulation. *Chest* 2003;124:292–6.
- Gerovasili V, Stefanidis K, Vitzilaios K, et al. Electrical muscle stimulation preserves the muscle mass of critically ill patients: a randomized study. *Crit Care* 2009;13:R161.
- Routsis C, Gerovasili V, Vasileiadis I, et al. Electrical muscle stimulation prevents critical illness polyneuropathy: a randomized parallel intervention trial. *Crit Care* 2010;14:R74.
- Abu-Khabeer HA, Abouelela AMZ, Abdelkarim EM. Effect of electrical muscle stimulation on prevention of ICU acquired muscle weakness and facilitating weaning from mechanical ventilation. *Alexandria J Med* 2013;49:309–15.
- Kho ME, Truong AD, Zanni JM, et al. Neuromuscular electrical stimulation in mechanically ventilated patients: a randomized, sham-controlled pilot trial with blinded outcome assessment. *J Crit Care* 2015;30:32–9.
- Goll M, Wollersheim T, Haas K, et al. Randomised controlled trial using daily electrical muscle stimulation (EMS) in critically ill patients to prevent intensive care unit (ICU) acquired weakness (ICUAW). *Intensive Care Med Exp* 2015;3:1–2.
- Fischer A, Spiegl M, Altmann K, et al. Muscle mass, strength and functional outcomes in critically ill patients after cardiothoracic surgery: does neuromuscular electrical stimulation help? the Catastim 2 randomized controlled trial. *Crit Care* 2016;20:1–13.
- Fontes Cerqueira TC, Cerqueira Neto MLde, Cacao LdeAP, et al. Ambulation capacity and functional outcome in patients undergoing neuromuscular electrical stimulation after cardiac valve surgery: a randomised clinical trial. *Medicine* 2018;97:e13012.
- Koçan Kurtoğlu D, Tastekin N, Birtane M, et al. Effectiveness of neuromuscular electrical stimulation on auxiliary respiratory muscles in patients with chronic obstructive pulmonary disease treated in the intensive care unit. *Turk J Phys Med Rehab* 2015;61:12–17.
- Gojda J, Waldauf P, Hrušková N, et al. Lactate production without hypoxia in skeletal muscle during electrical cycling: crossover study of femoral venous-arterial differences in healthy volunteers. *PLoS One* 2019;14:e0200228.
- Doucet BM, Lam A, Griffin L. Neuromuscular electrical stimulation for skeletal muscle function. *Yale J Biol Med* 2012;85:201–15.
- Bauman WA, Spungen AM, Adkins RH, et al. Metabolic and endocrine changes in persons aging with spinal cord injury. *Assist Technol* 1999;11:88–96.
- Kjaer M, Pollack SF, Mohr T, et al. Regulation of glucose turnover and hormonal responses during electrical cycling in tetraplegic humans. *Am J Physiol* 1996;271:R191–9.
- Gorgey AS, Dolbow DR, Dolbow JD, et al. The effects of electrical stimulation on body composition and metabolic profile after spinal cord injury—Part II. *J Spinal Cord Med* 2015;38:23–37.
- Parry SM, Berney S, Warrillow S, et al. Functional electrical stimulation with cycling in the critically ill: a pilot case-matched control study. *J Crit Care* 2014;29:695.e1–695.e7.
- Waldauf P, Gojda J, Urban T, et al. Functional electrical stimulation-assisted cycle ergometry in the critically ill: protocol for a randomized controlled trial. *Trials* 2019;20:724.
- Sommers J, Engelbert RHH, Dettling-Ihnenfeldt D, et al. Physiotherapy in the intensive care unit: an evidence-based, expert driven, practical statement and rehabilitation recommendations. *Clin Rehabil* 2015;29:1051–63.
- Berney S, Hopkins RO, Rose JW, et al. Functional electrical stimulation in-bed cycle ergometry in mechanically ventilated patients: a multicentre randomised controlled trial. *Thorax* 2021;76:656–63.
- Kayambu G, Boots R, Paratz J. Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial. *Intensive Care Med* 2015;41:865–74.
- Wyrwich KW, Tierney WM, Babu AN, et al. A comparison of clinically important differences in health-related quality of life for patients with chronic lung disease, asthma, or heart disease. *Health Serv Res* 2005;40:577–92.
- Denehy L, de Morton NA, Skinner EH, et al. A physical function test for use in the intensive care unit: validity, responsiveness, and predictive utility of the physical function ICU test (scored). *Phys Ther* 2013;93:1636–45.
- Ziak J, Krajcova A, Jiroutkova K, et al. Assessing the function of mitochondria in cytosolic context in human skeletal muscle: adopting high-resolution respirometry to homogenate of needle biopsy tissue samples. *Mitochondrion* 2015;21:106–12.
- Fossat G, Baudin F, Courtes L, et al. Effect of in-bed leg cycling and electrical stimulation of the quadriceps on global muscle strength in critically ill adults: a randomized clinical trial. *JAMA* 2018;320:368–78.
- Eggmann S, Verra ML, Luder G. Physiological effects and safety of an early, combined endurance and resistance training in mechanically ventilated, critically ill patients. *PLoS One* 2018;101:e344–5.
- Amundadóttir OR, Jónasdóttir RJ, Sigvaldason K. Effects of intensive upright mobilisation on outcomes of mechanically ventilated patients in the intensive care unit: a randomised controlled trial with 12-months follow-up. *Eur J Physiother* 2019;0:1–11.
- Denehy L, Skinner EH, Edbrooke L, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. *Crit Care* 2013;17:R156.
- Dall'Acqua AM, Sacchetti A, Santos LJ, et al. Use of neuromuscular electrical stimulation to preserve the thickness of abdominal and chest muscles of critically ill patients: a randomized clinical trial. *J Rehabil Med* 2017;49:40–8.
- Nordon-Craft A, Schenkman M, Edbrooke L, et al. The physical function intensive care test: implementation in survivors of critical illness. *Phys Ther* 2014;94:1499–507.
- Parry SM, Denehy L, Beach LJ, et al. Functional outcomes in ICU – what should we be using? – an observational study. *Crit Care* 2015;19:127.
- Hickmann CE, Roeseler J, Castanares-Zapatero D, et al. Energy expenditure in the critically ill performing early physical therapy. *Intensive Care Med* 2014;40:548–55.
- Bahouth MN, Power MC, Zink EK, et al. Safety and feasibility of a neuroscience critical care program to mobilize patients with primary intracerebral hemorrhage. *Arch Phys Med Rehabil* 2018;99:1220–5.

Supplementary Appendix

to paper Waldauf et. al.: Functional Electrical Stimulation-Assisted Cycle Ergometry-Based Progressive Mobility Programme for Mechanically Ventilated Patients: Randomised Controlled Trial with Six Months Follow Up

Table of Contents

Supplementary Methods	3
Full list of Enrolment Criteria	3
Inclusion Criteria:	3
Exclusion Criteria:.....	3
Individualised Rehabilitation Protocol	4
Protocolised rehabilitation in the intervention group (EMIR Trial).....	4
Details of rehabilitation delivered per treatment day and per study day	6
Reasons for days without rehabilitation	7
Richmond Agitation Sedation Scale (RASS)	8
Reflex locomotion therapy	8
Screening strategy	8
Randomisation procedure details	9
Strategy to minimise loss of follow-up	9
Details on power analysis and primary outcome measurement	10
Details of secondary outcome measurements	10
Supplementary Results	13
Recruitment curve	13
Primary outcomes – how it was collected	13
Primary outcome normality testing and descriptive statistics	14
Means with 95% confidence intervals	14
Physical function score.....	14
RAND SF-36 at 6 months	15
Comparison of primary outcome in this trials with other rehabilitations RCTs reporting 6 months outcomes	Error! Bookmark not defined.
Mental component score in subgroups with and without traumatic brain injury	17
Exploratory data analysis	18
Linear regression: MCS ~ group * TBI:	18

ICU and hospital length of stay – Tabular views of descriptive data	18
Doses of drugs used for sedation and analgesia.....	19
Sedation heatmap in tabular view	20
Detailed description of the influence of intervention on intracranial pressure.....	21
Consensus on Exercise Reporting Template (CERT) Self-evaluation Result (16 item checklist)	22
Supplementary references	26

Supplementary Methods

Full list of Enrolment Criteria

Inclusion Criteria:

- (1) ≥ 18 years;
- (2) mechanical ventilation, or imminent need of it at presentation;
- (3) predicted ICU length of stay ≥ 7 days;

Exclusion Criteria:

- (1) known primary systemic neuromuscular disease or spinal cord lesion at admission.
- (2) severe lower limb injury or amputation;
- (3) bedridden premorbid state (Charleston Comorbidity Score >4)
- (4) approaching imminent death or withdrawal of medical treatment within 24 h;
- (5) pregnancy;
- (6) presence of external fixator or superficial metallic implants in lower limb;
- (7) open wounds or skin abrasions at electrode application points;
- (8) presence of pacemaker, implanted defibrillator or another implanted electronic medical device;
- (9) predicted as unable to receive first rehabilitation session within 72 hours of admission or transferred from another ICU after more than 24 hours of mechanical ventilation;
- (10) Presence of other condition preventing the use of FESCE or considered unsuitable for the study by a responsible medical team;
- (11) prior participating in another functional outcome-based intervention research study.

