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Decreased isometric skeletal muscle force in critically ill patients

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Summary

Question under study: Critically ill patients can develop muscle weakness that prolongs recovery. The aim of this study was to evaluate contractile parameters of the involuntary isometric skeletal muscle forces as measures of muscle weakness in critically ill patients.

Methods: Prospective, controlled trial performed in an intensive care unit (ICU) of a university hospital. Subjects: 19 critically ill patients (diagnoses: intracranial bleeding n = 9; sepsis n = 6; others n = 4), who were ventilated and completely immobilised for one week. 20 healthy volunteers served as controls. We measured peak torques (PT), contraction times, half-relaxation times, peak rates of torque development and decay and torque latencies of the ankle dorsiflexors of the foot after peroneal nerve stimulation.

Results: Patients (median Acute Physiology and Chronic Health Evaluation II score 21) had reduced PTs, medians 3.3 Nm (interquartile range 2.5 Nm) vs 4.1 Nm (2.0 Nm) in controls (P = 0.0003) for single pulse, 4.9 (4.7) vs 8.1 Nm (3.8) (P = 0.0001) for 2-pulse, 6.1 (6.3) vs 10.3 Nm (3.9) (P = 0.0009) for 3-pulse and 7.3 (6.4) vs 11.6 Nm (7.8), (P = 0.006) for 4-pulse stimulations, respectively. Contraction times were reduced and half-relaxation times increased compared with controls.

Conclusions: Assessment of involuntary isometric skeletal muscle forces can be readily measured in critically ill patients. After one week of critical illness, these patients have decreased force compared with healthy controls. This assessment approach will be further evaluated in a long-term study with a larger patient population.

Key words: muscle; skeletal; isometric contraction; torque

Introduction

Critically ill patients in intensive care units (ICU) can develop skeletal muscle weakness, which can subsequently result in difficulties in weaning them from a respirator and/or be associated with disease prolongation. Apart from primary neuromuscular diseases there are secondary causes of muscle dysfunction that can lead to muscle weakness which include endocrine disorders and metabolic and electrolyte disturbances. In addition, a number of drugs can lead to muscle weakness [1]. Moreover, weakness in the critically ill patient can be caused by protein catabolism during an induced hypercatabolic state and/or might be associated with a de novo neuromuscular disorder; this latter state is described as critical illness polyneuromyopathy, which preferentially exists in septic patients and patients with systemic inflammatory response syndrome. Typically, such patients exhibit associated limb weakness that can begin during the early stages of the disease [1–3]. There have been few attempts to quantify such muscle weakness for either diagnostic purposes or to better understand the underlying disease aetiologies [4].

A primary reason for an absence of data is that evaluating voluntary muscle force requires a subject's cooperation and this is impracticable in ventilated and sedated critically ill patients. We hypothetised that an early decrease in muscle force

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Alphabetic list of abbreviations:

APACHE	Acute Physiology and Chronic Health Evaluation II score
ICU	intensive care unit
IQR	interquartile range
MVC	maximum voluntary contractions
Nm	Newtonmetre
PT	peak torque
R	correlation coefficient
r^2	determination coefficient

could be accurately measured and to accomplish this, we employed stimulated muscle force assessment during the early stage of critical illness. Such values would constitute baseline-values (data base) for a long-term investigation. After one week of complete immobilisation and ventilation, we measured contractile parameters of the involuntary isometric skeletal muscle torques of the ankle dorsiflexors utilising nerve stimulations. We used a special device that was originally developed for muscle force assessments of neurological patients and which had been previously evaluated in anaesthetised patients [5–7].

Methods

Study design and subjects

The Human Studies Committee of the University of Basel approved the experimental protocol. During a 2-year study period we recorded and analysed the involuntary, isometric skeletal muscle forces of the ankle dorsiflexor muscle groups evoked by peroneal nerve stimulation. The patients studied included 20 critically ill individuals who were ventilated and completely immobilised (= bed rest) for one week. Ventilation and immobilisation begun the day of admission to ICU. Some but not all patients were ill for a few days prior to their admission to the ICU. Exclusion criteria were pre-existing neuromuscular diseases, burns, patients with severe endocrinological or consuming diseases (eg, diabetes, cancer, AIDS), patients requiring regular skeletal muscle relaxation and patients older than 70 years or younger than 20 years. The severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score. Analgesia in all patients was achieved with morphine titration and sedation with propofol. Informed consent was obtained from the patients' relatives. To both evaluate our measuring device approach and to obtain baseline values, similar torque data were obtained and analysed from 20 healthy volunteers (controls).

