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Critical illness myopathy is frequent – accompanying neuropathy protracts ICU discharge

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Running head: CIM frequent - CIP protracts discharge

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ABSTRACT

Objectives: Neuromuscular dysfunction in critically ill patients is attributed to either critical illness myopathy (CIM) or critical illness polyneuropathy (CIP) or a combination of both. But it is unknown whether differential diagnosis has an impact on prognosis. This study investigates whether there is an association between the early differentiation of CIM versus CIP and clinical prognosis.

Methods: We included mechanically ventilated patients who featured a Simplified Acute Physiology Score II (SAPS-II) $\geq 20$ on three consecutive days within the first week after ICU admission. 53 critically ill patients were enrolled and examined by conventional nerve conduction studies and direct muscle stimulation (184 examinations in total). The first examination was conducted within the first week after admission to the intensive care unit (ICU).

Results: In this cohort of critically ill patients, CIM was more frequent (68%) than CIP (38%). Electrophysiological signs of CIM preceded electrophysiological signs of CIP (median at day 7 in CIM patients vs. day 10 in CIP patients, $p<0.001$). Most patients with CIP featured concomitant CIM. At discharge from ICU, 25% of patients with isolated CIM showed electrophysiological signs of recovery and significantly lower degrees of weakness. Recovery could not be observed in patients with combined CIM/CIP even though ICU length of stay was significantly longer (mean 35 days in CIM/CIP vs. mean 19 days in CIM, $p<0.001$).

Conclusion: Prognoses of patients differ depending on electrophysiological findings during early critical illness: Early electrophysiological differentiation of ICU acquired neuromuscular disorder enhances the evaluation of clinical prognosis during critical illness.

Keywords: critical illness myopathy, critical illness polyneuropathy, direct muscle stimulation, intensive care unit
**Abbreviations:** CIM = Critical Illness Myopathy; CIP = Critical Illness Polyneuropathy; dmCMAP = Compound Muscle Action Potential after direct muscle stimulation; ICU = Intensive Care Unit; MFCV = Muscle Fibre Conduction Velocity; MUAP = Motor Unit Action Potential; neCMAP = Compound Muscle Action Potential after nerve stimulation; SAPS-II = Simplified Acute Physiology Score; SNAP = Sensory Nerve Action Potential; SOFA = Sequential Organ Failure Assessment score.
Introduction

Since the early description of critical illness myopathy (CIM)\cite{1} and critical illness polyneuropathy (CIP)\cite{2,3}, the primary cause of these Intensive Care Unit (ICU) acquired weaknesses remains unresolved.\cite{4} ICU acquired weakness complicates recovery in critically ill patients and prolongs duration of mechanical ventilation and length of stay in ICU.\cite{5,6} Some authors advise against differentiation of CIM and CIP, as differentiation is complicated and may not result in consequences.\cite{7,8}

Electrophysiological abnormalities such as low compound muscle action potentials or pathological spontaneous activity can be detected within one week of ICU admission but do not allow for distinguishing CIM and CIP.\cite{9,10} In sedated patients without voluntary muscle contraction electrophysiological differentiation between CIM and CIP is difficult. CIM diagnosis relies on direct demonstration of muscle membrane dysfunction.\cite{11,12} Authors using this technique of direct muscle stimulation found myopathy to be more frequent in critically ill patients.\cite{7,11-15} CIP with associated sensory nerve involvement is assessed by a reduction of sensory nerve amplitudes, whereas assessment of motor CIP remains difficult. Rich and colleagues introduced a ratio that divides nerve evoked compound muscle action potentials (neCMAP) by direct muscle evoked compound muscle action potentials (dmCMAP) in order to differentiate between myopathy (this ratio is expected to be near 1) and motor CIP axonopathy (this ratio is expected to be small and near zero).\cite{16}

In this longitudinal study of 53 critically ill patients, conventional nerve conduction studies and direct muscle stimulation were combined to determine whether there is an association between the early differentiation of CIM versus CIP and clinical prognosis.
Methods

The study was approved by our local ethics committee. Written informed consent of legal proxies was obtained according to the Declaration of Helsinki.

We performed this observational study in a 14-bed surgical ICU over a period of 18 months. Patients who required mechanical ventilation and featured a Simplified Acute Physiology Score II $\geq 20$ (SAPS-II)[17] on three consecutive days within the first 7 days after ICU admission were eligible for inclusion. Pre-existing neuromuscular disorders, severe head trauma or bleeding diathesis were previously defined as exclusion criteria. All patients were treated according to our standard operating procedures of intensive care medicine, adopting evidence based bundles for severe sepsis.[18,19] Severity of illness was monitored daily by repeated ratings of SAPS-II and Sequential Organ Failure Assessment score (SOFA).[20]

Every three days after admission to the ICU electrophysiological bedside studies were recorded by portable 2-Channel Keypoint Medtronic equipment (Skovlunde, Denmark). Once either CIM or CIP was detected or once patients showed adequate awareness, diagnostic testing was repeated once a week. Given that patients featured sufficient awareness at ICU discharge (Ramsay score $\leq 2$)[21], muscle strength of upper and lower limbs was evaluated and graded according to the Medical Research Council score.[22] Whenever possible, we examined two proximal/distal muscles in each extremity and divided the total by the number of muscles examined.

