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RESEARCH ARTICLE

Lactate production without hypoxia in skeletal muscle during electrical cycling: Crossover study of femoral venous-arterial differences in healthy volunteers

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Abstract

Background

Aim of the study was to compare metabolic response of leg skeletal muscle during functional electrical stimulation-driven unloaded cycling (FES) to that seen during volitional supine cycling.

Methods

Fourteen healthy volunteers were exposed in random order to supine cycling, either volitional (10-25-50 W, 10 min) or FES assisted (unloaded, 10 min) in a crossover design. Whole body and leg muscle metabolism were assessed by indirect calorimetry with concomitant repeated measurements of femoral venous-arterial differences of blood gases, glucose, lactate and amino acids.

Results

Unloaded FES cycling, but not volitional exercise, led to a significant increase in across-leg lactate production (from -1.1±2.1 to 5.5±7.4 mmol/min, $p<0.001$) and mild elevation of arterial lactate (from 1.8±0.7 to 2.5±0.8 mM). This occurred without widening of across-leg veno-arterial (VA) O_2 and CO_2 gaps. Femoral SvO_2 difference was directly proportional to VA difference of lactate ($R^2 = 0.60$, $p = 0.002$). Across-leg glucose uptake did not change with either type of exercise. Systemic oxygen consumption increased with FES cycling to similarly to 25W volitional exercise (138±29% resp. 124±23% of baseline). There was a net uptake of branched-chain amino acids and net release of Alanine from skeletal muscle, which were unaltered by either type of exercise.

Competing interests: The authors have declared that no competing interests exist.

Conclusions

Unloaded FES cycling, but not volitional exercise causes significant lactate production without hypoxia in skeletal muscle. This phenomenon can be significant in vulnerable patients' groups.

Introduction

Functional electrical stimulation-assisted cycling (FES cycling) is a method originally developed over 30 years ago for patients with spinal cord injury [1]. It uses computer-driven electrical pulses delivered by transcutaneous electrodes and directly activating muscle contractions, independently on functionality of the physiological pathway between upper motoneuron and the neuromuscular junctions. The method is now commercially available in the form of both stationary and mobile devices [2], used by patients with a wide range of conditions incl. spinal cord injury [3], stroke [4,5], and multiple sclerosis [6]. FES cycling was demonstrated to improve cardiovascular fitness, insulin sensitivity [7] bone density and muscle strength [2,8]. In recent years, FES-cycling has become particularly attractive for sedated critically ill patients. Early mobilization is the only intervention, which can partially prevent the development of intensive care unit-acquired weakness [9–14]—the major long-term consequence in the survivors of protracted critical illness [15,16]. Muscle atrophy [17,18] and dysfunction [18] occur very early in the critically ill and FES cycling can help to deliver exercise before the patient can co-operate with a physiotherapist [19].

Although FES cycling seems to be feasible in intensive care unit patients [19], before its effect on meaningful clinical outcomes can be tested in the critically ill and other vulnerable patients groups, important physiological questions need to be addressed. Metabolic efficacy (i.e. power output divided by metabolic cost) of the FES cycling is typically very low, around 5–10%, as compared to 25–40% in volitional cycling [20–22]). This is likely due to non-physiological pattern of muscle activation, where large muscle groups are activated simultaneously rather than small well-coordinated units [2,23]. Despite FES cycling increases cardiac output [24] and leg blood flow to the same extent [25] or even more [26] than volitional cycling and consequently oxygen delivery to the muscle should be normal, there are features suggesting early switch to anaerobic metabolism: early fatigue [23,27], rapid intramyocellular glycogen depletion [28], increase of respiratory quotient (RQ) >1 [20] and even a mild increase in arterial lactate levels [29]. Increased lactate production could be caused by microcirculation impairment during electrically stimulated asynchronous contraction [30] or by a mismatch between glycogenolysis activated by electrical stimulation [31] and pyruvate oxidation.

Nonetheless, a direct evidence of the presence of anaerobic metabolism in skeletal muscle during FES cycling is lacking. In addition, whilst the influence of volitional resistance exercise on amino acid metabolism has been extensively studied [32–36] there is no such data for FES cycling, although one study demonstrated activation of anabolic signalling in electrically stimulated gastrocnemius muscle in a rat [31]. These questions may be particularly relevant before FES-assisted exercise is introduced to critically ill patients, who are in profound protein catabolism and may be less able to clear lactate from systemic circulation.

In light of this we conducted a crossover study of volitional and FES supine cycling in healthy postprandial volunteers, where we combined indirect calorimetry with across-leg venous-arterial (VA) difference studies. We hypothesized that FES-cycling as compared to light volitional exercise would lead to increased production of lactate in correlation with

widening of VA-CO_2 gap (as the measure of anaerobic metabolism), and with increased amino-acid efflux from skeletal muscle during exercise.

Materials and methods

Study subjects

Our experimental group consisted of 14 young (31±8 years), non-obese (23.7±3.7kg/m^2) healthy volunteers (gender M/F = 11/3). University Hospital Kralovske Vinohrady's Research Ethics Board reviewed the protocol and approved the study. Prior to the enrolment, all subjects gave their written informed consent in accordance with the Declaration of Helsinki.

Overview of study design

The study was performed during two visits performed 1 week apart. Subjects were asked to attend the visit at 08:00 AM after an overnight fast. In between these visits, the subjects were advised to take their usual diet and avoid strenuous exercise. During the first visit, the volunteers underwent a physical examination and body composition measurement. After 30 min bed rest, their energy expenditure was measured using indirect calorimetry with a ventilated canopy system. Afterwards, in each subject's VO_{2MAX} was determined on a cycle ergometer with stepwise load by 25 W increments until exhaustion. During the second visit, subjects were given a standardized breakfast containing 70 g of carbohydrates, 10 g protein and 15 g of fat. Afterwards, femoral vein and radial artery were cannulated. After 30 min rest, the subjects were exposed in random order to one of two supine exercise protocols, separated by 3 hours rest. Both protocols begun with baseline measurements (AV difference studies and calorimetry) followed by 5 min of passive cycling. Then, the subjects either performed three 10 min cycles of volitional cycling (at 10, 25 and 50 W, respectively) separated by 5 min of passive cycling (Group A), or FES cycling (Group B). The exercise protocols are outlined in Fig 1.

Methods

Indirect calorimetry and body composition assessment. Resting energy expenditure and RQ were measured after overnight (12 h) fast and 30 min bedrest using canopy as a mixing chamber with 10 sec sampling (Quark RMR device, Cosmed, Italy). To determine peak oxygen uptake (VO_{2max}) exhaustive exercise test was performed in each subject on an electromagnetically braked bicycle ergometer Ergoline Ebike (Ergoline Gmbh, Germany). After 5 min warm-up period, a workload of 50W was initiated and increased by 25 W every minute continuously until fatigue despite the verbal encouragement. Oxygen uptake was measured using mask, breath-by-breath, 10 sec sampling period (Quark RMR device, Cosmed, Italy. ECG was monitored continuously. Gas analysers (container 5% CO_2, 16% O_2 and room air) and flow analyser were calibrated prior to each measurement. Body fat was assessed using bioimpedance analysis (NutriGuard 2000, Bodystat, Germany).

Cannulations. Femoral vein was cannulated 2–3 cm below inguinal ligament under ultrasound guidance. In order to avoid the admixture of blood from saphenous and pelvic veins [37], a single-lumen central venous catheter (B-Braun, Germany) was inserted retrogradely to the depth of 10–15 cm so that the tip was deep in the femoral muscular compartment. For arterial sampling, we used a 22 F catheter (BBraun, Germany) inserted into the radial artery.

Cycling protocols. For both volitional and FES cycling we used RT-300 bikes (Restorative Therapies Ltd., USA) and the exercise was performed in supine position. *Volitional cycling* consisted of three 10 min intervals of active cycling: 10W (13 revolutions/min, resistance 7 N/m), 25W (31 revolutions/minute, 7.6 N/m), 50W (35 revolutions/min, and resistance 13.4 N/

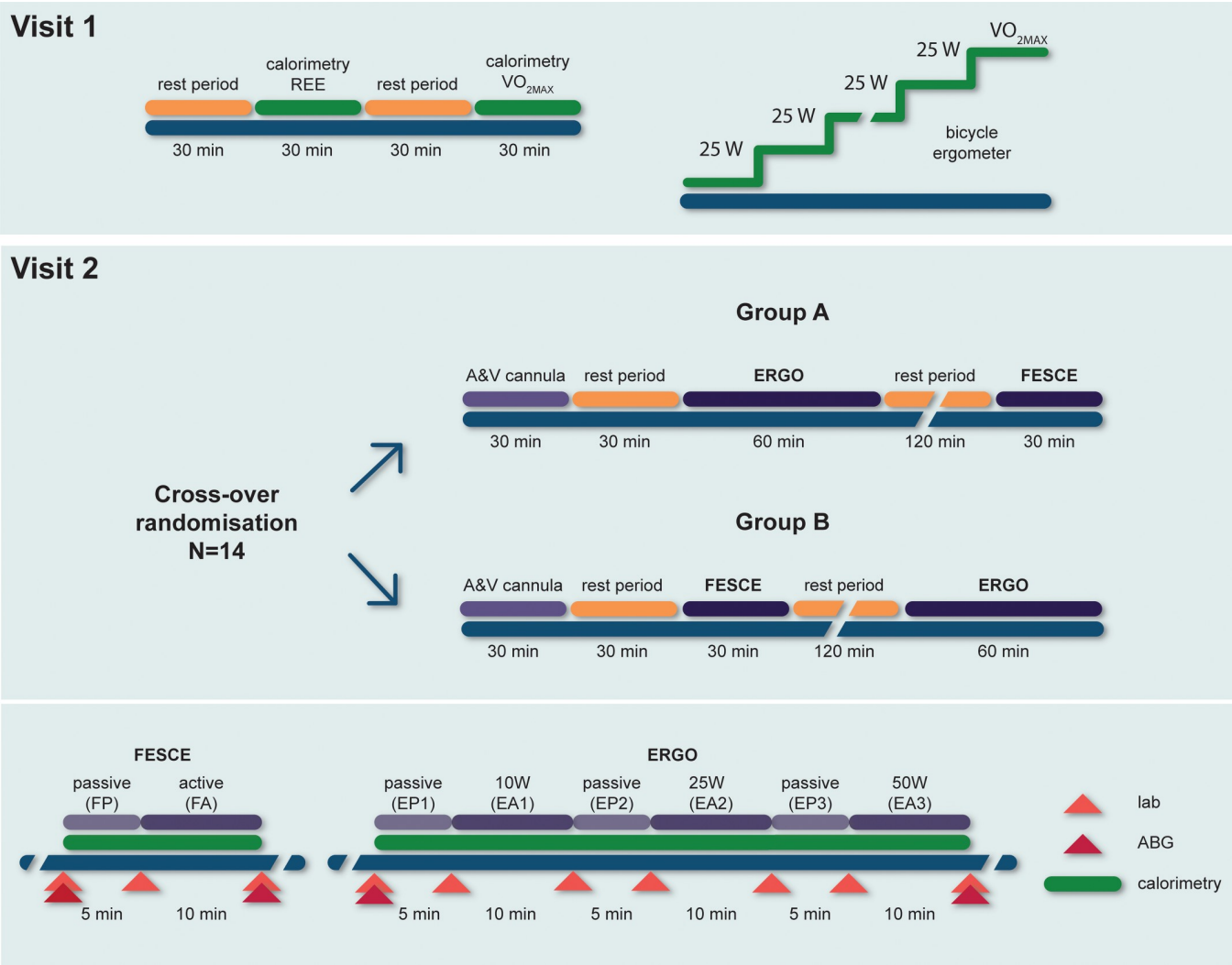

Fig 1. Overview of study design. Arrows designate arterial and venous blood sampling times. Note: ERGO = volitional cycling, FESCE = functional electrical stimulation cycling. Details of exercise are shown in the inlet at the bottom.

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m). These period were preceded (warm up) and separated by 5 min of passive cycling at 25 revolutions/min. *FES cycling*: Three pairs of transcutaneous electrodes (3 x 4", Restorative Therapies, Ltd., USA) electrodes were applied on each leg over quadriceps, hamstrings and gluteus maximus muscles, as per manufacturer's instructions. Prior to electrode placement, we measured the thickness of fat layer between the skin and muscle by ultrasound. After 5 min passive warm up (25 revolutions/min), the target speed was changed to 30 revolutions/min and stimulation gradually (1%/s) started to achieve 25 mA. Then, in each subject, the stimulation current was gradually increased to reach subjectively tolerated maximum. Oxygen uptake was measured continuously in both volitional and FES assisted cycling using mask breath-by-breath system (Quark RMR device, Cosmed, Italy). Gas analysers (container 5% CO_2, 16% O_2 and room air) and flow analyser were calibrated prior to each measurement.

Laboratory methods. Arterial and venous blood samples were analysed for blood gases, lactate and haemoglobin using POCT analyser Cobas b221 (Roche Diagnostics Limited, USA). For other analysis blood samples were centrifuged and frozen at -80˚C until analysed. Serum

creatine kinase and myoglobin was measured in a certified institutional laboratory (Cobas system, Roche Diagnostics Ltd., USA). Serum amino acid concentration in arterial/venous blood was analysed using capillary electrophoresis as described [38].

Calculations and statistics

Metabolic efficacy. Metabolic efficacy of volitional cycling was calculated as power output divided by the increase of energy expenditure [2]. Veno-arterial gap in the total content of carbon dioxide ($ctCO_2$ gap) was calculated according to equations used in ABL 900 Analyser (by Radiometer, Copenhagen, Denmark).

$$ctCO_2(B) = 9.286 \times 10^{-3} \times pCO_2 \times ctHb \times \left[1 + 10^{(pHEry - pKEry)}\right] + ctCO_2(P) \times \left(1 - \frac{ctHb}{21.0}\right)$$

where $ctCO_2$ (B) = CO_2 content in blood in mmol/L; $ctCO_2$ (P) = CO_2 content in plasma in mmol/L and equals to 0.23 x pCO2 + $cHCO_3^-$(P); pCO_2 is partial pressure in kPa, ctHb = haemoglobin content in mmol/L. $ctCO_2$(P). pH_{ERY} = estimated intracellular pH in red blood cells, which equals to 7.19+0.77 x (pH-7.4)+0.035 x (1-SO_2), where SO_2 is haemoglobin saturation with oxygen; and finally pK_{ERY} is a negative decadic logarithm of bicarbonate dissociation constant:

$$pK_{ERY} = 6.125 - \log\{1 + 10^{[pHEry - 7.84 - (0.06 \times SO_2)]}\}$$

Blood flow. In both FES and volitional cycling, leg oxygen uptake represents a relatively fixed proportion (76±8% and 78±9%, respectively) of whole-body oxygen uptake [39]. Therefore, an index of blood flow through the leg was calculated as whole-body oxygen consumption divided by the difference of oxygen content in arterial and femoral-venous blood. Blood oxygen content was calculated in mmol/L as 0.00983*pO_2 + SO_2[%]/100 * Hb *0.06206*(1-COHb [%]/100 –metHb[%], where SO_2 is saturation of haemoglobin with oxygen [%], Hb is haemoglobin [mmol/L], CO-Hb and met-Hb are fractions of carbonyl and methemoglobin, respectively, and pO_2 is partial pressure of oxygen [kPa].

Statistics. We used linear mixed effect model for 2x2 crossover design processed with software Stata 15 (Stata Corp., LLC, U.S.A.) [40,41]. The model consists of fixed and random part. In the fixed part, the model contained following parameters: (1) Sequence, i.e. order in which subject performed volitional and FES cycling protocols. Had this parameter been significant, a carry-over effect would have been present; (2) Period, basal vs. active, a parameter exploring the effect of the exercise, regardless whether volitional or FES; (3) Treatment, exploits the difference between volitional and FES cycling; and (4) Interaction Period#Treatment exploits whether FES cycling differs from volitional cycling during exercise period. Random part of the model contains subject number in order to take into account repeated measurements. Binary data are showed as frequency + %, continuous data as means ± SD. P value <0.05 was considered as significant. Whenever another test was used we specified this in the text. Sample size determination was performed prior commencement of the protocols with VA lactate difference as a primary outcome.

Results

Characteristics, tolerability and signs of muscle damage

All 14 subjects finished the protocol without adverse events; baseline (visit 1) calorimetry data are available for 13 subjects only due to a technical problem. Baseline characteristics are

outlined in Table 1. Sequence parameter of linear mixed effect model was not significant in any of analysed parameters (p = 0.14–0.94), so we assume no carry over effect from previous cycling protocol.

Maximum tolerated stimulation current of FES was 45±13 mA (range 25–67 mA). Although FES cycling caused a degree of discomfort, post-exercise serum myoglobin remained within reference range (<85 ng/mL) in all subjects (33±15 pg/mL, range 21–74). Nonetheless, there was a positive correlation between maximal stimulation current and post-exercise serum myoglobin (Spearman's $R^2 = 0.57$, p = 0.002).