Individualised Rehabilitation Protocol

Protocolised rehabilitation in the intervention group (EMIR Trial)

Stage and RASS score	Progressive mobility component	Supine cycle component (incl. the use of FESCE)	Total
0 unstable RASS -5 to -3 +/- neuromuscular blocking agents	2x15 minutes Passive/active exercises: passive and active range of motion, application of stretch reflex to upper and lower extremities and activation of global motor response, positioning in bed Respiratory-related activity	2x20 minutes Warm-up phase: about 5 minutes of passive cycling Therapeutic phase: functional electric stimulation (duration to aim for 90 min of total exercise per day, typically 10 min per session) Relaxation phase: about 5 minutes of passive cycling	Aim for 2 sessions a day and total 90 min of exercise a day (both FESCE and progressive mobility component)
1 sedated RASS -5 to -3	1x30 minutes Passive/active exercises: passive and active range of motion, application of stretch reflex to upper and lower extremities and activation of global motor response, positioning in bed Respiratory-related activity	2x20 minutes Warm-up phase: about 5 minutes of passive cycling Therapeutic phase: functional electric stimulation (duration to aim for 90 min of total exercise per day, typically 10 min per session) Relaxation phase: about 5 minutes of passive cycling	Aim for 2 sessions a day and total 90 min of exercise a day (both FESCE and progressive mobility component)
2 transition phase RASS -1 or 1, borderline cooperation	If cooperative: 2x10 minutes Passive/active exercises: active range of motion/lightly resisted upper and lower extremities, activation of global motor response, positioning in bed Respiratory-related activity 2x5 minutes Passive/active exercises (sit up in bed) If delirious: Individualise approach max. 30 minutes	2x20 minutes Warm-up phase: about 5 minutes of passive cycling Therapeutic phase: duration to aim for 20 minutes of functional electric stimulation (typically 10 min per session), attempt active cycling if cooperative Relaxation phase: about 5 minutes of passive cycling	Aim for 2 sessions a day and total 90 min of exercise a day (both FESCE and progressive mobility component)

	<p>If resedated: 1x15 minutes</p> <p>Passive/active exercises:</p> <p>passive and active range of motion, application of stretch reflex to upper and lower extremities and activation of global motor response, positioning in bed</p> <p>Respiratory-related activity</p>		
<p>3 weak</p> <p>RASS 0, cooperative</p>	<p>2x10 minutes</p> <p>Active exercises: active range of motion/lightly resisted upper and lower extremities</p> <p>2x5 minutes</p> <p>Progressive mobility: mobility activities progressing from less difficult activity in bed, active sitting on the bed</p> <p>2x60 minutes</p> <p>Active exercise: sit out with assistance**</p>	<p>2x20 minutes</p> <p>Warm-up phase: about 5 minutes of passive cycling</p> <p>Therapeutic phase: active cycling if able or functional electric stimulation (duration to aim for 90 min of total exercise per day, typically 10 min per session)</p> <p>Relaxation phase: about 5 minutes of passive cycling</p>	<p>Aim for 2 sessions a day and total 90 min of exercise a day (both FESCE and progressive mobility component)</p>
<p>4 able to stand with assistance</p> <p>RASS 0, cooperative</p>	<p>2x10 minutes</p> <p>Active exercises: active range of motion, low to moderate resistance against upper and lower extremities</p> <p>2x30 minutes</p> <p>Progressive mobility: mobility activities progressing from less difficult activity in bed to more difficult out of bed activities such as up to chair and ambulation</p>	<p>Warm-up phase: about 5 minutes of passive cycling</p> <p>Therapeutic phase: active cycling if able or functional electric stimulation (duration to aim for 90 min of total exercise per day, typically 10 min per session)</p> <p>Relaxation phase: about 5 minutes of passive cycling</p>	<p>Aim for 2 sessions a day and total 90 min of exercise a day (both FESCE and progressive mobility component)</p>

Table S1: Protocolised rehabilitation in the intervention group. Notes: FESCE functional electrical stimulation-assisted cycle ergometry; RASS = Richmond agitation and sedation scale. Categories of interventions were re-defined according to Consensus on exercise reporting template in the intensive care unit (Reid et al., 2018), dose and intensity according to Perme C, Chandrashekar R., 2009; * The setup of FES cycling is not included in FESCE time. This (e.g., electrode placement, achieve muscle contractions, start cycling) took the physiotherapists about 10 - 15 minutes. Take down time was approximately 10 minutes. ** Mobilisation into a chair is included in exercise time, sitting out time is not unless further exercise in sitting position.

Details of rehabilitation delivered per treatment day and per study day

	Groups	n	mean	SD	min	max	range	Q0.25	median	Q0.75	Wilcoxon
ICU [Days]	Intervention	75	13.7	8.5	1	31	30	7	12	20.5	0.674
	Control	75	13.9	10.5	2	63	61	5.5	12	19	
Number of treatment days/patient	Intervention	75	10.8	8.1	0	27	27	4	10	16	0.052
	Control	75	8.2	6.9	0	22	22	2	7	13	
Number of FESCE treatment days/patient	Intervention	75	6.5	6.1	0	24	24	2	5	9	N/A
	Control	N/A									
FESCE [min/treatment day]:	Intervention	63	31.1	10.1	8.7	50	41.3	22	33.1	39	N/A
	Control	N/A									
FESCE [min/study day]:	Intervention	75	14.7	11.5	0	41.7	41.7	5.7	14	23.7	N/A
	Control	N/A									
Physiotherapy duration [min/ treatment day]	Intervention	69	56.9	15	21.3	104.4	83	48.1	55	63.8	0.381
	Control	66	54.5	10	29.5	78.8	49.2	50.1	53.3	57.1	
Physiotherapy duration [min/ study day]	Intervention	75	45.4	21.2	0	94.2	94.2	36.1	48.8	54.6	<0.001
	Control	75	33.2	17.5	0	67.4	67.4	22.7	37.1	45.3	
Total duration of rehabilitation [min/ treatment day]	Intervention	71	79.6	24	15	139.1	124.1	65.6	82.2	96.6	<0.001
	Control	66	54.5	10	29.5	78.8	49.2	50.1	53.3	57.1	
Total duration of rehabilitation [min/ study day]	Intervention	75	60.2	27.2	0	121.4	121.4	48.7	61.9	77.7	<0.001
	Control	75	33.2	17.5	0	67.4	67.4	22.7	37.1	45.3	

Table S2A: Duration of rehabilitation calculated either per treatment day (i.e. excluding days without rehabilitation in analogy with Wright et al., 2018) or per study day (i.e. including days without rehabilitation).

	Groups	n	mean	SD	min	max	range	Q0.25	median	Q0.75	Wilcoxon
Passive exercise [min/treat.day]	Intervention	69	22.3	10	0	60.1	60.1	15	23.7	27	<0.001
	Control	66	15.7	8.5	0	30	30	10.1	15	23.2	
Passive exercise [min/study day]	Intervention	75	17.7	10.8	0	60.1	60.1	11.4	18.9	23.9	<0.001
	Control	75	9.5	7.1	0	30	30	4.3	8.5	15	
Supine resistance exercises [min/treat.day]	Intervention	69	23.3	9.6	0	44.3	44.3	17.7	24	30	0.104
	Control	66	26.9	7.9	8.2	50	41.8	22.8	27.1	30	
Supine resistance exercises [min/study day]	Intervention	75	18	10	0	44.3	44.3	12.2	18.3	25.5	0.25
	Control	75	16.1	9	0	35.3	35.3	10.7	17.3	22.3	
Supine aerobic exercise [min/treat.day]	Intervention	69	8.9	12.2	0	51.7	51.7	0	3	14	0.255
	Control	66	8.7	7.4	0	30	30	0.1	7.5	15	
Supine aerobic exercise [min/study day]	Intervention	75	7.6	11.4	0	50.7	50.7	0	2.4	12.2	0.714
	Control	75	5.5	5.9	0	30	30	0	5	8.7	

Exercise whilst sitting [min/treat.day]	Intervention	69	0.5	1.2	0	7.3	7.3	0	0	0	0.179
	Control	66	0.4	1.5	0	7.7	7.7	0	0	0	
Exercise whilst sitting [min/treat.day]	Intervention	75	0.4	1.1	0	6.8	6.8	0	0	0	0.138
	Control	75	0.3	1.2	0	7.5	7.5	0	0	0	
Mobilising into chair [min/treat.day]	Intervention	69	1.8	4.1	0	25	25	0	0	1.7	0.161
	Control	66	2.7	3.9	0	15	15	0	0	4	
Mobilising into chair [min/study day]	Intervention	75	1.6	3.8	0	25	25	0	0	1.1	0.379
	Control	75	1.8	3	0	13.1	13.1	0	0	2.2	
Stand-up and/or walking exercise [min/treat.day]	Intervention	69	0.2	0.6	0	2.9	2.9	0	0	0	0.656
	Control	66	0.2	0.5	0	2.2	2.2	0	0	0	
Stand-up and/or walking exercise [min/study day]	Intervention	75	0.2	0.5	0	2.9	2.9	0	0	0	0.574
	Control	75	0.1	0.4	0	1.8	1.8	0	0	0	

Table S2B: Detailed description of phases of protocolised rehabilitation calculated either per treatment day (i.e. excluding days without rehabilitation in analogy with Wright et al., 2018) or per study day (i.e. including days without rehabilitation).

