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Can functional electrical stimulation-assisted cycle ergometry replace insulin infusion in critically ill patient? A nested sub-study in a randomised controlled trial with 6 months follow-up

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Complete List of Authors:	Waldauf, Petr; Charles University, Fac Med 3, Dept. of Anaesthesia and Intensive Care Medicine; University Hospital Kralovske Vinohrady Urban, Tomas; Charles University, Fac Med 3, Dept. of Anaesthesia and Intensive Care Medicine; University Hospital Kralovske Vinohrady, Dept. of Burns Krajcova, Adela; Charles University, Fac Med 3, Dept. of Anaesthesia and Intensive Care Medicine Jiroutkova, Katerina; Charles University, Fac Med 3, Dept. of Anaesthesia and Intensive Care Medicine; University Hospital Kralovske Vinohrady Bakalar, Bob; Charles University, Fac Med 3, Dept. of Anaesthesia and Intensive Care Medicine; University Hospital Kralovske Vinohrady, Dept. of Burns Blahutova, Barbora; Charles University, Fac Med 3 Rasova, Kamila; Charles University, Fac Med 3, Dept. of Rehabilitation; University Hospital Kralovske Vinohrady Lippertova-Grunerova, Marcela; Charles University, Fac Med 3, Dept. of Rehabilitation; University Hospital Kralovske Vinohrady Gojda, Jan; Fakultni Nemocnice Kralovske Vinohrady, Department of Internal Medicine ; Charles University, Fac Med 3, Laboratory of Clinical Physiology Duska, Frantisek; Charles University, Fac Med 3, Dept. of Anaesthesia and Intensive Care Medicine; University Hospital Kralovske Vinohrady, Laboratory of Bioenergetics
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Abstract:	Background: Functional electrical stimulation-assisted cycle ergometry (FESCE) can deliver active exercise to critically patients including those who are sedated. Aerobic exercise is known to stimulate skeletal muscle glucose uptake. We asked whether FESCE can reduce intravenous insulin requirements and improve insulin sensitivity in intensive care patients. Method: We performed an a priori planned secondary analysis of data from an outcome-based randomised-controlled trial (NCT 02864745) of FESCE-based early mobility programme vs. standard of care in mechanically ventilated patients. We analysed glucose profile, glucose intake and insulin requirements during ICU stay in all enrolled patients.

	In a nested subgroup we performed hyperinsulinemic (120 mIU.m-2.min-1) euglycemic clamp at days 0, 7 and 180 (n=30, 23 and 11, respectively). Results: We randomised 150 patients 1:1 to receive intervention or standard of care. Seventeen (23%) patients in each study arm had a history of diabetes. During ICU stay patients received 137±65 and 137±88 g/day of carbohydrates (p=0.97), and 31 vs. 35 (p=0.62) of them required insulin infusion to maintain blood glucose 8.61±2.82 vs. 8.73±2.67 mM (p=0.75, n= 11254). In those treated with insulin, median daily dose was 53 (IQR 25-95) vs. 62 (IQR 26-96) IU in the intervention and control arm, respectively (p=0.44). In the subgroup of patients undergoing hyperglycaemic clamps, insulin sensitivities improved similarly and significantly from acute and protracted critical illness towards 6 months post discharge. Conclusion: Functional electrical stimulation-assisted cycle ergometry-based early mobility programme does not significantly reduce insulin requirements in critically ill patients on mechanical ventilation.

Can functional electrical stimulation-assisted cycle ergometry replace insulin infusion in critically ill patient? A nested sub-study in a randomised controlled trial with 6 months follow-up

Petr Waldauf, MD[1*], Tomáš Urban MSc[1*], Adéla Krajčová, MD, PhD[1], Kateřina Jiroutková, MD, PhD[1], Barbora Blahutová MD[1], Bob Bakalář MD[1], Kamila Řasová PhD[2], Marcela Grünerová-Lippertová MD, PhD[2], Jan Gojda MD, PhD[3] and František Duška MD, PhD[1]

[1] Department of Anaesthesia and Intensive Care Medicine, Charles University, The Third Faculty of Medicine and FNKV University Hospital Prague, Czech Republic

[2] Department of Rehabilitation, Charles University, The Third Faculty of Medicine and FNKV University Hospital Prague, Czech Republic

[3] Department of Medicine, Charles University, The Third Faculty of Medicine and FNKV University Hospital Prague, Czech Republic

[*]TU and PW contributed equally and shall be considered joint first authors

Corresponding author:

Frantisek Duska,

Dept. of Anaesthesia and Intensive Care Medicine

Srobarova 50

10034 Prague, Czech Republic

E-mail: frantisek.duska@lf3.cuni.cz

Phone: +420608405541

Abstract

Background: Functional electrical stimulation-assisted cycle ergometry (FESCE) can deliver active exercise to critically patients including those who are sedated. Aerobic exercise is known to stimulate skeletal muscle glucose uptake. We asked whether FESCE can reduce intravenous insulin requirements and improve insulin sensitivity in intensive care patients.

Method: We performed an *a priori* planned secondary analysis of data from an outcome-based randomised-controlled trial (NCT 02864745) of FESCE-based early mobility programme vs. standard of care in mechanically ventilated patients. We analysed glucose profile, glucose intake and insulin requirements during ICU stay in all enrolled patients. In a nested subgroup we performed hyperinsulinemic (120 $mIU.m^{-2}.min^{-1}$) euglycemic clamp at days 0, 7 and 180 (n=30, 23 and 11, respectively).

