Risk factors in critical illness myopathy during the early course of critical illness: a prospective observational study

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Abstract

Introduction: Non-excitable muscle membrane indicates critical illness myopathy (CIM) during early critical illness. We investigated predisposing risk factors for non-excitable muscle membrane at onset of critical illness.

Methods: We performed sequential measurements of muscle membrane excitability after direct muscle stimulation (dmCMAP) in 40 intensive care unit (ICU) patients selected upon a simplified acute physiology (SAPS-II) score ≥ 20 on 3 successive days within 1 week after ICU admission. We then investigated predisposing risk factors, including the insulin-like growth factor (IGF)-system, inflammatory, metabolic and hemodynamic parameters, as well as suspected medical treatment prior to first occurrence of abnormal dmCMAP. Nonparametric analysis of two-factorial longitudinal data and multivariate analysis were used for statistical analysis.

Results: 22 patients showed abnormal muscle membrane excitability during direct muscle stimulation within 7 (5 to 9.25) days after ICU admission. Significant risk factors for the development of impaired muscle membrane excitability in univariate analysis included inflammation, disease severity, catecholamine and sedation requirements, as well as IGF binding protein-1 (IGFBP-I), but did not include either adjunctive hydrocortisone treatment in septic shock, nor administration of neuromuscular blocking agents or aminoglycosides. In multivariate Cox regression analysis, interleukin-6 remained the significant risk factor for the development of impaired muscle membrane excitability (HR 1.006, 95%-CI (1.002 to 1.011), \( P = 0.002 \)).

Conclusions: Systemic inflammation during early critical illness was found to be the main risk factor for development of CIM during early critical illness. Inflammation-induced impairment of growth-factor mediated insulin sensitivity may be involved in the development of CIM.

Introduction

ICU-acquired muscle weakness is a serious complication of critical illness. It has been recognized as the clinical manifestation of an ICU-acquired peripheral neuromuscular pathology [1] that, with regard to muscle pathology, is characterized by atrophy of type II muscle fibres and thick filament myopathy [2].

Diagnosis of critical illness myopathy (CIM) is either based on clinical proof of muscle weakness after awaken-
Materials and methods

This study presents a subanalysis of 40 patients of a recent prospective observational study [5] that investigated the predictive value of certain electrophysiological measurements on the development of ICU-acquired weakness. Validating muscle membrane excitability at the onset of critical illness turned out to be most valuable for an early prediction of ICU-acquired weakness in immobile, sedated patients adding important information to clinical estimation of the patients’ motor function upon emergence from sedation. Mechanically ventilated ICU patients on an operative ICU who featured simplified acute physiology (SAPS-II) scores of 20 or higher on three successive days within one week after ICU admission were included in the study. Sequential electrophysiological measurements including measurement of muscle membrane excitability had been performed at study enrollment and every three days until pathological findings were detected or clinical evaluation of muscle strength by Medical Research Council (MRC) score was possible.

Details of electrophysiological measurements are reported elsewhere [5], in brief we assessed the compound muscle amplitude with concentric needle electrodes after direct stimulation of the muscle. Comparable with measurement of compound muscle amplitude after nerve stimulation, this is a quantitative method and the normal data in critically ill patients are 3 mV or more [3]. Patients with non-excitable muscle membrane after direct muscle stimulation showed reduced amplitudes of less than 3 mV, whereas patients with an acute neuromuscular weakness show normal amplitudes within the muscle after direct muscle stimulation. Measurement of muscle membrane excitability diagnoses myopathy but cannot exclude an additional axonal motor neuropathy. Here we focused on a risk factor analysis of non-excitable muscle membrane from the beginning of critical illness until first proof of non-excitable muscle membrane. Hence, we excluded patients being pretreated on other ICUs for more than 24 hours and only included values of risk factors of the first eight days of critical illness in the analysis. The study was approved by our local review board. Written informed consent was obtained from legal proxies.