Reasons for days without rehabilitation

The intervention occurred in 817/932 days; standard care occurred on 615/895 days. The reasons for no-physiotherapy days were:

1. Day of enrollment was recorded as the day in the study, but no rehabilitation was delivered as the study subjects were usually randomized in the afternoon.
2. Day where rehabilitation was considered unsafe (patient not meeting safety criteria) or not feasible (e.g. patient transferred to operating room)
3. Out-of-bed mobilization were occasionally skipped particularly for obese patients, when there was no assistance available to physios from the nurses due to staff shortages or workload on the unit.
4. (In standard of care only): Unlike study physios, hospital physios do not work on Sundays.

Richmond Agitation Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation communicate or follow commands

Table S3: Richmond Agitation and Sedation Scale

Reflex locomotion therapy

There are many different physical therapy interventions available and views about what physical therapy entails differ. Some therapists emphasize the role of stimuli application (neuroproprioceptive „facilitation and inhibition“ while others emphasize physical therapy as a problem-solving educational process (Motor/skill acquisitions). Different views could influence both the delivery and outcome of therapy. For example, Vojta reflex locomotion or the Perfetti approach are considered key interventions in one region (Vojta reflex locomotion in the Czech Republic while Perfetti approach in Spain), but may be unknown to some physical therapists in other regions (Rasova et al., 2020).

Reflex locomotion therapy developed by prof. Vojta (Vojta V., 1973) is routinely used in the Czech Republic. Patients are set up into the precisely given initial position with defined angular setting of extremities (prone, supine and kneeling position) and activation zones (trunk, acromion, scapula, epicond. med. humeri, proc. styl. radii, spina iliaca sup. ant., mus. gluteus, epicond. med. femoris, calcaneum) are stimulated with precise localization and pressure direction. This sustained manual pressure stimulation of specific points on the skin surface gradually evokes a widespread involuntarily motor response (reflex creeping, reflex turning and process of verticalization), and moreover sensory and autonomic response is activated [2]. Such approach is implemented not only in bedridden patients, but also in fully active patients with aim to qualitatively improve their movement.

Screening strategy

Research nurses (5 persons in 2.5 full-time working equivalents) were responsible for pre-screening potentially eligible patients and notifying investigators, who were approaching the family at or immediately after the first family meeting with medical team. In case legal representative was not available, eligible patients have been enrolled without consent as per article 38 of the Declaration of Helsinki. In this case, an independent physician confirmed patient's lack of capacity

and fulfilment of the entry criteria. Pre-screening during week days was performed by a research nurse who has always been physically present at morning rounds. During weekend and bank holidays pre-screening research nurses used remote access to clinical information system (MetaVision, IMD Soft, Israel).

Randomisation procedure details

When entering screening baseline data and checking against inclusion and exclusion criteria, the process of randomisation was performed automatically in an electronic case-report form. The computer was programmed to generate a randomisation sequence at <http://randomisation.com> in permuted blocks of four in each of four strata based on (1.) presence or absence of sepsis and (2.) specific consent to muscle biopsy studies.

Strategy to minimise loss of follow-up

1. Protocol was designed to allow primary outcome be obtained over the phone.
2. Contact details + 2 back-ups: When consenting the relatives, we not only took contact details of patients, but also contact detail of the next of kin and a back-up contact for other family member. Contact details were checked when research nurses performed discharge visits.
3. Plan A: Re-join interview: 4-6 weeks before the 6 months follow up was due the research nurses (who were known to the patients or the family) phoned and arranged the date for the follow up phone call. During this pre-interview, the main objective was to determine who is the best to phone (whether the patient or the carer should be interview) and schedule time and date of this phone call. Patients/carers were also reminded not to disclose whether they used bike or not during their hospital stay when speaking with blinded outcome assessor.
4. Plan B: Use of back-up contacts: In case patients/relatives were not available, the attempts to re-join interview continue, with eventual use of back-up contacts.
5. Plan C: In cases this failed, the blinded study assessors themselves tried to contact patients/carers directly at 6 months.
6. Plan D: Physical visits of patients: In remaining cases (n=6) it was necessary to physically visit patients at their homes or long-term care facilities. In 5 cases, it was in patients who remained hospitalised in long term facilities, whose family agreed with gathering the data but did not know the necessary details about patient's current condition, which nursery personnel refused to give over the phone. In one case, it was necessary to visit a patient suffering from self-neglect in his home.

Details on power analysis and primary outcome measurement

Power analysis is based on the study of Kayambu et al. 2015, who studied a rehabilitation intervention in patients with sepsis and reported in the control group the mean **physical function (PF) score** 60 points with a standard deviation of 29.4 points. We aimed to be able to detect changes of health-related quality of life that are clinically important for patients. In order to determine “moderately clinically important” difference for our patients, we used per analogiam data from a study on patients with COPD, asthma and myocardial infarction (Wyrwich et al., 2005), which determined this difference to be in the range of 15-20 points by a Delphi consensus of stakeholders. In order to get 80% probability to detect (at $p < 0.05$) a difference of 15.8 points in the population with physical function score of 60.0 ± 29.4 points, we would require 108 patients ($n=54$ in each group). We used two-sided test at <https://clincalc.com/stats/samplesize.aspx> to calculate this. In order to compensate for non-survivors (mortality of unselected patients in our unit in 2014 was 28%), we planned for and also randomised 150 patients.

Please note that although PF is an important determinant of the study primary outcome, **physical component score (PCS)**, there are other elements of physical health, which we believed could also have been influenced by the intervention and thus better reflects the answer to our research question. Namely, $PCS = (10PF + 4RP + 2BP + 5GH) / 21$, where RP is role limitation due to physical health, BP=bodily pain and GH = general health. There was no study published in 2014 to report on PCS and its standard deviation in populations similar to our cohort and therefore it should be noted that power analysis of our study is based on surrogate (PF).

Details of secondary outcome measurements

- Four-item Physical Fitness in Intensive Care Test (PFIT-s) was measured as per Denehy et al., 2013 with using ordinal scale ranging from 0 to 12 (see table S4).

Assistance	Cadence [steps/min]	Shoulder Strength	Knee Strength
0=unable	0=unable	0=<gr 3	0=<gr 3
1=assists x 2	1= <49	1=gr 3	1=gr 3
2=assist x 1	2=50-80	2=gr 4	2=gr 4
3=no assistance	3=>80	3=gr 5	3=gr 5

Table S4: Components of PFIT-s test. Note gr.= grade referring to Oxford muscle power scale (see below on MRC score)

- A trained study physiotherapist unblinded to patient's treatment allocation was obtaining these scores at D28 or ICU discharge, whichever occurred earlier. Data were entered into the electronic CRF in the form of scroll-down list.

Figure S1: PFIT-s entry into electronic case report form.

- Rectus muscle cross-sectional diameter was measured by ultrasound (Vivid G5, GE Healthcare) as described by Montes R., 2001. Linear 9MHz probe was placed in transverse plane perpendicular to the skin in the midpoint between patella and anterior superior iliac spine and rectus femoris muscle identified and its antero-posterior diameter measured. See Fig. S2.