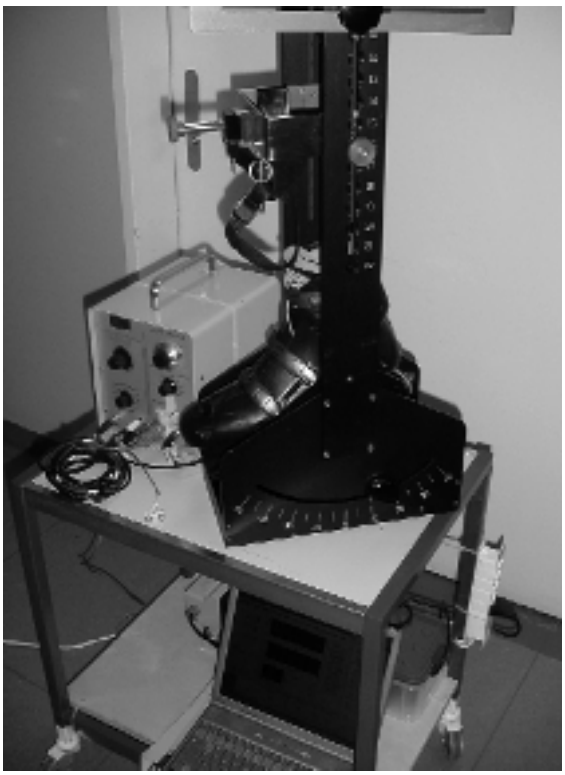

Figure 1

Muscle force assessment system to determine isometric torque in humans [5–9]. The system has four main components: (i) A stabilising device consisting of two metal bars, straps and a boot. The boot is fixed on a foot plate that can be rotated and fixed at any position between –40° to 40°; (ii) A strain gauge system with a Wheatstone bridge circuit that detects the evoked torque produced by the stimulated ankle dorsiflexor group; (iii) A stimulator/amplifier unit that can supply variable stimulus pulse amplitudes and pulse durations and can amplify the voltage changes evoked by the torque of the stimulated muscle; (iv) A computer with data acquisition software for simultaneously recording, analysing, and displaying all signals.

Techniques for force assessment

A stimulator (S11, Grass Medical Instruments, Quincy, MA, USA) was used for peroneal nerve stimulation. A special device that securely held the subject's leg was used for quantification of muscle torque (Fig. 1) [5–9]. The torques applied to this device were measured by incorporated strain gauges (SG-2/350-LY41 Strain Gauges, OMEGA Engineering, Inc., Stamford, CT, USA) attached to an aluminium bar that restrained movement of the footplate. The output of the strain gauge was amplified (amplifier: Grass Medical Instruments, Quincy, MA, USA); voltage changes proportional to the muscle torque were digitised through a data acquisition card (DAQ-Card™-1200, National Instruments, Austin, TX, USA), and then stored in a computer. All data acquisition and analysis programs were written with LabVIEW 2 (National Instruments, Austin, TX, USA).

The muscle force assessment system was secured to the subjects while they remained in a supine position in bed; one leg was strapped to the stabilising device that was adjusted to their individual body dimensions and one foot was secured into a boot which was fixed to the torque plate. If the cutaneous temperature of the leg was lower than 31 °C, a convective warm-air system was employed to elevate the temperature to 31–32 °C (surface temperature probe Genius™, infrared thermometer, Sherwood-Davis & Geck, Gosport, UK). After cleaning the skin with an alcoholic wipe, a pair of small ball-shaped electrodes was pressed tightly against the skin behind the fibula's head so to deliver the superficial common peroneal nerve stimulations.