Patients were treated following standard operating procedures of intensive care incorporating severe sepsis bundles [15]. Systemic inflammation, sepsis or severe sepsis [see Table E1 in Additional file 1] accompanied by organ dysfunction [see Table E2 in Additional file 1] was classified according to consensus conference criteria [16,17]. Inflammatory cytokines (IL-6 and IL-10), IGF-1 and its binding proteins (IGFBP-I, IGFBP-III) were analysed from blood samples, drawn between days 3 and 7 as well as between days 8 and 10 after ICU admission.

Hemodynamic parameters and blood glucose levels were recorded four times daily considering least favorable values within six-hour intervals. Illness severity, SAPS-II [18], sepsis-related organ failure assessment (SOFA) [19] and other clinical data were recorded on a daily basis. Methods are further described in Additional file 1.

Statistical analysis

Results are expressed as median and 25th/75th percentiles for continuous variables and proportions for qualitative parameters, respectively. We used nonparametric tests for statistical testing.

Changes in interesting clinical outcomes with respect to time were analyzed using nonparametric analysis of longitudinal data in a two-factorial design (1st factor: compound muscle action potential after direct muscle stimulation (dmCMAP) normal versus dmCMAP abnormal; 2nd factor: repetitions in time), focusing on values during the first eight days after ICU admission or within a first interval between days 3 and 7, and a second interval between days 8 and 10 after ICU admission. Therefore, we compared all time points simultaneously on the corresponding response curves [20].

In univariate and subsequently in multivariate Cox’ proportional hazard regressions (stepwise backward procedure), we tested risk factors impairing muscle membrane excitability (as a dependent variable). For all parameters we included values from days of first IL-6 measurements in the analysis. Hazard ratios (HR) with their 95% confidence intervals (CI) and the corresponding P values were calculated for each risk factor. P values less than 0.05 (two-sided) were considered as statistically significant.

We evaluated the diagnostic test performance of IL-6 and SOFA to indicate the development of myopathy by
receiver operating characteristics (ROC) analysis using abnormal dmCMAP amplitude less than 3 mV as electrophysiological parameter for diagnosis of myopathy and IL-6 as well as SOFA as test variables. We combined the diagnostic tests regarding sensitivity and specificity of SOFA and IL-6 to indicate myopathy with the help of the known ‘believe-the-positive’ rule.

All tests should be understood as constituting exploratory data analysis, such that no adjustments for multiple testing have been made. We used SPSS, Version 14 (SPSS, Inc., Chicago, IL, USA), and SAS, Version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient characteristics

Forty patients at the onset of critical illness were enrolled in the study. Twenty-two patients developed abnormal muscle membrane excitability in terms of reduced compound muscle action potential after direct muscle stimulation (dmCMAP abnormal) within 7 (5 to 9.25) days after admission to ICU as reported earlier [5]. Eighteen patients showed normal muscle membrane excitability (dmCMAP normal). Patients with abnormal dmCMAP revealed significant paresis (MRC 2.6 (1.84 to 3.27)) after emergence from sedation compared with patients with normal dmCMAP (MRC 4.1 (4 to 4.84); \( P < 0.0001 \)).

ICU length of stay was significantly prolonged in dmCMAP abnormal patients (26 (18 to 38) days) compared with dmCMAP normal patients (13 (8 to 18) days; \( P < 0.0001 \)).

Patients’ characteristics upon admission and within the first eight days after ICU admission are shown in Table 1.

Risk factors of critical illness myopathy in dmCMAP normal and dmCMAP abnormal patients within the first week after ICU admission.

Within the first eight days after ICU admission, patients with abnormal dmCMAP had significantly more days with systemic inflammatory response syndrome, severe sepsis, and dysfunction of two or more organs compared with patients with normal dmCMAP (Table 1 and Figure 1).