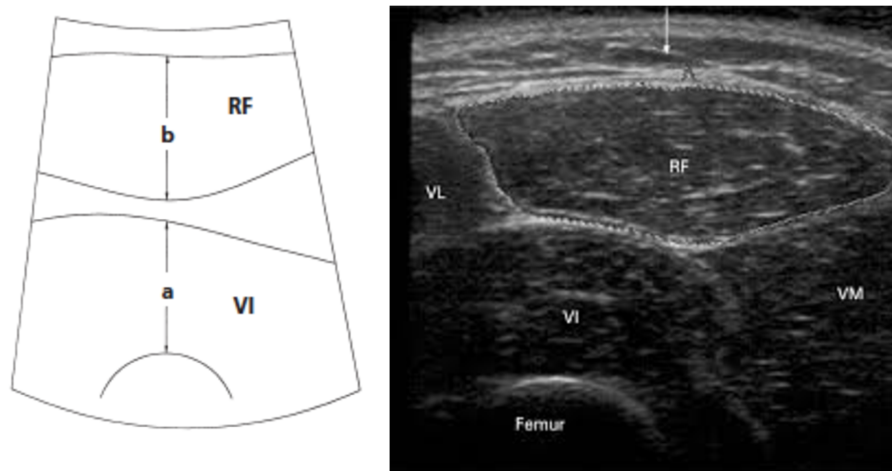


Figure S2: Measurement of rectus femoris cross-sectional diameter – adapted from Montes [6]. Note: RF = rectur femoris muscle, VI = vastus intermedius muscle.

- Daily nitrogen balance was calculated as a difference between nitrogen intake minus nitrogen excretion. Nitrogen intake was calculated automatically (Metavision 5.0, IMD Soft Israel) by multiplying N-content of the feeding formulas and their intake. Nitrogen excretion has been measured by multiplying output of urine (and/or dialysis fluid) and its nitrogen content. Nitrogen content was calculated as a sum of nitrogen in urea, creatinine and

ammonia. No preservation of urine has been used before ammonia measurement. We have not measured nor estimated non-urinary nitrogen losses.

- Muscle power as per the Medical Research Council (MRC) score has been assessed as a sum of 5-grade Oxford scores on 3 muscle groups on four limbs. Oxford score is measured as 0, paralysis; 1, only a trace or flicker of muscle contraction is seen or felt; 2, muscle movement is possible with gravity eliminated; 3, muscle movement is possible against gravity; 4, muscle strength is reduced, but movement against resistance is possible and 5, full power. Therefore, MRC score ranges from 0 (quadriplegia) to 60 (normal muscle strength).
- Number of ventilator-free days has been calculated for each patient as a count of days when a patient is alive and disconnected from invasive or non-invasive mechanical ventilation for entire 24 hours period. This includes patients with tracheostomies ventilating all day long on Ayre T-piece and patients supported by high-flow nasal oxygen cannula. Ventilator-free day is not counted when the patient requires non-invasive ventilation or in patients on end-of-life pathway after terminal extubation.
- ICU length of stay was measured at discharge from ICU or at day 28, whichever occurred earlier.
- Number of episodes of elevated intracranial pressure (Pre-specified safety outcome): Rehabilitation intervention (with or without FESCE) could have been delivered per protocol to patients with ICP measurement in place whose ICP is normal and stable and who are not on second or third-tier therapy for intracranial hypertension. ICP has been measured by intraparenchymal probe (Codman®, Life Sciences, USA) inserted in right midpupillary line and zeroed at tragus. An elevation of ICP has been defined as any elevation above 20 mmHg lasting for 5 or more minutes or requiring any intervention. ICP has been watched carefully during and after rehabilitation interventions and noted in electronic case report form. In addition, ICP waveforms were checked manually in retrospect from clinical information system (Metavision 5, IMD Soft, Israel) in all patients with ICP monitor in place, who were enrolled into the study.
- Number of dialysis interruptions (Pre-specified safety outcome): This was defined as unplanned termination of continuous renal replacement therapy for any reason that requires resetting the circuit or reinsertion of venous access cannula.

Supplementary Results

Recruitment curve

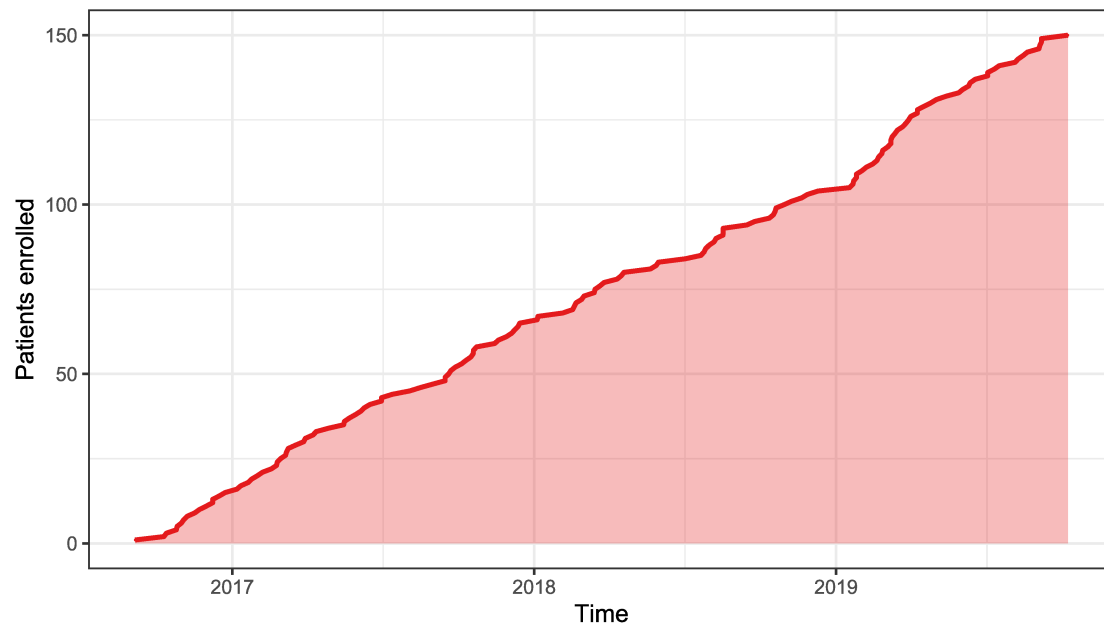


Figure S3: Recruitment curve = number of enrolled patients over time.

Primary outcomes – how it was collected

Eighty eight (59%) out of 150 enrolled patients were alive at 6 month. Primary outcome was collected from 88 (100%) of them following way:

- Eleven out of 31 patients who consented to metabolic substudy came to hospital for follow-up exercise testing, insulin clamp and muscle biopsies.
- 53 patients were interviewed face-to-face at their convenience next to their scheduled unrelated hospital appointment or were visited at home by outcomer assessors
- In 24 patients, primary outcome data were gained by structured telephone interview with patients themselves (n=10) or their carers (n=14).

Primary outcome normality testing and descriptive statistics

Primary outcome = Physical Component Summary Score of SF-36 QoL questionnaire at 6 months deviated from normal distribution in our population.

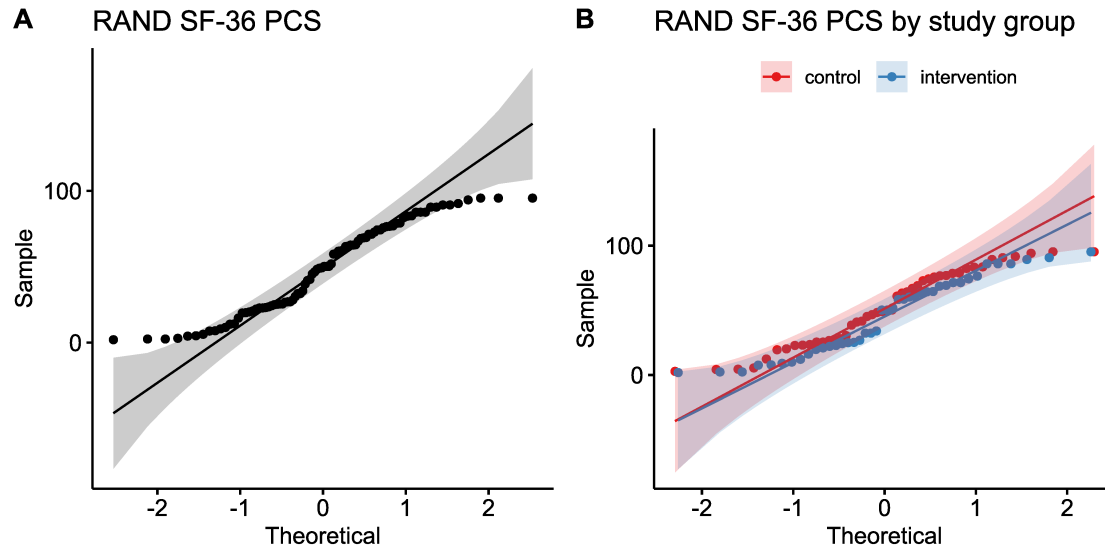


Figure S4: PCS SF-36 (primary outcome) normality of distribution.

In the paper, Wilcoxon test was used to test the differences and results presented as medians (interquartile range).