Motor nerve conduction velocity and compound muscle action potential amplitude after nerve stimulation (neCMAP) were unilaterally performed in median, peroneal as well as in tibial nerves and recorded from abductor pollicis brevis, extensor digitorum brevis and abductor hallucis muscles. Sensory nerve conduction studies were unilaterally conducted in sural and
median nerves. Surface electrodes were used for stimulation and recording. In case of missing recordings or in presence of oedema, subdermal electrodes were used in all patients. Nerve conduction measurements were compared to normal values from age-matched individuals that were provided by the neurophysiological laboratory of the Charité.

During sedation, electromyography was performed in deltoid, biceps brachii, extensor digitorum longus, abductor pollicis brevis, rectus femoris, and tibialis anterior muscles using concentric needle electrodes to assess pathological spontaneous activity. As soon as patients showed sufficient awareness and voluntary muscle contraction was possible, quantitative electromyography was applied whenever possible in extensor digitorum longus and tibialis anterior muscles. A total of 20 different motor unit action potentials (MUAP) was sampled by random insertion of a concentric needle electrode into four different regions of an examined muscle, each recorded at 10ms, 50µV and filter settings of 500 Hz and 10 kHz.[23,24] Mean duration of collected non-polyphasic MUAPs was compared to normal values from healthy age-matched volunteers.[23,25]

Assessment of compound muscle action potential amplitudes following direct muscle stimulation (dmCMAP) was performed by longitudinal placement of either conventional stimulating surface electrodes or by subdermal electrodes along muscle fibres just proximal of the distal tendon insertion in case of oedema. Muscles were stimulated by gradually increasing strength (from 10 to 100mA) at 1Hz and a pulse duration of 0.1ms. For recordings, disposable concentric needle electrodes (length 25mm or 37mm; diameter 0.46mm) and/or disposable gel surface electrodes were used and placed 15–50 mm proximal of the stimulating electrode, guided by muscle twitch. Whenever no twitch was visible, the recording concentric needle electrode was pointed at four different directions in order not to miss small amplitudes. Muscles were assumed to be inexcitable if responses could still not be obtained. dmCMAP amplitudes were measured peak to peak. Filter settings were 500 Hz and 10 kHz. Limbs’
temperature was ensured to be >32°C. The examination included tibialis anterior and abductor pollicis brevis. According to Trojaborg and colleagues, dmCMAP amplitudes recorded by concentric needle electrodes <3mV were considered to be pathologic and consistent with myopathy.[11]

Electrophysiological measurements of tibialis anterior and abductor pollicis brevis muscles of healthy volunteers (age 22 – 74 years) in our laboratory provided reference values for dmCMAP amplitudes using surface electrodes (n=17) or concentric needle electrodes (n=8). To assess motor CIP we calculated neCMAP/dmCMAP ratios (recorded in tibialis anterior muscle with peroneal nerve stimulation at the knee AND in abductor pollicis brevis muscle with median nerve stimulation at the wrist) as introduced by Rich and colleagues: ratios <0.5 indicate motor neuropathy; ratios >0.5 in combination with reduced dmCMAP amplitudes indicate myopathy, while ratios >0.5 in presence of normal dmCMAP amplitudes display normal findings.[13]

To determine muscle-fibre conduction velocity (MFCV), latencies of muscle-fibre action potentials were determined and calculated for the measured distance between electrodes. Perpendicular position of recording needle electrodes was ensured. Responses earlier than 8 ms were likely to be conducted via intramuscular nerve twigs and not included.[11,12,14]

Diagnostic criteria for electrophysiological examination were as follows:

**ICU control:** patients presenting no pathology;

**ICU unspecific:** patients presenting unspecific pathology (pathological spontaneous activity and reduced neCMAP) not verifying myopathy or neuropathy;

**CIM patients:** patients presenting reduced dmCMAP in at least one muscle examined in addition to unspecific findings and normal sensory/motor nerve conduction velocity (isolated CIM);

**CIP patients:** patients presenting reduced SNAP and/or ne/dmCMAP ratio <0.5 in addition to unspecific findings (isolated CIP),
CIM/CIP patients: patients presenting characteristics of combined CIM and CIP - reduced
dmCMAP AND reduced SNAP and/or ne/dmCMAP ratio <0.5.
Patients were classified according to their most severe electrophysiological findings during
their ICU stay. To compare electrophysiological data between patient groups, findings of the
first examination presenting the most severe electrophysiological classification were chosen
for each patient.