Moreover, patients with abnormal dmCMAP received significantly higher doses of norepinephrine within the first week after ICU admission (Figure 2). Hemodynamic stability in terms of circulatory shock was significantly impaired within the first eight days compared with dmCMAP normal patients (Figure 2). There was no difference regarding frequency and cumulative dosage of adjunctive hydrocortisone therapy within the first week after ICU admission between the two groups (Table 1).

DmCMAP abnormal patients received significantly higher doses of analgesics and sedation and more neuromuscular blocking agents; however, the cumulative dosage of neuromuscular blocking agents was low within both groups (Table 1).

IL-6 plasma levels were significantly higher within the first week (day 5 (3 to 7)) in patients with abnormal dmCMAP. In the second week (day 8 (6 to 10.25)), IL-6 decreased in both groups but remained significantly higher in dmCMAP abnormal patients. There was no difference between the two groups regarding IL-10 plasma levels (Figure 3).

Daily blood glucose levels (Figure 4), total carbohydrate intake, insulin requirement (Table 1), and the insulin per kcal carbohydrate intake (Figure 4) were not significantly different between the two groups within the first week. Patients with abnormal dmCMAP had a significantly higher plasma osmolarity and sodium plasma levels during the first eight days after ICU admission than dmCMAP normal patients (Figure 5).

IGF-I was reduced in dmCMAP abnormal patients at both test intervals (87.2 ng/ml (65.9 to 119.5) versus 104.5 ng/ml (74.4 to 136.9) and 76.1 ng/ml (55.1 to 119.5) versus 87.2 ng/ml (65.8 to 122)), but differences did not reach statistical significance. Plasma levels of IGFBP-III were not different between both groups whereas IGFBP-I as a marker reflecting impaired insulin sensitivity was significantly higher in dmCMAP abnormal patients at both test intervals (Figure 6).

Cox’ regressions analysis

Separate (univariate) Cox regression analyses for risk factors impairing muscle membrane excitability are shown in Table 2. Analyses included values from day of first IL-6 measurements.

In univariate analysis severity of illness, sepsis-related organ dysfunction, inflammation, catecholamine requirements, sedation requirements and an impaired insulin sensitivity turned out as significant risk factors for the development of impaired muscle membrane excitability within the early course of critical illness. An increased osmolarity, adjunctive hydrocortisone treatment in septic shock, administration of neuromuscular blocking agents and aminoglycosides were not significantly correlated with the development of impaired muscle membrane excitability.

In the backward selection of multivariate Cox regression analysis (Figure 7) the extent of inflammation as reflected by IL-6 plasma levels and the fentanyl dosage remained as independent risk factors for the development of impaired muscle membrane excitability.

Sensitivity and specificity

Sensitivity and specificity of SOFA score to predict abnormal membrane excitability was highest on day 4 at a cut-off value of 10 (sensitivity = 65% and specificity = 93.8%). The cut-off value for IL-6 predicting abnormal membrane excitability was observed at 230 pg/ml, featuring sensitivity of 71.4% and specificity of 93.3%. According to the ‘believe the positive’ rule applied in a combined
Table 1: Patients’ characteristics within the first week after ICU admission in patients without and with critical illness myopathy