Results: We randomised 150 patients 1:1 to receive intervention or standard of care. Seventeen (23%) patients in each study arm had a history of diabetes. During ICU stay patients received 137±65 and 137±88 g/day of carbohydrates (p=0.97), and 31 vs. 35 (p=0.62) of them required insulin infusion to maintain blood glucose 8.61±2.82 vs. 8.73±2.67 mM (p=0.75, n= 11254). In those treated with insulin, median daily dose was 53 (IQR 25-95) vs. 62 (IQR 26-96) IU in the intervention and control arm, respectively (p=0.44). In the subgroup of patients undergoing hyperglycaemic clamps, insulin sensitivities improved similarly and significantly from acute and protracted critical illness towards 6 months post discharge.

Conclusion: Functional electrical stimulation-assisted cycle ergometry-based early mobility programme does not significantly reduce insulin requirements in critically ill patients on mechanical ventilation.

Key words: critically ill; glucose control; insulin resistance; hyperinsulinaemic clamp

Abbreviations: BMI = body mass index; ICU = intensive care unit; IQR = interquartile range; FESCE = functional electrical stimulation-assisted cycle ergometry; M-value = insulin-mediated glucose disposal; RAPA score = rapid assessment of physical activity

Conflict of interests: None declared.

Clinical Relevancy Statement: Treatment of hyperglycaemia of the critically ill with continuous intravenous insulin infusion is not without risks. In this paper we show how the delivery of early mobility programme, which includes electrical exercise, influences insulin sensitivity and glucose control in enterally fed general ICU patients. In addition, this study is the first one to show natural evolution of critical illness-induced insulin resistance measured by serial hyperinsulinaemic clamps in the ICU and 6 months afterwards.

Introduction

Insulin resistance is a well-recognized phenomenon in critically ill patients [1]. Acute injury, inflammation, and catecholamine surge induce a catabolic response where glycogen, fat and proteins are degraded to provide substrates for immune cells and wound healing. Bedrest, insulin counter-acting drugs such as steroids or vasopressors, and carbohydrate delivery in the form of artificial nutrition may further exacerbate hyperglycaemia, which has repeatedly been associated with ICU morbidity and mortality, even after adjustments to disease severity [2]. Insulin infusion is effective in controlling blood glucose levels, but it may increase risk of hypoglycaemia and mortality [3,4]. In healthy subjects skeletal muscle is the main organ responsible for insulin-mediated glucose disposal and even a short bout of aerobic exercise increases glucose uptake up to 5-fold[5]. Animal studies suggest that mechano-signalling pathways exist in skeletal muscle and can circumvent molecular pathways affected by insulin resistance[6]. Technology advances, such as functional electrical stimulation-assisted cycle ergometry (FESCE) allow delivery of active exercise even before the patient regains consciousness[7,8] and it is tempting to hypothesise that compared to standard of care, a FESCE-based early mobility programme delivered to mechanically ventilated patients would reduce intravenous insulin requirements and increase insulin-mediated glucose disposal during hyperinsulinaemic clamp. In this study, we also aimed to investigate the dynamics of insulin sensitivity during and 6 months after critical illness.

Materials & Methods

We performed an *a priori* planned secondary analysis of an outcome-based prospective randomised controlled trial Electric Mobility & Insulin Resistance (EMIR, NCT02864745) performed in intensive care of FNKV University Hospital in Prague. Clinical

outcomes are reported elsewhere [Waldauf, Thorax 2021], full protocol of the study has been published[7] and details can also been found in Supplementary Appendix.

In brief: Mechanically ventilated adult critically ill patients, who were expected to need a protracted (>7 days) ICU stay were recruited within 72 hours of hospital admission. Exclusion criteria include bedridden pre-morbid status and contraindications to FESCE such as limb fractures or pacemaker. The standard care arm underwent standard rehabilitation delivered by personnel not involved in the study. In the intervention arm, the rehabilitation is protocolled according to patient's condition and degree of cooperation with a dedicated full-time study physiotherapists aiming to deliver 90 min of exercise a day, 7 days a week. Before patients re-gained the ability to engage in the mobilisation programme, they received 2 sessions of FESCE (RT-300, Respiratory Therapies, USA) per day. This technique involved synchronised transcutaneous electrical stimulations of the gluteal, hamstrings and quadriceps muscles on both legs to produce a coordinated pattern of movements on a supine bicycle. The exercise intervention continued until day 28 or ICU discharge, whichever occurred earlier. All other aspects of intensive care (including nutrition and insulin treatment) were driven by clinical team, who were not directly involved in the study, but not blinded to patient's treatment allocation. Nutrition was delivered preferably enterally (Supportan, Fresenius Kabi, Germany) as tolerated with the aim to deliver 1.5 g of protein/kg/day. Insulin was started when blood glucose level reached 11 mM and sliding scale insulin infusion rate was then adjusted by a bedside nurse aiming blood glucose levels 6-8 mM. Arterial blood glucose levels were checked in all patients at 05:00, 17:00 and 22:00 by blood gas analyser ABL-90 (Radiometer, Denmark) and ad hoc as needed as per bedside nurse discretion by a portable glucometer. Patient's vital functions, all laboratory data incl. blood glucose levels and data from syringe drivers are automatically and in real time uploaded into the clinical information

system (MetaVision, ver. 5, IMD-Soft, Israel). We have extracted data on blood glucose levels, glucose intake and insulin dose from these (See Supplementary Appendix and Fig. S1 for details).