Optimal joint position: the optimal muscle length for maximum isometric contraction (in this case, the ankle-joint position) was determined by moving the torque plate until twitch torques were at their maximal levels [10]. This position of the torque plate was then fixed and used for all subsequent stimulations. Since torque results from the dorsiflexion of the ankle (Mm. tibialis anterior, together with the extensor hallucis longus, extensor digitorum longus and peroneus tertius) minus plantarflexion produced by the peroneal muscles, joint positions can vary between individuals. If a patient required muscle relaxation for the initial operating procedures (eg, trepanation for cranial haematoma), subsequent repetitive nerve stimulation ruled out residual neuromuscular blockade.

Supramaximal stimulation: the supramaximal voltage (approximately 50–90 V) and supramaximal current (approximately 40–90 mA) were determined by increasing the voltage until maximum twitch torque and maximum electromyogram signal of the ankle dorsiflexor muscle group were evoked.

Stimulation protocol

The session study protocol included single-, double-, triple-, and quadruple-pulse peroneal nerve stimulations. These were unidirectional depolarising pulse stimuli with a duration of 0.3 ms; the interpulse intervals were 5 ms.

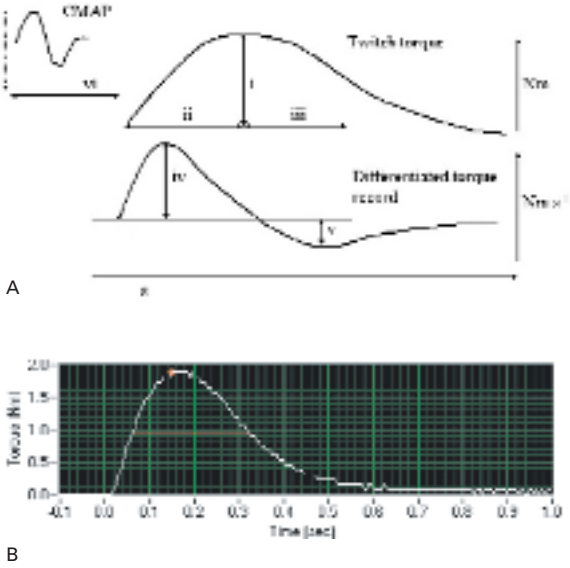

Figure 2

A Record of the twitch torque and differentiated torque of the ankle dorsiflexor group. Compound muscle action potential (CMAP) is schematic; the stimulus is indicated by the dashed arrow. (i) Peak torque (PT); (ii) Contraction time; (iii) Half-relaxation time; (iv) Peak rate of torque development; (v) Peak rate of torque decay; (vi) Torque latency; Nm: Newtonmetre; s: seconds
B Screen display of the data acquisition unit with a typical twitch torque; the red point marks the peak torque.

To avoid any possible fatigue phenomena or twitch-to-twitch potentiation, 2-min rest periods between stimuli were provided; 8 values (two values for each stimulation described above to calculate the intrasession variability) were obtained.

Variables

(i) Peak torque (PT) (newtonmeter, [Nm]): the maximum amount of developed involuntary isometric muscle torque; (ii) Contraction time (ms): time from onset of torque to time of PT; (iii) Half-relaxation time (ms): time from PT to time when torque decays to half of PT; (iv) Peak rate of torque development (Nm s^{-1}): the maximum rate (first derivative) of torque development; (v) Peak rate of torque decay (Nm s^{-1}): the maximum rate of torque decay; (vi) Torque latency (ms): the time from stimulus to the onset of torque development (figure 2).

Maximum voluntary contraction

We also measured the maximum voluntary contractions (MVC) in the control individuals. Subjects were asked to perform a maximum voluntary dorsiflexion and the ratios between MVC and PTs evoked by electrical stimulation were calculated. During the MVC, a superimposed supramaximal single stimulus (interpolated twitch) was delivered as a means to assess the level of voluntary contraction. Torque was regarded as maximum when the interpolated twitch was less than 10% of a following single twitch [11]. All measurements were repeated twice.

Statistical analysis

StatView program (ADEPT™, Hertfordshire, UK) was used for statistical evaluation. Age, ankle-joint positions and the measured variables were analysed using the Mann-Whitney rank-sum test for nonparametric variables. Gender was compared with contingency tables. Correlation coefficients were calculated. A P value <0.05 was regarded as significant.