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Abnormal</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>Total 40</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>42 (24.3/58.5)</td>
<td>58 (42.5/68.3)</td>
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</tr>
<tr>
<td>Gender</td>
<td>male/female</td>
<td>12/6</td>
<td>15/7</td>
</tr>
<tr>
<td>Survival</td>
<td>survivor/non-survivor</td>
<td>17/1</td>
<td>14/8</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>24.8 (20.5/26.6)</td>
<td>25.4 (23.3/29.7)</td>
<td>0.19b</td>
</tr>
<tr>
<td>Reason of ICU admission</td>
<td>Multiple trauma. total n (%)</td>
<td>11 (61.1)</td>
<td>10 (45.5)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia. total n (%)</td>
<td>3 (16.7)</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td></td>
<td>Abdominal cancer. total n (%)</td>
<td>2 (11.1)</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>SAPS-II</td>
<td>31.5 (23.8/42)</td>
<td>41.0 (36.3/48.3)</td>
</tr>
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<td></td>
<td>SOFA</td>
<td>8.0 (5.8/10.3)</td>
<td>10.0 (7/12.5)</td>
</tr>
<tr>
<td></td>
<td>White blood cell count (1/nl)</td>
<td>9.6 (8.4/12.6)</td>
<td>8.8 (6.5/11.6)</td>
</tr>
<tr>
<td></td>
<td>Plasma urea (mg/dl)</td>
<td>17.1 (11.03/23.9)</td>
<td>17.2 (10.8/26.1)</td>
</tr>
<tr>
<td></td>
<td>Plasma creatinine (mg/dl)</td>
<td>33 (21/53.8)</td>
<td>55.5 (33.8/102.5)</td>
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<tr>
<td></td>
<td>PaO2/FIO2</td>
<td>205.5 (183/247.5)</td>
<td>177.4 (91/215.6)</td>
</tr>
<tr>
<td></td>
<td>Plasma lactate (mmol/l)</td>
<td>2.15 (1.5/2.5)</td>
<td>3.35 (2.02/6.02)</td>
</tr>
<tr>
<td></td>
<td>Plasma pH</td>
<td>7.36 (7.3/7.47)</td>
<td>7.28 (7.2/7.48)</td>
</tr>
<tr>
<td>Inflammation day 1-8 (cum. %)</td>
<td>SIRS</td>
<td>75.0 (52.2/100)</td>
<td>87.5 (71.9/100)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>25.0 (0/62.5)</td>
<td>68.8 (9.4/87.5)</td>
<td>0.075a</td>
</tr>
<tr>
<td>Septic shock</td>
<td>12.5 (0/50)</td>
<td>56.2 (0/87.5)</td>
<td>0.022a</td>
</tr>
<tr>
<td>Organ dysfunction day 1-8 (cum. %)</td>
<td>Coagulation</td>
<td>18.75 (0/77.7)</td>
<td>62.5 (9.4/100)</td>
</tr>
<tr>
<td>Lung</td>
<td>33.3 (18.75/75)</td>
<td>68.75 (25/100)</td>
<td>0.15a</td>
</tr>
<tr>
<td>Renal</td>
<td>0 (0/0)</td>
<td>0 (0/56.3)</td>
<td>0.21a</td>
</tr>
<tr>
<td>Liver</td>
<td>0 (0/31.3)</td>
<td>25 (0/50)</td>
<td>0.12a</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>0 (0/18.75)</td>
<td>12.5 (0/50)</td>
<td>0.08a</td>
</tr>
<tr>
<td>GCS &lt; 13</td>
<td>0 (0/7.14)</td>
<td>6.25 (0/75)</td>
<td>0.22a</td>
</tr>
<tr>
<td>Organ dysfunction &gt; 2</td>
<td>0 (0/0)</td>
<td>37.5 (0/62.5)</td>
<td>0.003a</td>
</tr>
<tr>
<td>Drugs days 1 to 8 (% patients; cum dosage per patient)</td>
<td>Norepinephrine (mg)</td>
<td>61.1; 295 (259/501)</td>
<td>91; 60.1 (27.5/84.1)</td>
</tr>
<tr>
<td>Dobutamine (mg)</td>
<td>27.8; 581 (259/951)</td>
<td>54.5; 1975 (958/4399)</td>
<td>0.12b; 0.019b</td>
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<tr>
<td>NMBA (mg)</td>
<td>55.6; 10 (9/320)</td>
<td>63.6; 27; 514 (175/45)</td>
<td>0.75b; 0.016b</td>
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<td>Aminoglycosides (mg)</td>
<td>16.7; 1440 (1260/1440)</td>
<td>27; 420 (320/620)</td>
<td>0.48b; 0.024b</td>
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<tr>
<td>Hydrocortisone (mg)</td>
<td>16.7; 719 (501/719)</td>
<td>36.4; 836 (598/963)</td>
<td>0.29b; 1.0b</td>
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<tr>
<td>Carbohydrates (kcal/kg)</td>
<td>94.4; 64.7 (29.2/103.2)</td>
<td>95.5; 59.7 (50.6/83.4)</td>
<td>1.0b; 0.95b</td>
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<tr>
<td>Insulin (IU)</td>
<td>100; 237.8 (165/370)</td>
<td>95.5; 331.2 (155/590)</td>
<td>1.0b; 0.2b</td>
</tr>
<tr>
<td>Fentanyl (mg)</td>
<td>94.4; 18.4 (7/26.5)</td>
<td>95.5; 36 (19.8/69.5)</td>
<td>1.0b; 0.006b</td>
</tr>
<tr>
<td>Midazolam (mg)</td>
<td>77.8; 726 (318/1292)</td>
<td>90.9; 1702 (810/3593)</td>
<td>0.38b; 0.05b</td>
</tr>
</tbody>
</table>

