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Passive Cycling Limits Myofibrillar Protein Catabolism in Unconscious Patients: A Pilot Study

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Abstract

Background: To test the effects of passive cycling on muscle protein metabolism in unconscious patients.

Materials and Methods: Twenty-seven patients (age 61.0 ± 16.4 years) admitted for coma (n=21) or with respiratory insufficiency requiring prolonged sedation were randomized to standard care (n=8) or passive cycling (2×30 minutes/day for 7 days, n=7). Longer-duration cycling (2×60 minutes/day, n=6) or passive cycling plus a hypercaloric hyperprotein diet (n=6) were assessed in separate groups. Ultrasound, biochemical and electrophysiological data were collected for 7 days. The thicknesses of the rectus femoris and of the vastus intermedius were measured by ultrasound. Myofibrillar protein catabolism was assessed by the urine 3-methylhistidine/creatinine ratio (3MH/creat).

Findings: Passive cycling was well tolerated and resulted in a faster decrease in 3MH/creat and a slightly less negative nitrogen balance than standard care. These changes were not influenced by a longer duration of passive cycling or by a hypercaloric hyperprotein diet. There were no differences in muscle thicknesses or electromyographic data between standard care and passive cycling groups.

Conclusions: Passive cycling in comatose or sedated patients was associated with less myofibrillar proteolysis. If confirmed in larger trials, this approach could help to prevent the long-term muscular consequences of prolonged inactivity in critically ill patients.

Keywords: Passive cycling,; Muscle; Bedrest; Intensive care; Muscular atrophy; Mobilization

Introduction

During prolonged critical illness, muscular weakness is very frequent and can ultimately lead to difficulty in weaning from mechanical ventilation and loss of functional autonomy. Muscular weakness increases the rate of complications contributing to longer lengths of stay in the intensive care unit (ICU) [1,2]. Loss of muscle function and bulk, proximal weakness and fatigue are the most frequent long-term complaints of patients who have received prolonged mechanical ventilation. Even after 5 years, significant functional disability was present in survivors of the acute respiratory distress syndrome (ARDS), as assessed by the 6-minute walking distance and the physical functioning section of the Short Form 36 Health Survey (SF-36) questionnaire [3].

The development of muscle weakness in ICU patients is associated with multiple factors, including bed rest [4], multiple organ failure, muscle inactivity, hyperglycemia, and use of corticosteroids and neuromuscular blockers [5,6]. The combination of these factors likely results in increased muscular proteolytic activity [7], largely exceeding the protein synthesis rate [8].

Several therapeutic approaches to limit ICU-acquired muscle weakness have been investigated. Early exercise and mobilization (physical and occupational therapy) during periods of daily interruption of sedation were associated with better functional outcomes at hospital discharge, evaluated by the ability to perform six activities of daily living and to walk independently [9]. Resistance exercise increased the acute amplitude of mitochondrial and sarcoplasmic protein synthesis and resulted in a robust, but delayed stimulation of myofibrillar protein synthesis [10]. Burtin et al. reported that passive or active exercise training sessions using a bedside ergometer were associated with improvements in the 6-min walking distance, the isometric quadriceps force, and the subjective feeling of functional and physical well-being (SF-36 questionnaire) at hospital discharge [11]. These effects of passive cycling could be partially related to an increase in muscle blood flow and to the prevention of joint stiffness.

When active techniques cannot be used, passive techniques may provide some benefit. In one study, passive stretching of one leg was reported to preserve the architecture of muscle fibers, although

prevention of muscle wasting was uncertain [12]. Passive mobilization, such as cycling, can trigger muscular contraction after stimulation of stretch receptors, even in the absence of neural stimulation.

The present study aimed to define the intrinsic effects of passive cycling on muscle metabolism and function in patients with prolonged minimal muscular activity. Specifically, this pilot trial aimed to assess: 1) the effects of mobilization by passive cycling on muscle thickness, electrophysiological features and myofibrillar protein catabolism; 2) whether there was a dose-effect relationship between the intensity and duration of exercise and the magnitude of changes in muscle catabolism and thickness; and 3) whether there was a synergistic effect of increased calorie and protein intake with passive mobilization.