Group	n	mean	SD	min	max	range	se	Q0.25	Median	Q0.75
Controls	46	51.65	28.81	2.86	95.24	92.38	4.25	25.77	49.17	76.85
Intervention	42	45.3	29.19	1.9	95.24	93.33	4.5	21.25	50.24	69.13

Table S5: Descriptive statistics of the primary outcome (PCS-SF36 at 6 months is as follows)

Means with 95% confidence intervals

Means with 95% Confidence intervals for primary outcome (PCS/SF36) are: Intervention 45.3 (35.1-55.5), Control 51.7 (41.9-61.4)

Physical function score

Median physical function score of SF-36 at 6 months was 47.5 (IQR 20; 84) points and 42.5 (IQR 25; 80) in intervention vs. control groups ($p=0.65$, Wilcoxon). This was not a prespecified outcome and we report this to enable meta-analyses.

RAND SF-36 at 6 months

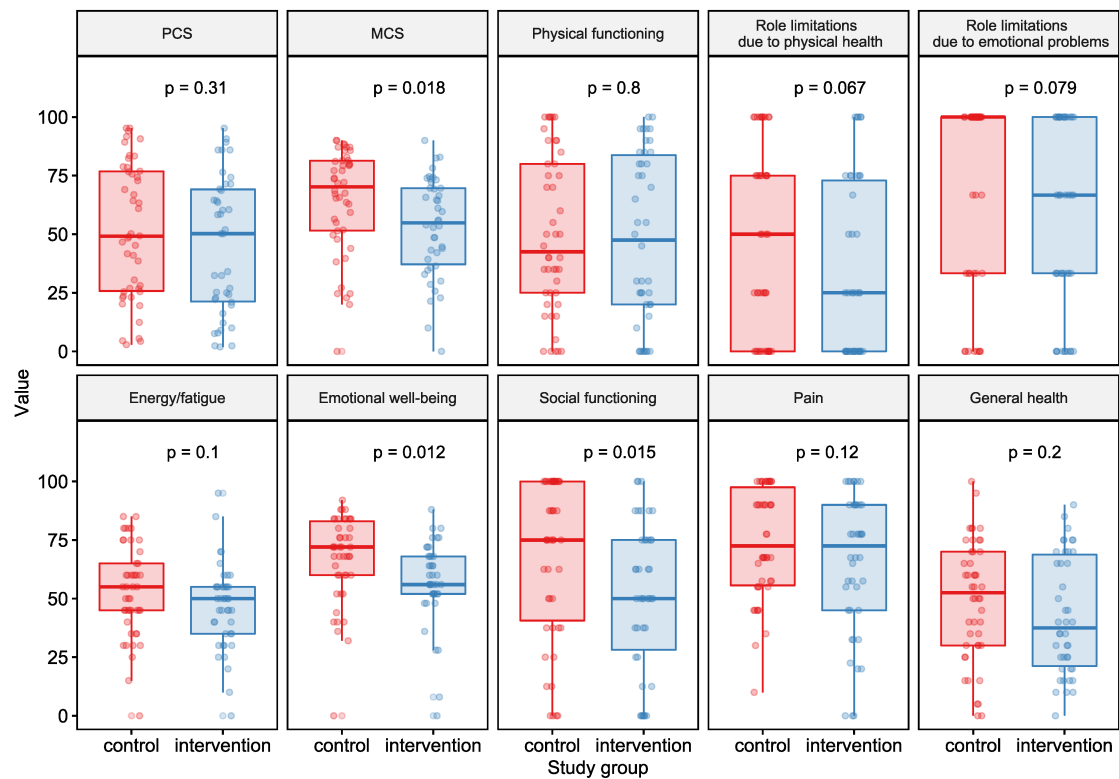


Figure S5: Results of SF-36 at 6 months (p values are from t-test) and data are calculated as per version 1 of RAND methodology https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html

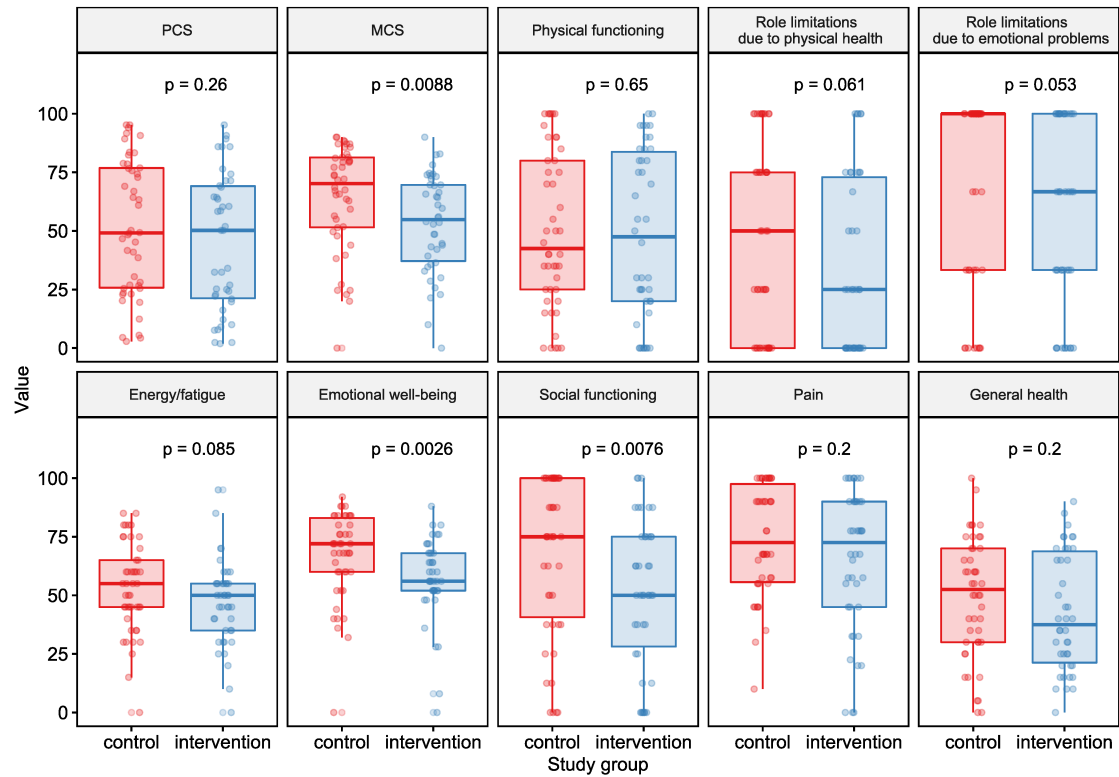


Figure S6: Results of SF-36 at 6 months (p values are from Wilcoxon test) and data are calculated as per version 1 of RAND methodology https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html

Mental component score in subgroups with and without traumatic brain injury

Note: This was not a prespecified outcome and the study was not powered to investigate this. Data below must be interpreted as hypothesis generating only.

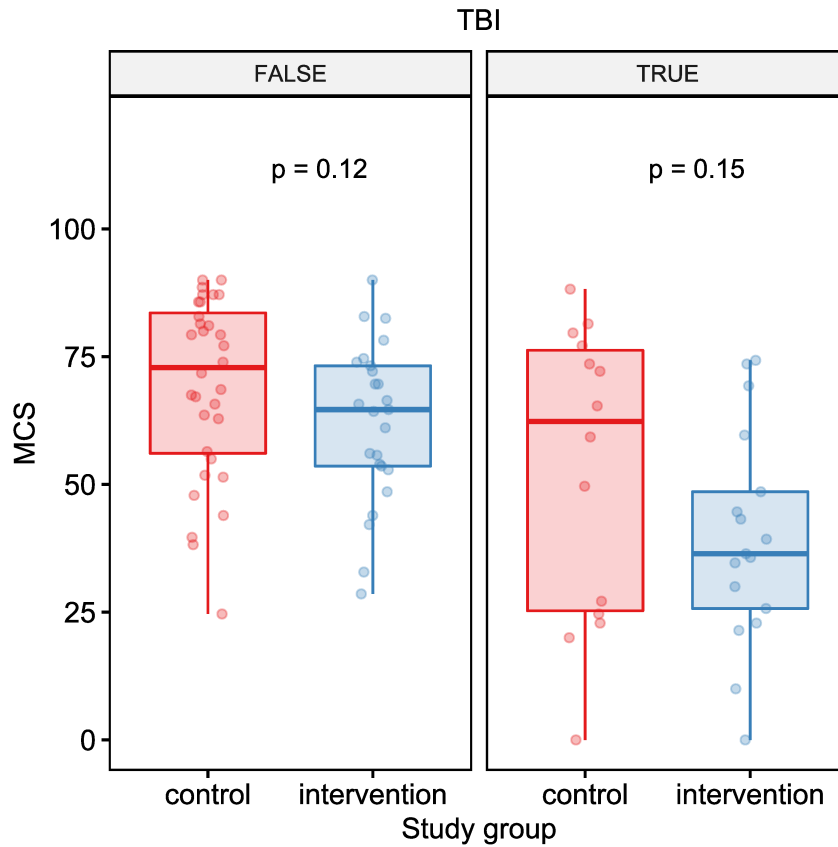


Figure S7: Mental component summary score at 6 months in patients with and without traumatic brain injury. P-values are from Wilcoxon test.