Myopathy according to direct muscle stimulated compound muscle action potential (dmCMAP) at onset of critical illness, normal (≥3 mV) and abnormal (< 3 mV); parameters are calculated upon ICU admission or within eight days after ICU admission.

BMI, body mass index; CRP, C-reactive protein; GCS, Glasgow Coma Scale; NMBA, neuromuscular blocking agent; PaO2/FIO2, index of arterial oxygenation efficiency corresponding to ratio of partial pressure of arterial O2 to the fraction of inspired O2; SAPS-II, simplified acute physiology score; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment score; (cum. %), cumulative fractions of presented parameters calculated by sum of days fulfilling criteria of a particular parameter divided by total days of ICU presence within the first eight days after ICU admission; (% patients), proportion of patients; (cum. dosage), cumulative drug dose within the first eight days after ICU admission. Qualitative data are given as proportions (%). Continuous data and cumulative fractions are given as median and 25%/75% percentile; aFisher’s exact test, bMann-Whitney U rank test.
cross tabulation of patients with SOFA scores of 10 or more at day 4 after ICU admission and/or IL-6 plasma levels of 230 pg/ml or more, we observed a sensitivity of 85.7% and a specificity of 86.7% of this combination for predicting development of abnormal dmCMAP.

Discussion
In this observational study we investigated predisposing risk factors leading to non-excitable muscle membrane indicating CIM during early critical illness. The main finding was a significant relation between muscle membrane inexcitability, disease severity and IL-6 plasma levels.

In the absence of a reliable clinical parameter identifying patients at risk of developing CIM during early critical illness, when motor function is not assessable due to analgesia and sedation, current data on risk factors leading to CIM are derived mostly from prospective cohort studies relating data from ICU admission with patients' motor function once assessable [6]. One excellent study investigating risk factors for combined critical illness neuromyopathy [9] during early critical illness showed that illness severity, determined through acute physiology and chronic health evaluation (APACHE) III scores, predicted the later development of critical illness neuromyopathy. In our study, sequential measurements of muscle membrane excitability offers the opportunity to focus on CIM and to determine the time frame in which CIM originates during early critical illness, thereby improving stratification of predisposing risk factors for CIM.

Univariate analysis indicated illness severity, IL-6, hemodynamic impairment, decreased insulin sensitivity as well as analgesia and sedation as predisposing risk factors. However, only IL-6 and dosage of analgesia emerged as independent risk factors from multivariate analysis. Interestingly, we did not observe any significant relation between development of non-excitable muscle membrane and application of low-dose hydrocortisone, aminoglycosides or neuromuscular blocking agents, which have frequently been incriminated as being involved in the development of CIM.