Metabolic studies. In a subgroup of patients whose representatives specifically consented to it (see Flowchart in Supplementary Fig. S1), we performed hyperglycaemic euglycemic clamps at fasting state in the morning of day 1 (baseline). These studies were repeated in ICU after 7 day (n=23) and in outpatients after 180 days (range 171-186, n=11). At baseline arterial blood sample for measurement of fasting blood glucose, insulin and C-peptide was taken. After a 10-min priming infusion at a double rate, insulin infusion (1 unit/ml in 0.9% saline) was held constant at 120 $mIU \cdot min^{-1} \cdot m^{-2}$ BSA for consequent 110 min. Blood glucose concentration was determined every 5 min using StatStrip (Nova Biomedical, Waltham, MA, USA). Blood glucose concentration was clamped at ~5 mmol/L by infusion of variable amounts of glucose. The total body glucose disposal rate (M-value) was calculated from the final 30 min (steady-state) and was used as a measure of insulin sensitivity after adjustment to body weight. Insulin clamps at follow-up visit (Day 180) were performed similarly, with two intravenous cannulas, one in an antecubital vein for the infusion of insulin and glucose, and the other retrograde into a dorsal hand vein for sampling of arterialised blood using heated hand technique.

Calculations and statistics. Differences between groups were tested using two-sided Welch t-test, Wilcoxon rank sum test, or linear mixed effect model with random intercept, where appropriate, and $p<0.05$ is considered significant. All calculations were performed in R and R Markdown, version 4.0.3.

Results:

We enrolled 150 patients into the trial, out of which 31 consented to undergo serial insulin clamps. Baseline characteristics of enrolled subjects is given in Table 1.

	All patients (n=150)	Subgroups				P value
		Intervention group (n=75)		Control group (n= 75)		
		Consent to clamp YES (n=16)	Consent to clamp NO (n=59)	Consent to clamp YES (n=15)	Consent to clamp NO (n=60)	
Age (mean±SD)	**61.1±15.2**	58±17	61±15	64±11	62±16	0.665
Sex (M/F)	**110/40**	12/4	41/18	10/5	47/13	0.663
BMI	**30.1±7.4**	29.2±5.9	29.4±6.5	33.3±8.1	29.9±8.1	0.428
APACHE II (median [IQR])	**21.8±6.4**	22±5	23±5	27±7	22±7	0.045
Days from ICU admission to recruitment	**1.2 (IQR 0.8-1.8)**	1.4±0.8	1.3±0.8	1.4±0.7	1.2±0.8	0.895
History of diabetes* (%)	**34 (23%)**	6/10 (38%)	11/48 (19%)	7/8 (47%)	10/50 (17%)	0.003
Pre-admission Charlson comorbidity score (median [IQR])	**3 (IQR1-4)**	2.9±2.0	2.7±2.4	3.7±2.8	3.2±2.2	0.405
RAPA Score (median [IQR])	**1 (IQR 1-4)**	2.7±2.3	2.4±2.0	2.9±2.3	3.0±2.4	0.556
Diagnostic category (trauma/surgical/medical)	**51/19/81**	8/3/5	20/3/36	4/1/10	19/12/29	0.087
Sepsis or septic shock on admission (Yes/No [%Yes])	**37 (24.7%)**	5/11 (31%)	14/45 (24%)	5/10 (33%)	13/47 (22%)	0.742

Table 1: Baseline study subject characteristics.

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) and received 137±65 and 137±88 g/day of carbohydrates (p=0.97) and 80±24 vs 50±10 min (p<0.001) of rehabilitation a day. In total, there were 5659 and 5595 blood glucose measurements in the study. There was no difference in blood glucose control between groups as average blood glucose was 8.61±2.82 vs. 8.73±2.67 (p=0.75) in the intervention vs. control groups, respectively. There were 11 (0.2%) and 16 (0.3%) blood glucose values were below 3.4 mM in intervention and control arms, respectively (Odds ratio of hypoglycaemia 0.7 [95%CI 0.3/1.6], p=0.44). To control blood

glucose, 31 (41%) and 35 (47%) patients needed insulin infusion during their ICU stay (Odds ratio of needing insulin in intervention arm 0.81 (95%CI 0.4-1.6, p=0.62). The median daily dose in those who received insulin was 53 (IQR 25-95) and 62 (26-96) IU of insulin in intervention and control arms, respectively (p=0.44). Mean daily dose of insulin in all patients adjusted to actual body weight was 0.25±0.35 and 0.27±27 $IU.kg^{-1}.day^{-1}$ (n=150, p=0.67), whilst mean adjusted doses in patients receiving insulin were 0.60±0.28 vs. 0.58±0.34 $IU.kg^{-1}.day^{-1}$ (n=66, p=0.83).

Insulin-mediated glucose disposal. As shown in Figure 1 insulin-mediated glucose disposal during hyperinsulinaemic clamp improved significantly in both groups throughout the course of critical illness and continued during recovery phase to reach levels measured for normal subjects[9]. In order to rule out the effect of non-survivors, we have also separately analysed only patients who survived ICU until day 7 and the improvement of insulin sensitivity remained significant (See Table S2 in the Supplementary appendix). There were no significant differences between intervention and control groups.