Results are expressed as arithmetic mean ± standard deviation (SD) for electrophysiological
data, median and (25/75) percentiles (if number of patients <4 only median) for categorical or
non-normally distributed data, or frequencies [%] for qualitative data, respectively. Statistical
tests were conducted with non-parametric tests by Mann-Whitney-U test for two independent
samples, Kruskal-Wallis test for three or more independent samples, and Fisher’s exact test
for qualitative data. In case of small samples, greater differences in sample sizes, large but
unbalanced groups, data sets containing ties, or sparse data, tests were carried out in an exact
version. Diagnostic test performance was evaluated by receiver operating characteristics
(ROC) analysis using MUAP duration in tibialis anterior muscle <11.1 ms as
electrophysiological gold standard for diagnosing myopathy in patients capable of voluntary
muscle contraction or, alternatively, using amplitudes of dmCMAP in tibialis anterior muscles
of sedated patients not being capable of voluntary muscle contraction.
Kaplan-Meier curves were estimated to show the cumulative incidence of different
electrophysiological disorders developing over time and to estimate probabilities for ICU
discharge after first day of awareness in CIM and CIM/CIP patients. Differences between
groups considering cumulative incidences were tested by univariate Log-Rank test.
In univariate Cox’ proportional hazard regressions we tested the impact of CIM respectively
CIM/CIP as well as illness severity on the duration between first day of adequate awareness
and ICU discharge (as dependent variable). In Cox’ regressions with time dependent
covariates, dmCMAP and SNAP amplitudes were included as indicators of myopathy respectively neuropathy while repeated recordings of SAPS-II and SOFA score during adequate awareness were included as indicators of illness severity. These variables were also analysed by stepwise (backward) procedure of multivariate Cox’ regression accounting for time dependent covariates. Hazard ratios (HR) with 95%-confidence intervals (95%-CI (HR)) and corresponding p-values were calculated for each risk factor. p<0.05 (two-sided) was considered as statistically significant. Statistical analysis was performed using SPSS, Version 14, Copyright© SPSS, Inc., Chicago, Illinois 60606, USA, and SAS, Version 9.1, Copyright© SAS Institute, Inc., Cary, NC, USA.
Results

212 patients required mechanical ventilation and featured SAPS II $\geq 20$ on three consecutive days within the first 7 days after ICU admission and were therefore eligible for inclusion. Patients with pre-existing neuromuscular disorder (n=24), severe head trauma (n=14) or bleeding diathesis (n=33) (thrombocytopenia <20,000/µl) were excluded. 16 patients could not be included due to logistical reasons. Written informed consent by legal proxy could not be obtained in 72 patients. Finally, 53 patients were included and a total of 184 electrophysiological examinations were conducted. One or two examinations were conducted in nine patients each, three exams in 12 patients and four or more examinations in 23 patients.

Patient classification is shown in Figure 1. Only one patient with pre-existing Wilson's disease and two previous liver transplantations showed reduced SNAP amplitudes without evidence of motor CIP or CIM at both exams. However, pre-existing sensory polyneuropathy could not be ruled out.[26] To prevent confusion, all three patients classified as ICU unspecific as well as the only patient with isolated sensory nerve involvement were not considered in tables and figures.