Metabolic efficacy of volitional vs. FES cycling

Metabolic efficacy of volitional cycling was 39.2±5.6%. Unloaded FES cycling led to an increase of metabolic rate to 138±29% from baseline, which was comparable to the increase with 25 W volitional exercise (124±23%). See Fig 2. Energy gain from anaerobic glycolysis was negligible or negative for volitional cycling and 5.0±6.2 W for FES cycling.

Blood flow index

At rest before volitional and FES cycling, blood flow index was 6.6±2.4 vs. 6.3±3.4 (p = 0.57), and increased significantly (p<0.01) and similarly (p = 0.77) to 160% and 165% of baseline after volitional and FES exercise.

Exploring muscle metabolism during FES cycling

VA differences of both O_2 and CO_2 contents (ctO_2 and $ctCO_2$) tended to widen with volitional exercise (Fig 3A and 3B), whilst the opposite trend was seen for FES cycling. In line, there was no change in oxygen saturation of haemoglobin in femoral venous blood neither with volitional exercise (from 63.9±12.7% to 64.3±8.7%), whilst there was an increase after FES cycling (from 62.6±11.3 to 70.3±8.7%; p = 0.02). Across-leg respiratory exchange ratio (i.e. the ratio between VA differences of CO_2 and O_2 contents) although different at baseline (Fig 3C) tended to increase with volitional cycling, but this change was not significant. There was no change from baseline in across-leg glucose uptake of glucose (FES -5.5±3.9 to -5.9±3.6mmol/min; volitional -7.0±3.6 to -6.9±6.1mmol/min). Whole body RQ increased with FES cycling (0.88±0.02 to 0.95±0.02, p = 0.001, but did not change with volitional exercise (0.87±0.02 to 0.85±0.02, p = 0.55; See Fig 3D) and only FES cycling led to an increase in across-leg lactate VA differences and production (from -1.1±2.1 to 5.5±7.4 mmol/min, p<0.001 vs. from -0.9 ±1.1 to -0.4±1.2 mmol/min, p = 0.70 Fig 3E) with very high inter-individual variability (See

Table 1. Baseline characteristics of study subjects.

Parameter	Mean±SD	N
Age (years)	31±8	14
Sex (M/F)	11/3	14
BMI (kg/m^2)	23.7±3.7	14
Body fat (%)	14±6	14
REE (kcal/day)	1901±356	13
RQ at rest	0.90±0.10	13
VO_{2MAX} (ml/kg/min)	41±6	13

Note: BMI = body mass index, REE = resting energy expenditure, RQ = respiratory quotient, VO_{2max} = peak oxygen consumption. Baseline data from one subject are unavailable due to technical problem with the machine.

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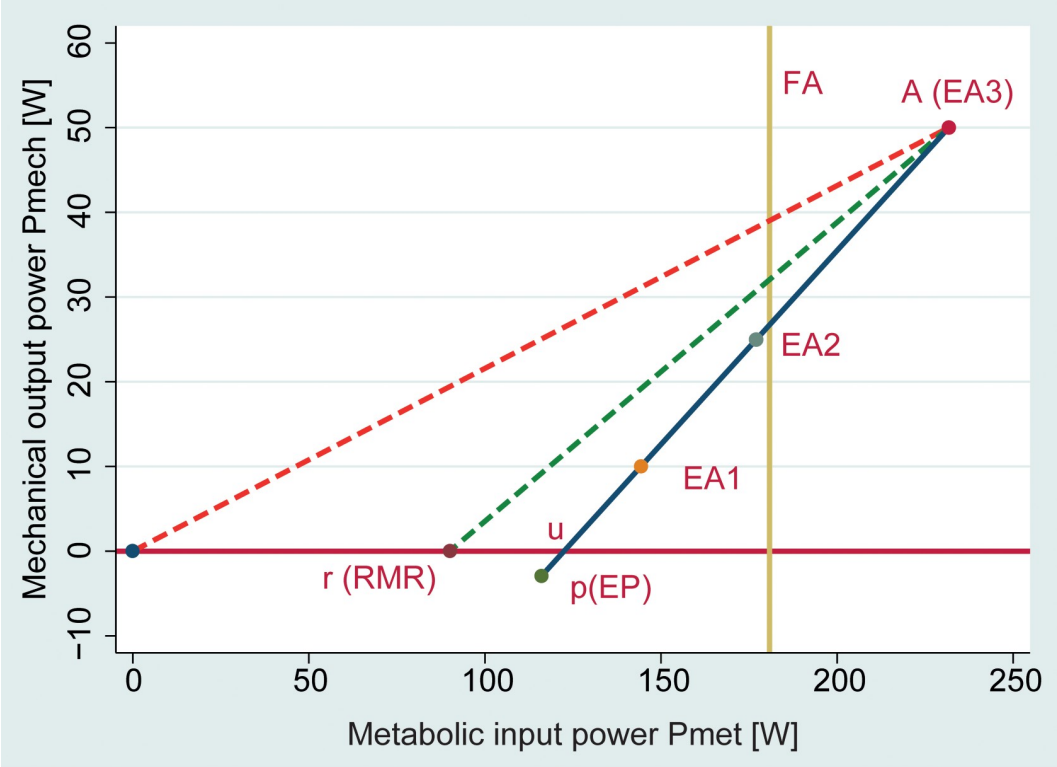

Fig 2. Hunt's diagram [2,22] outlining the efficacy of volitional exercise relative to metabolic cost of unloaded FES cycling (yellow line). Note: Metabolic efficiency is the gradient of the line joining the active cycling operating point (A) to one of the baseline conditions: u is unloaded cycling; r is rest, p is passive cycling.

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Fig 3F). Systemic arterial lactate levels remained normal after volitional cycling (from 1.6±0.6 mmol/l to 0.9±2.1 mmol/l, p = 0.887), and increased after FES cycling (from 1.6±0.7 mmol/l to 2.3±0.8 mmol/l, p<0.001).

Analysing lactate production

With FES cycling, there was a significant positive correlation between VA lactate difference and femoral venous haemoglobin saturation with oxygen (Spearman's R^2 = 0.6, p = 0.002, Fig 3G). Lactate producers had smaller veno-arterial difference in CO_2 content of the blood (R^2 = 0.3, p = 0.046, Fig 3H), effectively ruling out oxygen delivery problem. Subjects with femoral VA lactate difference >0.5 mmol/L ("lactate producers", n = 5, see Fig 3F) were compared with the rest of the group (n = 9) but no difference was found besides lactate having higher RQ at baseline (0.94±0.06 vs., 0.86±0.07, p = 0.034). Of note, stimulation current used during FES cycling was not different in lactate producers (42±10 vs. 44±16 mA, p = 0.87).

Amino acid metabolism

As expected in postprandial volunteers, at baseline resting skeletal muscle was taking up branched-chain amino acids (BCAAs) whilst producing Alanine (Ala). Skeletal muscle only produced Glutamine (Gln) at baseline in the volitional cycling group, otherwise the change was not significantly different from zero (Fig 4). Neither type of exercise led to a significant change of amino acid metabolism, but it is apparent from Fig 4 that with volitional cycling there was a trend to an increase in Ala production and a decrease of glutamine production,

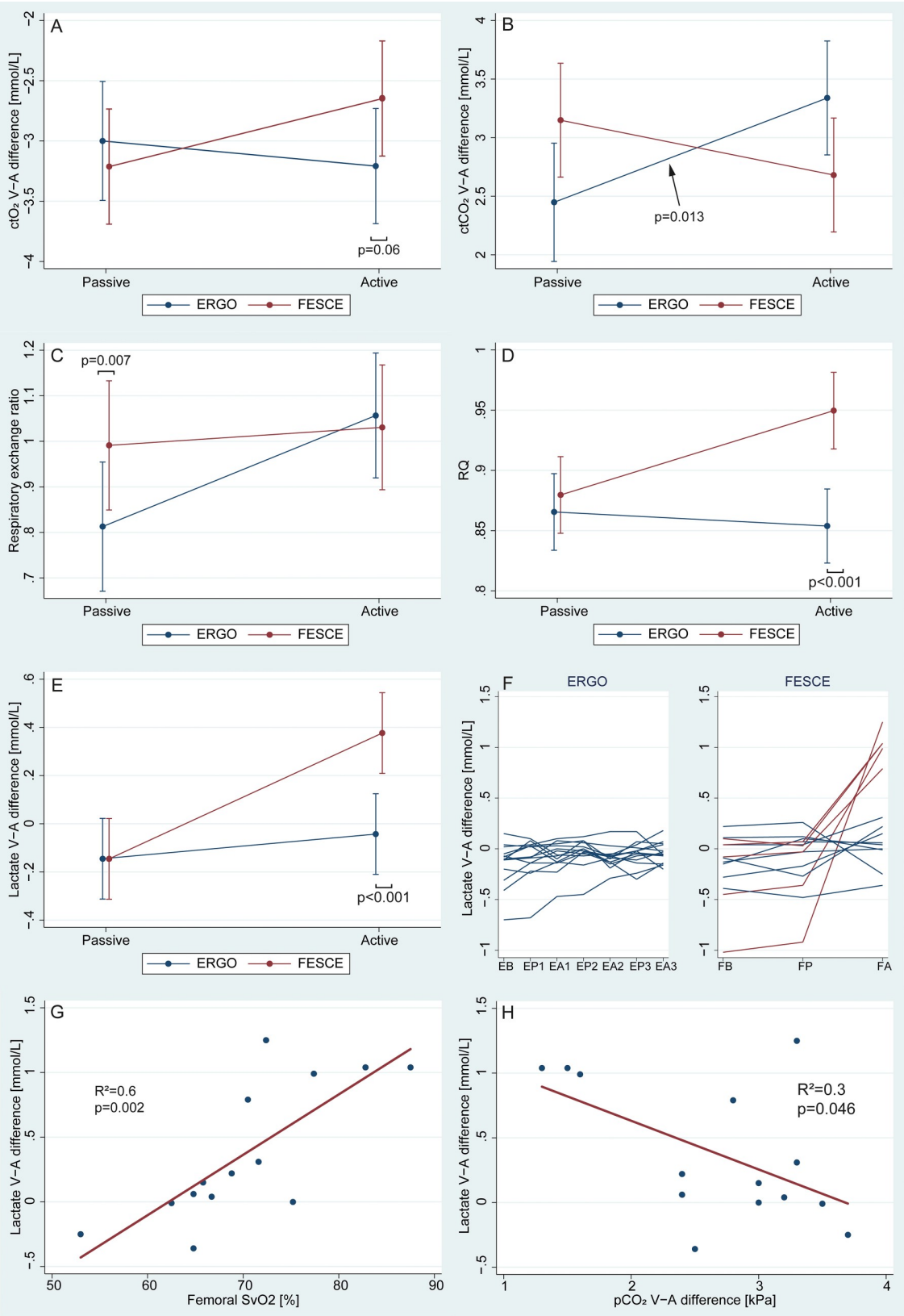
A
ctO₂ V−A difference [mmol/L]
p=0.06
Passive
Active
ERGO
FESCE
B
ctCO₂ V−A difference [mmol/L]
p=0.013
C
Respiratory exchange ratio
p=0.007
D
RQ
p<0.001
E
Lactate V−A difference [mmol/L]
p<0.001
F
ERGO
FESCE
EB EP1 EA1 EP2 EA2 EP3 EA3
FB FP FA
G
R²=0.6
p=0.002
Femoral SvO2 [%]
H
R²=0.3
p=0.046
pCO₂ V−A difference [kPa]

Fig 3. Venous-arterial (VA) differences studies. Lactate VA difference is derived from multiplying femoral VA differences of concentrations and calculated leg blood flow. See text for further details. Linear regression was used in G and H. Note: ctO_2 and $ctCO_2$ = total blood content of oxygen and carbon dioxide; RQ = whole body respiratory quotient; SvO_2 = femoral venous saturation of haemoglobin with oxygen. ERGO = volitional cycling; FESCE = functional electrical stimulation-assisted cycling; Passive period vs Active FES/50W volitional period.

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whilst after FES cycling no such a trend was apparent (across-leg amino acid exchange remained unaffected). Uptake of BCAAs continued and did not change with either type of exercise ($p = 0.83$ and $p = 0.86$).

Discussion

The major finding of our study is that unloaded supine FES cycling leads to lactate production without signs of muscle hypoperfusion, as low blood flow through exercising limbs would have caused femoral venous haemoglobin desaturation (Esaki et al., 2005; Sun et al., 2016) and widening of VA-CO_2 gap [42], which were not observed in our subjects. Moreover, there was a significant positive correlation between across-leg lactate production and femoral venous oxygenation, suggesting that subjects producing lactate did so whilst extracting less oxygen from (and producing less CO_2 into) the local circulation. There was a marked interindividual variability in metabolic response to FES cycling: some subjects responded to FES similarly to volitional cycling, whilst others produced so much lactate that it elevated systemic (arterial) lactate concentrations well above the normal range. We have not found any convincing characteristics of the subjects producing lactate during FES, although they seemed to be oxidizing more carbohydrates at baseline. Notably there was no correlation between the amplitude of stimulation current used and the production of lactate.

Tissue dysoxia and femoral venous desaturations are known to accompany lactate production during high intensity volitional exercise (i.e. > approx. 60% $VO_{2\ MAX}$) [43, 44, 45], at which oxidative phosphorylation becomes oxygen dependent. At lower exercise intensities, there is a concomitant lactate production in fast twitch glycolytic muscle fibres and consumption in slow twitch fibres [46] and—as seen in our subjects—during a steady low intensity volitional exercise, skeletal muscle may become a net lactate consumer [47].

The most obvious explanation of FES-driven lactate production would be tissue dysoxia, occurring despite adequate flow of oxygenated blood through major vessels. Non-physiological asynchronous contractions of large muscle units activated by FES [2,23] could have caused an inhomogeneous perfusion at the level of microcirculation, with hypoxic regions and units with luxurious perfusion acting as functional AV shunts. The increase in whole-body RQ with FES cycling, would support the presence of some degree of anaerobic metabolism, but it could also be explained by impaired fatty acid oxidation with the preference of carbohydrate substrates [39] or by primary increased ventilation. The major argument against microcirculatory impairment and anaerobic lactate generation is the absence of widening of venous-arterial CO_2 gap. Carbon dioxide is produced also anaerobically and released from bicarbonate as the consequence of buffering acid load in hypoxic tissue, and because CO_2 diffuses rapidly even from poorly perfused tissue, VA-CO_2 gap is regarded as a very sensitive marker of tissue hypoxia caused by impaired microvascular flow [48]. Not only VA CO_2 gap was not widened after FES cycling, but in was inversely proportional to lactate production. Moreover, the 138±29% increase in the whole body oxygen consumption after FES-cycling observed by us and others [49] would also argue against major oxygen delivery problem.

Lactate production without tissue dysoxia may occur as a result of the dysbalance between pyruvate production from glycolysis and its conversion to acetyl-CoA and oxidation in tricarboxylic acid cycle [46,47]. Muscle contraction instantly triggers, via the increase in $Ca^{2+}{}_{[IC]}$,

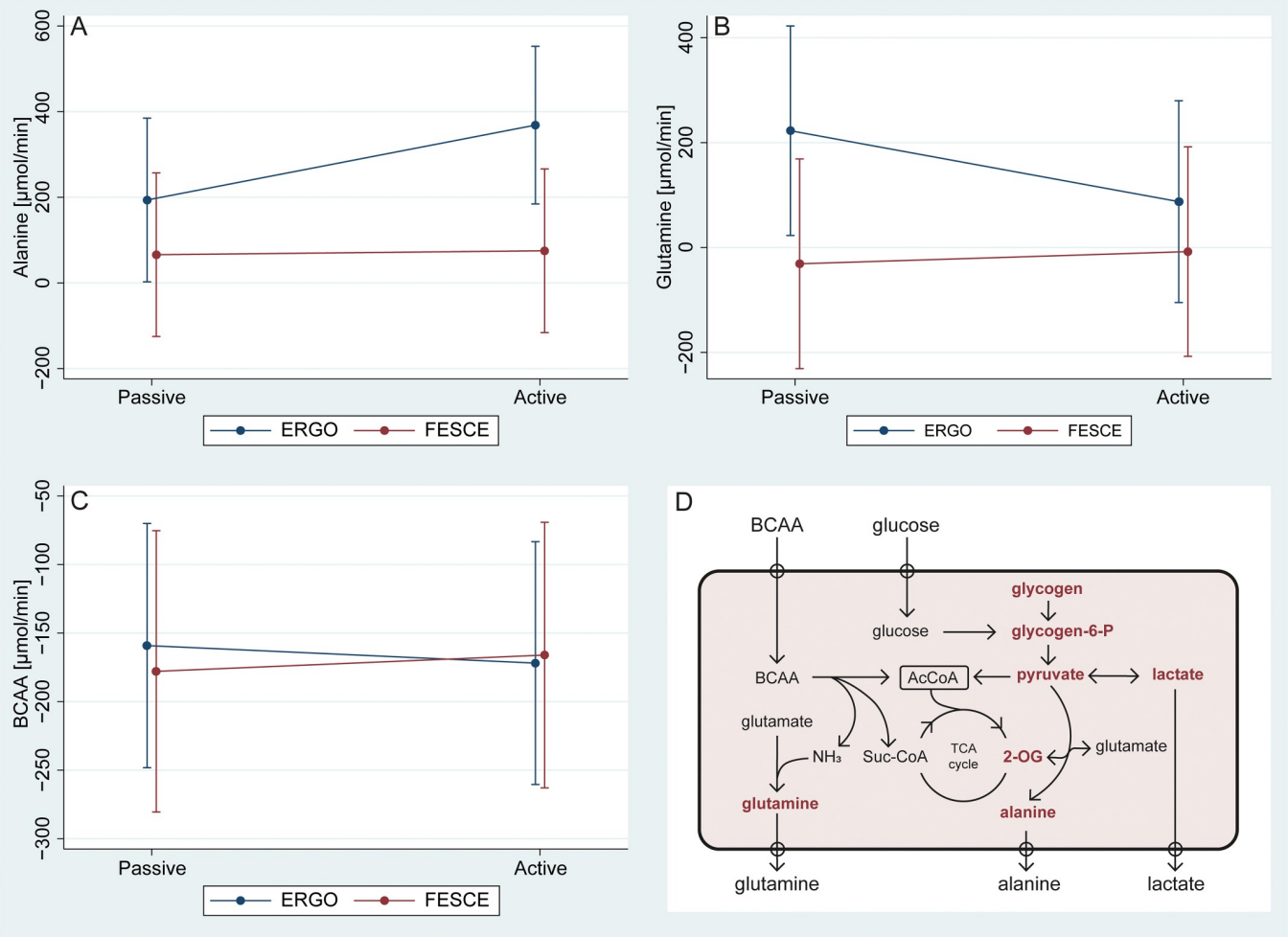

Fig 4. Amino acid metabolism during volitional and FES cycling. Values are derived from multiplying femoral VA differences of concentrations and calculated leg blood flow. Note: BCAA = branched-chain amino acids (i.e. the sum of Valine, Leucine, and Isoleucine); ERGO = volitional cycling; FESCE = functional electrical stimulation-assisted cycling; Passive period vs Active FES/50W volitional period. TCA = tricarboxylic acid cycle, 2-OG = 2-oxoglutarate.