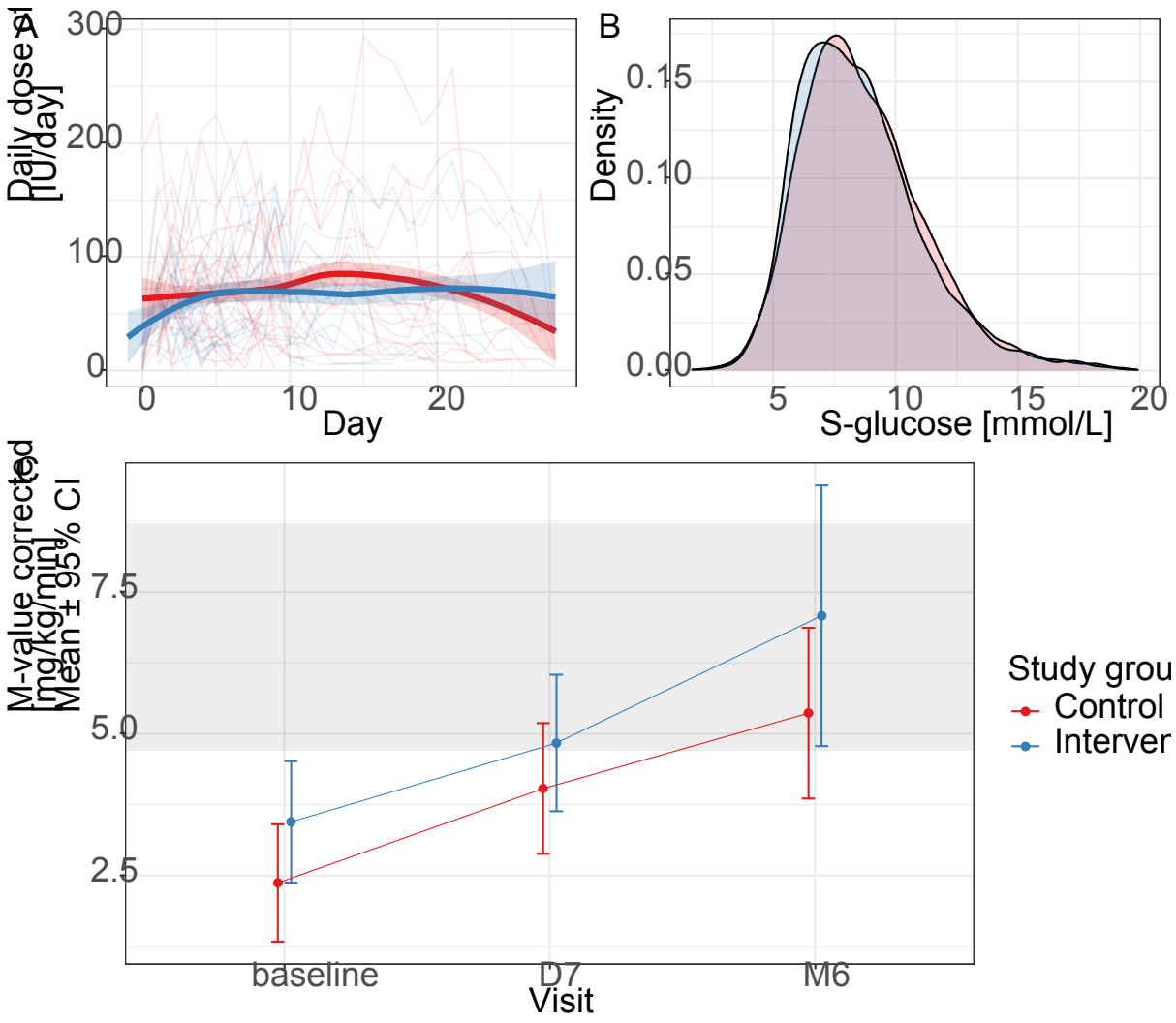

Figure 1: A) Mean insulin doses in all patients with 95% confidence of intervals. B) Density diagram of blood glucose levels. C) Prediction of difference in study groups of M-value corrected over different time visits. Note: M-value is expressed as glucose infusion rate space corrected, units = $mg.kg^{-1}.min^{-1}$. Grey zone represents published [9] normal range in age-matched population.

Discussion

There are two main finding of this study. Firstly, early mobility programme does not significantly improve glucose control or reduce insulin requirements in critically ill patients. This is despite exercise intervention has successfully been delivered and there is a clear and

significant separation of rehabilitation duration between treatment groups, which mostly consists of 29 min/day of FESCE. There are few possible explanations of this results, which contrasts with previous studies showing that early mobilization could decrease insulin requirements in ICU patients[10]. In healthy volunteers, unloaded FESCE increased energy expenditure similarly to 25W aerobic exercise[9], but across-leg metabolic characteristics differ from volitional cycling and it is possible that it also fails to activate mechano-signalling pathways[6] that would activate glucose uptake. In addition, it seems from glucose profiles that glucose control strategy was quite liberal compared to Patel's study [10]. This, together with the fact that 23% of our cohort had pre-existing diabetes, resulted in relatively high insulin requirements in those who needed insulin trestment (~0.6 $IU.kg^{-1}.day^{-1}$), whilst in Patel's study[10] the effect of early mobilization was only seen in low-insulin subgroup (<0.15 $IU.kg^{-1}.day^{-1}$). In fact, we have seen a trend to a reduction of proportion of patients needing insulin infusion in the intervention arm and it should be stressed that with 150 subjects and 47% insulin treatment in the control group, our study was only powered to detect (at α=0.05 and β=0.2) a reduction of the need of insulin treatment below 24% (or <18 out of 75 patients) in the intervention group. Lastly, the dose of exercise in the control group (50 min/day) in our study was unusually and unexpectedly high, possibly due to Hawthorne effect[11].