Methods

The studies were performed in two Belgian ICUs located in the University Hospital of Liège and in a Liège University-affiliated hospital, the Centre Hospitalier Régional de La Citadelle. The study was approved by the institutional review boards of both hospitals, and signed informed consent was requested from the patients' relatives.

Inclusion criteria were the following: Adult (> 18 years at admission); period of unconsciousness and/or sedation and mechanical ventilation anticipated to last at least 7 days; and hemodynamic stability (i.e., no requirement for increasing doses of vasopressor agents). Exclusion criteria were: No signed consent; systemic treatment with steroids (intravenous or oral); contra-indication to mobilization of the lower limbs, including pelvic instability, leg fractures, or recent deep venous thrombosis. Standard care included manual mobilization of the limbs and passive turning twice daily by the nurse and the physiotherapist, mechanical ventilation, and nutritional support (Nutrison® Standard, Nutricia, Zoetermeer, NL) preferentially provided continuously by the enteral route, with target calories and nitrogen set at 25 kcal/kg/day and 1.2 kcal/kg/day, respectively. Enteral nutrition was considered as successful when at least 60% of the prescribed amount was delivered. The study was discontinued in patients who recovered spontaneous motor activity, could be weaned from mechanical ventilation, or died.

Sub-study 1: Effects of passive cycling (Figure 1)

Patients were randomized (sealed envelopes) into two groups: A (standard care) or B (passive cycling). Patients randomized to group B received, in addition to standard care, two 30-min sessions of passive cycling per day during the 7-day study period, using a bedside cycle ergometer (MOTOmed®, Letto-2, RECK-Technik GmbH, Betzenweiler, Germany) set at 20 cycles/min. After careful cleaning and disinfection of the pedals, the patient's feet were securely strapped to the pedals and the cycle adjusted to the leg length.

Sub-study 2: Long-duration cycling

A further set of patients (group C) was treated in the same way as the patients of group B, except that the duration of cycling was increased to 60 mins twice daily.

Sub-study 3:

A further set of patients (group D) was treated in the same way as the patients of group B, except that target calories and nitrogen were set at 35 kcal/kg/day and 1.8 kcal/kg/day, respectively. A hyperenergetic hyperprotein solution (Fresubin HP Energy, Fresenius

and Bad-Homburg, Germany) was used to achieve these nutritional goals.

Figure 1: Example of passive cycling in an unconscious patient.

Collected variables (Figure 2)