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glycogenolysis and glycolysis, producing pyruvate. Sudden increase in cytosolic pyruvate concentration shifts the near-equilibrium reaction: *Pyruvate* + *Glutamate* ↔ *Alanine* + *2-oxoglutarate*, rightwards. Alanine is increasingly released during exercise and 2-oxoglutarate is believed to increase the functional capacity of tricarboxylic acid cycle [50] allowing for increase in oxidative ATP production. BCAAs uptake in skeletal muscle continues or even increases during exercise, providing carbons for oxidative pathways and nitrogen for Alanine and Glutamine formation (Fig 4D). Although non-significant, we have observed some trends to these responses after volitional cycling, but no rearrangement at all of amino acid metabolism was seen with FES exercise. Glycolytic compartment is known to respond much faster compared to oxidative phosphorylation and a rapid increase in cytosolic pyruvate concentration could lead to lactate release from cells even in the absence of tissue hypoxia [46]. Moreover, FES cycling compared to volitional exercise is known to activate glycogenolysis and glycolysis disproportionally faster than oxidative pathways [20,39]. In light of this, our data are consistent with aerobic lactate generation due to a dysbalance between pyruvate generation from glycogenolysis and glycolysis and its oxidation in citric acid cycle. Indeed, skeletal muscle is not a

metabolically homogenous tissue [47] and FES may preferentially trigger muscle contraction in glycolytic fast twitch fibres, whilst lactate oxidizing slow fibres may have been less sensitive to electrical stimulation. The sensitivity of different muscle fibres to external stimulation is unknown and remains to be studied, but a higher sensitivity of fast twitch fibres would be in keeping with the finding, that a long-term external electrical stimulation of a denervated muscle restores its mass and contractile power, but not fatigability [51].

From clinical point of view we found important the absence of venous haemoglobin desaturation during FES-cycling as decreased central venous saturation impairs systemic oxygenation in patients with a degree of intrapulmonary shunt. Mild lactic acidosis could be of concern in patients with impaired lactate clearance (e.g. liver failure). Unloaded FES cycling led to VO_2 response comparable to 25W volitional exercise, which would represent a very significant exercise load for critically ill patients, who tend to have even higher metabolic cost for a given power output [52] and only tolerated cycling at 3–6 W in one study [52]. Lastly, although the absence of laboratory signs of muscle damage and amino acid release is reassuring, the positive association of post-exercise serum myoglobin with stimulation current amplitude suggest a risk of muscle damage from the use of stimulation currents above 70mA, which are often needed to elicit visible contractions in sedated critically ill patient, perhaps due to their impaired muscle excitability [16].

The major weakness of our study is that we have not used direct measurements of leg blood flow and tissue oxygenation. We only use indirect indices, which prevents us from drawing any conclusions about the influence of FESCE on blood flow, which might have been altered, eg. by altered function of muscle pump. However, effects of FES exercise on leg blood flow are known [17,25] and the main finding of the study, i.e. lactate production without evidence of tissue hypoxia, can be supported by across-leg VA differences alone. Muscle tissue oxygen concentrations are known to be closely reflected by femoral venous oxygen content [43,53].

In conclusion, we have demonstrated that 10 min of supine FES cycling in healthy volunteers leads to production of lactate without features suggestive oxygen consumption/delivery mismatch, which are known to accompany lactate production during high intensity voluntary exercise [42,43]. Despite a significant increase in systemic oxygen consumption (proportional to 25W of volitional exercise) and unaltered across-leg glucose uptake with FES cycling, we have not observed the rearrangement of amino acid metabolism towards anaplerosis.

Supporting information

S1 Table. Dataset spreadsheet.
(XLSX)

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Formal analysis: Jan Gojda, Petr Tůma, Kamila Řasová, František Duška.

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Software: Petr Waldauf, Natália Hrušková, Barbora Blahutová, Adéla Krajčová, Petr Tůma.

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Příloha 2:

Originální článek k projektu B publikovaný v časopise Critical Care Medicine s infografikou a editoriálem

Effects of Rehabilitation Interventions on Clinical Outcomes in Critically Ill Patients: Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Objectives: To assess the impact of rehabilitation in ICU on clinical outcomes.

Data Sources: Secondary data analysis of randomized controlled trials published between 1998 and October 2019 was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Study Selection: We have selected trials investigating neuromuscular electrical stimulation or cycling exercises or protocolized physical rehabilitation as compared to standard of care in critically ill adults.

Data Extraction: Mortality, length of stay in ICU and at hospital, days on mechanical ventilator, and adverse events.

Data Synthesis: We found 43 randomized controlled trials (nine on cycling, 14 on neuromuscular electrical stimulation alone and 20 on protocolized physical rehabilitation) into which 3,548 patients were randomized and none of whom experienced an intervention-related serious adverse event. The exercise interventions had no influence on mortality (odds ratio 0.94 [0.79–1.12], $n = 38$ randomized controlled trials) but reduced duration of mechanical ventilation (mean difference, −1.7 d [−2.5 to −0.8 d], $n = 32$, length of stay in ICU (−1.2 d [−2.5 to 0.0 d], $n = 32$) but not at hospital (−1.6 [−4.3 to 1.2 d], $n = 23$). The effects on the length of mechanical ventilation and ICU stay were only significant for the protocolized physical rehabilitation subgroup and enhanced in patients with longer ICU stay and lower Acute Physiology and Chronic Health Evaluation II scores. There was no benefit of early start of the intervention. It is likely that the dose of rehabilitation delivered was much lower than dictated by the protocol in many randomized controlled trials and negative results may reflect the failure to implement the intervention.

Conclusions: Rehabilitation interventions in critically ill patients do not influence mortality and are safe. Protocolized physical rehabilitation significantly shortens time spent on mechanical ventilation and in ICU, but this does not consistently translate into long-term functional benefit. Stable patients with lower Acute Physiology and Chronic Health Evaluation II at admission (<20) and prone to protracted ICU stay may benefit most from rehabilitation interventions. (*Crit Care Med* 2020; XX:00–00)

Key Words: cycling; critically ill; exercise; neuromuscular electrical stimulation; outcome; physical rehabilitation

Mortality from most ICU syndromes is decreasing despite the increasing frailty and age of the patients being admitted to intensive care. Growing number of survivors suffer from poor long-term functional outcomes related to neuromuscular weakness and fatigability (1–4). Although ICU-acquired weakness is multifactorial (5), immobility plays an important role in its pathophysiology (6–9). Over the last two decades, there has been a paradigm shift away from providing "rest for recovery" to early mobility for patients in the ICU (5, 10–12). Since the landmark study by Schweickert et al (13), the concept of protocolized physical rehabilitation (PPR) has been shown to be safe (14–17) and physiologically plausible (13, 16–26). In addition, semiautomated instruments have been developed to deliver exercise to critically ill patients independently on their level of consciousness or constant presence of a physiotherapist. Namely, passive and active supine cycling on a bicycle ergometer (18, 25, 27–29) or neuromuscular electrical stimulation (NMES) (30–38), during which cutaneous electrodes placed over specific muscle groups electrically trigger muscle contractions.

As of today, it is difficult to offer a clear clinical guidance as to how and in whom to use which rehabilitation techniques

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at the bedside in ICU. Data from randomized controlled trials (RCTs) are quickly emerging as 14 new RCTs have been published since the topic has been last reviewed (39, 40), but a lot remained to be done regarding the individualized approach that could have been tailored to the patient's need and circumstances In light of this, we set out to systematically review all RCTs reporting clinical outcomes investigating all types of rehabilitation interventions in adult critically ill patients. In order to gain insight into the sources of heterogeneity of the results, we also performed a meta-regression analysis of factors that may have influenced the results of the RCTs.

METHODS

Registration

This meta-analysis is fully compliant with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (41), and systematic review has been prospectively registered in an international database of prospectively registered systematic reviews Prospero (No CRD42019132255, http: https://www.crd.york.ac.uk/prospero/).

Eligibility Criteria

We searched for RCTs in critically ill patients, which investigated a rehabilitation intervention defined as any form of PPR, NMES, or supine cycling. RCTs were included if they reported on at least one clinical endpoint such as mortality, days on mechanical ventilation (or ventilator-free days), lengths of stay in intensive care or in hospital, or long-term functional outcome. We have included all papers without language limitation that were accepted for publication or published between 1 January 1998 and 1 October 2019.

Information Sources and Search Strategy

Two researchers (A.K., K.J.) independently conducted a comprehensive literature search using PubMed, the Cochrane Central Register of Controlled Trials, MEDLINE, Web of Science, Physiotherapy Evidence Database, Scientific Electronic Library Online and Latin American & Caribbean Health Sciences Literature databases. Additionally, we searched the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov via their dedicated search portal for studies that might have been missed. Step-by-step strategy and full search terms sequence used in PubMed database can be found in **Supplemental Data File—Detailed Search Strategy** (Supplemental Digital Content 1, http://links.lww.com/CCM/F484). We adopted the PubMed search strategy when searching in other databases.

Selection of Studies and Data Extraction

Two authors (A.K., K.J.) independently extracted the data from the full text of papers into sheets designed a priori by the data analyst (P.W.). The two versions were compared, and any discrepancies are resolved by a third assessor (F.D.). Rationales for study exclusion are given in **Figure 1**.

Data Items

We extracted patients' age, sex, disease severity (Acute Physiology and Chronic Health Evaluation [APACHE] II, mortality in the control group), diagnostic category (medical, surgical, mix, specific disease only), and the proportion of patients with sepsis. We categorized the type of intervention as cycling, NMES or any form of PPR), timing (days after ICU admission or beginning of mechanical ventilation [MV]), and per-protocol exercise dose (in min/d, days/patient and whether or not the intervention was delivered >5 d per week). Outcomes included ICU- and end-of-study mortality (defined as mortality at the last follow-up point), the length of stay (LOS) in ICU and in hospital, the duration of mechanical ventilation and/or ventilator-free days at day 28, and any long-term functional outcome.

Risk of Bias

Risk of publication bias (small study effect) was assessed by Eggers test (with $p < 0.05$ considered significant) and by funnel plots, which were constructed in addition to forest plots for all meta-analyses (**Supplemental Table 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/F485; and **Supplemental Additional Results**, Supplemental Digital Content 3, http://links.lww.com/CCM/F486).

Summary Measures

Mantel-Haenzel odds ratios (ORs) and 95% CIs were calculated for death in ICU and death at the end of the study for each RCT. The OR was chosen because of the large variation in baseline event rates between the RCTs (mortality in the control groups ranges from 0% to 78%), implying that the relative risk would not be a good summary measure. Differences in means (95% CIs) between intervention and control groups were calculated for the LOS in ICU, LOS at hospital, duration of MV, and ventilator-free days. Where these outcomes were reported as median (interquartile range [IQR]) or median (range) and in the absence of access to record-level data, we used transformation to means (SD) as described by Wan et al (42).

Synthesis of Results and Measures of Consistency

Apart from the synthesis of the outcomes from all the RCTs, we separately analyzed three prespecified subgroups of RCTs based on the intervention studied: (NMES, cycling, and PPR). Heterogeneity of treatment effect between RCTs was assessed using a standard chi-square test, and, if appropriate, a weighted estimate of the typical treatment effect across all RCTs was calculated.

Additional Analyses

In order to gain insight into the sources of heterogeneity, prespecified subgroup analyses were performed to determine whether the treatment effect varies with the following: 1) intervention exposure (defined as mean ICU-LOS multiplied by per-protocol daily dose of rehabilitation [min]) and timing of initiation (>72 vs ≤72 hr within ICU admission),

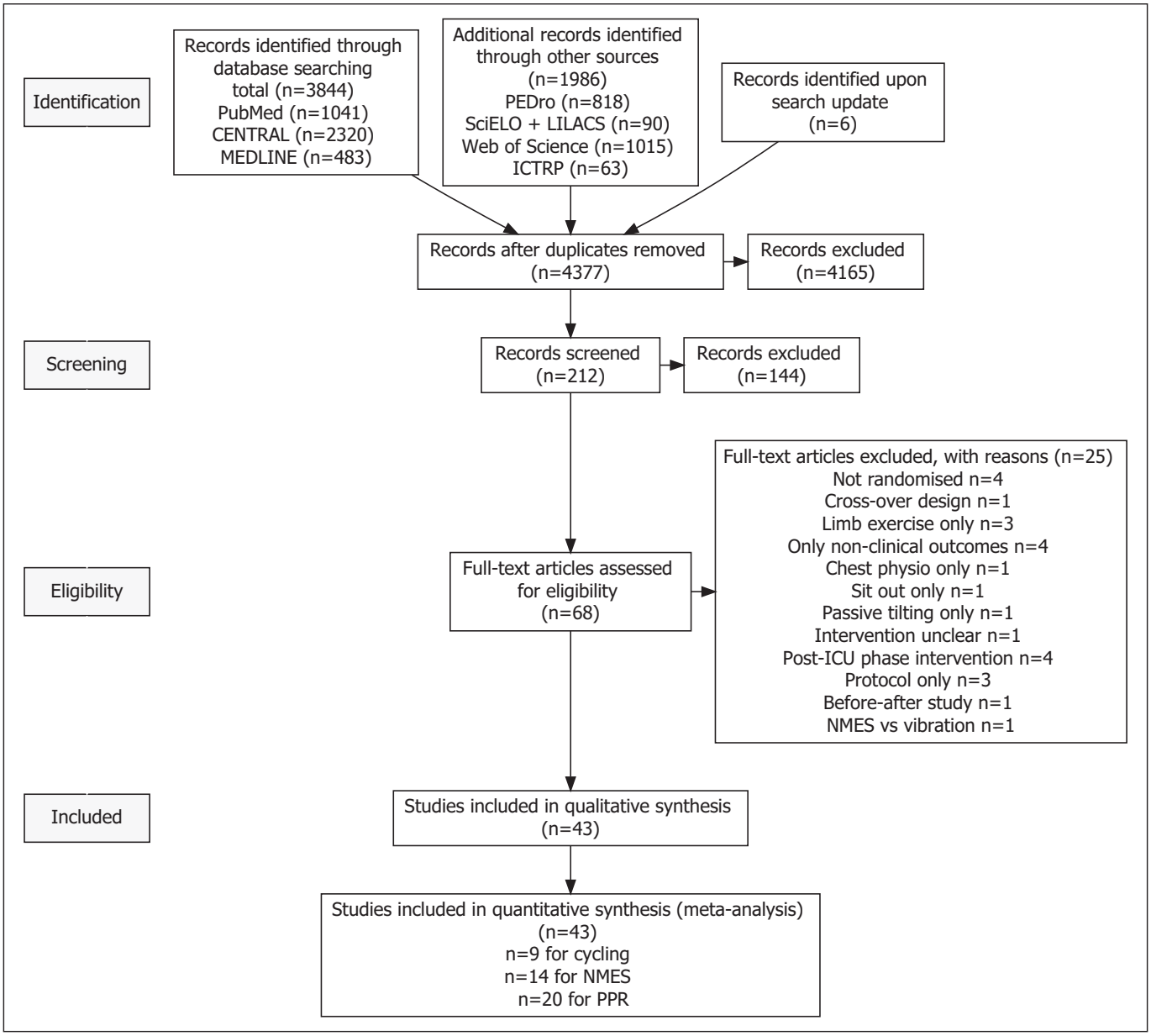

Figure 1. Search and selection process flowchart. Other sources include Physiotherapy Evidence Database (PEDro [*n* = 818]), Scientific Electronic Library Online (SciELO) and Latin American & Caribbean Health Sciences Literature (LILACS) databases (*n* = 90), World Health Organization International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov (*n* = 63) and secondary search within references of retrieved full texts (*n* = 6). CENTRAL = Cochrane Central Register of Controlled Trials, NMES = neuromuscular electrical stimulation, PPR = protocolized physical rehabilitation.