Second important and innovative finding of this study is that we, to our knowledge for the very first time, assessed by serial euglycaemic hyperinsulinaemic clamps the evolution of insulin sensitivity in acute and protracted critical illness, and then 6 months afterwards. We have seen clear and significant increases of insulin-mediated insulin sensitivity over time that were not significantly affected by treatment group allocation. After 6 months high-dose-insulin-mediated glucose disposal was significantly better than during protracted critical illness and reached values comparable to patients with type 2 diabetes[12] or cancer[13], but

remained lower than in lean healthy subjects of similar age in some[14], but not all[9] studies. It should be stressed that although most baseline characteristics of patients consenting to insulin clamps were not different to overall study population, there seems to be a selection bias towards patients with diabetes.

In conclusion, insulin sensitivity increases during the transition from acute to chronic phase of critical illness and further improves after 6 months. Early mobility programme based on functional electrical stimulation-assisted supine cycle ergometry does not significantly influence glucose control or insulin requirements in mechanically ventilated critically ill patients.

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Authorship Statement. P. Waldauf and T. Urban equally contributed to the conception and design of the research; F. Duska, J. Gojda and M. Grünerová-Lippertová contributed to the design of the research; P. Waldauf, B. Bakalář, B. Blahutová, K. Jiroutková contributed to the acquisition and analysis of the data; all authors contributed to the interpretation of the data; and F. Duška drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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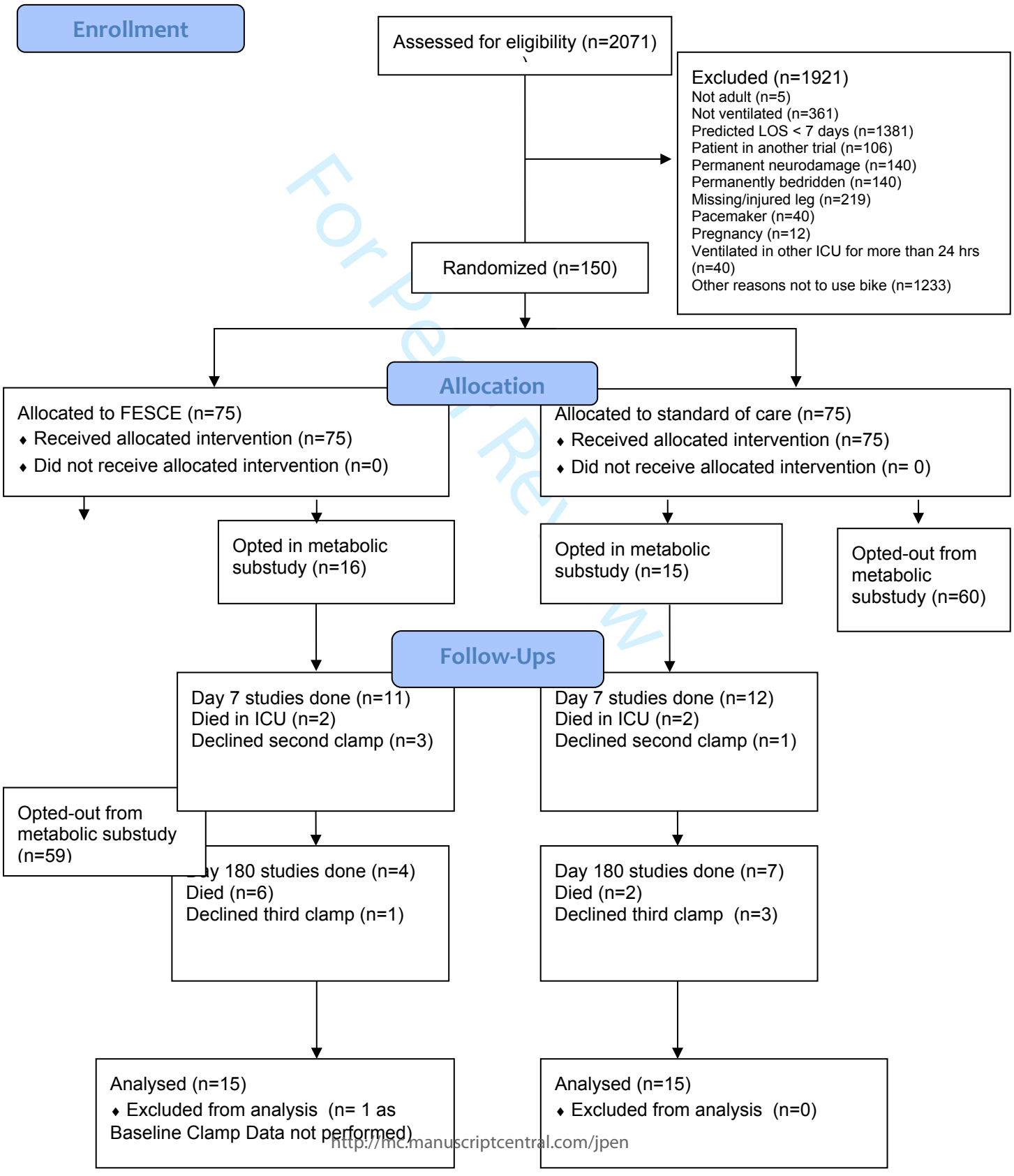
Supplementary Appendix

To paper Waldauf at al.: Can functional electrical stimulation-assisted cycle ergometry-based early mobility programme replace insulin infusion in critically ill patient? A nested sub-study in a randomised controlled trial with 6 months follow