Results

We initially recorded data from 20 patients, but one patient was excluded from our final analyses because of the subsequent diagnoses of a previously unknown neuromuscular disease. There were no differences in gender, age or ankle-joint positions between patients and control populations. There was an overall intrasession variability of median 6%. The median APACHE II score was 21 (Interquartile range [IQR] 8.8). Fifteen out of 19 patients (79%) were sedated with propofol for one week (table 1). Patients had reduced PTs, reduced PT development and decay, reduced contraction times and prolonged half-relaxation times compared with controls (table 2). PT values between patients with sepsis (n = 6) and intracranial bleeding (n = 9) were not significantly different. The frequency histograms show the distribution of the PT values (figure 3). The PT / MVC correlation in controls was R = 0.5 for overall stimulation, with 3-pulse stimulation eliciting the highest correlation, R = 0.7, determination coefficient r^2 = 0.5 (figure 4).

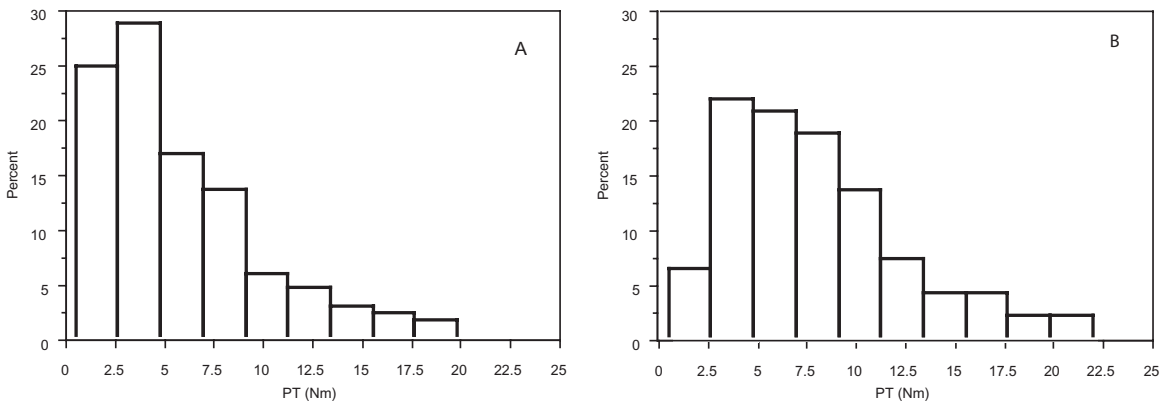

Figure 3

Frequency histograms of the electrically evoked peak torque (PT) values of the ankle dorsiflexor group in 20 critically ill patients (A) and 20 healthy controls (B). In the control patients, there was a shift towards higher PT values: more than 50% of the PT values were >7.0 Newtonmetre (Nm); In contrast, more than 50% of PT values in the critically ill patients were ≤5.0 Nm.

Table 1
Patient clinical data.

Patient	age (years)	diagnosis	APACHE II score	propofol sedation*	steroids (total dose)	28-day-outcome
1	67 M	Sepsis (Pneumococcus), MOF	39	yes	no	S
2	49 M	SAH	27	yes	no	S
3	59 F	SDH	33	yes	no	S
4	23 M	SAH	26	no	no	S
5	44 M	SAH	19	yes	dexamethasone 72 mg	Died week 1
6	70 M	Intracerebral haemorrhage	25	no	prednisone 360 mg	S
7	35 F	EDH; intracerebral haemorrhage	25	yes	no	S
8	23 F	ARDS, Sepsis	17	yes	no	S
9	70 F	Sepsis (Legionella), MOF	15	yes	no	S
10	52 M	EDH; SDH;	20	yes	no	S
11	30 F	SDH	21	no	no	S
12	46 M	Sepsis (Streptococcus), MOF	21	yes	no	Died week 2
13	52 F	Sepsis of urinary tract origin	15	yes	no	S
14	53 M	Sepsis, ventricular assist device, MOF	15	yes	no	Died week 4
15	68 M	Polytrauma	19	yes	no	S
16	65 M	Pneumonia	23	yes	no	S
17	65 M	Intracerebral haemorrhage	21	no	no	Died week 2
18	50 M	Aortic dissection	16	yes	no	S
19	64 F	Pneumonia	16	yes	methylprednisolone 80 mg	S