Exploratory data analysis

Groups	n	mean	SD	min	max	range	se	Q0.25	Median	Q0.75
TBI = FALSE, control	32	69.1	17.6	24.6	90.0	65.4	3.1	56.1	72.9	83.6
TBI = FALSE, intervention	25	62.3	15.5	28.6	90.0	61.4	3.1	53.6	64.6	73.2
TBI = TRUE, control	14	52.9	28.6	0.0	88.2	88.2	7.6	25.3	62.3	76.3
TBI = TRUE, intervention	17	39.4	21.1	0.0	74.3	74.3	5.1	25.7	36.4	48.6

Table S7A: Mental component summary scores at 6 months.

term	estimate	std.error	statistic	p.value
(Intercept)	70.181	3.22	21.797	<0.001
group: intervention - control	-9.227	4.252	-2.17	0.033
TBI: TRUE - FALSE	-19.626	4.447	-4.414	<0.001

Table S7B: Linear regression analysis: MCS ~ group + TBI:

Linear regression: MCS ~ group * TBI:

term	estimate	std.error	statistic	p.value
(Intercept)	69.14	3.512	19.688	<0.001
group: intervention - control	-6.854	5.303	-1.293	0.2
TBI: TRUE - FALSE	-16.206	6.366	-2.546	0.013
group intervention : TBI TRUE	-6.711	8.917	-0.753	0.454

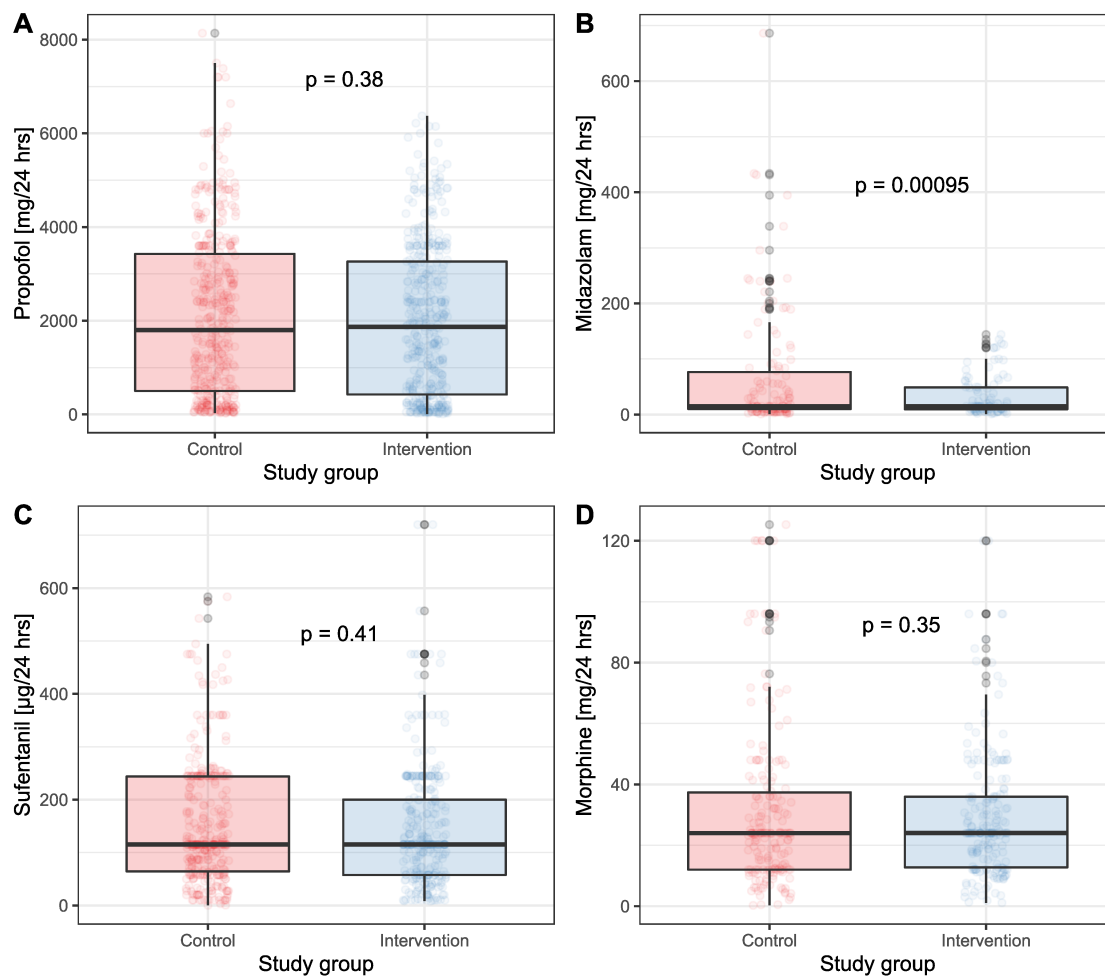
Table S8: Linear regression analysis: MCS ~ group * TBI:

ICU and hospital length of stay – Tabular views of descriptive data

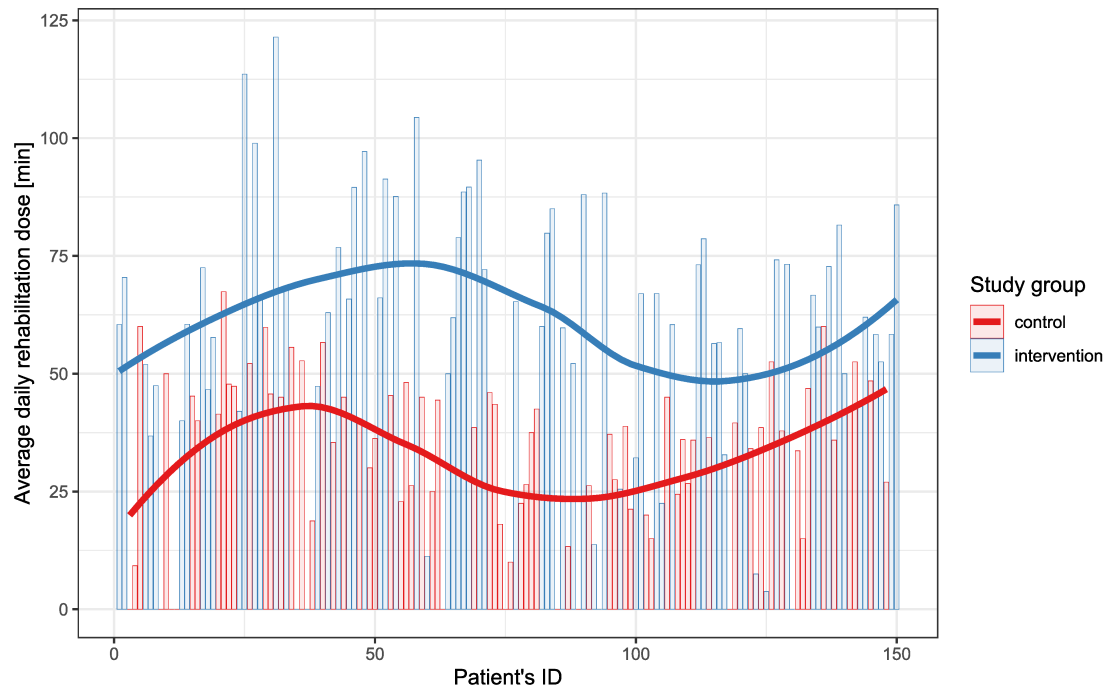
		N	Mean ± SD	Median (IQR)	Min	Max
ICU LOS [days]	Intervention	75	13.7±8.5	12 (7-21)	1	31
	Control	75	13.9±10.5	12 (6-19)	2	63
Hospital LOS [months]	Intervention	70	2.2±2.0	1.4 (0.5-2.6)	0.1	6.0
	Control	69	2.0±1.9	1.4 (0.5-4.0)	0.1	6.2

Table S9: Tabular view of uncensored lengths of stay. Please note that this table contains descriptive uncensored data unlike Figure 3C and 3D of the main manuscript containing death-censored Kaplan-Meier curves.

Doses of drugs used for sedation and analgesia



Supplementary Figure S8: Doses of sedatives



Supplementary Figure S9: Duration of rehabilitation vs. study number that were given consecutively and represent time. Individual bars represent mean rehabilitation duration in individual subjects, the line is Loess curve (local regression).