Patients’ characteristics are shown in Table 1.
<table>
<thead>
<tr>
<th></th>
<th>ICU –control (n=13)</th>
<th>CIM (n=16)</th>
<th>CIM/CIP (n=20)</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (years)</td>
<td>34 (23/51)</td>
<td>59 (37/67)</td>
<td>51 (41/58)</td>
<td>0.063</td>
<td>0.301</td>
</tr>
<tr>
<td>gender (m / f)</td>
<td>10/3</td>
<td>8/8</td>
<td>17/3</td>
<td>0.061</td>
<td>0.034</td>
</tr>
<tr>
<td>BMI kg/m² on admission</td>
<td>24.7 (21.6/26.3)</td>
<td>25 (22/28.5)</td>
<td>26 (21.9/31.2)</td>
<td>0.445</td>
<td>0.404</td>
</tr>
<tr>
<td>Sepsis on admission (%)</td>
<td>0%</td>
<td>44%</td>
<td>55%</td>
<td>0.002</td>
<td>0.738</td>
</tr>
<tr>
<td>Diagnosis on admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple trauma</td>
<td>76.9% (n=10)</td>
<td>37.5% (n=6)</td>
<td>50% (n=10)</td>
<td>0.017</td>
<td>0.047</td>
</tr>
<tr>
<td>Cancer surgery</td>
<td>7.7% (n=1)</td>
<td>37.5% (n=6)</td>
<td>5% (n=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARDS / sepsis</td>
<td>7.7% (n=1)</td>
<td>25% (n=4)</td>
<td>45% (n=9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>others</td>
<td>7.7% (n=1)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS-II on admission</td>
<td>26 (22/40)</td>
<td>39 (31/48)</td>
<td>41 (33/50)</td>
<td>0.227</td>
<td>0.539</td>
</tr>
<tr>
<td>SAPS-II peak (first 10 days)</td>
<td>36 (24/44)</td>
<td>40 (31/52)</td>
<td>54 (40/65)</td>
<td>0.048</td>
<td>0.243</td>
</tr>
<tr>
<td>SOFA on admission</td>
<td>8 (6/9)</td>
<td>9.5 (7/12)</td>
<td>11 (8/14)</td>
<td>0.006</td>
<td>0.149</td>
</tr>
<tr>
<td>SOFA peak (first 10 days)</td>
<td>8 (7/9)</td>
<td>10 (8/14)</td>
<td>12 (10/14)</td>
<td>0.002</td>
<td>0.523</td>
</tr>
<tr>
<td>Acute renal failure on admission</td>
<td>0%</td>
<td>18.8%</td>
<td>25%</td>
<td>0.157</td>
<td>0.709</td>
</tr>
<tr>
<td>survival (%)</td>
<td>100%</td>
<td>62.5%</td>
<td>80%</td>
<td>0.045</td>
<td>0.285</td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>8 (7/15)</td>
<td>19 (14/33)</td>
<td>35 (23/47)</td>
<td>&lt;0.001</td>
<td>0.004</td>
</tr>
</tbody>
</table>

p-value<sup>a</sup> compares all three groups (Kruskal-Wallis-test / Fisher’s exact test), whereas p-value<sup>b</sup> (Mann-Whitney-U test / Fisher’s exact test) compares data between CIM- and CIM/CIP-patients. Values are shown as median and (25/75 percentiles) or as absolute numbers. BMI = Body Mass Index, ARDS = Acute Respiratory Distress Syndrome, SAPS-II = Simplified Acute Physiology Score, SOFA = Sepsis related Organ Failure Assessment, ICU length of stay = Intensive Care Unit length of stay.
Amplitudes of nerve conduction studies are shown in Table 2. Predominant involvement of the lower limbs was observed in all patients. Parameters such as motor/sensory nerve conduction velocity, distal motor latency or F-Wave did not deviate from normal values in any of the examined patients. Pathological spontaneous activity such as fibrillation potentials or positive sharp waves were mostly of moderate activity and could be observed in different muscles from patients classified as “ICU unspecific”, “CIM” and “CIM/CIP”. Tibialis anterior and extensor digitorum longus muscles were most frequently affected.

Table 2 Motor and sensory amplitudes for ICU control, CIM - and CIM/CIP patients.

<table>
<thead>
<tr>
<th>Nerve</th>
<th>ICU – control (n=13)</th>
<th>CIM (n=16)</th>
<th>CIM/CIP (n=20)</th>
<th>p-value \textsuperscript{a}</th>
<th>p-value \textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>neCMAP (mV)</td>
<td>Median (10.1 \pm 4.3) (n=11)</td>
<td>(6 \pm 4.5) (n=11)</td>
<td>(4.5 \pm 2.9) (n=15)</td>
<td>0.003</td>
<td>0.51</td>
</tr>
<tr>
<td>Peroneal</td>
<td>(5.3 \pm 3.7) (n=13)</td>
<td>(2.3 \pm 3.4) (n=15)</td>
<td>(1 \pm 1.2) (n=19)</td>
<td>0.003</td>
<td>0.32</td>
</tr>
<tr>
<td>Tibial</td>
<td>(11.8 \pm 6.1) (n=13)</td>
<td>(3.2 \pm 4.1) (n=15)</td>
<td>(3.7 \pm 4.2) (n=13)</td>
<td>0.013</td>
<td>0.16</td>
</tr>
<tr>
<td>SNAP (µV)</td>
<td>Median (22.1 \pm 7.9) (n=11)</td>
<td>(17.3 \pm 6.7) (n=11)</td>
<td>(15.4 \pm 7.6) (n=17)</td>
<td>0.058</td>
<td>0.4</td>
</tr>
<tr>
<td>Sural</td>
<td>(6.5 \pm 3.4) (n=12)</td>
<td>(12.8 \pm 21.8) (n=15)</td>
<td>(1.5 \pm 2) (n=18)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

p-value \textsuperscript{a} compares all three groups (Kruskal-Wallis-test), whereas p-value \textsuperscript{b} (Mann-Whitney-U test) compares data between CIM- and CIM/CIP-patients. Values are given as mean ± SD. neCMAP = nerve evoked Compound Muscle Action Potential amplitude, SNAP = Sensory Nerve Action Potential amplitude.
Muscle specific electrophysiological data are shown in Table 3. In quantitative electromyography we observed an increased incidence of polyphasic potentials and the recruitment pattern at maximum effort was fully or only mildly reduced despite severe weakness in patients classified as “CIM / CIP” respectively “CIM” indicating a myopathy. We did not find signs of denervation such as a reduced recruitment pattern or elevated MUAP amplitudes.