Acute respiratory distress syndrome (ARDS); acute physiology and chronic health evaluation score II (APACHE II); multi-organ failure (MOF); epidural haemorrhage (EDH); subarachnoid haemorrhage (SAH); subdural haemorrhage (SDH); female (F); male (M); survived (S); * 1–4 mg kg^{-1} h^{-1} for the first two days
Day 3–7: only intermittent doses of 10–30 mg if required

Table 2
Evaluation of isometric muscle force variables of the ankle dorsiflexors; critically ill patients after one week of ventilation and immobilisation vs controls.

Variables	patients (n = 19)	controls (n = 20)
PT 1 (Nm)	3.3 (2.5)	4.1 (2.0)[a]
PT 2 (Nm)	4.9 (4.7)	8.1 (3.8)**
PT 3 (Nm)	6.1 (6.3)	10.3 (3.9)***
PT 4 (Nm)	7.3 (6.4)	11.6 (7.8)[b]
Contraction time 1 to 4 (ms)	104 (37)	116 (53)**
Half-relaxation time 1 to 4 (ms)	115 (45)	110 (31)[c]
Peak rate of torque 1 to 4 development (Nm s^{-1})	128 (128)	180 (137)*
Peak rate of torque 1 to 4 decay (Nm s^{-1})	–38 (38)	–75 (84)*
Torque 1 to 4 latency (ms)	22 (3)	23 (5)
Ankle-joint position (degrees)	18 (15)	17 (10)

Peak torque (PT): the maximum amount of developed nonvolitional isometric muscle torque; Contraction time: time from onset of torque to time of PT; Half-relaxation time: time from PT to time when torque decays to half of PT; Peak rate of torque development: the maximum rate of torque development; Peak rate of torque decay: the maximum rate of torque decay. Torque latency: time from stimulus to onset of torque development. 1 = single pulse; 2 = double pulse; 3 = triple pulse; 4 = quadruple pulse.
* P <0.0001 vs controls; ** P 0.0001; *** P 0.0009; [a] P 0.0003; [b] P 0.006; [c] P 0.01.
Values are medians (parentheses interquartile range)

Discussion

Our aim was to quantify isometric skeletal muscle forces in critically ill patients after one week of ventilation and immobilisation. The approach described here permitted quantification and characterisation of involuntary evoked forces. These patients elicited reduced torques, shorter contraction times and prolonged relaxation times of the ankle dorsiflexors compared to the control patients. These preliminary results indicated that muscle weakness can begin at a very early stage of critical illness in patients who are both immobilised and ventilated.

Generalised muscle strength can have an important influence on the weaning process from a respirator and on the recovery of ICU patients [1–3, 12]. Apart from neuromuscular diseases,

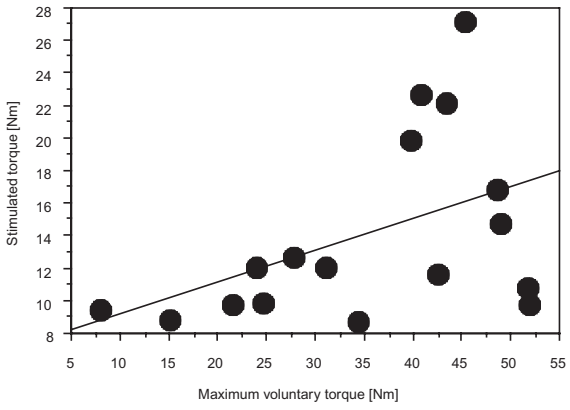

Figure 4

Correlation between maximum voluntary muscle torque of the ankledorsiflexors and torque evoked by peroneus nerve stimulation in control population. The correlation was R = 0.5 for overall stimulation (single- to quadruple-pulse nerve stimulations) with 3-pulse stimulation eliciting the highest correlation, R = 0.7. Nm = Newton-metre