2) patient characteristics (sex, disease severity expressed as APACHE II score, proportion of patients with sepsis), and 3) risk of bias (whether MV duration or ICU and hospital LOS were reported in intention-to-treat population or only in survivors). Test for differences in subgroups were based on random effect models and DerSimonian-Laird method to calculate τ^2 (underlying between-study variability). In addition, for continuous independent variables, we also performed meta-regression to estimate its influence on the treatment effect.

All calculations were performed using statistical packages meta_4.9-5 (43) and metafor_2.1-0 (44) programmed in R, version 3.6.1 2019-07-05 R.app 1.65 (45). Further details of the methods and step-by-step analyses can be found in Supplemental Additional Results (Supplemental Digital Content 3, http://links.lww.com/CCM/F486).

RESULTS

Characteristics of Studies Analyzed

The search strategy (Fig. 1) yielded 43 RCTs. Of these, nine investigated some form of in-bed cycling, 14 NMES, and 20 PPR. One RCT (17) investigated combination of PPR with NMES, and it was further grouped with PPR. Individual RCTs processed in this meta-analysis are summarized in **Supplemental Table 2** (Supplemental Digital Content 4,

http://links.lww.com/CCM/F487). The RCTs were relatively small (median number of subjects is 55) and selective (median of 13% of admitted patients were recruited), often excluding patients with common comorbidities such as obesity (18, 25, 32, 46). Randomized patients (n = 3,548) were 59.5 years old (IQR, 56.5–62.5 yr old), had APACHE II score 19.6 (IQR, 17.9–23.7), and spent a median of 15 days (IQR, 10–21 d) in ICU and 10 days (IQR, 7–13 d) on mechanical ventilation.

Treatment Effects on In-Hospital Clinical Outcomes

Exercise interventions had no influence on ICU mortality (OR 1.02 [0.84–1.24]) or end-of-study mortality (OR, 0.94 [0.79–1.12]) (**Fig. 2**). This lack of effect on survival was homogenous in pooled RCTs (n = 38 RCTs, p for heterogeneity = 0.73 and 0.50, respectively) and across subgroups according to the type of exercise delivered. None of the RCTs reported a severe or life-threatening complication of the intervention. "ICU LOS" was marginally shorter in the intervention group as compared to controls (mean difference, –1.2 [–2.5 to 0.0] days, n = 31 RCTs), mostly due to the effect of RCTs investigating PPR (n = 16 RCTs, mean difference –2.0 [–3.6 to –0.3] days). The "duration of MV" reflected the treatment effects on ICU LOS (mean difference –1.7 d [–2.5 to –0.8 d], heterogeneity $p < 0.01$, n = 32 RCTs) (**Fig. 3**). "Hospital LOS" was not significantly different (mean difference –1.6 d [–4.3 to 1.2 d], n = 23 RCTs). See also Supplemental Additional Results (Supplemental Digital Content 3, http://links.lww.com/CCM/F486).

Treatment Effects on Long-Term Functional Outcomes

Twelve RCTs reported on some form of functional outcomes (Supplemental Table 2, Supplemental Digital Content 4, http://links.lww.com/CCM/F487). The timeframes and outcomes reported were diverse. In nine RCTs, there was no measurable effect of the intervention on functional variables, whereas three RCTs reported an improvement in physical function (17, 47) or the degree of independence (48). Most commonly reported parameter (in seven RCTs (17, 18, 24, 28, 47, 49) available from 768 patients) was physical component summary score component of The 36-Item Short Form Health Survey at 6 months, which was not significantly changed by rehabilitation intervention (mean difference, where positive value favors intervention 1.5 [-2.1; 5.1]). Other important patient-oriented outcomes such as return to work of cognitive function were only reported in few RCTs (19, 22, 50, 51).

Patients' Factors Influencing the Treatment Effect

Patients' age, male-to-female ratio, and proportion of septic patients did not influence the treatment effect on ICU LOS (p = 0.53, p = 0.49, p = 0.56, respectively). The meta-regression analyses suggest that the treatment effect on ICU LOS (**Fig. 4*A***) and MV duration (**Fig. 4*B***) might be reduced in RCTs on patients with higher APACHE II score. In line, the treatment reduced MV duration and ICU LOS in subgroup of RCTs enrolling patients with mean APACHE II below the median of 20 (mean differences –1.7 d [–3.3 to –0.1 d], –2.9 d [–4.4 to –1.3 d], respectively), whereas the treatment effect was not seen in RCTs on patients with APACHE II greater than or equal to 20 (mean differences –1.4 d [–3.3 to 0.5 d] and –0.4 d [–2.5 to 1.6 d], respectively). Importantly, there was no relation between APACHE II score in treatment effect on mortality (**Fig. 4*E***).

Intervention Characteristics Influencing the Treatment Effect

There is a strong association between the length of exposure to intervention and treatment effect on MV duration and ICU LOS ($p < 0.05$ for both) (**Fig. 4 C, D**). We have not found, however, any differences in treatment effects on ICU LOS between prespecified subgroups of the RCTs with or without early start (within 3 d of ICU admission, p = 0.46) (**Fig. 4*F***) or with the total per protocol extra rehabilitation dose in the intervention arm (p = 0.97). Nonetheless, only few RCTs monitored and reported delivered dose of intervention (19, 34, 47, 51–53), and in these, the delivered dose was invariably smaller than the dose prescribed in the protocol, sometimes as low as 25% of prescribed dose (19).

Risk of Bias

Risk of bias within RCTs is shown **Figure 5**, with details for individual RCTs in Supplemental Table 1 (Supplemental Digital Content 2, http://links.lww.com/CCM/F485). For neither of four main outcomes (mortality, ICU and hospital LOS, MV duration), the risk of publication bias (small study effect) was significant. Funnel plots can be seen with each forest plot in Supplemental Additional Results (Supplemental Digital Content 3, http://links.lww.com/CCM/F486). Only 10 RCTs reported ventilator-free days. There was no influence of study subjects' mortality on ICU LOS (p = 0.48), and MV duration was shortened in RCTs reporting it in intention-to-treat population (n = 19, mean difference –1.7 d [–2.5 to –0.8 d]) similarly to the RCTs reporting it only in survivors (n = 13, mean difference –1.4 d [–2.9 to 0.12 d]). Three RCTs (14, 17, 34) were stopped prematurely. Primary outcome was measured on average in 71% (range 31%–100%) of enrolled patients, but assessor was blinded to subject's treatment allocation only in three of 43 RCTs.

DISCUSSION

The main finding of this meta-analysis is that rehabilitation interventions in ventilated critically ill patients significantly reduce the duration of mechanical ventilation and the LOS in ICU by 1.7 and 1.2 days, respectively. Protocolized physical therapy (i.e. individualized physical exercise that is adjusted according to patient's tolerance and performance capacity) was more efficient that NMES alone or supine cycling-based treatment in reducing MV or ICU days. All forms of exercise seem to be safe, as none of the RCTs reported a serious or life-threatening complication. RCTs focused on physiologic outcomes showed no effect (54–56) or a reduction (29) in systemic inflammation, very modest changes in gas exchange and hemodynamics (38, 55, 57), and preservation or improvement

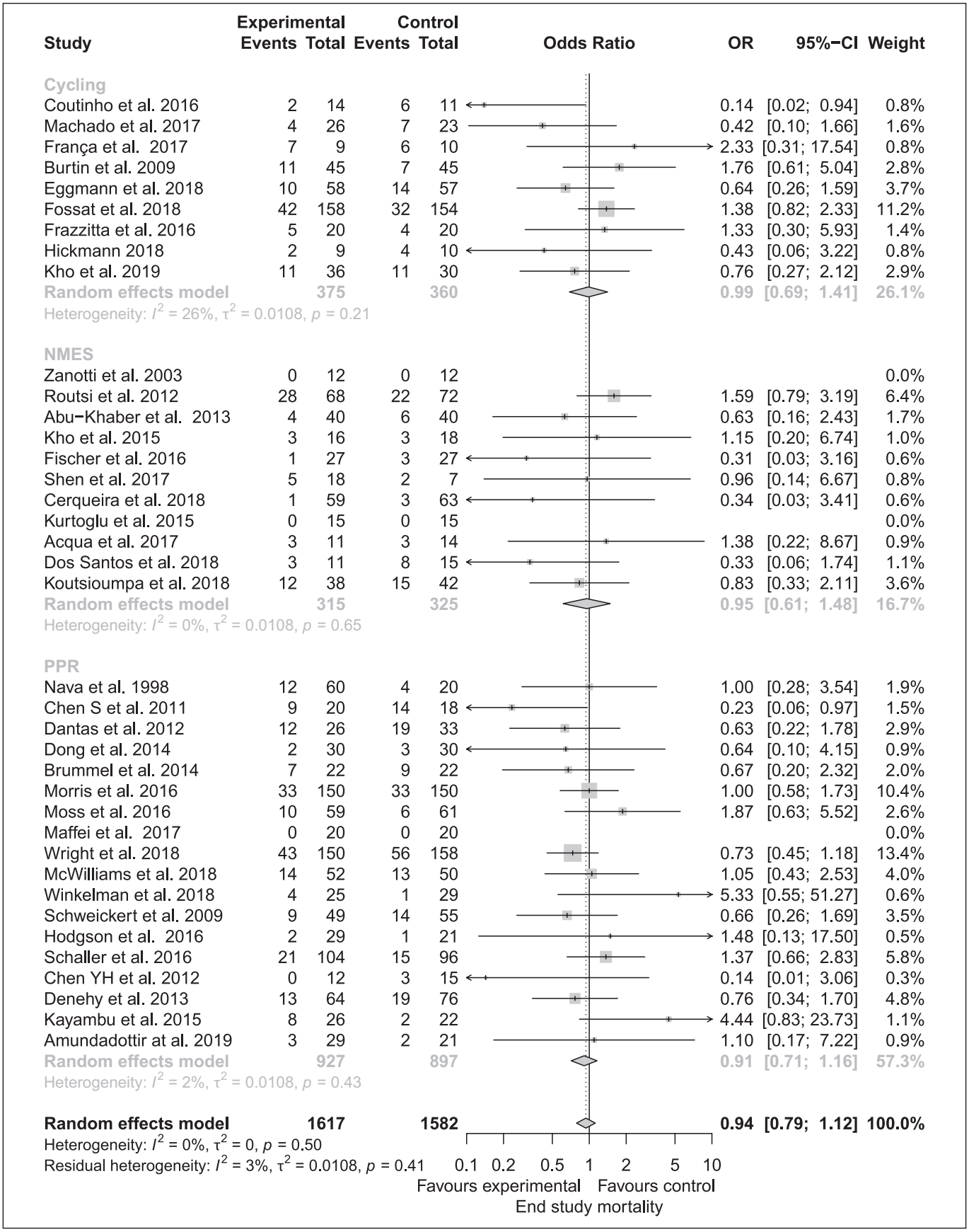

Figure 2. Forrest plot of the influence of intervention on end-of-study mortality. NMES = neuromuscular electrical stimulation, OR = odds ratio of death, PPR = protocolized physical rehabilitation.

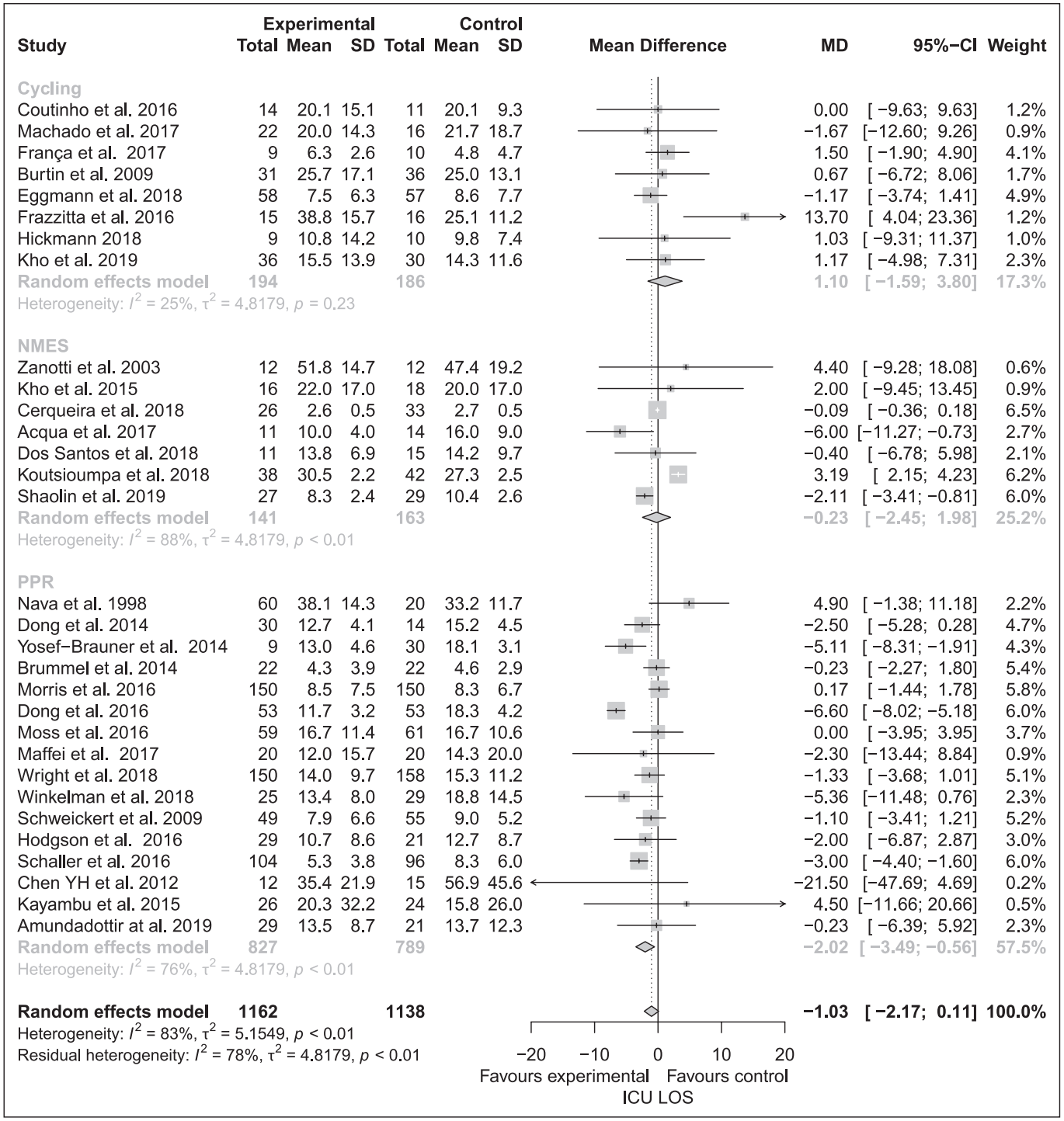

Figure 3. Forrest plot of the influence of intervention on ICU length of stay. LOS = length of stay, NMES = neuromuscular electrical stimulation, PPR = protocolized physical rehabilitation.

of muscle power in some (27, 30, 32, 35, 36), but not all (28, 33, 34) RCTs.