In healthy subjects (age 22 – 74 years) dmCMAP amplitudes were not below 0.6mV when recorded by surface electrodes and not below 3mV when recorded by concentric needle electrodes. For surface electrodes 95% CI were between 0.9mV and 6mV for tibialis anterior muscle and between 0.6mV and 20mV for abductor pollicis brevis muscle. Considering concentric needle electrodes, the according 95% CI were between 4mV and 19mV and between 6.8mV and 13mV, respectively. MFCV was positively correlated with dmCMAP amplitude, reduced amplitudes indicating slower MFCV (Rho = 0.55 and R Quadrate = 0.401).

We did not observe isolated motor CIP in any patient, as ne/dmCMAP ratios were consistently >0.5, which indicates either myopathy in presence of reduced dmCMAP amplitudes (CIM- and CIM/CIP patients) OR normal findings in presence of normal dmCMAP amplitudes (healthy subjects and ICU-controls). ROC analysis verified dmCMAP in tibialis anterior muscle during sedation as predictor of myopathy as later diagnosed by MUAP duration in the same muscle once voluntary contraction was applicable. The best relationship of sensitivity (70%) to specificity (83.3%) was observed at the cut-off value of 3.2mV for dmCMAP, which is compatible to standard values from Trojaborg and colleagues.[11]
Table 3 Muscle specific data for healthy volunteers, ICU control-, CIM- and CIM/CIP patients

<table>
<thead>
<tr>
<th>muscle</th>
<th>healthy volunteers (n=17)</th>
<th>ICU controls (n=13)</th>
<th>CIM (n=16)</th>
<th>CIM/CIP (n=20)</th>
<th>p-value (^a)</th>
<th>p-value (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dm CMAP (mV) (concentric needle electrode) lower limit =3mV</td>
<td>Tib ant</td>
<td>8 ± 2.1 (n=8)</td>
<td>5.6 ± 1.8 (n=12)</td>
<td>2.2 ± 2.3 (n=15)</td>
<td>1.6 ± 1.9 (n=19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Abd poll brev</td>
<td>9.3 ± 2.3 (n=6)</td>
<td>4.3 (n=2)</td>
<td>4.2 (n=2)</td>
<td>2.6 ± 5 (n=10)</td>
<td>0.136</td>
</tr>
<tr>
<td>dm CMAP (mV) (surface electrode) lower limit =0.6mV</td>
<td>Tib ant</td>
<td>2.8 ± 0.4 (n=17)</td>
<td>1.6 ± 0.5 (n=9)</td>
<td>0.3 ± 0.1 (n=9)</td>
<td>0.1 ± 0.1 (n=8)</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>Abd poll brev</td>
<td>7.1 ± 5.3 (n=12)</td>
<td>4.5 ± 4.1 (n=5)</td>
<td>1.3 ± 1.7 (n=6)</td>
<td>0.7 ± 1.6 (n=6)</td>
<td>0.044</td>
</tr>
<tr>
<td>MFCV (m/s)</td>
<td>Tib ant</td>
<td>-</td>
<td>5.9 ± 1.6 (n=3)</td>
<td>5.2 ± 1.1 (n=8)</td>
<td>4.6 ± 1.1 (n=9)</td>
<td>0.454</td>
</tr>
<tr>
<td>ne/dmCMAP ratio</td>
<td>Tib ant</td>
<td>1.79 ± 1.02 (n=7)</td>
<td>2.2 ± 0.7 (n=9)</td>
<td>13.8 ± 14.6 (n=4)</td>
<td>4.9 ± 3.9 (n=9)</td>
<td>0.018</td>
</tr>
<tr>
<td>MUAP duration (ms)</td>
<td>Tib ant</td>
<td>-</td>
<td>11.2 ± 0.6 (n=8)</td>
<td>9.0 ± 2.6 (n=7)</td>
<td>6.9 ± 1.8 (n=10)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Ext dig com</td>
<td>-</td>
<td>10 ± 1 (n=8)</td>
<td>6.3 ± 3.1 (n=9)</td>
<td>5.6 ± 1.1 (n=12)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