many endocrine disorders and metabolic dysfunctions associated with electrolyte disturbances can cause muscle weakness. In addition, a number of agents/drugs (eg, aminoglycosides, steroids, and residual neuromuscular blocking agents) can potentially impair muscle function [1]. Moreover, muscle weakness in itself can be caused by a critical illness polyneuromyopathy, immobilisation, or a combination of both. Neuromuscular dysfunction can last up to 5 years after ICU discharge [13]. In general, muscle wasting can result from any intervention that reduces mechanical muscle activity (microgravity, bed rest, etc.) even in the absence of severe illness. It is important to distinguish such disuse atrophy from the muscle atrophy found in critically ill patients [2].

Previously, several approaches have been used to quantify muscle force in vivo [14–18]. Coakely et al. used a grading system according to the investigator's subjective assessment of limb movement in patients [14]. Zifko and colleagues evaluated muscle force in 62 patients with the critical illness polyneuropathy according to the British Medical Research Council scale; severe muscle weakness in distal and proximal muscles occurred in 43 and 40%, and mild weakness in 24 and 27% of the muscles, respectively [16]. De Letter et al. measured decrease of muscle force in ICU patients by motor sum scores of three upper and three lower limb muscles and in noncooperative patients by motor sum scores of pain stimuli and tendon reflexes [17]. Similarly, De Jonghe et al. also evaluated muscle force using the Medical Research Council score and found an incidence of 25% for ICU-acquired paresis. Proximal muscle force was significantly less than distal force in both upper and lower limbs [18] but, as with most of such scoring systems, these measurements require a patient's cooperation and cannot be applied to patients who are sedated and ventilated.

One approach to investigate the muscle force in non-conscious subjects is to stimulate the nerve-muscle unit. Previously, Harris et al. described a twitch reduction of the adductor pollicis muscle in 12 ICU patients [11]. Muscle tension was elicited by electrical and magnetic stimulation of the ulnar nerve. Our present approach was comparable with their system; however, we determined the torque of the foot.

Nevertheless, our results confirmed those of Harris et al.; we observed bell-shaped torque curves (figure 2) that are characteristic of those from in vitro investigations for single fibres or isolated muscles [19, 20]. Based on the intrasession variability of 6% as observed here and in previous studies from our group [6], we regard this clinical assessment approach as reliable. However, measurements were only done at one time point during the critical state. Thus, it was unclear as to whether patients lost their force because of their critically ill state or whether the underlying disease that lead to admission to the ICU was the cause. This question can only be answered by evaluating patients, eg with pneumonia, who are not yet critically ill. An immobilisation period prior to ICU admission was excluded in 13 patients. One patient was in a wheelchair for two months while an incomplete immobilisation of about one week was found in five patients. This profile represents the immobilisation periods that were relevant to measured torque values.

In the clinical setting described here, no patient was able to generate a true maximum voluntary contraction, thus we could not verify the use of this isometric torque system as being useful to measure voluntary muscle forces in ICU patients. However, we demonstrated this correlation for the controls. Moreover, Day et al. evaluated our device by using the Medical Research Council score and found that it has a good reliability [5]. As the 3-pulse stimulation pattern most accurately reflects voluntary force, we believe this to be the preferable pattern for future investigations relative to maximal torque outputs. Electrically evoked torques will always be smaller than voluntary force values due to both dorsiflexors and plantarflexors [10]. Because of the size of the patient groups we studied, we were unable to show whether skeletal muscle force values can be used to differentiate between diagnoses and/or ultimate outcomes. In addition, as employed here our device would not allow one to readily differentiate between axonal, neuromuscular, and pure muscular lesions. Recently, Bednarik et al. described a direct muscle stimulation technique that they consider to be useful for differentiating between muscular and nerve lesions in patients with complex polyneuromyopathy [4].

One explanation for the decreased torques we observed in our patient population could be that they elicited a reduced membrane excitability of either their muscle and/or nerve cells, as has been described during critical illness and sepsis [21, 22]. Moreover immobilisation impairs calcium uptake in the sarcoplasmic reticulum, which can result in an increased relaxation time [23].

