Intensive care unit-acquired weakness: early diagnosis, symptomatology and prognosis

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CHAPTER 5

FEASIBILITY AND DIAGNOSTIC ACCURACY OF EARLY ELECTROPHYSIOLOGICAL RECORDINGS FOR ICU-ACQUIRED WEAKNESS: AN OBSERVATIONAL COHORT STUDY

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Submitted
ABSTRACT

Objective
An early diagnosis of ICU-acquired weakness (ICU-AW) is difficult because disorders of consciousness frequently preclude muscle strength assessment. The aim of this study was to investigate feasibility and diagnostic accuracy of electrophysiological recordings to diagnose ICU-AW early in non-awake critically ill patients.

Design
Single-center, prospective, observational cohort study

Patients and Setting
Newly admitted patients, mechanically ventilated ≥2 days and not reactive to verbal stimuli were recruited in a mixed medical-surgical ICU.

Interventions
Electrophysiological recordings comprised nerve conduction studies (NCS) of 3 nerves and, if coagulation was normal, myography in 3 muscles. Upon awakening, strength was assessed (ICU-AW: average Medical Research Council score <4), blinded for electrophysiological recordings. Feasibility was expressed as the percentage of recordings that were both possible and had sufficient technical quality. Diagnostic accuracy of feasible recordings was analyzed based on cut-off values from healthy controls and from critically ill patients at the ICU without ICU-AW.

Measurements and Main Results
Thirty-five patients were included (17 with ICU-AW). Recordings were obtained on day 4 (IQR: 3-6). Feasibility was 95 % for ulnar motor recordings, 80 % for ulnar sensory recordings, 88 % for peroneal recordings (extensor digitorum brevis muscle), 80 % for peroneal recordings (tibialis anterior muscle), and 35 % for sural recordings and for myography. Diagnostic accuracy based on cut-off values from healthy controls was low for all recordings. When using cut-off values from critically ill patients with and without ICU-AW, the peroneal compound muscle action potential (extensor digitorum brevis muscle) amplitude and ulnar sensory nerve action potential amplitude had good diagnostic accuracy.

Conclusion
Nerve conduction studies of the ulnar and peroneal nerve are feasible in critically ill patients. The diagnostic accuracy is low using cut-off values from healthy controls. Cut-off values validated specifically for discrimination between critically ill patients with and without ICU-AW may improve diagnostic accuracy.
INTRODUCTION

Intensive Care Unit–acquired weakness (ICU–AW) is a frequent and important complication of critical illness, occurring in approximately 50% of critically ill patients. According to expert-based criteria, ICU-AW is diagnosed by assessing muscle strength manually using the Medical Research Council (MRC) score. Manual muscle strength assessment is easy to perform and has good intra- and inter-observer reliability in awake and attentive patients. However, early after ICU admission, consciousness or attentiveness is frequently impaired, potentially causing a diagnostic delay. This may withhold important prognostic information from physicians and families. Moreover, it is thought that early abnormalities in muscles and nerves of patients with ICU-AW are reversible and potential therapeutic interventions could therefore be more effective when started early.

Electrophysiological recordings can be used to diagnose muscle and/or nerve disorders underlying ICU-AW. As awake and attentive patients are not necessary for most electrophysiological recordings, they may be useful to diagnose ICU-AW before this can be done with manual muscle strength assessment. For daily clinical care, a small subset of electrophysiological recordings would be preferable. It is uncertain, however, which subset has the highest diagnostic yield. Direct muscle stimulation (DMS) has been proposed and may be a diagnostic option, however the validity of this recording has been questioned. DMS is technically more demanding than conventional electrophysiological recordings and may therefore not be very practical. Regardless which electrophysiological recordings are used, feasibility in the ICU may be an issue because of electrical interference, discomfort and edema, albeit that this has not been formally studied.

The aims of this study were to study feasibility and diagnostic accuracy of early conventional electrophysiological recordings for diagnosing ICU-AW in non-awake critically ill patients.