p-value \(^a\) compares ICU-controls, CIM- and CIM/CIP-patients (Kruskal-Wallis-test), whereas p-value \(^b\) (Mann-Whitney-U test) compares data between CIM- and CIM/CIP-patients. Values are given as mean ± SD. dmCMAP = direct muscle stimulated Compound Muscle Action Potential amplitude, MFCV = Muscle Fibre Conduction Velocity, ne/dmCMAP ratio = nerve evoked compound action potential amplitude divided by direct muscle stimulated compound action potential amplitude, MUAP = Motor Unit Action Potential, Tib ant = tibialis anterior muscle, Abd poll brev = abductor pollicis brevis muscle, Ext dig com = extensor digitorum communis muscle.
Onset of electrophysiological pathology is shown in Figure 2. Six patients could not be included in analysis due to treatment in external hospitals prior to ICU admission. Abnormal dmCMAP amplitudes occurred significantly earlier than abnormal SNAP (p < 0.001), indicating that CIM occurs prior to CIP with associated sensory nerve involvement during early critical illness. CIM patients showed reduced dmCMAP amplitudes median at day 7 (5/11) while CIM/CIP patients showed reduced SNAP amplitudes median at day 10 (4/13).

Confounders prolonging ICU length of stay showed that classification as CIM or CIM/CIP independently influenced ICU length of stay whereas illness severity was comparable between both groups (p=0.005) (Table 4). Once sedation was ended, patients classified as CIM/CIP stayed significantly longer than patients classified as CIM (p = 0.05) (Figure 3).
Table 4 Confounders prolonging ICU length of stay between end of sedation and ICU discharge

<table>
<thead>
<tr>
<th>Univariate Cox’ regression with time dependent covariates</th>
<th>Hazard Ratio [HR]</th>
<th>95%-CI [HR]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIM and CIM/CIP</td>
<td>0.33</td>
<td>0.16 – 0.66</td>
<td>0.001</td>
</tr>
<tr>
<td>SOFA</td>
<td>1.05</td>
<td>0.95 – 1.17</td>
<td>0.34</td>
</tr>
<tr>
<td>SAPS-II</td>
<td>0.99</td>
<td>0.97 – 1.03</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Multivariate Cox’ regression with time dependent covariates

(after backward selection)

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Univariate and multivariate Cox’ proportional hazard regression accounting for time dependent covariates as potential confounders prolonging ICU length of stay between end of sedation and ICU discharge (dependent variable) is shown. Analyses included dmCMAP and SNAP amplitudes as indicators of CIM and/or CIP, respectively as well as repeated SAPS-II and SOFA score ratings during awareness as indicators of critical illness severity. Hazard ratios (HR) with 95%-confidence intervals (95%-CI[HR]) and p-values for each variable.

SAPS-II = Simplified Acute Physiology Score, SOFA = Sepsis related Organ Failure Assessment, ICU = Intensive Care Unit, dmCMAP = direct muscle stimulated Compound Muscle Action Potential amplitude, SNAP = Sensory Nerve Action Potential amplitude.

At discharge from ICU, some patients classified as CIM featured amplitude recovery of dmCMAP in tibialis anterior muscles (Figure 4a) and neCMAP in tibialis and peroneal nerves, while patients classified as CIM/CIP consistently showed reduced amplitudes of dmCMAP and neCMAP (Figure 4b).

At ICU discharge, muscle strength according to the MRC-score was significantly lower in patients classified as CIM/CIP (n=14; examination was precluded in 4 patients due to death and in 2 patients due to logistical reasons; mean MRC-score in upper limbs 3.5; mean MRC-
score in lower limbs 3.25) than in patients classified as CIM (n=8; examination was precluded in 6 patients due to death and in 2 patients due to logistical reasons; mean MRC-score in upper limbs 4.5, p=0.002; mean MRC-score in lower limbs 4.0, p=0.004).
Discussion

Direct muscle stimulation facilitates diagnosis of CIM in the early course of critical illness. During analgesia and sedation, other methods of clinical assessment are not applicable. Electrophysiological signs of CIM precede electrophysiological signs of CIP. Isolated CIP was not observed in any patient, it occurred only in combination with myopathy. Clinical courses of patients classified as CIM respectively CIM/CIP differ. Both CIM and CIM/CIP independently influence ICU length of stay after the end of sedation. However, patients classified as CIM/CIP feature significantly higher degrees of weakness at ICU discharge and longer ICU lengths of stay than patients classified as CIM. Electrophysiological recordings displayed that some patients classified as CIM showed signs of recovery at discharge from ICU while all patients classified as CIM/CIP consistently featured electrophysiological pathology at ICU discharge.

Technical aspects

By comparing dmCMAP amplitudes with MUAP duration in quantitative electromyography - the gold standard of proving myopathy [23,24] - we could show that assessment of dmCMAP amplitudes represents a valuable tool to differentiate between CIM and CIP during the early course of critical illness, when voluntary muscle contraction is not applicable due to sedation (sensitivity 70%, specificity 83.3%).