Large prospective randomized studies have shown that glycemic control is associated with the development of neuromuscular dysfunction [11,12]. In our study, we did not observe a difference in blood glucose levels between dmCMAP normal and abnormal patients because we aimed for glycemic control below 150 mg/dl in all of our patients. However, despite comparable blood glucose levels between the groups, IGFBP-1 was significantly higher in abnormal dmCMAP patients. In agreement with other
Figure 2 Critical illness myopathy and hemodynamic variables. Normal (≥3 mV) and abnormal (< 3 mV) direct muscle stimulation compound muscle action potentials (dmCMAP), (a) mean shock index and (b) daily norepinephrine dosage on the first eight days after ICU admission. Patients with impaired muscle membrane excitability had significantly higher shock indices and required significantly higher daily norepinephrine dosages during the first eight days after ICU admission.

Figure 3 Critical illness myopathy and systemic inflammation. Normal (≥3 mV) and abnormal (< 3 mV) direct muscle stimulation compound muscle action potentials (dmCMAP), (a) IL-6 plasma levels, (b) IL-10 plasma levels at median day (25th/75th percentile) 5 (3 to 7) and median day 8 (6 to 10,25). Patients with impaired muscle membrane excitability had significantly higher IL-6 plasma levels but no significant differences of IL-10 plasma levels at both measurement intervals.
reports [21,22] we consider increased IGFBP-1 as a parameter indicative of impaired insulin sensitivity. Hence, our data suggest that significantly impaired insulin sensitivity during early critical illness was related to development of abnormal muscle membrane excitability.

In parallel, dmCMAP abnormal patients revealed a significant hyperosmotic state within the first days of critical illness. Hyperosmolality is related to illness severity [23] and has been described as a risk factor for critical illness neuropathy [24]. It is worth noting that the study by Gar-nacho-Montero and colleagues [24] did not differentiate between myopathy and neuropathy. In our study, hyperosmolality during the first days after ICU admission was significantly related to electrophysiological-proven muscle pathology. It can be speculated that this hyperosmotic state may have led to osmotic stress-induced reduction of cellular insulin sensitivity in our patients, which has been shown in adipocytes under experimental conditions [25].

However, alteration of insulin sensitivity and plasma osmolality are most likely related to systemic inflammation in our study. Our data are in agreement with the general perception that systemic inflammation and sepsis-related organ dysfunction are major triggers for the development of CIM [6,8,9,26]. Earlier experimental data inducing inflammation in rats by intravenous inoculation of endotoxin showed that IL-6 increased muscle fatigue [27] and decreased muscle contractility of the diaphragm [28]. Interestingly, recent clinical data indicate a relation between IL-6 and reduced muscle strength in elderly people [29]. Our data reveal a possible role of IL-6 in the development of non-excitable muscle membrane during early critical illness finally leading to muscle weakness.

IL-6 seems to be an important mediator leading to muscle protein breakdown [30]. One mechanism may lie in the inhibition of growth factor-mediated (e.g. IGF-I) intracellular signaling by IL-6 [13,31]. IGF-I plays a central role in glucose uptake and protein synthesis, and was shown to be downregulated in inflammation and sepsis [13]. Impairment of IGF-I may be due to inflammation-induced upregulation of high-affinity IGFBP-1 which prevents IGF-I receptor binding [32]. In vitro [33] and later in vivo [14], it has been shown that an increase of IGFBP-1 reduced the IGF-I-mediated glucose uptake and reduced protein synthesis in skeletal muscle within an experimental setting. In line with this, our data suggest that impaired growth factor-mediated intracellular signaling due to systemic inflammation may be involved in the development of CIM.

Corticosteroids are controversially discussed as aggravating factors of CIM [6,7,9,34]. It is well established that high-dose application of corticosteroids, for example in patients with chronic obstructive pulmonary disease, results in selective loss of thick myosin filaments in skele-
tal muscle fibers [35], a so-called steroid-induced myopathy [36].