Sex, age, date and reason for ICU admission were recorded at the time of inclusion in the study. Patient monitoring included heart rate, blood pressure and pulse oximetry. Nutritional intake (calories and nitrogen) was recorded daily during the study period. Ultrasound, biochemical and electrophysiological data were collected at the time of study start and at the end of the 7-day study period. In patients from groups C and D, the thicknesses of the rectus femoris and of the vastus intermedius was measured by ultrasound (10 Hz probe) performed by the same dedicated radiologist, with the patient in a supine position and the legs relaxed lying flat in extension. A Philips HD11 Ultrasound machine linear probe (L12-5 MHz, 50 mm broadband linear array) was used. An Ultrasound Gel Pad was applied directly on the thigh for optimal transducer contact and signal penetration The position of the probe was marked and angulation was carefully checked to ensure the highest possible reproducibility of the measures. Urinary aliquots were sampled daily from patients of groups A and B for determination of urea, protein and creatinine concentrations. Daily and cumulative nitrogen balances were calculated using the Lee and Harvey formula (Urea mmol/24h×0.036) and the total nitrogen intake expressed in g/day. A 10-ml aliquot was sampled from day 0 and day 7 urines for determination of 3-methylhistidine (3MH) by high performance liquid chromatography (HPLC) with an ion-exchange column. The 24-h urine output was recorded. The 3MH/creatinine ratio was calculated as an index of muscle protein catabolism; the upper limit of the normal range is 0.01. A surface electromyogram (Neuropack®, Nikoh Kohden, Japan) was recorded in patients from groups A and B after placement of the electrodes on the external edge of the tibia (negative electrode), calf (neutral) and internal malleolus (positive electrode) and stimulation of the common fibular nerve by currents of 2-mA incremental intensity. The maximal muscular response (amplitude and area) of each action potential was recorded (measurements in triplicate) as an index of the number of excitable muscle fibres.
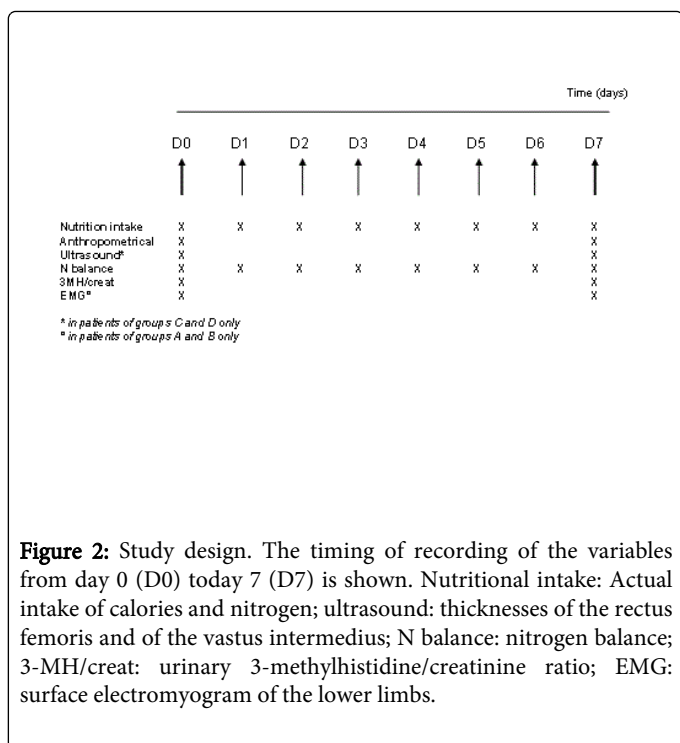
Figure 2: Study design. The timing of recording of the variables from day 0 (D0) today 7 (D7) is shown. Nutritional intake: Actual intake of calories and nitrogen; ultrasound: thicknesses of the rectus femoris and of the vastus intermedius; N balance: nitrogen balance; 3-MH/creat: urinary 3-methylhistidine/creatinine ratio; EMG: surface electromyogram of the lower limbs.

Statistical Analysis

A per protocol analysis was conducted; i.e., data from patients in whom the study was discontinued before day 7 were not used. Baseline characteristics were compared using non-parametric tests, chi-square tests, analysis of variance, Student's t-test or non-parametric testing, as appropriate (Statistica ® software). No power calculation or sensitivity analysis was carried out, in relation with the "proof-of-concept" aim of this pilot study. The effects of the intervention were analyzed by analysis of variance, as a function of time and group and time x group. A p value $< .05$ was considered as significant.

Results

A convenience sample of 27 patients was enrolled (8, 7, 6 and 6 patients in groups A, B, C and D, respectively).

Pt nb	Group	Age	Sex		SAPS II score	Time from admission (days)
1	A	72	M	Complicated cardiac surgery	22	23
2	A	60	M	Head trauma	20	8
3	A	77	M	Complicated cardiac surgery	70	4
4	A	53	F	Cerebral hemorrhage	72	2
5	A	62	M	Complicated cardiac surgery	62	7
6	A	86	F	ARDS	39	3
7	A	55	F	Cerebral hemorrhage	51	4
8	A	70	M	Cerebral hemorrhage	27	7
Mean ± SD		67 ± 11			45 ± 21	7 ± 7
9	B	40	M	Cerebral hemorrhage	32	7
10	B	68	F	Brain tumor	26	7
11	B	76	F	Stroke	41	4
12	B	72	F	ARDS	63	3
13	B	72	M	Head trauma	48	22
14	B	42	F	Post-anoxic encephalopathy	78	2
15	B	78	M	Immune encephalopathy	34	9
Mean ± SD		57 ± 24			43 ± 19	7 ± 7
16	C	44	M	Head trauma	25	30
17	C	69	F	Post-anoxic encephalopathy	40	46
18	C	80	M	Cerebral hemorrhage	46	5
19	C	67	M	Stroke	41	36
20	C	41	F	Stroke	27	10
21	C	54	M	ARDS	23	4
Mean ± SD		59 ± 15			34 ± 10	22 ± 18
22	D	67	M	Immune encephalopathy	18	8
23	D	69	M	Stroke	36	9
24	D	34	M	Head trauma	21	22
25	D	48	F	Cerebral hemorrhage	41	7
26	D	73	F	Cerebral hemorrhage	21	17
27	D	18	F	Head trauma	26	8
Mean ± SD	52 ± 21				27 ± 9	12 ± 6
ARDS: acute respiratory distress syndrome: M: male; F: female						