The technique of direct muscle stimulation has been evaluated in healthy subjects[27,28] and patients suffering from weakness and/or weaning failure caused by critical illness.[7,11-13,29] Published reference data for dmCMAP depend on recording characteristics of electrodes: concentric needle electrodes (Trojaborg et al., 2001: 8.0 ± 0.9mV, lower limit ≥ 3mV, n = 18; Lefaucheur et al., 2006: 9.61 ± 2.36mV, lower limit ≥ 4.88mV, n = 12 AND our data: 8.0 ± 2.1mV, lower limit ≥ 3mV, n = 8), subdermal electrodes (Trojaborg et al.,
2001: 4.5 ± 1.7 mV, lower limit ≥ 1 mV, n = 18), or surface electrodes (our data: 2.8 ± 0.4, lower limit ≥ 0.6 mV, n = 17). Assessing dmCMAP with surface electrodes may be of advantage in patients with bleeding diathesis. However, measurements with concentric needle electrodes have the advantage of also recording smaller activity from within the deeper muscle.

MFCV values of healthy subjects (Troni et al., 1983: 3.53 – 4.24 m/s male and 2.96 – 3.74 m/s female; Trojaborg et al., 2001: 6.4 ± 0.3 m/s; Allen et al., 2008: 3.0 – 5.5 m/s) and CIM patients (Trojaborg et al., 2001: 4.5 ± 0.2 m/s; Allen et al., 2008: 2.32 ± 1.12 m/s, our data: 5.2 ± 1.1 m/s) are various. Interestingly, patients classified as ICU control showed a reduction of MFCV (5.9 ± 1.6 m/s, n = 3) and dmCMAP amplitude (5.6 ± 1.8 mV, n = 12) compared to healthy volunteers (our data and Trojaborg et al., 2001), possibly indicating early impairment of muscle membrane excitability on a subclinical level that is not accompanied by distinct levels of weakness after the end of sedation.[15] This indicates, that critical illness in general causes impairment of muscle membrane excitability, however, in order to cause muscle organ failure an additional pathomechanism is essential.

Ne/dmCMAP ratios <0.5 are supposed to indicate motor axonopathy.[16] Since this ratio was >0.5 in all of our patients the presence of motor axonopathy is questionable. Z’Graggen and colleagues assessed the existence of membrane depolarization in motor nerves by applying nerve excitability testing[30], proving a nerve membrane affection but not finally proving the existence of a motor axonopathy.

It should be emphasised that SNAP abnormalities indicate sensory neuropathy and cannot serve as definite evidence towards neuropathic involvement in clinical weakness. Early reports attributed weakness in critically ill patients mostly to distal motor axonopathy on the basis of non-specific electrophysiological abnormalities and neglected the possibility of
primary muscle fibre disorder.[3,31] By applying the technique of direct muscle stimulation,
we and others, were able to show that CIM is frequent in critically ill patients.[7,11-15]
However, ne/dm CMAP ratios did not add further information to the diagnosis of myopathy
than dmCMAP amplitudes.

Clinical aspects

Onset and incidence of neuromuscular disorder

To the best of our knowledge, this is the first study reporting that CIM is verified significantly
earlier than CIP. Unspecific findings such as pathological spontaneous activity or reduced
neCMAP amplitudes do not differentiate CIM and CIP and were observed within the first
week after ICU admission. This is in line with three earlier studies describing early onset of
neuromuscular dysfunction in the ICU without differentiating between myopathy and
neuropathy.[9,10,32] We presume that early pathological spontaneous activity is related to
muscle membrane depolarization leading to elevated excitability.

Coexistence of pathological spontaneous activity and reduced dmCMAP amplitudes was
surprising to us, as we expected a reverse relationship due to contrary pathology. However,
this is in line with findings from a rat-model of CIM describing concomitant membrane
depolarization and reduced excitability, which was attributed to voltage-gated sodium-channel
dysfunction.[33,34] It was furthermore reported, that endotoxin of gram-negative bacteria
causes a hyperpolarized shift in the gating of voltage-gated sodium channels in human
skeletal muscle,[35] which in presence of muscle membrane depolarization in critically ill
patients [36] will finally cause muscle membrane inexcitability.

We observed both systemic inflammation and illness severity during early critical illness to
present significant risk factors for development of CIM or CIM/CIP. It nevertheless remains
unresolved why some patients show more severe or combined affection of muscles and nerves
than others.
Recovery from neuromuscular disorder

Some authors advise against adoption of electrophysiological differential diagnosis [7,8] since distinguishing between CIM and CIP would not be associated with clinical prognosis. We recently reported that CIM constitutes the primary reason for ICU acquired weakness presenting in critically ill patients suffering from sepsis, systemic inflammatory response syndrome or multiple organ failure once sedation is ended.[15] For the first time we report that ICU length of stay is markedly prolonged in patients classified as CIM/CIP compared to patients with isolated CIM and that this does not result from illness severity after sedation was ended. Expecting subsequent prolongation of recovery time, it was interesting to observe that patients classified as CIM/CIP still featured severe weakness at ICU discharge in contrast to CIM patients. This is consistent with observations by Guarneri and colleagues describing better long-term prognosis (one year after hospital discharge) in patients diagnosed with isolated CIM.[37] It should nevertheless be mentioned that patients classified as CIM/CIP showed more pronounced dmCMAP amplitude reduction and shorter MUAP duration, both characteristics of pronounced myopathy, than patients with pure CIM.