Nevertheless, these reports refer to steroid myopathy as a result of high-dose steroid application. A link between 'low-dose hydrocortisone' treatment as adjunctive therapy during septic shock and development of CIM has been postulated [15], but never proven. Several data indicate that moderate doses of steroids do not prolong mechanical ventilation due to muscle weakness but are related to significantly more ventilator-free days and ear-

**Figure 5.** Critical illness myopathy and plasma homeostasis. Normal (≥3 mV) and abnormal (< 3 mV) direct muscle stimulation compound muscle action potentials (dmCMAP), (a) plasma sodium, (b) plasma osmolarity, (c) plasma pH and (d) plasma urea (multiply by factor 0.46 for blood urea nitrogen (BUN) conversion) over the first eight days after ICU admission. Patients with impaired muscle membrane excitability had significantly higher plasma sodium, plasma osmolarity, plasma pH and plasma urea during the first eight days after ICU admission.
Critical illness myopathy and insulin sensitivity

Figure 6

(a) Insulin-like growth factor binding protein (IGFBP)-1 plasma levels, (b) IGFBP-3 plasma levels at median day (25th/75th percentile) 5 (3 to 7) and median day 8 (6 to 10,25). Patients with impaired muscle membrane excitability had significantly higher IGFBP-1 plasma levels but no significant differences of IGFBP-3 plasma levels at both measurement intervals.

Table 2: Risk factors leading to impaired muscle membrane excitability

<table>
<thead>
<tr>
<th>Cox' regression with time dependent covariates</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>LL</td>
<td>UL</td>
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<tr>
<td><strong>Univariate</strong></td>
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<tr>
<td>SOFA</td>
<td>1.175</td>
<td>1.042</td>
<td>1.324</td>
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<td>SAPS-II</td>
<td>1.019</td>
<td>0.998</td>
<td>1.04</td>
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<td>Norepinephrine</td>
<td>1.006</td>
<td>1.002</td>
<td>1.011</td>
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<td>Dobutamine</td>
<td>1.000</td>
<td>1.000</td>
<td>1.001</td>
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<td>Midazolam</td>
<td>1.001</td>
<td>1.000</td>
<td>1.001</td>
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<td>Fentanyl</td>
<td>1.026</td>
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<td>1.048</td>
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<td>HC in septic shock</td>
<td>1.001</td>
<td>0.999</td>
<td>1.003</td>
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<td>NMBA (Cisatracurium)</td>
<td>1.027</td>
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<td>Aminoglycoside (Tobramycin)</td>
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<td>Osmolarity</td>
<td>1.012</td>
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<td>IGFBP-1</td>
<td>1.012</td>
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<td>C-reactive protein</td>
<td>1.058</td>
<td>0.994</td>
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<td>IL-6</td>
<td>1.006</td>
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Univariate Cox' proportional hazard regression with time dependent covariates for variables considered risk factors impairing muscle membrane excitability (as dependent variable) are shown. For the particular parameter repeated measures of daily cumulative dosages, daily plasma levels or daily score values until first proof of reduced muscle membrane excitability in compound muscle action potential after direct muscle stimulation (dmCMAP) abnormal patients or until ICU discharge in dmCMAP normal patients were included in the analysis. HC, adjunctive hydrocortisone treatment in septic shock; IGFBP-1, insulin-like growth factor–binding protein–1; IL-6, interleukin–6; NMBA, neuromuscular blocking agent; SOFA, sequential organ failure assessment score; SAPS-II, simplified acute physiology score. Hazard ratios (HR) with LL (lower limit) and UL (upper limit), 95% confidence intervals (95% CI) and P values for each variable.
lier spontaneous breathing capacity [37]. In an earlier study we did not observe an association between low-dose hydrocortisone application and development of paresis [5,34]. In this study we were able to show that low-dose hydrocortisone application does not provoke impaired muscle membrane excitability, suggesting that steroid involvement in CIM development is dose dependent [8].