Sedation heatmap in tabular view

Group	Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	RASS	perc	perc	perc	perc	perc	perc	perc	perc	perc	perc	perc	perc	perc	perc
Control	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	1.4	0	0	0	0	0	0	0	0	0	0	0
	2	2.7	0	1.4	1.6	1.8		2.1	4.5	9.5	2.4	2.6	0	0	3.3
	1	2.7	2.7	4.3	4.9	7.3	8.0	10.6	9.1	4.8	7.1	13.2	8.6	6.2	3.3
	0	10.7	16.4	21.4	19.7	25.5	38.0	38.3	31.8	40.5	47.6	36.8	14.3	6.2	16.7
	-1	10.7	6.8	11.4	11.5	10.9	10.0	14.9	18.2	21.4	14.3	21.1	31.4	46.9	43.3
	-2	12.0	23.3	20.0	21.3	16.4	16.0	12.8	11.4	7.1	4.8	7.9	25.7	21.9	10.0
	-3	28.0	17.8	12.9	13.1	7.3	4.0	4.3	6.8	4.8	2.4	2.6	8.6	3.1	3.3
	-4	21.3	23.3	17.1	18.0	16.4	12.0	6.4	6.8	4.8	4.8	5.3	2.9	9.4	10.0
Intervention	-5	12.0	9.6	10.0	9.8	14.5	12.0	10.6	11.4	7.1	16.7	10.5	8.6	6.2	10.0
	4	1.3	1.4	0	0	0	1.8	2.0	0	0	5.1	0	0	0	0
	3	1.3	2.8	4.4	1.5	3.3	3.6	2.0	2.2	4.8	7.7	5.3	2.8	5.7	3.1
	1	6.7	2.8	5.9	7.6	11.5	7.1	10.2	20.0	2.4	17.9	5.3	2.8	11.4	21.9
	0	6.7	9.9	14.7	18.2	14.8	17.9	20.4	20.0	21.4	15.4	21.1	11.1	11.4	28.1
	-1	4.0	8.5	5.9	12.1	13.1	5.4	14.3	13.3	23.8	23.1	23.7	13.9	22.9	9.4
	-2	14.7	12.7	13.2	10.6	13.1	16.1	14.3	13.3	21.4	7.7	18.4	16.7	22.9	15.6
	-3	13.3	21.1	14.7	16.7	8.2	12.5	6.1	6.7	7.1	7.7	13.2	27.8	14.3	3.1
	-4	32.0	19.7	17.6	10.6	11.5	17.9	16.3	11.1	4.8	5.1	2.6	16.7	2.9	3.1

	-5	20.0	21.1	23.5	22.7	24.6	17.9	14.3	13.3	14.3	10.3	10.5	8.3	8.6	15.6
--	----	------	------	------	------	------	------	------	------	------	------	------	-----	-----	------

Table S10: Distribution of patients into Richmond Agitation and Sedation Scale categories. Note: perc = percentage of patients

[Detailed description of the influence of intervention on intracranial pressure.](#)

The Protocol followed standard safety criteria (Sommers et al., 2015) for both intervention and control group. This means that planned rehabilitation session was omitted in case patient had unstable ICP or was receiving neuroprotective regimen (i.e. 2nd or 3rd tier of treatments for intracranial hypertension).

There were 15 days with ICP monitoring in place in 3 patients in the control group and 15 days with ICP monitoring in 4 patients in the intervention group. In all patients and intraparenchymatous ICP probe (Codman, Germany) was inserted through a burr hole in right midpupillary line and zeroed at tragus. Sustained ICP elevation was defined as ICP>20 torr for >5 mins or any elevation that required intervention.

All rehabilitation sessions were initiated on patients who were fulfilling safety criteria. There were no ICP elevations in the 3 patients in the control group, but in total 23 elevations were recorded in two out of four patients in the interventional group. These two patients are described in more detail.

Patient A was 27-year-old man with blunt severe TBI. He begun FESCE exercises on day 3 when the decision to wake him up was made. He suffered 3 elevations of ICP, which occurred 4, 6.5 and 22 hours after last FESCE exercise. The patient was alive with severe neurological disability 6 months after

Patient B was 73-year-old man with severe blunt isolated TBI. He was randomised into interventional arm, but was not receiving any exercises due to unstable ICP up until day 6 when his ICP stabilised. Then he received one 15 min FESCE intervention throughout which ICP remained stable. However, 55 mins after this, ICP begun to rise again, requiring reescalation of treatment. Thereafter, there were 20 more ICP elevations, which resulted in the necessity of a decompressive craniectomy. Afterwards, the patients resumed rehabilitation program, but remained comatose and died 2.5 months after the injury.

Consensus on Exercise Reporting Template (CERT) Self-evaluation Result (16 item checklist)

Here we provide the results of paper self-evaluation according to minimum standards published for reporting exercise interventions (Slade et al., 2016). In case some details were not included in the manuscript due to word count restrictions, they can be found here.

1 Detailed description of the type of exercise equipment:

Functional electrical stimulation-assisted cycle ergometry (RT300 System, © Restorative Therapies Inc. 2005-2016. LB100108 Version 37)

2 Detailed description of the qualifications, expertise and/or training

Educated (MSc.), experienced (10 years of clinical practice) and certified (underwent special training how to use Functional electrical stimulation-assisted cycle ergometry) physical therapist delivered the therapy.

3 Describe whether exercises are performed individually or in a group.

Exercises was performed individually.

4 Describe whether exercises are supervised or unsupervised; how they are delivered

Exercise was supervised by senior physical therapist (Ph.D., 20 year of clinical practice, trained in FESCE) and medical doctor (specialised in critical illness, Ph.D., 20 year of clinical practice). The details of therapy are described in Table S1 above.

5 Detailed description of how adherence to exercise is measured and reported

Adherence to exercise was measured by following ways:

- Immediately after the intervention was delivered, the physiotherapist recorded the duration and content of the therapy in electronic case-report form (see Figure S10)
- Throughout the study 20 randomly selected sessions were observed by a hidden observer and objective data on progressive mobility programme time were recorded with physiotherapists self-reported data
- FESCE device automatically records and stores exercise duration, distance travelled (in meters), and energy load (calories).

Therapy session 1		Therapy session 2	
Standard therapy			
From	<input type="text" value="9:00"/>	To	<input type="text" value="9:30"/>
Passive movement	<input type="text" value="20"/>	min	
Activated movement in a lying position	<input type="text" value="15"/>	min	
Activated movement in a sitting	<input type="text" value="0"/>	min	
Activated movement in a standing	<input type="text" value="0"/>	min	
Active movement in a lying position	<input type="text" value="0"/>	min	
Active movement in a sitting	<input type="text" value="0"/>	min	
Active movement in a standing	<input type="text" value="0"/>	min	
Lactate before standard therapy	<input type="text"/>	mmol/L	
FESCE			
From	<input type="text" value="10:40"/>	To	<input type="text" value="11:05"/>
FESCE dose	<input type="text" value="20"/>	min	<input style="border: 1px solid gray;" type="text" value="?"/>
Lactate before FESCE	<input type="text"/>	mmol/L	
FESCE			
From	<input type="text" value="11:10"/>	To	<input type="text" value="11:33"/>
FESCE dose	<input type="text" value="20"/>	min	<input style="border: 1px solid gray;" type="text" value="?"/>
Lactate after FESCE	<input type="text"/>	mmol/L	

Figure S10: Electronic Case Report Form to record exercise times

6 Detailed description of motivation strategies

Motivation strategies were dependent on the sedation score. There was no extra motivation for deeply sedated patients, who received passive, reflex and FESCE exercises. Once patients regained consciousness, the therapists talked to them explaining the role of the therapy and gave them psychological support. Motivation strategies, enjoyment of the progress and psychological support were not protocolized in this study. Patients using FESCE had the possibility to observe on the monitor animation of a cyclist and together with the distance travelled, speed and heart rate. Motivation strategies, enjoyment of the progress and psychological support were not protocolized in this study.

7a Detailed description of the decision rule(s) for determining exercise progression

Progression in meeting milestones (such as sitting on the bed, sitting out, stand etc) were dependent on patient's consciousness, cooperativity, muscle power (this can be inferred from Table S1). In addition, the decision to actively mobilise the patient was determined according to consensus recommendations regarding safety criteria for mobilization of adult, mechanically ventilated patients in the ICU (Hodgson et al., 2014).

Most importantly: a fraction of inspired oxygen less than 0.6 with a percutaneous oxygen saturation more than 90% and a respiratory rate less than 30 breaths/minute and normal and stable intracranial pressure were required for in- and out-of-bed mobilization.