The meta-regression analysis suggests that patients with lower APACHE II scores at admission might gain more benefit (in terms of a reduction of MV and ICU days) than sicker patients. The lack of association of intervention with mortality is consistent across RCTs recruiting patients with a range of mean APACHE II scores (Fig. 4E). There was no signal of difference in treatment effect with any other patients' characteristics. Most benefit was seen in patients that stayed in ICU long enough to receive effective dose of the intervention. For example, for any additional day on MV in the control group, exercise intervention was able to shorten it by 0.3 d (0.1–0.5 d). The length of exposure could

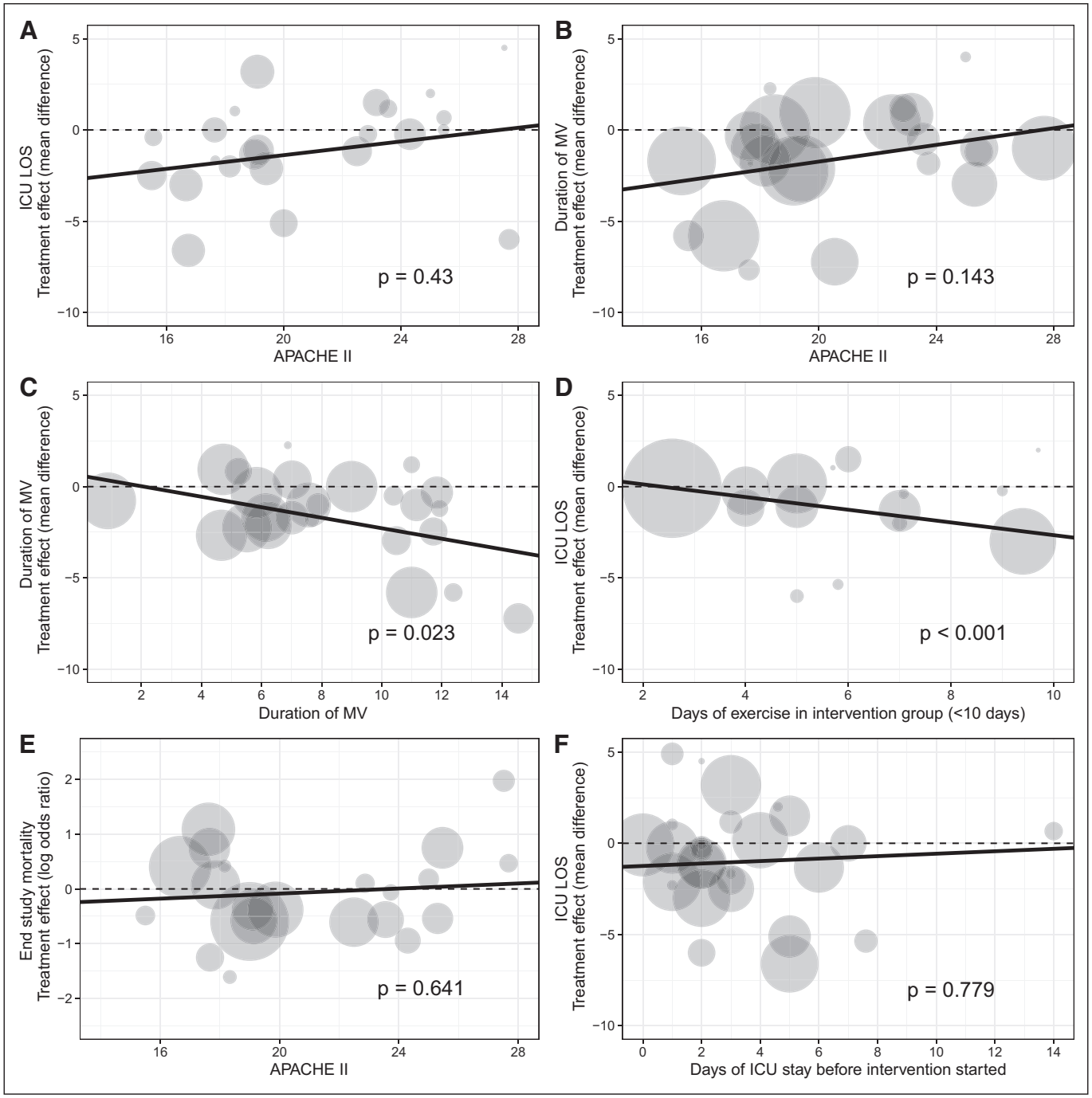

Figure 4. Meta-regression bubble plots. **A**, Acute Physiology and Chronic Health Evaluation (APACHE) II score versus treatment effect on ICU length of stay (LOS). **B**, APACHE II score versus treatment effect on mechanical ventilation (MV) duration. **C**, MV duration versus treatment effect on MV duration. **D**, Days of exercise versus treatment effect on ICU stay. **E**, APACHE II score versus treatment effect on study subjects' mortality. **F**, Mean number of days in ICU before intervention started versus treatment effect on ICU LOS.

not be compensated by more frequent rehabilitation (>5 d/wk), early start, or increased prescribed daily dose of exercise (measured in min/day). Yet, the shortening the time on ventilator and in ICU did not translate into a significant shortening of hospital LOS or consistent improvements of long-term functional outcomes. This suggests that for a lasting effect, rehabilitation intervention may need to be extended beyond ICU (14)

The evidence summarized in this review is limited to RCTs. In addition, 73% of patients in this meta-analysis were recruited into single-center phase II RCTs with less than 150 patients, testing primarily physiologic endpoints and safety or feasibility of interventions in diverse patient populations. Only five RCTs had greater than 150 subjects (14, 19, 22, 28, 50), and only two (19, 47) were adequately powered to investigate the effect of interventions on the patient-centered outcomes. Furthermore,

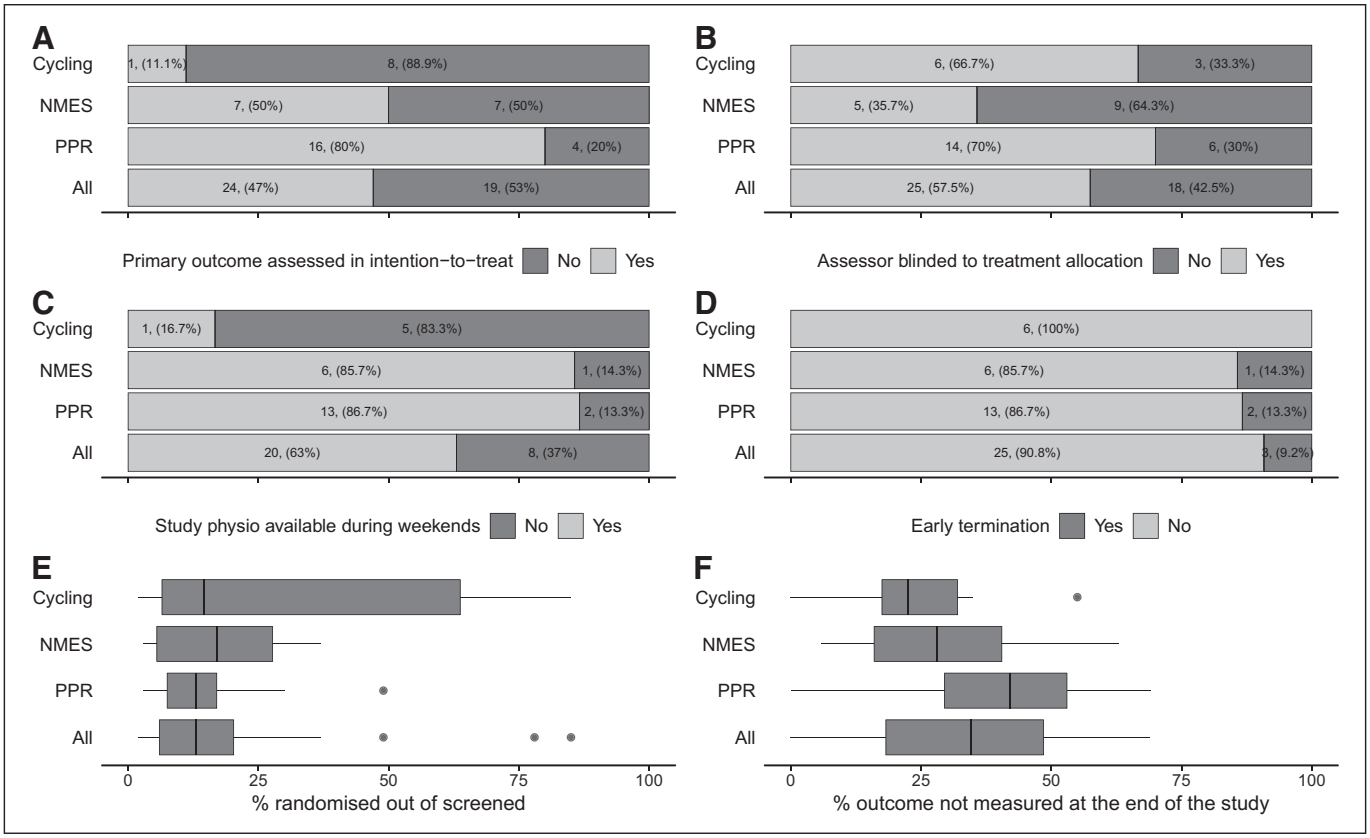

Figure 5. Risk of bias in individual randomized controlled trials displayed as the proportion at risk. **A**, Primary outcome assessed in intention-to-treat population. **B**, Assessor of primary outcome blinded to patient's treatment allocation. **C**, Study physiotherapist was reported to be available during the weekend. **D**, The randomized controlled trial was terminated early, that is, before reaching prespecified target number of participants. **E**, Proportion of randomized patients out of screened. **F**, Proportion of patients in whom the primary outcome was not measured for any reason. Detailed table with risk of bias for individual RCTs is available in the table S208 in Supplemental Additional Results (Supplemental Digital Content 3, http://links.lww.com/CCM/F486). NMES = neuromuscular electrical stimulation, PPR = protocolized physical rehabilitation.

37 RCTs did not monitor and report rehabilitation dose delivered to patients, and in six RCTs that did (19, 34, 47, 51–53), it was invariably smaller than the dose prescribed per protocol. Indeed, the lack of treatment effect even in adequately powered studies may either be true or represent a failure of protocol implementation. In addition, implementation failures could lead to superimposed selection bias, that is, that even physiotherapists consciously or subconsciously may have selected less sick patients for rehabilitation and in turn, within each trial less sick patients might have received more rehabilitation. This is an alternative explanation of the inverse relation of treatment effect and APACHE II score seen in the meta-regression analysis. Further confounding factor was the variability of per-protocol rehabilitation in the control groups. It ranged from no exercise at all (13, 29, 58), through passive limb movements (30, 46, 48, 59) to once-daily PPR (22, 53, 54, 60, 61) up to 60 minutes per day of exercise (62).

Meta-regressions results should be interpreted with caution and only as hypothesis generating. Although the original studies are RCTs, the meta-regression is across RCTs and is prone to the effect of confounders and aggregation bias, that is, the relationship with patient averages across RCTs may not be the same as the relationship for patients within RCTs. Further limitation of meta-regression analysis is inherent to the quality and completeness of source data. Important cofounders to the treatment effect might have been missed because they are were not reported by RCTs (such as preadmission frailty or functional status) or failures of protocol implementation render them invalid (such as per-protocol daily rehabilitation dose or early start). In addition, most trials only included patients with a certain pre-specified expected LOS—however understandable, this fact introduced selection bias and left the study population skewed toward long-stay patients.

From clinical point of view, it is important to notice that 24 of 43 RCTs report having a physiotherapist available 7 days a week, which is unlikely to be reproduced in routine clinical care, where a physiotherapist is often a scarce resource. At this time, there is no evidence from the pooled data to support the use of automated devices such as NMES or cycling-based interventions (18, 25, 27, 55, 56) even combined (28) or coordinated (63, 64). Hence, the individualized physical rehabilitation remains the only intervention with proven benefit in critically ill patients. With limitations noted above, it is likely that patients, regardless of age or sex, who are already stable and likely to require protracted stay in the ICU are those who benefit most from exercise interventions. On the other hand, goal-directed rehabilitation is safe and potentially beneficial for all ICU patients meeting the established safety criteria (65).

TABLE 1. Recommendation for Future Clinical Trials in Critical Care Rehabilitation

Patients	Report Patient's Premorbid Functional Status and Trajectory Report Reason for Admission Diagnosis
Intervention	Monitor and report on protocol implementation, that is,. the dose of exercise delivered to individual patients.
	Consider qualitative aspects/studies, that is, analyzing barriers to protocol implementation as a part of routine care.
	Consider studying rehabilitation interventions extending beyond ICU.
Control	Measure and report on rehabilitation intervention delivered in the control group.
	Monitor and report on sedation holds planned and performed.
Outcomes	Adhere to recommended core outcome set for trials in critical care rehabilitation (66).
	Make anonymized patient-level data set available in public databases accessible to secondary analyses.

The evidence in the field of critical care rehabilitation consists mainly of small single centre studies, often underpowered to measure the effect of intervention on patient-centered outcomes and even more often failing to implement the protocol and report on the dose of exercise and other important information. Indeed, performing RCTs in the critically ill is challenging mainly due to the inherent heterogeneity in these patients and due to the presence of many confounders mitigating the casual link between the immobility (or lack of exercise) and clinical outcomes. Based on our analysis of existing data, we formulated several recommendations for the design of future trials, which are summarized in **Table 1**.

CONCLUSIONS

The evidence available in the field is mostly derived from the synthesis of the results of small, single-center RCTs. PPR, but not supine cycling or NMES alone, shortens the time spent on MV and in the ICU. Long-term ICU patients with lower APACHE II scores seem to benefit most, and exposure time to rehabilitation may be more important than the acuteness of intervention initiation. Summary of evidence for the main finding is provided in **Supplemental GRADE Table** (Supplemental Digital Content 5, http://links.lww.com/CCM/F488).

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Critical Care Medicine

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Rehabilitation interventions in critically ill patients are safe and do not influence mortality

Title Effects of Rehabilitation Interventions on Clinical Outcomes in Critically Ill Patients: Systematic Review and Meta-Analysis of Randomized Controlled Trials

Objective
To assess the impact of rehabilitation in ICU on clinical outcomes

Study Selection
Neuromuscular electrical stimulation (NMES), cycling exercises, or protocolized physical rehabilitation as compared to standard care

Data Source
Secondary data analysis of randomized controlled trials published between 1998 and 2019

Data Extraction
Mortality, length of stay in ICU and at hospital, days on mechanical ventilator, and adverse events

Data Synthesis

43 Randomised Control Trials
- 9 Cycling
- 14 NMES
- 20 Protocolized Physical Rehab

3548 Patients
No serious adverse event
No influence on mortality
odds ratio 0.94 [0.79–1.12]

-1.7 Days
Mechanical Ventilation
[−2.5 to −0.8 d]

-1.2 Days
ICU Length of Stay
[−2.5 to 0.0 d]

-1.6 Days
Not Significant
Hospital Length of Stay
[−4.3 to 1.2 d]

Significant effects only seen in **Protocolized Physical Rehab**

Enhanced in patients with **Longer ICU Stay** **Lower APACHE II**

"Dose" delivered **Much lower than prescribed by protocol**

No benefit in **Early Start of Intervention**

Data from Waldauf P, et al: *Crit Care Med*, 2020

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Mobilizing to Restore the Lives of Critically Ill People*

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The current global public health crisis demonstrates the value of preventative care enacted early, reduce patient harms, and to avoid overwhelming ICUs with more patients than available beds (1). Preventative interventions rely on our ability to project into the future and change our behavior to avoid damaging consequences—a leap of faith toward potential improvements. Bed rest and deep sedation in the ICU are known to cause profound weakness and delirium that can delay weaning from mechanical ventilation, lengthen ICU and hospital length of stay, and contribute to prolonged disability for survivors of critical illness (2–5). Lack of muscular strength correlates with higher mortality across a spectrum of illnesses (6). Preventing muscle loss is vital, and providing ICU patients an opportunity to move, is a logical strategy to avoid delayed ICU discharge with a future of disability. Mobility is so intuitive and important that the Society of Critical Care Medicine (SCCM) Clinical Practice Guidelines for the Prevention of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) include a section devoted to assuring mobility is a safe, recommended practice (7). Additionally, SCCM offers the ICU liberation bundle for applying the PADIS Guidelines (8), and Hodgson et al (9) published an expert consensus article providing specific clinical variables to mobilizing ICU patients.

Together the PADIS Guidelines and Hodgson expert consensus article are the skeletal framework ICU early mobility randomized clinical trials (RCTs) attempt to fill out with dosage, intensity, and duration of patient activity. Prescribing mobility as medicine prevents damage in and beyond the ICU, such as patients unable to return to work 6 months after discharge (3). Looking to systematic reviews for answers to the ICU mobility as medicine questions is problematic. In a 2018 Cochrane Review of the effects of early intervention (mobilization or active exercise), initiated in the ICU, compared with delayed exercise or usual care, on improving physical function or performance, muscle strength and health-related quality of life, Doiron et al (10) found too much heterogeneity in outcomes reporting to perform a meta-analysis, and due to small sample sizes, inherent biases, and inadequate descriptions of interventions, they could not draw meaningful conclusions from their systematic review. In a systematic review evaluating the quality of description of ICU mobility protocols for replication by de Queiroz et al (11), none of the 16 eligible RCTs for review sufficiently reported their interventions dosage, volume, frequency, progression, adherence, or other important components to guide clinicians wanting an evidence-based process to optimize ICU patient mobility in their own setting.

Into this paradox of nebulous ICU mobility practice amidst incomplete evidence; comes an enlightening new systematic review and meta-analysis by Waldauf et al (12), in this issue of *Critical Care Medicine*, on the effects of rehabilitation interventions on outcomes in critically ill patients. This review distinguishes itself from the pack with specific intervention guidance and a larger number of included RCTs. Forty-three RCTs published between 1998 and 2019 met inclusion criteria for a total number of 3,548 subjects with no adverse events, no effect on mortality or hospital length of stay, but a significant reduction of time on mechanical ventilation and reduction of ICU stay. Noting the variation in choices of intervention across the studies, this review seeks to untangle the heterogeneous literature with a comparative analysis of three specific mobility modalities—in bed cycling, neuromuscular electrical stimulation, and protocolized physical rehabilitation (PPR). The improved outcomes were only significant for PPR with the best results noted for patients with a longer ICU stay and a lower Acute Physiology and Chronic Health Evaluation II score. The authors provide comprehensive statistical analysis of the data from these RCTs and conclude that: "individualized physical rehabilitation remains the only intervention with proven benefit in critically ill patients. In light of the lack of evidence that the early start would be associated with more benefit, physiotherapy should be preferentially allocated to patients, regardless of age or sex, who are already stable and likely to require protracted stay in the ICU" (12).