Table of Contents

Supplementary Methods

Flowchart of subjects in the study



Analysis
(metabolic subgroup)

Full list of Enrolment Criteria

Inclusion Criteria:

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

Exclusion Criteria:

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

Individualised Rehabilitation Protocol

Table S1 Protocolised rehabilitation in EMIR Trial (recommendation)

Stage and RASS score	Control group = goal-directed standard physiotherapy	Intervention group = FESCE in addition to the goal-directed standard physiotherapy
0 unstable	2x 15 minutes	FESCE 2x45 minutes*

RASS -5 to -3 +/-muscle relaxants	Passive/active exercises: passive and active range of motion, application of stretch reflex to upper and lower extremities and activation of global motor response, positioning in bed Respiratory-related activity	Preparation phase: about 5 minutes of passive cycling Therapeutic phase: about 35 minutes of functional electric stimulation Relaxation phase: about 5 minutes of passive cycling
1 sedated RASS -5 to -3	1x30 minutes Passive/active exercises: passive and active range of motion, application of stretch reflex to upper and lower extremities and activation of global motor response, positioning in bed Respiratory-related activity	FESCE 2x45 minutes* Preparation phase: about 5 minutes of passive cycling Therapeutic phase: about 35 minutes of functional electric stimulation Relaxation phase: about 5 minutes of passive cycling
2 transition phase RASS -1 or 1, borderline cooperation	If cooperative: 2x10 minutes Passive/active exercises: active range of motion/lightly resisted upper and lower extremities, activation of global motor response, positioning in bed Respiratory-related activity 2x5 minutes Passive/active exercises (sit up in bed) If delirious: Individualise approach max. 30 minutes If resedated: 1x15 minutes Passive/active exercises: passive and active range of motion, application of stretch reflex to upper and lower extremities and activation of global motor response, positioning in bed Respiratory-related activity	FESCE 2x45 minutes* Preparation phase: about 5 minutes of passive cycling Therapeutic phase: functional electric stimulation (about 30 min) with active cycling (about 5 min) Relaxation phase about 5 minutes of passive cycling
3 weak RASS 0, cooperative	2x10 minutes Active exercises: active range of motion/lightly resisted upper and lower extremities 2x5 minutes Progressive mobility: mobility activities progressing from less difficult activity in bed, active sitting on the bed 2x60 minutes Active exercise: sit out with assistance	FESCE 2x45 minutes* Preparation phase: about 5 minutes of passive cycling Therapeutic phase about: functional electric stimulation (about 15 min) with active cycling (about 20 min) Relaxation phase: about 5 minutes of passive cycling
4 able to stand with assistance RASS 0, cooperative	2x10 minutes Active exercises: active range of motion, low to moderate resistance against upper and lower extremities 2x30 minutes Progressive mobility: mobility activities progressing from less difficult activity in	FESCE 2x45 minutes* Preparation phase: about 5 minutes of passive cycling Therapeutic phase: functional electric stimulation (about 5 min) with active cycling (about 30 min)

	bed to more difficult out of bed activities such as up to chair and ambulation	Relaxation phase: about 5 minutes of passive cycling

Notes: FESCE functional electrical stimulation-assisted cycle ergometry, RASS = Richmond agitation and sedation scale. Categories of interventions were defined according to Consensus on exercise reporting template in the intensive care unit (Reid et al., 2018), dose and intensity according to Perme C, Chandrashekar R., 2009.
**Conducting FES cycling for set up (e.g., electrode placement, achieve muscle contractions, start cycling) took the physiotherapists about 10 - 15 minutes and take down (e.g., removing the patient from the bike and electrode removal) about next 10 minutes in addition to FES cycling.*

Table S2 Description of an average treatment days

*an average treatment day were defined as the number of days when the participant received physical rehabilitation in ICU. Data are “median of mean”, that is a mean time was calculated for each participant and then, as a data were not normally distributed, a median was calculated for each trial arm (Wright et al., 2018)
Abbreviations: ICU LOS (intensive care unit length of stay), Standard (goal-directed standard physiotherapy), FESCE (Functional electrical stimulation-assisted cycle ergometry)
Note: Real time composition of the control (goal-directed standard physiotherapy) and the intervention group (FESCE in addition to the goal-directed standard physiotherapy) was influenced according to actual patient’s conditions and workload on the unit.

Table S3 Richmond Agitation Sedation Scale (RASS)