Table 1: Patient demographics

Nutritional intake

All but one of the patients were successfully fed by the enteral route in groups A, B, C or a hypercaloric hyperprotein solution in group D. Only one patient in group A received supplemental parenteral nutrition (Structo-Kabiven®, Fresenius, Bad-Homburg, Germany) for

2 days. During the 7-day study period, the amount of calories and proteins provided averaged 1357 ± 270 kcal/day and 52 ± 18 g of proteins/day (mean ± SD of the values recorded in patients from groups A, B and C), respectively.

Tolerance to passive cycling

Cycling was well tolerated by all patients; no cycling session was interrupted. No episode of hypoxemia or hemodynamic instability was reported during the intervention.

Sub-study 1 (groups A and B)

Daily nitrogen balance did not differ between groups (Table 2, p= 0.53). The cumulative nitrogen balance was slightly more negative in group A than in group B (-50.6 ± 6.3 vs -35.2 ± 7.4 g, p=0.09). The 3MH/creatinine ratio decreased in both groups (from 0.056 ± 0.026 to 0.037 ± 0.045 in group A, p<0.05, and from 0.074 ± 0.031 to 0.036 ± 0.054 in group B, p<0.01); the decrease was steeper in group B than in group A (p<0.05) (Figure 3). The amplitude and area of the maximal muscular responses to electrical stimulation did not change over time (Table 2). The time course of these electrophysiological parameters did not differ in groups A and B.

Sub-study 2 (group C)

The 3MH/creatinine ratio decreased from 0.026 ± 0.043 to 0.017 ± 0.026 (p=0.02) over the study period. This decrease was similar to that seen in group B (Figure 3). There was no significant change in muscle thickness (Table 2).
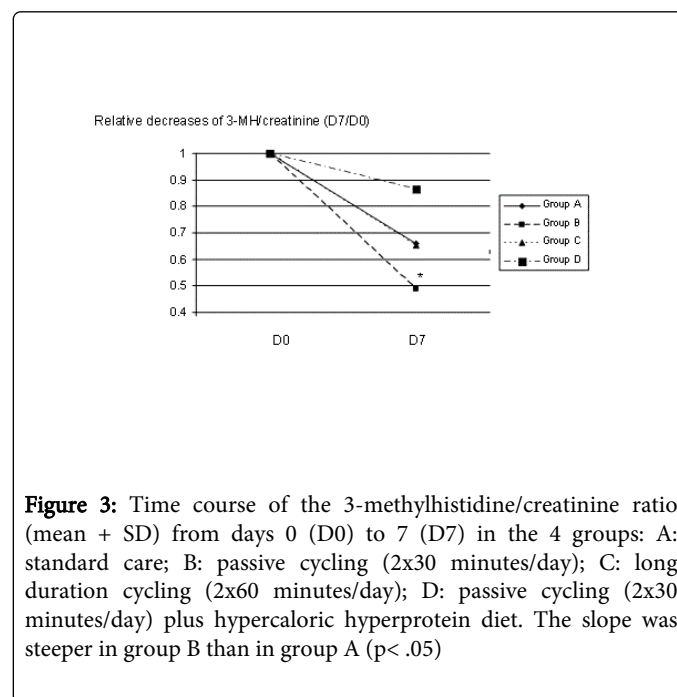
Day 7 (from 0.022 ± 0.087 to 0.019 ± 0.091, p > .05) (figure 3).). There was no significant change in muscle thickness (Table 2).