As some CIM patients show recovery of dmCMAP amplitude reduction at ICU discharge, we presume inactivation of voltage-gated sodium channels in structural intact muscle fibres to be reversible after successful treatment/elimination of potentially involved factors, which would explain return to normal function within days.[7,11,13,38] Recovery was not observed in patients classified as CIM/CIP, which may be either due to pronounced muscle dysfunction with selective myosin-filament loss in fast twitch muscle fibres OR due to muscle denervation causing muscle membrane depolarization potentially counteracting recovery.[11,36,38,39]

In conclusion, we were able to show that clinical prognosis differs according to electrophysiological differential diagnosis during early critical illness. CIM in combination
with CIP was associated with more severe weakness at ICU discharge and longer ICU length of stay than isolated CIM. During the early course of critical illness, when voluntary muscle contraction is not applicable due to sedation, we recommend conventional electrophysiological recordings in combination with direct muscle stimulation (adds another 5-15 min) to maintain precise differential diagnosis. This supports better prediction of weaning difficulties which occur in both CIM and CIM/CIP patients and furthermore assists clinicians in estimating motor function recovery at ICU discharge.

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Legends for figures

Figure 1 Consort Diagram for electrophysiological characteristic. SAPS-II = Simplified acute physiology score, ICU = Intensive care unit, neCMAP = nerve evoked compound action potential amplitude, dmCMAP = direct muscle stimulated compound action potential amplitude, SNAP = sensory nerve action potential amplitude.

Figure 2 Cumulative incidence of neuromuscular affection in days after onset of critical illness. Probability 0.5 for pathological spontaneous activity (short/long dashed line n=34) is median 5 days (4.82/ 7.18  95% CI), for reduction of neCMAP amplitudes (short/long dashed line (n=40) 6 days (3.88 / 6.12 95% CI); for reduction of dmCMAP amplitudes (solid line, n = 30) 9 days (6.38 / 11.6 95% CI) and for reduction of SNAP amplitude (short dashed line, (n=17) 18 days (4.01 / 31.9 95% CI). Time differences are significant for dmCMAP vs. pathological spontaneous activity and neCMAP (p < 0.01) and vs. SNAP (p< 0.001, Log Rank test). Crosses per line denote censored observation without showing pathological signs.

Figure 3 Cumulative Probability for ICU length of stay counted from the day after awakening from sedation until discharge from ICU for CIM – patients (solid line) and CIM/CIP – patients (dashed line) (p = 0.054; Log Rank test).

Figure 4 Time course for dmCMAP after onset till discharge of ICU stay organized in time groups (1-3 days, 4-6 days, 7-9 days, 14-18days, 19-24 days and 25-31 days) for ICU-control, CIM- and CIM/CIP-patients; for (A) dmCMAP amplitude of tibialis anterior muscle, reference mark at 3mv (normal ≥ 3mV); box plots show median and (25%/75%) percentile. ICU-control (black boxes), purely CIM- (diagonal Boxes) and CIM/CIP patients (blank Boxes). (B) Difference of neCMAP and dmCMAP amplitude at discharge from ICU
for ICU-control, CIM- and CIM/CIP-patients. Differences are shown for CIM/CIP patients vs. purely CIM-patients (Kruskal-Wallis test). neCMAP = nerve evoked compound action potential amplitude, dmCMAP = direct muscle stimulated compound action potential amplitude.
53 patients included

Normal electrophysiological findings

13 ICU control patients

Unspecific pathological electrophysiological findings / pathological spontaneous activity, reduced neCMAP

and reduced dmCMAP

3 ICU unspecific patients

and reduced SNAP

1 CIP patient

16 CIM patients

20 CIM/CIP patients

Figure 1
Figure 2
Figure 3

Probability of ICU discharge vs. number of ICU days after adequate awareness.

- CIM+CIP-
- CIM+CIP+
Figure 4a
Figure 4b

Comparison of amplitudes (mV) for different groups: ICU-control, CIM, and CIM/CIP. The box plots show the distribution of amplitudes for neCMAP N peroneus, neCMAP N tibialis, and dmCMAP tibialis anterior muscle. The p-values (0.007, 0.027, and 0.031) indicate statistically significant differences between the groups.