Furthermore, dosage of analgesics and sedatives was significantly associated with the development of non-excitable muscle membrane. Interpreting higher doses of analgesics and sedatives as higher degrees of immobilization, this finding is in line with recent studies describing that immobilization aggravated neuromuscular weakness in an experimental setting [38] and that early physical mobilization resulted in a better clinical outcome of motor function [10].

For clinicians it is difficult to estimate patients at risk for the development of CIM. The APACHE-III score has been cited as being able to identify patients at risk for critical illness neuromyopathy [9]. In our study we used the SOFA score because it is widely accepted in the ICU setting, and has been validated to monitor organ dysfunction-related to sepsis [19]. Our results indicate that a SOFA score of 10 or above and/or IL-6 plasma levels of 230 pg/ml or more at the onset of critical illness disclose high-risk patients for the development of non-excitable muscle membrane.

The following limitations of this study need to be addressed. Although we observed a statistically significant effect for IL-6 as a main risk factor for non-excitable muscle membrane, it has to be stressed that the overall effect was small, which may be due to small sample size. It also needs to be mentioned that blood samples were col-
lected at two different time points only and that the
course of inflammatory parameters was not followed
daily. However, this was designed as a pilot study for
hypothesis generation. The clinical significance has to be
addressed in further studies.

Conclusions
Systemic inflammation during early critical illness turned
out to be the main risk factor for the development of non-
excitable muscle membrane indicating CIM. It may be
hypothesized that inflammation-induced impairment of
growth factor-mediated intracellular signaling is involved
in the pathophysiology of CIM. Furthermore, adjunctive
treatment with low-dose hydrocortisone during septic
shock was not associated with development of CIM.

Key messages
• Non-excitable muscle membrane indicates CIM
during early critical illness.
• Inflammation, disease severity, decreased insulin
sensitivity, catecholamine and sedation requirement
turned out to be significantly related to the develop-
ment of impaired muscle membrane excitability.
• IL-6 and dosage of analgesia emerged as indepen-
dent risk factors from multivariate analysis.
• Inflammation-induced impairment of growth-factor-
mediated insulin sensitivity may be involved in
the development of CIM.
• In contrast to prior assumptions we could not
observe any significant relation between development
of CIM and application of low-dose hydrocortisone in
septic shock.

Additional material

Additional file 1 Further description of methods and definitions. The
additional file contains additional information on exclusion criteria, electro-
physiologic measures, general ICU care, and laboratory testing [39].
Two tables within this file explain the conditions required for defining sys-
temic inflammatory response syndrome, sepsis, severe sepsis, or septic
shock (E1) and organ dysfunction (E2).

Abbreviations
APACHE: acute physiology and chronic health evaluation; CI: confidence in-
ternal; CIM: critical illness myopathy; dCMAP: compound muscle action poten-
tial after direct muscle stimulation; HR: hazard ratio; IGF: insulin-like growth
factor, IGF-BP: insulin-like growth factor binding protein, IL: interleukin, MRC: 
Medical Research Council, ROC: receiver operating characteristic; SAPS: simpli-
fied acute physiology score; SOFA: sepsis-related organ failure assessment.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
SW-C conceived of the study, performed data and statistical analysis, wrote the
final manuscript and is head of the project, which is funded by the Deutsche
Forschungsgemeinschaft. MD and DK participated in the design of the study,
data analysis and in writing the final manuscript. SK performed the electro-
physiological measurements and analysis. JS and DK performed laboratory
data measurements and analysis. FB programmed the data base and partici-
pated in data collection and analysis. KW prepared the statistical part of the
manuscript and performed the statistical analysis. CS critically revised the man-
uscript and gave final approval. SS critically revised the electrophysiological
data analysis and participated in writing the paper. All authors read and
approved the final manuscript.

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