Figure 3: Time course of the 3-methylhistidine/creatinine ratio (mean + SD) from days 0 (D0) to 7 (D7) in the 4 groups: A: standard care; B: passive cycling (2x30 minutes/day); C: long duration cycling (2x60 minutes/day); D: passive cycling (2x30 minutes/day) plus hypercaloric hyperprotein diet. The slope was steeper in group B than in group A (p< .05)

Discussion

The most salient findings of our study are that mobilization by passive cycling resulted in a faster decrease in myofibrillar protein catabolism than with standard care without a detectable change in muscle thickness or in electromyographic variables and that no significant dose-effect of passive cycling or synergism with increased calories/protein intake and passive mobilization was found.

The model used in this clinical study is unique, as only patients with minimal muscular activity for a period of at least 7 days were studied. The increased rate of myofibrillar protein catabolism was confirmed by the supra-normal values of the 3-MH-to creatinine ratio. Admittedly, pure passive stretch was not investigated when neuromuscular blockade was not used. Therefore, these results may be confounded by the reflex arc and upper neuronal influences on tone and spasticity. However, the design of this study is a reflection of the current standard of care, since muscle paralysis is rarely used in the type of patient included in this study. The effects of standard physiotherapy only (passive mobilization and turning twice a day) on protein catabolism are probably minimal, as suggested by the slight decrease in the 3-MH-to creatinine ratio observed in group A. No potentially confounding factors, such as new sepsis, surgery or hypoxemia, were noted during the study period. However, in patients with ongoing sepsis or recent surgery, acute inflammatory changes in muscle metabolism may differ from those present in long-stay neurological patients. These patients were probably representative of a typical ICU population of long-stayers, in whom acquired weakness is a major issue. Nevertheless, as most patients were admitted for a neurological diagnosis, whether the findings of this study can be applied to non-neurological patients is unclear.

The use of the 3-MH-to creatinine ratio as an index of myofibrillar protein catabolism, was described in 1978 [13] and validated in 1981

Group	Nitrogen balance (g/24h)		Amplitude (mV)		Area (mV.ms)			
	D0	D7	D0	D7	D0	D7		
A	-5.2 ± 2.0	-3.5 ± 1.9	7.9 ± 1.2	6.9 ± 1.1	68 ± 8	70 ± 12		
B	-4.8 ± 1.8	-2.2 ± 3.0	8.0 ± 1.1	7.0 ± 1.1	75 ± 9	70 ± 12		
	Muscle thickness measured by echography (mm)							
	Left Rectus Femoris		Right Rectus Femoris		Left Vastus intermedius		Right Vastus Intermedius	
	D0	D7	D0	D7	D0	D7	D0	D7
C	9.9 ± 2.8	9.5 ± 2.4	9.6 ± 2.7	11.2 ± 4.2	11.1 ± 3.3	11.0 ± 3.7	10.5 ± 2.5	11.2 ± 4.0
D	13.8 ± 6.5	11.7 ± 6.2	15.2 ± 5.9	13.4 ± 6.1	15.8 ± 3.1	14.7 ± 4.2	16.4 ± 4.0	15.4 ± 5.3

Table 2: Anthropometric data, muscle thickness and nitrogen balance (mean ± SD)

Sub-study 3 (group D)

As expected, patients receiving the hypercaloric hyperprotein diet (n=6) received higher amounts of calories and proteins (2027 ± 424 kcal/day and 101 ± 21 g proteins/day) than did patients in the other groups (1357 ± 270 kcal/day and 52 ± 18 g proteins/day, both p<0.01). The 3MH/creatinine ratio did not change significantly from Day 0 to

for critically ill patients with sepsis or trauma [14]. The 3-MH-to creatinine ratio has been shown to decrease over time after surgical injury [15]. The faster decrease in the 3-MH-to creatinine ratio in patients treated with passive mobilization compared to standard care (sub-study 1) reflects the decreased myofibrillar protein catabolism, and is consistent with the slight decrease in nitrogen balance. Admittedly, some unrecorded changes in renal function may have influenced the 3-MH-to creatinine ratio [14, 16]. The influence of changes in non-muscular protein metabolism, including changes in the protein turnover of the gastrointestinal tract, can also not be assessed from the present data. Indeed, the rate of muscle loss follows a logarithmic curve, implying a decreased rate of muscle loss after the acute inflammatory phase. The differences in time interval between admission in the ICU and study inclusion may have introduced a risk of 'lead-time bias'.