Propofol can block skeletal muscle sodium channels and the central part of the motor nerve system [24–26] and its use may lead to a reduced torque. However, we have previously found that propofol does not alter torque [6]. In the present study, propofol was administered for a longer du-

ration and at a higher cumulative dosage that could have influenced torque. Unfortunately, we did not determine propofol plasma concentration in our patients and work is ongoing to look at such potential interactions. Since only patient 8 was given aminoglycosides for 3 days and no patient was given calcium antagonists, this could not have influenced torque values [1]. However, such medications administered before ICU admission cannot be excluded. A residual neuromuscular blockade by relaxants was ruled out. Steroids affect muscle force [27]; however the number of patients who received steroids was presumably too small in our study to detect a difference. All patients required catecholamines; it was reported by Thiele et al. that catecholamine support and sepsis were associated with the development of the critical illness polyneuropathy [28]. However, it is not clear whether catecholamines themselves impair muscle force.

There are potential limitations in the present study. The assessment device that was used weighs approximately 15 kg, which can make handling and application cumbersome in a clinically challenging environment. Further, adjustment of the device, ie, determination of the optimal ankle-joint position, can be time consuming. With ongoing immobilisation optimal ankle-joint position can vary due to the extensibility of the structures around the muscle (eg, fascia, conjunctive tissue). In patients with severe oedema, electrode position and supramaximal stimulation is often difficult to determine; moreover, excessive sweating can alter conductance. The nerve stimulation employed here may be considered by some individuals as uncomfortable and the investigator must be aware of this: this discomfort can be generally avoided by insuring proper patient sedation. Moreover, the ankle dorsiflexors represent only one muscle group and other important muscles, such as those for respiration, cannot be measured with our device. In animal experiments artificial ventilation results in respiratory muscle atrophy and reduced force [29]. However, it is not clear whether this also occurs in humans. At present, no satisfactory method to measure respiratory strength exists in the ICU. New techniques, eg, magnetic stimulation of phrenic nerves, combined with the measurement of transdiaphragmatic, oesophageal and endotracheal tube pressure, are being developed. There are ongoing efforts to assess the adductor pollicis, arm flexors, and sternocleidomastoid muscles with the methodologies described here [7–9]. Thus, the approach we employed here is as versatile and can be easily configured to investigate multiple muscle groups.

In conclusion, we analysed the involuntary isometric skeletal muscle forces of the ankledorsiflexors in critically ill patients after one week of ventilation and immobilisation. In general, these patients elicited significantly reduced torques, shorter contraction times, and prolonged relaxation times when compared with controls. These results indicated that muscle weakness begins during the early stages of critical illness for patients who are immobilised and ventilated. Additional studies with more patients are needed to verify whether the method employed in our study has the potential to quantitate muscle force during clinical stay.

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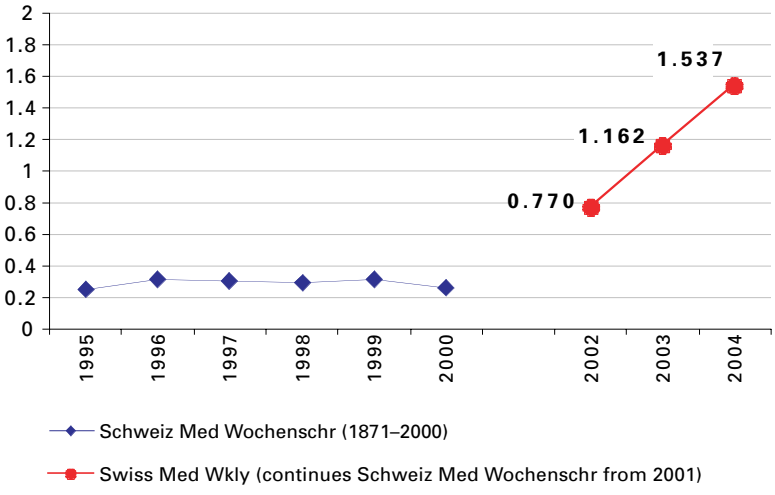

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