This recommendation based on the review appears logical, however, examining the details with an eye on weak quality evidence, invites skepticism. The authors note a small number of subjects enrolled in the RCTs (on average 13% of admitted ICU patients) selection bias. Performing a meta-regression on the cumulative data, they noted no difference in treatment effects between studies that initiated rehabilitation early versus more than 72 hours after admission, and no difference for extra dosage of mobility interventions (12). At the same time, only 14% of the 43 RCTs reported dosage and if it was reported, it invariably was delivered in a smaller dose than the protocol—as low as 25% in one of the few reporting studies. Primary outcome was measured on average in 71% of enrolled patients.

*See also p. 1055.

Key Words: critically ill; intensive care unit early mobility; outcomes; physical activity; preventative medicine; rehabilitation; systematic review

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Heterogeneity of patient population can be assumed when mortality rate reporting for the control groups varied from 0% to 78% and reporting bias an issue given the assessors were blinded in only 7% of studies. Only two of the RCTs were adequately powered (12). This means there is a high probability the longer stay less sick ICU patients benefitted most not as a key demographic in greatest need with best response to ICU mobility, rather as the one group who actually received and were reported on the interventions, while the rest remains an unknown. Well established barriers to providing ICU rehabilitation need to be reported in these incomplete RCTs. The crucial impact of sedation and delirium should be an imbedded and reported component of all ICU mobility protocols given their profound impact on the delivery of mobility interventions (13).

If this pattern in ICU rehabilitation research continues, how can the field advance and how can clinicians determine the optimal timing, mode, and dose of mobility to restore critically ill patients? The solution begins with universal core outcomes to improve reporting and reduce heterogeneity in ICU early mobility research. The process has begun both by Needham et al (14) and a mixed methods review plus Delphi consensus process led by Connolly et al (15) to inform ICU providers and researchers of standardized outcomes for physical rehabilitation interventions during critical illness and recovery. Uniform standards of reporting outcomes provides reliable data, while survivors and families offer us insights for meaningful measures of recovery. The perspectives of ICU survivors and families are reported in a 2018 survey by Dinglas et al (16) with domains of physical function, cognitive function, return to work and prior activities, and mental health being the four highest out of 19 rated domains agreed upon by patients and researchers. While researchers find mortality to be a most important outcome, patients ranked it lowest. Complete evidence-based mobility prescriptions will need to wait for future research in a common language. Meanwhile, an urgency exists for researchers to thoroughly examine, and clinicians to deliver, ICU rehabilitation beyond survival to restore patient lives. Avoiding long-term disability is a vital domain impossible to achieve without some way for critically ill patients to be awake and mobile during their ICU stay, regardless of how sick or how long their struggle under our care.

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Příloha 3:

Originální článek k projektu C publikovaný v časopise Trials

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Trials

STUDY PROTOCOL Open Access

Functional electrical stimulation-assisted cycle ergometry in the critically ill: protocol for a randomized controlled trial

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Abstract

Background: Intensive care unit (ICU)-acquired weakness is the most important cause of failed functional outcome in survivors of critical care. Most damage occurs during the first week when patients are not cooperative enough with conventional rehabilitation. Functional electrical stimulation-assisted cycle ergometry (FES-CE) applied within 48 h of ICU admission may improve muscle function and long-term outcome.

Methods: An assessor-blinded, pragmatic, single-centre randomized controlled trial will be performed. Adults ($n = 150$) mechanically ventilated for < 48 h from four ICUs who are estimated to need > 7 days of critical care will be randomized (1:1) to receive either standard of care or FES-CE-based intensified rehabilitation, which will continue until ICU discharge. Primary outcome: quality of life measured by 36-Item Short Form Health Survey score at 6 months. Secondary outcomes: functional performance at ICU discharge, muscle mass (vastus ultrasound, N-balance) and function (Medical Research Council score, insulin sensitivity). In a subgroup ($n = 30$) we will assess insulin sensitivity and perform skeletal muscle biopsies to look at mitochondrial function, fibre typing and regulatory protein expression.

Trial registration: ClinicalTrials.gov, NCT02864745. Registered on 12 August 2016.

Keywords: Early rehabilitation, Critically ill, Intensive care unit, Functional electrical stimulation-assisted cycle ergometry, Mobility, Physical therapy

Background

Functional disability, a natural consequence of weakness, is a frequent and long-lasting complication in survivors of critical illness [1–3]. Over recent decades, mortality from acute critical illness has decreased with a consequent increasing number of ICU survivors. Understanding the post-ICU morbidity experienced by these survivors has become increasingly important. The greatest burdens that survivors of critical illness face are related to neuromuscular dysfunction and neuropsychological maladjustment [4]. In particular, neuromuscular abnormalities during critical illness are common, with a median prevalence of 57% [1]. In both patients with chronic critical illness and survivors of severe critical illness, neuromuscular weakness may be substantial and persistent [5], resulting in important decrements in physical function and quality of life for years after discharge [1, 2].

In the past, routine features of general care provided in the ICU included liberal use of sedation and immobilization of the patient, which were thought to be necessary for facilitating interventions to normalize physiological function by artificial means. Over the last decade, there has been a paradigm shift away from this approach towards a more conservative treatment philosophy for patients in the ICU [4, 6, 7]. This paradigm shift is consistent with the observation that long-term physical problems in survivors of critical illness, particularly those with respiratory failure, may result from the protracted ICU stay and period of immobilization during which the patient is receiving organ support that is

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essential for survival [2, 4]. In line with this, a daily interruption of sedation policy has been widely adopted and proven to be beneficial [8] and early mobilization culture is spreading quickly across ICUs [9–13]. Indeed, these strategies, together with early physical therapy [9, 11, 12, 14–20], are the only safe [12, 20–22] and effective interventions in the prevention of long-term neuromuscular disability in survivors of intensive care. It should be stressed that in these studies early rehabilitation is defined as starting between days 2 and 5 of the ICU stay [9, 11, 12, 14–19] or as an activity beginning before ICU discharge [20].

Standard "early" rehabilitation cannot be started early enough, and FES-CE may be a solution to this dilemma. The first week in the ICU is critical as muscle mass and function is lost quickly. Immobility-associated muscle loss is evident as early as within 18–48 h of onset of acute critical illness or severe injury [23, 24] and is greatest during the first 2–3 weeks of critical illness [25, 26]. Up to 40% loss of muscle strength can occur within the first week of immobilization, with a daily rate of strength loss between 1.0 and 5.5% [27]. A 10–14% decrease in cross-sectional measurements of the rectus femoris muscle has been observed within the first week of the ICU stay [26]. Conventional rehabilitation during the first few days in the ICU is indeed limited in patients who are sedated and mechanically ventilated, and typically consists of passive limb movements, with or without the use of stretch reflex [16, 20]. Schweickert et al. [16] provided the earliest (within 48 h of intubation) and largest (26 ± 14 min a day for patients on mechanical ventilation) dose of rehabilitation and reported improvements of physical function at hospital discharge, but no measurements beyond. Active rehabilitation is delayed until the neurological condition of the patient improves enough to facilitate participation. In the sickest patients, who are at particular risk of developing ICU-acquired weakness (ICUAW), sedation and immobility may be prolonged well beyond the first week, when established damage to the muscle has already occurred.

There are several ways to deliver more effective physical exercise therapy to patients who are sedated and mechanically ventilated. For example, physical exercise can be delivered effectively and safely by passive supine cycling on a bicycle ergometer [15, 18, 28–30]. More recently, electrical neuromuscular stimulation (NMES) has been developed to mimic active exercise in patients who lack voluntary muscle activity [31–39]. During NMES, cutaneous electrodes placed over specific muscle groups electrically trigger muscle contractions. In order to achieve maximum efficacy, passive cycling and NMES can be delivered simultaneously and synchronized to produce a coordinated pattern of movements. The technique is called FES-CE (functional electrical stimulation-assisted cycle ergometry). There is a large body of experience with these methods in the rehabilitation of patients with stroke and spinal cord injuries (reviewed in [40]). The method is effective in preventing the loss of muscle mass [41] and has been shown to improve anabolic resistance and insulin sensitivity in quadriplegic patients [42, 43].

The only study of FES-CE in critical illness is the pilot trial by Parry et al. [44], where the feasibility and safety of FES-CE was demonstrated in a small cohort of critically ill patients (eight patients received the FES-CE intervention, versus eight controls). Patients in the intervention group showed significant improvements in the Physical Function in Intensive Care Test and a faster recovery of functional milestones (e.g. time to stand from lying, walking on the spot). However, the mechanism by which this occurred is unknown. There are no data on the effect of FES-CE on long-term functional outcome in ICU survivors. In healthy volunteers [45] and patients with spinal cord injury [46], unloaded FES-CE can increase whole-body oxygen consumption. It is unknown whether these effects, including improving insulin sensitivity and protein metabolism [47], can also be achieved in critically ill patients.

Rationale

Mechanisms of muscle wasting and ICUAW

Pathophysiology of ICUAW is complex and multifactorial (reviewed in [4]), and there is a growing body of evidence suggesting the role of sarcopenia and metabolic derangement of skeletal muscle.

Firstly, *insulin resistance* is a well-known comorbidity in critical illness [48], contributing to and aggravating complications such as severe infections, organ dysfunction and death, and has also been implicated in the ICU-acquired weakness. Two main consequences of insulin resistance are hyperglycaemia and "anabolic resistance". It has been observed that the provision of protein and energy to support the enhanced hypermetabolic demands of ICU patients is unable to prevent the rapid loss of muscle mass [49]. Indeed, skeletal muscle insulin resistance is the likely reason why nutritional support further exacerbates hyperglycaemia. Insulin therapy is often used in ICU patients to try and combat this, but it appears to be ineffective in ICU-acquired weakness and its safety in the ICU setting has been questioned [50]. Physical activity is an attractive alternative intervention target as it has profound effects on substrate metabolism in contracting skeletal muscle, with a single bout of muscle contraction known to increase muscle glucose uptake several fold and sensitize the muscle to insulin and the anabolic effects of amino acids for up to 24 h, including in individuals where insulin and anabolic resistance is evident [51]. It is not known whether

intensified rehabilitation can improve the insulin effect on glucose uptake and whether it influences the stimulatory effect of insulin and amino acids on muscle protein synthesis.

Secondly, *mitochondrial dysfunction* in skeletal muscle may play a role in the development of ICUAW. Mitochondrial depletion and dysfunction of mitochondrial respiratory complexes I and IV has been demonstrated in acute severe sepsis in association with multiorgan failure and death [52], and early activation of mitochondrial biogenesis predicted survival [53]. Our group has recently demonstrated in two pilot studies [54, 55] that, compared to healthy controls, there is a 50% reduction of mitochondrial functional capacity in skeletal muscle in the patients with protracted critical illness and ICUAW. This is accompanied by a significant relative increase in the abundance and functional capacity of respiratory complex II, which delivers electrons to the respiratory chain from fatty acid oxidation [54]. Weber-Carstens et al. [48] demonstrated that insulin fails to activate GLUT-4 translocation to cellular membranes in patients with ICUAW, causing skeletal muscle "intracellular glucose starvation" and a failure of AMP-activated protein kinase to respond to the impairment of ATP production. Most notably, in five subjects, these abnormalities were alleviated by NMES. In light of this, the relative increase of complex II capacity observed in our pilot study may represent a functional adaptation of muscle to the increased reliance on fatty acid oxidation. It is not known whether the severity of mitochondrial functional alteration reflects the degree of insulin resistance and the severity of muscle weakness, and whether the delivery of very early FES-CE has a potential to influence these changes.

In the light of this, we hypothesize the following:

H_1: As most of the damage to the structure and function of skeletal muscle occurs during the first week, intensified goal-directed rehabilitation, which includes FES-CE and starts within 48 h after ICU admission, improves the functional outcome of ICU survivors at 6 months when compared to the standard of care.
H_2: The intervention, as compared to standard of care, shall preserve muscle mass and improve muscle power at ICU discharge.
H_3: The intervention, as compared to standard of care, shall increase insulin-mediated whole-body oxidative glucose disposal and mitochondrial functional indices.

Objectives

1. To investigate, in a pragmatic, prospective, randomized, controlled, assessor-blinded trial, the effects of very early intensive rehabilitation using a goal-directed protocol that includes FES-CE in mechanically ventilated ICU patients predicted to need a protracted ICU stay
2. To perform more detailed metabolic studies, including serial muscle biopsies and using euglycaemic hyperinsulinaemic clamps, in a nested subgroup. Insulin sensitivity in the whole study population will be compared by glucose control and consumption of intravenous insulin required to control blood glucose

Primary outcome

The primary outcome is the physical component of the SF-36 quality of life questionnaire measured in ICU survivors at 6 months. Based on the study by Kayambu et al. [12], where this measure was 60 ± 29 points in the control group, our study is powered to detect a change by 15 points or more, which is within the limits determined as clinically important for patients with COPD, asthma and myocardial infarction [56]. The SF-36 has been validated in the Czech Republic and endorsed by the Institution for Health Information and Statistics (https://www.uzis.cz/en/node/8159).

Secondary outcomes

- Four-item Physical Fitness in Intensive Care Test (time frame: at 28 days or discharge from the ICU, whichever occurs earlier) as the functional outcome at ICU D/C
- Muscle mass measured by rectus muscle cross-sectional area on B-mode ultrasound (time frame: at 7-day intervals up to day 28 or discharge from the ICU, whichever occurs earlier)
- Nitrogen balance measured in grams per metre-squared of body surface area (time frame: at 7-day intervals up to day 28 day or discharge from the ICU, whichever occurs earlier) and the cumulative the difference between nitrogen intake and output
- Muscle power as per the Medical Research Council (MRC) score (time frame: at 7-day intervals up to day 28 or discharge from the ICU, whichever occurs earlier)
- Number of ventilator-free days (time frame: at 28 days); that is, number of days, out of 28 days after admission, that the patient has NOT been supported by mechanical ventilation
- Number of rehabilitation interruptions due to physiological deterioration (time frame: at 28 days or discharge from the ICU, whichever occurs earlier)
- Number of episodes of elevated intracranial pressure (time frame: at 28 days or discharge from the ICU, whichever occurs earlier)

- Number of dialysis interruptions (time frame: at 28 days or discharge from the ICU, whichever occurs earlier)
- Length of ICU stay in days (time frame: at 6 months)

Study population

One hundred and fifty participants meeting the eligibility criteria will be recruited in four ICUs at FNKV University Hospital.

Inclusion criteria: age ≥ 18 years; mechanical ventilation, or imminent need of it at presentation; predicted ICU length of stay ≥ 7 days.

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

With the exception that we do not limit the study population with sepsis, we have intentionally chosen similar criteria to the only study underway on FES-CE in ICU patients, which is primarily focused on muscle structure and function [57].

Interventions

The flow of participants throughout the trial is shown in Fig. 1 and the study procedures in Fig. 2. As soon as informed consent has been obtained, and prior to randomization, baseline testing including anthropometric examination will be performed. In addition, in patients with specific consent, a muscle biopsy will be obtained and hyperinsulinaemic clamp will be performed on the first morning (8.00–11.00 a.m.) and prior to the start of enteral nutrition.

Standard care group

Both groups will receive usual best medical and nursing care in the ICU, which includes daily sedation holds when applicable and delirium 12-hourly monitoring (by CAM-ICU scale [58]) and management as usual in the routine practice. Respiratory physiotherapy will also be delivered without alterations. The routine standard care arm will undergo mobilization/rehabilitation delivered by personnel not involved in the study in a usual, routine way. Details of physiotherapy treatment will be recorded but not protocolled in the standard care arm.

Intervention group

In the intervention arm, early goal-directed rehabilitation is protocolled according to the patients' condition and degree of cooperation (Fig. 3), and there will be predefined safety criteria, which are in accordance with current recommendations for active rehabilitation of critically ill ventilated adults [13]. Whilst the safety criteria are binding for the study physiotherapist, the rehabilitation protocol is not and the delivery of physical exercise can be altered according to the actual patient's condition. However, any alteration and the reason for it will be recorded. The intervention will start as soon as possible and always within 72 h of ICU admission, continuing until ICU discharge. Supine cycling will be delivered as per protocol on a supine cycle ergometer attached to a neuromuscular stimulator. Surface electrodes will be applied to the gluteal, hamstring and quadriceps muscles on both legs. The intensity of muscle stimulation will be delivered at a level able to cause visible contractions (confirmed by palpation if uncertain) in all muscle groups without causing undue pain or discomfort to the participant, according to a regime specified by Parry et al. [44]. Once the patient is more alert, and able to participate, they will be provided with standardized encouragement to engage in therapy. To increase the intervention workload, resistance will be increased incrementally and cycling cadence. If a participant is readmitted to intensive care, the intervention will be re-initiated. The intervention continues until day 28 or ICU discharge, whichever occurs earlier.