Increased protein turnover involving an increased rate of protein synthesis followed by increased breakdown cannot be excluded. To evaluate the influence of these factors, more sophisticated or more invasive techniques, such as stable isotope methods or muscle biopsy, would be needed.

The absence of any effect of passive cycling on muscle thickness could be related to changes in the water and fat content of the muscles and surrounding tissues, perhaps related to changes in the muscle glycogen content. Muscle strength cannot anyway be deduced from measurements of muscle thickness, unlike muscular cross-sectional area. Others have shown slow changes in limb perimeters in critically ill patients [17]. Computerized tomography would probably have been ideal for accurate quantification of muscle mass [18], although this technique has not been widely used in ICU patients. Instead, we used echography with a 10-Hz probe, a technique that has been validated to assess the magnitude of ICU-acquired muscle wasting [19]. Variance in ultrasound measurements was minimized because the same, experienced radiologist collected these data and the technique used was standardized. The changes in muscle thicknesses seen in critically ill patients have been reported to be very heterogeneous [17]. Of note, after spinal cord injury in children, passive cycling increased muscle bulk only when associated with electrical stimulation of the quadriceps [20]. In the ICU, preliminary data suggest that neuromuscular electrical stimulation (NMES) provides some muscular activity even very early during critical illness, potentially helping preserve muscle mass [21] and increase muscle strength [22].

The lack of association between the interventions tested in sub-studies 2 and 3 (increased duration of cycling and increased intake of calories and proteins, respectively) and the ultrasound estimates of muscle thickness could also be related to the relatively short time interval (7 days) between the two measurements. In particular, the slope of the 3-MH-to creatinine ratio over time tended to be steeper in group C (long-duration cycling, decrease of 34 % from baseline) than in group B (27% from baseline), implying that the inclusion of a larger number of patients would allow a more accurate assessment of a dose-response effect, which was not the primary aim of the present study. The lack of a synergistic effect of increased calories and nitrogen with passive mobilization could be related to the amino-acid composition of the enriched formula, and/or to an excessive caloric load [23].

Interpretation of these data is limited because of the small number of patients who could be studied until the end of the 7-day period. The comparability of the groups at baseline is not established, because the proportion of primarily neurological patients differed, as did the time from ICU admission to study inclusion. However, the aim of the study was to assess the effects of passive cycling in all types of immobile patient at any time during the ICU stay. Differences in the concentrations of 3MH-to-creatinine ratio between sub-study 1 and sub-studies 2 and 3 could reflect lower muscle protein catabolism in groups C and D. Nonetheless, the relative change over time is probably a better reflection of the effect of the intervention than absolute values. For this reason, we preferred to use paired values (day 0 and day 7) to show the relative changes in the 3MH/creatinine ratio measured in samples processed simultaneously. The delay between admission to the ICU and inclusion in the study was also variable, in relation with the course of the disease: Some patients were awake at the time of admission and en developed a complication (loss of consciousness or requirement for sedation). This could confound our assessment of the effect of passive cycling, because muscle loss/protein catabolism could have begun well before the intervention. Unfortunately the doses of sedative used in some patients, the mean blood glucose level and the organ failure score during the study period were not recorded. No neuromuscular blocking agent was given during the study. However, regardless of the effects of passive mobilization, the set-up of the present trial might be helpful to evaluate and score the severity of muscular weakness.

Despite these limitations, we believe that our observations in this pilot "proof-of-concept" study, i.e., a decrease in myofibrillar protein catabolism and tolerance to passive cycling in patients with a prolonged period of minimal muscular activity, opens the way for further investigations. Changes in muscle blood flow, water/fluid shifts, stretching of the connective tissue or muscular contractions should be recorded in future evaluations. Obviously, larger study samples, longer periods of observation and intervention, and more frequent or longer duration sessions will be needed to fully evaluate the effects of passive mobilization on muscle function and recovery.

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