7b Detailed description of how the exercise program was progressed

Once the patient was more alert and able to participate, they were encouraged to engage in therapy. To increase the intervention workload, resistance and cycling cadence were increased incrementally. Therapists also corrected the trajectory of the movement by passive corrections or by techniques of neuroproprioceptive “facilitation, inhibition” (e.g. adaptive resistance).

8 Detailed description of each exercise to enable replication

Surface electrodes were applied to the gluteal, hamstrings and quadriceps muscles on both legs according to a regime specified by Parry et al., 2014. In brief, patients underwent warm-up phase (expected length about 5 minutes of passive cycling), therapeutic phase (i.e. functional electrical stimulation or active cycling lasting as driven by meeting daily duration goals and patient’s tolerance), and relaxation phase (expected length about 5 minutes of passive cycling). FES impulses had pulse width 250 μ s, pulse frequency 40 Hz, and the lowest output per channel (in a range 0- 60 mA) that allowed locomotive movement of lower extremities 60 mA.

9 Detailed description of any home programme component

Not applicable, the program was only delivered at hospital.

10 Describe whether there are any non-exercise components

There are any non-exercise components.

11 Describe the type and number of adverse events that occur during exercise

Pre-specified safety parameters (secondary outcomes) were dialysis interruptions and elevations of intracranial pressure in patients and these are described in the manuscript body.

There were no additional severe periprocedural events such as falls, inadvertent extubations or line removals in either group.

12 Describe the setting in which the exercises are performed

Face to face individualised physical therapy was delivered at two intensive care unit containing 10 and 11 level 3 beds of a large teaching hospital and admits approximately 1000/year of non-selected medical and surgical critically ill patients.

13 Detailed description of the exercise intervention

Patients were laying supine strapped to a cyclo-ergometer modified for use on a hospital bed. Intervention is in detail described in the Table S1.

14a Describe whether the exercises are generic (one size fits all) or tailored

Details about exercise can be inferred from Table S1. This was a pre-specified exercise programme where physical therapy and FESCE setting was tailored to patients condition.

14b Detailed description of how exercises are tailored to the individual

Interventions were tailored according to consciousness, cooperativity, muscle power and standard safety criteria for mobilization of critically ill patients [9]. Distance and duration of cycling was set by signs of muscle fatigue such as pain, grimace or increase in heart rate.

15 Describe the decision rule for determining the starting level

Starting level was determined according to consensus recommendations regarding safety criteria for mobilization of adult, mechanically ventilated patients in the ICU [9]. Most importantly: a fraction of inspired oxygen less than 0.6 with a percutaneous oxygen saturation more than 90% and a respiratory rate less than 30 breaths/minute and normal and stable intracranial pressure were required for in- and out-of-bed mobilization.

16a Describe how adherence or fidelity is assessed/measured

Adherence to exercise was measured by the FESCE. Parameters as the distance (in meters), the average session duration (seconds) and energy load (calories). Moreover, the therapist recorded detail information about each session into the study protocol. In addition, there was a concealed assessor, who checked the accuracy of self-reported times during 20 random exercises.

16b Describe the extent to which the intervention was delivered as planned

Intervention was delivered in 817 out of 932 (88%) ICU days. During the days where it was delivered, the average daily doses were 80 ± 35 , mean daily dose of FESCE was 32 ± 13 min (Figure 2 of the main manuscript).

Supplementary references

- 1 Eggmann S, Verra ML, Luder G, *et al.* Physiological effects and safety of an early, combined endurance and resistance training in mechanically ventilated, critically ill patients. *PLoS One* 2018;**101**:e344–5. doi:10.1016/j.physio.2015.03.553
- 2 Fossat G, Baudin F, Courtes L, *et al.* Effect of in-bed leg cycling and electrical stimulation of the quadriceps on global muscle strength in critically ill adults: A randomized clinical trial. *JAMA - J Am Med Assoc* 2018;**320**:368–78. doi:10.1001/jama.2018.9592
- 3 Kayambu G, Boots R, Paratz J. Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial. *Intensive Care Med* 2015;**41**:865–74. doi:10.1007/s00134-015-3763-8
- 4 Morris PE, Herridge MS. Early Intensive Care Unit Mobility: Future Directions. *Crit. Care Clin.* 2007;**23**:97–110. doi:10.1016/j.ccc.2006.11.010
- 5 Moss M, Nordon-Craft A, Malone D. A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. *Am J Respir Crit Care Med* 2016;**193**:1–57. doi:10.1164/rccm.201505-1039OC
- 6 Wright SE, Thomas K, Watson G, *et al.* Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): A multicentre, parallel-group, randomised controlled trial. *Thorax* 2018;**73**:213–21. doi:10.1136/thoraxjnl-2016-209858
- 7 Hodgson CL, Bailey M, Bellomo R, *et al.* A binational multicenter pilot feasibility randomized controlled trial of early goal-directed mobilization in the ICU. *Crit Care Med* 2016;**44**:1145–52. doi:10.1097/CCM.0000000000001643
- 8 Amundadóttir OR, Jónasdóttir RJ, Sigvaldason K, *et al.* Effects of intensive upright mobilisation on outcomes of mechanically ventilated patients in the intensive care unit: a randomised controlled trial with 12-months follow-up. *Eur J Physiother* 2019;**0**:1–11. doi:10.1080/21679169.2019.1645880
- 9 Berney S, Hopkins RO, Rose JW, *et al.* Functional electrical stimulation in-bed cycle ergometry in mechanically ventilated patients: a multicentre randomised controlled trial. *Thorax* Published Online First: December 2020. doi:10.1136/thoraxjnl-2020-215093
10. Reid, J.C., Unger, J., McCaskell, D. et al. Physical rehabilitation interventions in the intensive care unit: a scoping review of 117 studies. *j intensive care* 6, 80 (2018). <https://doi.org/10.1186/s40560-018-0349-x>
11. Perme C, Chandrashekar R. Early mobility and walking program for patients in intensive care units: creating a standard of care. *Am J Crit care an Off Publ Am Assoc Crit Nurses* 2009;**18**:212–21. doi:10.4037/ajcc2009598
12. Wright SE, Thomas K, Watson G, Baker C, Bryant A, Chadwick TJ, Shen J, Wood R, Wilkinson J, Mansfield L, Stafford V, Wade C, Furneal J, Henderson A, Huggill K, Howard P, Roy

A, Bonner S, Baudouin S. Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial. *Thorax*. 2018 Mar;73(3):213-221. doi: 10.1136/thoraxjnl-2016-209858.

13. Řasová K, Freeman J, Cattaneo D, et al. Content and Delivery of Physical Therapy in Multiple Sclerosis across Europe: A Survey. *Int J Environ Res Public Health* 2020;17. doi:10.3390/ijerph17030886
14. Vojta V. [Early diagnosis and therapy of cerebral movement disorders in childhood. C. Reflexogenous locomotion--reflex creeping and reflex turning. C1. The kinesiologic content and connection with the tonic neck reflexes]. *Z Orthop Ihre Grenzgeb* 1973;111:268-91.
15. Kayambu G, Boots R, Paratz J. Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial. *Intensive Care Med* 2015;41:865-74. doi:10.1007/s00134-015-3763-8
16. Wyrwich KW, Tierney WM, Babu AN, et al. A comparison of clinically important differences in health-related quality of life for patients with chronic lung disease, asthma, or heart disease. *Health Serv Res* 2005;40:577-91. doi:10.1111/j.1475-6773.2005.00373.x
17. Denehy L, de Morton NA, Skinner EH, et al. A physical function test for use in the intensive care unit: validity, responsiveness, and predictive utility of the physical function ICU test (scored). *Phys Ther* 2013;93:1636-45. doi:10.2522/ptj.20120310
18. Montes R. Changes in the cross-sectional diameter of muscle ultrasonography between relaxation and maximum voluntary isometric contraction in normal young subjects. *Physiotherapy* 2001;87:172-8. doi:10.1016/S0031-9406(05)60603-7
19. Sommers J, Engelbert RHH, Dettling-Ihnenfeldt D, et al. Physiotherapy in the intensive care unit: an evidence-based, expert driven, practical statement and rehabilitation recommendations. *Clin Rehabil* 2015;29:1051-63. doi:10.1177/0269215514567156
20. Slade SC, Dionne CE, Underwood M, et al. Consensus on Exercise Reporting Template (CERT): Explanation and Elaboration Statement. *Br J Sports Med* 2016;50:1428-37. doi:10.1136/bjsports-2016-096651
21. Hodgson CL, Stiller K, Needham DM, et al. Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. *Crit Care* 2014;18:658. doi:10.1186/s13054-014-0658-y
22. Parry SM, Berney S, Warrillow S, et al. Functional electrical stimulation with cycling in the critically ill: A pilot case-matched control study. *J Crit Care* 2014;29:695.e1-695.e7. doi:10.1016/j.jcrc.2014.03.017