Methods

Enrolment and randomization

All patients admitted to participating ICUs are screened daily by research nurses and all eligible patients or their representatives are approached by investigators as soon as possible, but always within 72 h of admission. Participants for whom informed consent was obtained will be randomly assigned (1:1) to receive either standard care or the intervention using offsite independent randomization protocols (www.randomization.com) embedded in the electronic case report form. Randomization will be stratified according to the presence or absence of sepsis and the availability of a biopsy at baseline. There is no restriction (blocking) during randomization.

Both the study team and clinical personnel will be made aware of subject treatment allocation. The outcome assessor is not involved in patient care and remains blinded to treatment allocations.

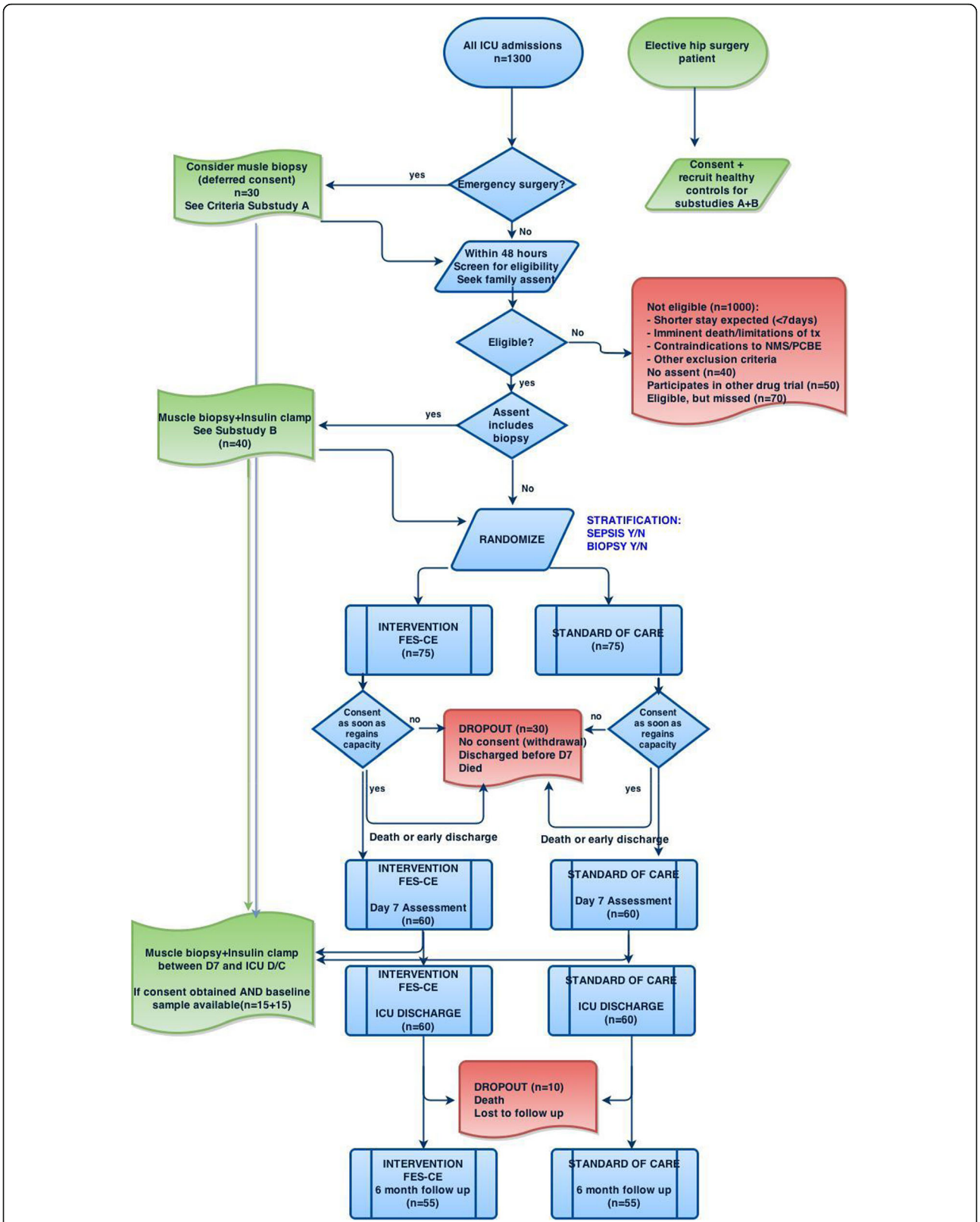

Fig. 1 Planned flowchart of patients enrolled into the trial. D7 day 7, D/C discharge, FES-CE functional electrical stimulation-assisted cycle ergometry, ICU intensive care unit, tx treatment, NMS neuromuscular stimulation, PCBE passive cycling-based exercise

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close out
TIMEPOINT**	*0-48h*	0	*D_{1-6}*	*D_7*	*D_{8-28}*	*ICU D/C*	*Post ICU D/C*	*F-up D_{180}*
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Sepsis Y/N, Biopsy Y/N	X							
Randomisation (stratified)		X						
INTERVENTIONS:								
Intervention (EGDR)			←	—	—	→		
Control (Standard RHB)			←	—	—	→		
Biopsy subgroup		Clamp + biopsy		Clamp + biopsy				Clamp + biopsy
ASSESSMENTS: Functional status	Before admission (CCS retrospect)	ROM		MRC		MRC PFIT		SF36 (primary outcome)
Adverse events		X	X	X	X	X	X	X
Vital functions		X	X	X	X	X		
SOFA, N-balance, Fluid balance			X	X	X	X		
Anthropometry		X		X				X
RHB Dose (min/day)	X	X	X	X	X	X		
MV, ICU, Hospital (Y/N)			X	X	X	X	x	X

Fig. 2 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure. D day, D/C discharge, EGDR early goal-directed rehabilitation, F-up follow-up, ICU intensive care unit, MRC Medical Research Council, MV mechanical ventilation, RHB rehabilitation, SF-36 Short Form 36, SOFA Sequential Organ Failure Assessment, CCS Charlson comorbidity score, ROM range of motion, PFIT physical function test for use in the intensive care unit

Clinical data retrieval and handling

The ICUs are paperless and fully computerized, so vital functions and other physiological parameters are monitored and data are routinely stored in secure hospital data bases via a protected dedicated network (MetaVision; IMD Soft Inc.). This includes data about nutritional intake and urinary output. On top of this, research nurses will input data into an electronic, secure, customized online case report form database (eCRF; accessible at https://195.113.79.251:9090/apex/f?p=103:101:14992036032980). Data protection and encryption is in accordance with the EU's General Data Protection Regulations as well as Czech data protection laws. The data will be audited by on a regular basis, but at least after each 10 patients are enrolled, by independent study monitor. After the database is locked upon study completion, patients' data will be de-identified and available in full in a public database.

Urine samples will be collected daily, surfaced with toluene and stored in a deep-freeze facility for later determination of nitrogen content and 3-methyl histidine levels (to calculate the muscle catabolism rate and nitrogen balance). In addition, all study patients will undergo assessment by a study physiotherapist, which includes a measurement of rectus muscle cross-sectional area on both legs and, whenever the patient regains consciousness, also muscle power by MRC score (standardized testing of muscle power (0–5) for 12 muscle groups on all four limbs, giving a score of 0–60 (60 suggesting normal muscle power)). Blood will be taken, and plasma

Stage	Condition	RASS score	Intervention	Frequency/da
0	Unstable (e.g. prone, FiO2>0.6, high inotropes)	-5 to -4 ± muscle relaxants	Passive Range of Motion with stretchreflex to upper and lower limbs.	2x15 minutes (min)
			Electrical neuromuscular stimulation to major muscle groups on UL+LL	1x60 min
1	Sedated	-3 to -2	As Stage 0 + FES---assisted leg cycle ergometry (FES---CE)	1x30 min
2	Transition phase: needing inotropes, ventilation	-1 or 1 Borderline cooperation	AM (before sedation hold): FES---CE	1x60 min
			PM (after sedation hold) If cooperative: Active range of motion/lightly resisted UL+LL Sit up in bed/on edge	2x10 min 2x5 min
			If delirious: Individualize approach	Aim to deliver >30 min
			If resedated: FES---CE Passive Range of Motion with stretch reflex to upper and lower limbs	1x60 min 1x15 min
3	Weak	0 Cooperative	Active Range of Motion/Lightly resisted with upper and lower limbs Sit on the edge of bed Sit out with assistance FES---CE or active CE (low resistance)	2x10 min 2x5 min 2x60 min 2x15 min
4	Able to stand with assistance	0 Cooperative	Active Range of Motion/Lightly resisted with upper and lower limb Sit out Active CE (low to moderate resistance) Ambulation with assistive device and 1---2 therapists	2x10 min 2x30 min 2x as tolerated 2x30 min

Fig. 3 Protocol of intensified goal-directed rehabilitation. FES-CE functional electrical stimulation-assisted cycle ergometry, FIO_2 fraction of inspired oxygen, LL lower limb, RASS Richmond Agitation and Sedation Scale, UL upper limb

separated and frozen at – 80 °C for later analysis of cytokines and hormone levels. This assessment will be repeated at day 7 intervals and at ICU discharge. At ICU discharge, the patients and relatives will be asked to provide contact details for follow-up. After 6 months, the patient or family will be contacted for structured interview as required for the SF-36 questionnaire, and collected using the RAND methodology (www.rand.org). Whilst participants and the intervention physiotherapist cannot be blinded to group allocation, research staff assessing the outcome will be from a separate clinical department (JG, BB, MH) and thus will remain blinded to treatment allocation. Outcome assessors are familiar with the SF-36, which is in routine use for other trials, and received SF-36 re-training at induction to this trial. Strategies to improve adherence to intervention mainly include the 24/7 availability of one of the team of five research nurses as well as one full-time physiotherapist equivalent only reserved for study interventions, with extra budgeting to cover physiotherapy sessions in the intervention group during the weekend. The time of physiotherapy sessions will be recorded by the physiotherapist and randomly checked by a hidden independent assessor (bedside ICU nurse receiving specific instructions). The primary outcome has been chosen also with respect to the fact that it can be collected over a structured telephone interview, thereby minimizing missing data.

Complementary studies: insulin resistance and mitochondrial function

These studies will be performed in addition to other study procedures in a nested subgroup of patients, who give specific consent. The first measurement will be performed at baseline prior to randomization, ideally the next morning after admission. Second measurement will be performed on day 7 of ICU stay, i.e. after at least 5 days of intervention.

Muscle biopsy

Muscle biopsy will be performed from the vastus lateralis muscle using the Bergstrom needle biopsy technique.

The sample will be separated into three parts (50–100 mg each). One part will be immediately frozen in liquid nitrogen for analysis of the protein/DNA ratio and for protein expression studies. The second part will be frozen in liquid nitrogen-cooled isopentone for muscle fibre typing and immunohistochemistry analysis. The third part put will be placed in BIOPS media on ice for the preparation of homogenates and measurement of citrate synthase activity, spectrophotometric analysis of the activity of respiratory complexes I–IV [52] and western blot analysis of respiratory complexes (as described in [55]). In the fresh muscle homogenates, we will use high-resolution respirometry (Oxygraph; Oroboros, Austria) to determine the function of individual respiratory complexes in the cytosolic context and measure basic functional metabolic indices by a method we have recently developed and calibrated against isolated mitochondria [59]. We will specifically look at the degree of mitochondrial uncoupling, the respiratory chain capacity and the function of individual complexes, including glycerol-3-phosphate shuttle. From the satellite cells we will prepare a culture of myotubes, which will serve as an in vitro model of skeletal muscle [60] and specifically measure the in vitro ability of myotubes to oxidize fatty acids by extracellular flux analysis (Seahorse Biosciences). Frozen muscle samples will be stored at − 80 °C for analysis of the DNA/protein ratio, mRNA and proteins involved in the regulation of proteolysis, substrate oxidation and anabolic pathways of skeletal muscle (MuRF, FOXO, atrogins) as well as immunohistochemistry and typing of muscle fibres. In order to determine which changes are caused by critical illness itself, we will also obtain control samples ($n = 15$) from age, sex and BMI-matched metabolically healthy volunteers undergoing elective hip surgery at the Department of Orthopaedic Surgery. In addition, we will look at the change of these indices after 7 days of critical illness and the influence of the intervention versus standard of care. We will look at correlation of these parameters with muscle power (i.e. compare the bioenergetics profile of skeletal muscle in those who develop ICUAW and in those who do not) and insulin resistance.

Insulin sensitivity and substrate oxidation will be measured after overnight fasting by hyperinsulinaemic euglycemic clamp (as described in [61]). We will compare the effect of intervention on insulin-mediated glucose disposal.

Statistical analyses

Sample-size calculation

In studies of critical illness outcome at 6 months using SF-36 scores, the standard deviation varied between 10 and 30 points. In order to have 80% power to detect a 15-point difference in SF-36 scores between control and intervention at the level of significance $p < 0.05$ in the population with a mean of 60 and SD of 30 [12], we would need 108 subjects (54 in each arm). In order to allow for deaths and dropouts, we plan to randomize 150 subjects.

Data analysis plan

The primary outcome and all secondary outcomes will be compared between the intervention and standard of care groups in an intention-to-treat population, with all tests two-sided and with the level of significance set at 5%, after the primary outcome has been collected in the last subject. There is no plan for any interim analysis. We will perform exploratory analyses in pre-specified subgroups of patients stratified according to APACHE II, and the length of intervention. We will also perform unadjusted analysis of odds ratio of being functionally independent (defined as ability to walk, use a telephone, self-care, use the toilet and groom) at 6 months after ICU admission in patients in the intervention and standard of care groups. We will perform adjustments on the disease severity (APACHE II score), admission diagnosis, baseline functional status and age. Missing data for primary outcome will be dealt by reporting both worst-case and per-protocol results; no imputation will be used.

Ethical considerations

This trial involves a two-tier consent process: first to the rehabilitation intervention and then additionally to the insulin clamp and muscle biopsies in a nested subgroup within the primary trial. All patients meeting the aforementioned criteria will be invited to participate and asked to provide written informed consent. It is expected that most screened patients will lack the capacity to provide informed consent. In this situation, the deferred consent policy will be applied: patient's next of kin (NOK) will be approached, and be given verbal and written information explaining the nature of the study given information leaflet and asked to provide assent. Discussion with the family will help inform the treating medical team regarding a best interest decision for assent to be recruited into the study. An option will be given to participate in the trial, but not to undergo insulin clamps and muscle biopsies. In a subgroup of patients when the family is unavailable within the first 48 h, an independent physician will be asked to review inclusion and exclusion criteria and weight benefits and risks of participation in the trial – all patients enrolled based on independent physician assent will proceed without insulin clamps and muscle biopsies. Participants themselves will be asked to provide ongoing consent as soon as they regain capacity. Again, they will be offered the option to continue participating in the trial without insulin clamps and/or muscle biopsies, if they so wish. Details of all

participants who refuse consent for muscle biopsy/insulin clams will be recorded. All serious adverse events that are suspected as being related to study interventions will be reposted to the Research Ethics Board and regulatory authorities as per local legislation. Other adverse events deemed to be related or possibly related to treatment intervention will be discussed at regular monthly meetings of the study team with the decision on further action, as there is no formal steering committee for this trial. The final decision-making and reporting responsibility is with the principal investigator (FD). All adverse events will be recorded in the eCRF. All protocol amendments, should they be required, will be subjected to a priori approval by the REB. Once implemented, protocol amendments will be reported to the sponsor and registration body (www.clinicaltrials.gov).

Replication of key aspects of trial methods and conduct

The trial is designed to be fully reproducible in an ICU setting in larger, but not necessarily teaching or academic, hospitals, where the FES-CE equipment and trained physiotherapists are available 7 days a week.

The sponsor of the study is a state-governed grant agency that has not had nor will have any role in study design; collection, management, analysis and interpretation of data; writing of the report; or the decision to submit the report for publication.

Dissemination of results

We will submit the main results of the trial in an open-access peer-reviewed journal within 6 months after the 150th subject has completed the 6-month follow-up visit, which is expected to happen in Q2 of 2020. We will make fully de-identified record-level raw data available in a public database Additional file 2.

Trial status

This trial is recruiting (recruitment began November 2016, expected finish November 2019) (first patient recruited 4 October 2016, expected end of study 1 July 2020), protocol version 2.0 as of January 2018. For the full WHO Trial Registration Data Set, see Additional file 1.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-019-3745-1.

Additional file 1. WHO Trial Registration data set.

Additional file 2. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents.

Abbreviations

D/C: Discharge; FES-CE: Functional electrical stimulation-assisted cycle ergometry; ICU: Intensive care unit; MRC: Medical Research Council; SF-36: 36-Item Short Form Health Survey

Authors' contributions

FD is the author of the main idea and overlooks the conduct of the study. PW, KJ, MF and PJ are responsible for consenting and recruiting patients and performing clinical procedures. JK is the study monitor. PW is the data analyst and biostatistician. NH and KR are the study physiotherapists. MH and BB are blinded outcome assessors. TU, JG and FS are investigators of the metabolic sub-studies. All authors will have access to record-level data and will contribute to publication of the results. All authors read and approved the final manuscript.

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Availability of data and materials

All cleaned de-identified raw data will be made available in an open online database (https://data.mendeley.com/datasets) within 6 months of publication of the main results of the trial.