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

		communicate or follow commands

Supplementary Results

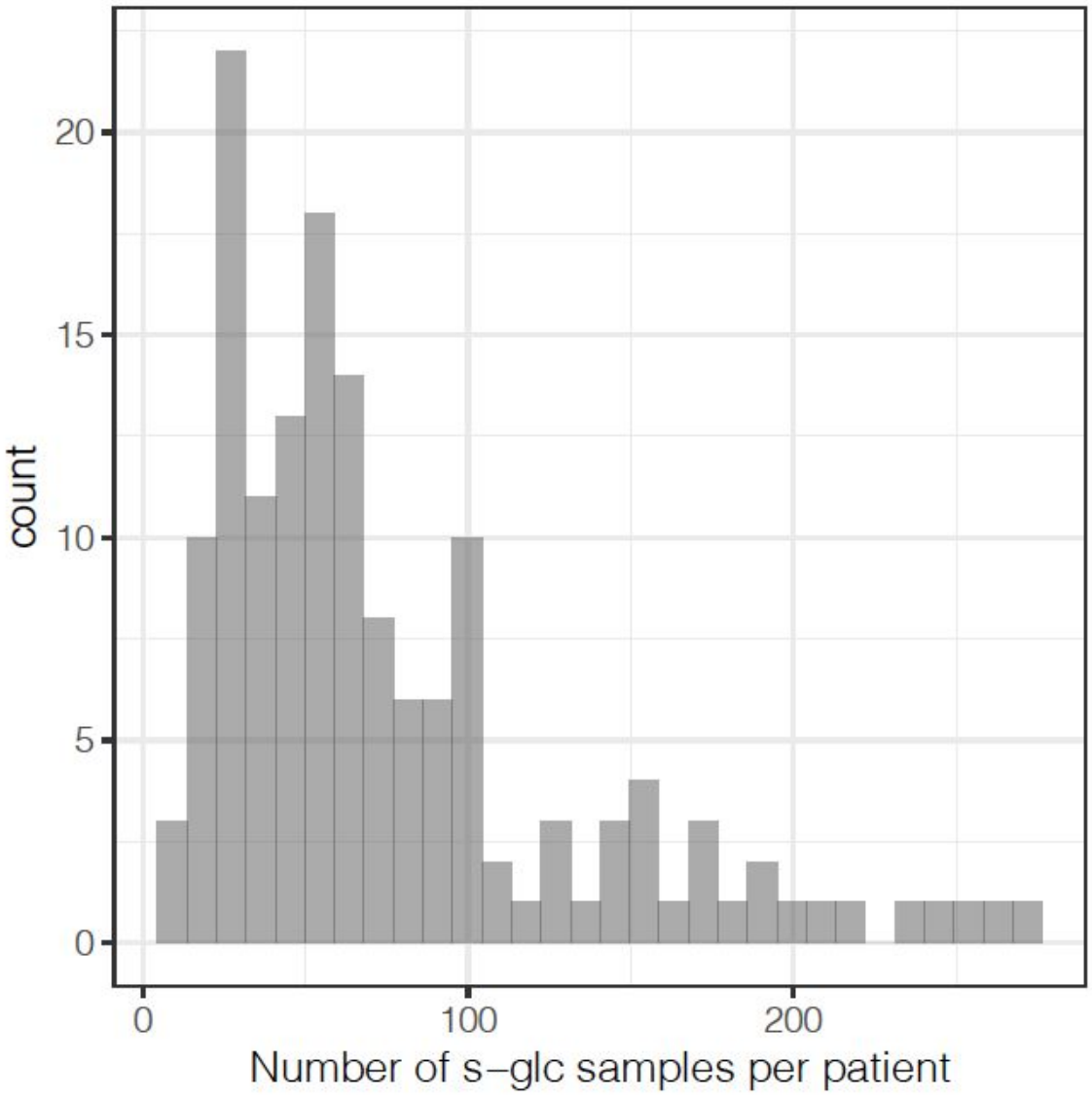
Table S4: Insulin sensitivity analyses.

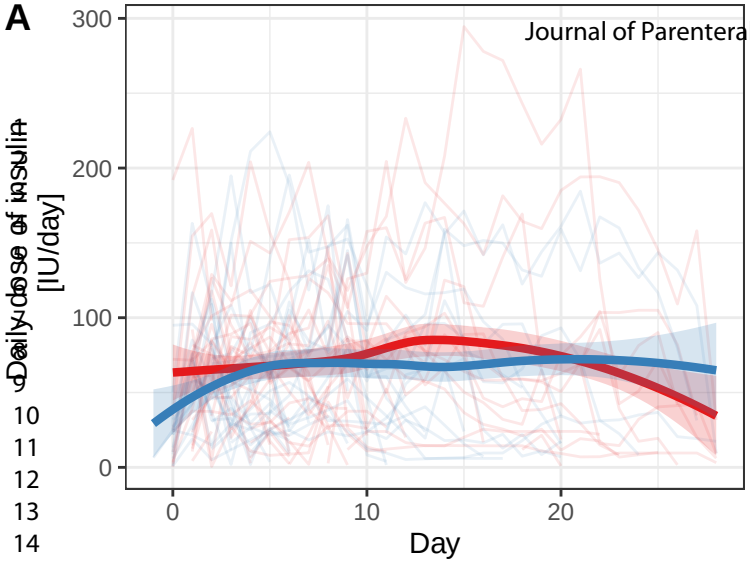
Glucose and insulin values are those measured in the end of the steady state of 120 mIU.min^{-1}.m^{-2} hyperinsulinaemic clamp, i.e. at 120th min.