Ethics approval and consent to participate

The trial design is in accordance with the 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.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Příloha 4:

Originální článek k projektu C publikovaný v časopise Thorax s editoriálem

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

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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/m^2 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.

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.

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]

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 diameter[15] 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

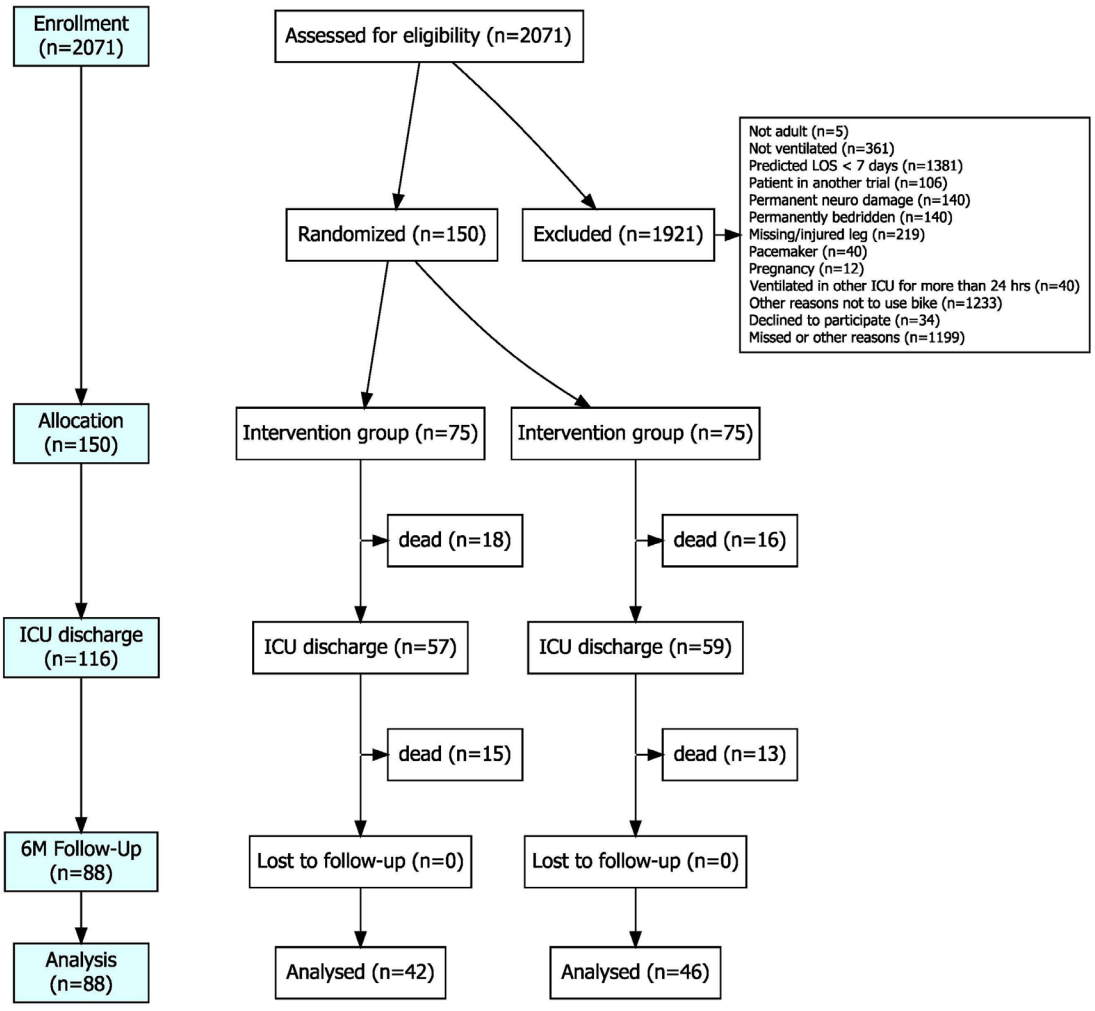

Figure 1 Flowchart of patients enrolled into the trial. Each patient could have one or more reasons not to be included and therefore the sum of reasons exceed the number of patients excluded. Other reasons included missed patients due to logistical reasons or patients who were deemed unlikely to survive; 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 mass[28] 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	0.80

CCS[31]; IAPA ranges 0–8 with higher number meaning higher functional independence[32]; 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 μs, 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

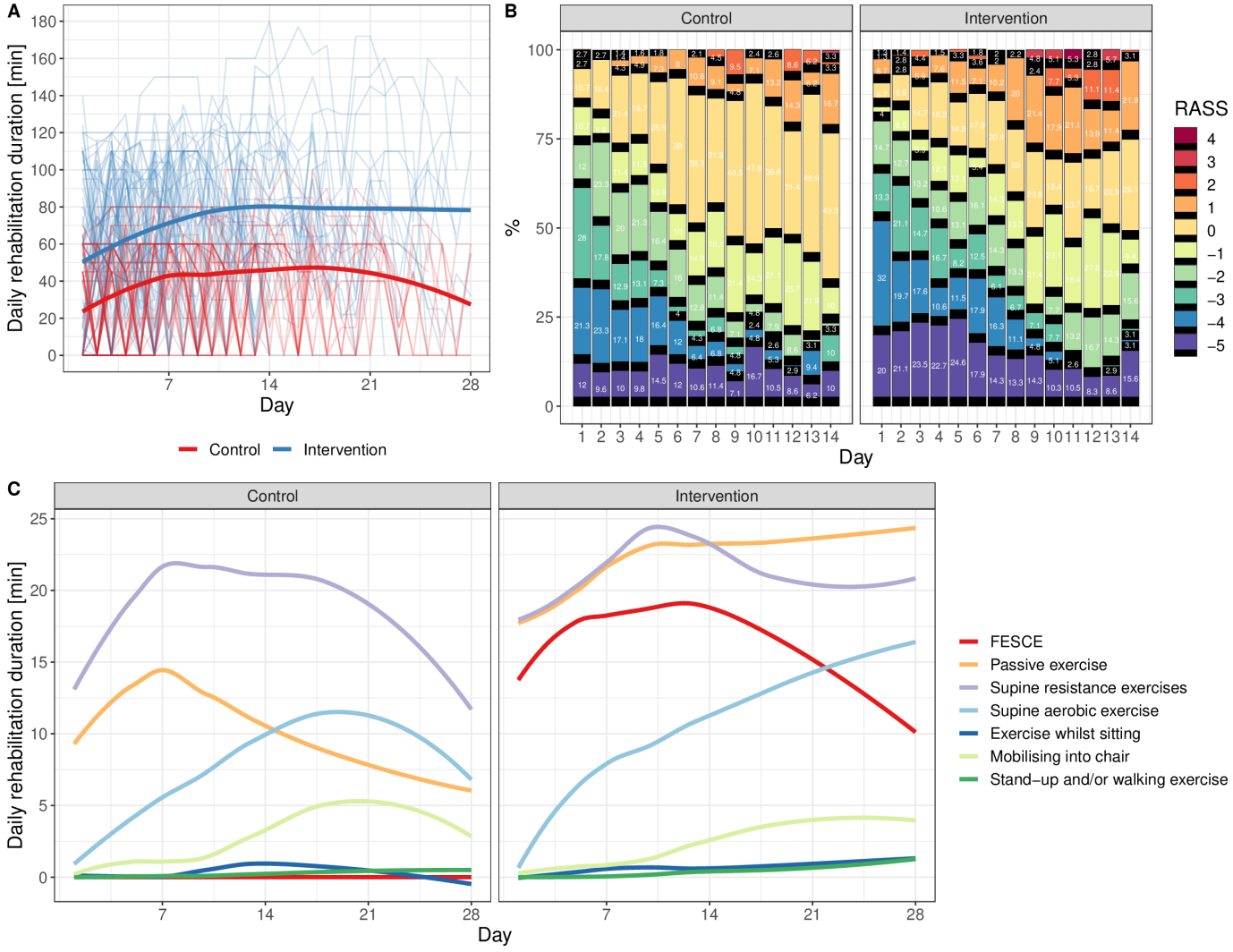

Figure 2 Protocol implementation indices. (A) Average duration of rehabilitation in intervention (blue line) and control (red line) groups in all days of all patients (ie, including days without rehabilitation). Thin lines are individual patients (one outlier received up to 180 min of rehabilitation 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

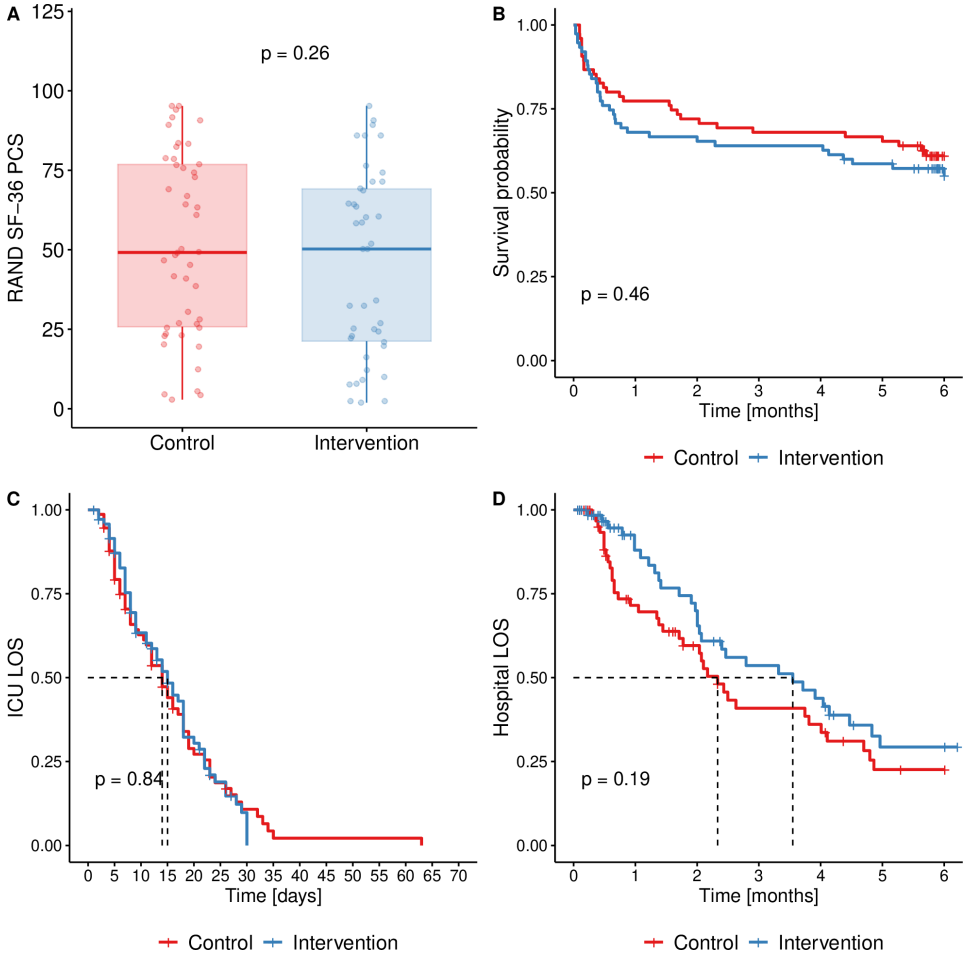

Figure 3 (A) Physical component summary of SF-36 score (primary outcome); (B) Kaplan-Meier curve of survival in the study; (C) Kaplan-Meier curve of patients in the ICU (censored for non-survivors); (D) Kaplan-Meier curve of patients at hospital (censored for non-survivors). P values are from Wilcoxon 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±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/m^2/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 implementation[6] 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 protocoled 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) then 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 volunteers[26] we have found that unloaded FESCE as used in our study can lead to aerobic lactate production and increase whole-body energy to 138%±29% and leg blood flow to 160%±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 patients[47] 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±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.

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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.

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ICU mobility and improved outcomes: still searching for the Holy Grail

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A growing number of patients are surviving critical illness, many of whom will experience long-term impairments in cognition and physical function. These enduring effects represent a significant burden for patients, their families and society. Unfortunately, interventions aimed at preventing the development of functional or cognitive disability due to critical illness are limited. Strategies to minimise sedation and initiate early physical rehabilitation have been associated with reductions in physical impairment and delirium, but the results of studies have been mixed and the impact on long-term outcomes has not been well established.[1] The implementation of rehabilitation with mobilisation within 72 hours of mechanical ventilation has the most promising results, but occurs in less than 10% eligible patients, with barriers, including the availability of trained physiotherapists and the ability of a patient to participate in rehabilitation sessions.[2 3] Therefore, there is intense interest in novel rehabilitation strategies to overcome these barriers.

Functional electrical stimulation-assisted cycle ergometry (FES-cycling) combines neuromuscular electrical stimulation (NMES) with in-bed cycling. FES-cycling offers theoretical advantages as it is feasible to integrate early in the course of critical illness, including in non-volitional patients, and mimics typical exercise by coupling the peripheral neuromuscular systems. Prior studies examining the effects of cycling and NMES delivered separately on functional outcomes have been mixed.[4] Pilot data have suggested that the combination of modalities in FES-cycling produces a robust physiologic response compared with usual intensive care unit (ICU) mobilisation and may improve muscle strength and reduce the incidence of delirium in critically ill patients.[5 6] Two randomised controlled trials recently published in the *Thorax Journal* studied the impact of multicomponent rehabilitation protocols with and without FES-cycling on short-term and long-term functional and cognitive outcomes.

Berney *et al* performed a multicentre randomised controlled trial of 162 mechanically ventilated patients with sepsis or systemic inflammatory response syndrome.[7] Patients were randomised to receive either 60 min of FES-cycling at least 5 days a week plus usual care rehabilitation or usual care alone. There were no significant differences in muscle strength at hospital discharge or cognitive impairment at 6 months, though it is notable that the study was underpowered for the 6-month cognitive impairment outcome. They also found no difference in secondary outcomes, including mortality, delirium and functional status.

Waldauf *et al* performed a single-centre randomised clinical trial involving 150 patients comparing an early multicomponent rehabilitation protocol, including FES-cycling to standard care in mechanically ventilated patients.[8] FES-cycling was performed for a maximum of 90 min a day, 7 days a week in the intervention group. Control patients received treatment by a multidisciplinary team two times per day, 6 days a week. The authors report no difference in the primary outcome 36-Item Short Form Health Survey (SF-36) physical component score at 6 months. There were also no differences in functional status, muscle area or strength at ICU discharge, or ICU length of stay.

Importantly, robust rehabilitation was provided in the control arms of both studies. The control group in the study by Waldauf *et al* received a median of 53 min of rehabilitation services per treatment day, far more than standard at most institutions. In the study by Berney *et al*, the incidence of ICU acquired weakness at hospital discharge in the control arm was lower than previously published rates. This suggests that the lack of difference in outcomes between the intervention and control groups may be in part due to high-quality standard care provided at the study sites, which may not be reflective of practice in many critical care settings.

Loss of muscle mass occurs early in critical illness; therefore, early interventions to prevent muscle wasting are theoretically beneficial.[9] As the safety threshold of initiating FES-cycling is likely lower than traditional therapy services, it is plausible earlier initiation of activity would improve discharge strength and other long-term functional outcomes. In the Berney *et al*'s study, FES-cycling was initiated at a median time of 3 days from intubation in the intervention group. Enrolment in the Waldauf *et al*'s study occurred around 30 hours after admission, with therapy initiation the following calendar day. While the implementation of FES-cycling took place earlier relative to traditional therapy, trials finding benefit of early rehabilitation were able to initiate traditional therapy services at a median of 1.5 days into their critical illness.[2] Thus, FES-cycling may have to be implemented earlier following intubation in the setting of a thoughtful safety protocol.

Early in the course of critical illness, patients' mental status frequently limits ability to actively participate in therapy. One possible advantage of FES-cycling is that nerves and muscles can be engaged without the involvement of the brain. However, lack of early central nervous system stimulation and input of executive function into exercise may limit the efficacy of FES-cycling. Prior studies demonstrating improved outcomes associated with early rehabilitation included interruption of sedation during therapy sessions.[2 10] Interruption of sedation may allow the central nervous system to engage peripheral nerves and skeletal muscle in a way that preserves function, prevents delirium and improves long-term outcomes. The improvement of nitrogen balance found in the intervention group of the Waldauf *et al*'s study implies FES-cycling slowed loss of muscle; however, strength and muscle mass were not significantly different. This finding perhaps supports that central nervous system attention to the therapy task is essential to improve physical outcomes. In addition, the absence of early sedation interruption may partially explain why a reduction in delirium and cognitive dysfunction were not seen. Future technology, which integrates the entire neuromuscular axis early in the course of critical illness, may have more clinically significant outcomes.

In summary, both studies were well designed and implemented without demonstrating FES-cycling provides a clear improvement in patient-centred outcomes. Possible explanations for the negative results include high-quality usual care rehabilitation services in the control arms, relatively late implementation of therapy services, and unclear integration of the brain with peripheral

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nerves and muscles. Of note, both studies were underpowered for the long-term outcomes. Future studies investigating the benefits of early rehabilitation may focus on early awakening and/or integration of the central nervous system to have clinically significant results.

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