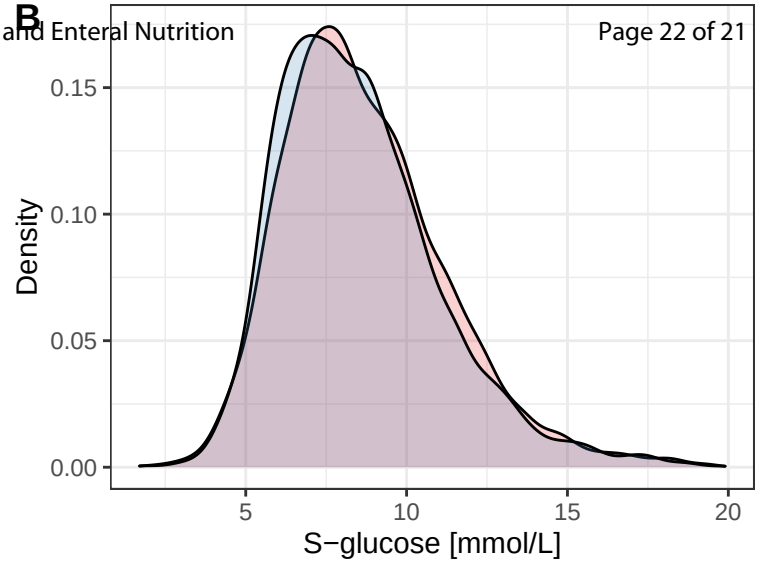
	Study group	Steady state glucose [mmol/L]	M value corrected [mg.kg^{-1}.min^{-1}]		Ln (M value/Insulin) [mg.L.kg^{-1}.min^{-1}IU^{-1}]	
All samples				p		P value
Baseline (n=30)	Intervention (n=15)	5.5±1.0	3.5±1.7	0.136	2.31±1.53	0.347
	Control (n=15)	6.4±1.5	2.5±2.0		1.84±1.50	
Day 7 (n=22)	Intervention (n=10)	5.6±0.7	5.3±2.2	0.126	2.67±1.05	0.510
	Control (n=12)	5.6±0.6	4.0±1.6		3.02±1.24	
Day 180 (n=11)	Intervention (n=4)	5.0±0.3	7.9±2.0	0.083	3.33±0.26	0.794
	Control (n=7)	6.7±1.4	5.7±2.1		3.12±0.50	
Only survivors						

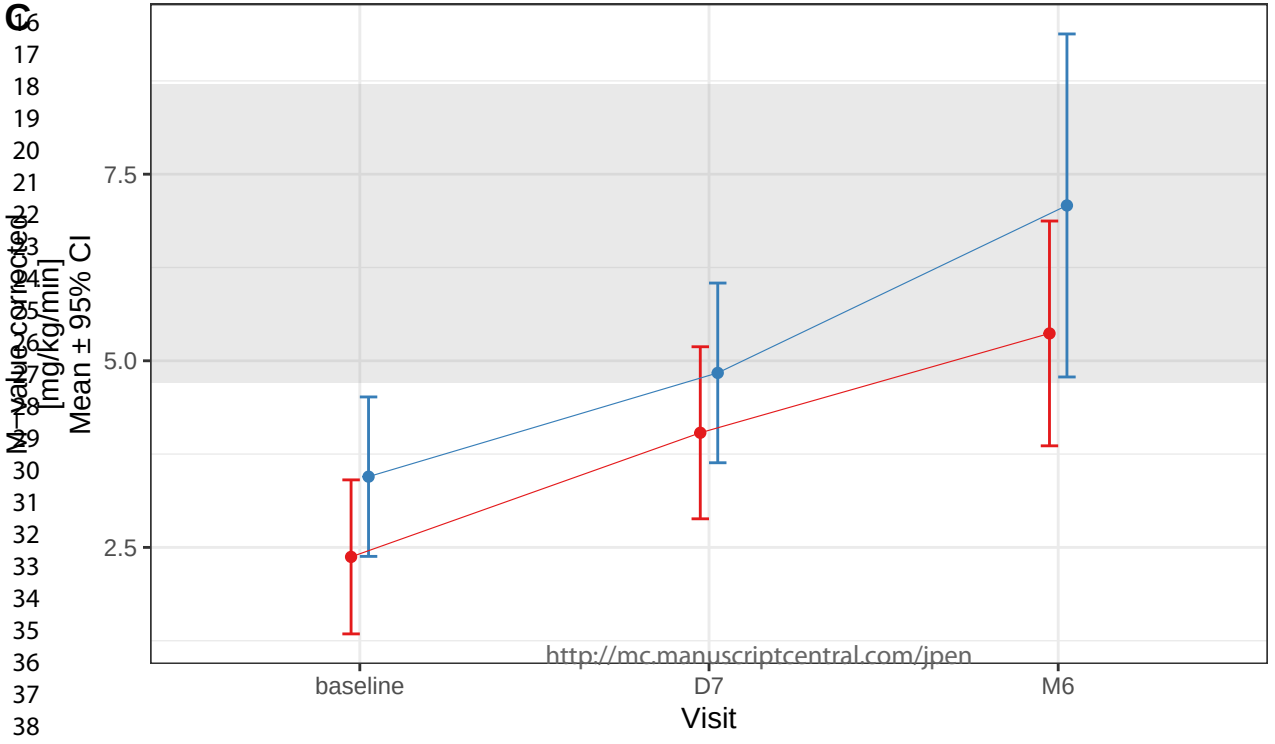
Baseline (n=23)	Intervention (n=11)	5.6±1.1	4.0±1.8	0.110	2.69±1.59	0.397
	Control (n=12)	6.6±1.7	2.6±2.2		2.15±1.52	
Day 7 (n=21)	Intervention (n=10)	5.6±0.7	5.3±2.2	0.124	2.67±1.05	0.428
	Control (n=11)	5.6±0.6	4.0±1.6		3.13±1.23	

Figure S2 Number of blood glucose samples per patient / distribution




A
Daily dose of insulin [IU/day]
300
200
100
0
0
10
20
Day


B
Density
0.15
0.10
0.05
0.00
5
10
15
20
S−glucose [mmol/L]


C
M-value corrected [mg/kg/min]
Mean ± 95% CI
7.5
5.0
2.5
baseline
D7
M6
Visit
Study group
Control
Intervention
http://mc.manuscriptcentral.com/jpen