METHODS

Design and ethical approval

A prospective observational cohort study was performed in the mixed medical-surgical ICU of the Academic Medical Center, Amsterdam, the Netherlands. The study was designed in accordance with the STARD criteria. The Institutional Review Board of the Academic Medical Center, Amsterdam, the Netherlands approved the study (NL33385.018.10; 10/219 #10.17.1630). Legal representatives of patients gave informed consent prior to inclusion in the study and informed consent was confirmed in patients who regained consciousness.

In- and exclusion criteria

Newly admitted critically ill patients who were mechanically ventilated for ≥2 days were eligible for inclusion. The level of sedation of eligible patients was evaluated and only patients who were unreactive to verbal stimuli (Richmond Agitation Sedation Scale (RASS) <-3) were included. Other exclusion criteria were a neuromuscular disorder (e.g. Guillain-Barré syndrome), stroke, cardiac arrest or spinal injury as reason for ICU admission. In addition, we excluded moribund patients, patients with a poor pre-hospital functional status (Rankin ≥4) and patients with preceding spinal injury.
Electrophysiological recordings (the index test):
Electrophysiological recordings were performed using a Medelec Synergy N2 (Carefusion, The Netherlands). Hand temperature was kept at >32°C and foot temperature was kept at >30°C. One investigator (LW), who was specifically trained for these recordings, performed the measurements without assistance of a technician. Recordings were done unilaterally. For all nerve conduction studies (NCS), supramaximal stimulation was sought. The compound muscle action potentials (CMAPs) were recorded with large surface electrodes at standardized sites defined by anatomical landmarks from the abductor digiti quinti when stimulating the ulnar nerve at the wrist and elbow. A 3-Hz train of 10 stimuli was given to exclude a decremental response (>10 % CMAP amplitude reduction) indicating neuromuscular blocking. If this was found, further recordings were postponed. Otherwise, CMAPs were recorded from the tibialis anterior (TA) and extensor digitorum brevis (EDB) muscles when stimulating the peroneal nerve at the ankle and distal and proximal from the fibular head. Sensory nerve action potentials (SNAPs) were recorded from the little finger when stimulating the ulnar nerve at the wrist and from the lateral malleolus when stimulating the sural nerve at the calf.

When clotting parameters were normal (activated partial thromboplastin time (aPTT) <45 seconds and platelet count >50x10⁹/L), myography was performed and abnormal spontaneous muscle activity was recorded with concentric needle electrodes of the dorsal interossei I/II, deltoid and TA muscles using standard methods. When clotting parameters were normal (activated partial thromboplastin time (aPTT) <45 seconds and platelet count >50x10⁹/L), myography was performed and abnormal spontaneous muscle activity was recorded with concentric needle electrodes of the dorsal interossei I/II, deltoid and TA muscles using standard methods. When clotting parameters were normal (activated partial thromboplastin time (aPTT) <45 seconds and platelet count >50x10⁹/L), myography was performed and abnormal spontaneous muscle activity was recorded with concentric needle electrodes of the dorsal interossei I/II, deltoid and TA muscles using standard methods. From the electrophysiological recordings, the following parameters were used for analyses: CMAP amplitude and duration (negative peak), SNAP amplitude (negative peak) and the presence of abnormal spontaneous activity (defined as grade ≥1 for either positive sharp waves or fibrillation potentials).

To assess feasibility, all recordings were reviewed off-line for technical quality by an experienced neurophysiologist (CV) who was blinded for muscle strength results. If a recording could not be performed, the reason for this was registered. Reasons were: severe local ischemia, a local infection, stimulation site not accessible or patient discomfort. Discomfort led to discontinuation of the recording protocol.

Medical Research Council score (the reference test):
When patients awoke (RASS between -1 (“drowsy”) and 1 (“restless”)) and were attentive (able to follow verbal commands with arms or eye-lids), a physical therapist, blinded for electrophysiological results, assessed strength of the following six muscle groups bilaterally: wrist dorsiflexors, elbow flexors, shoulder abductors, hip flexors, knee extensors and ankle dorsiflexors. Strength was scored using the Medical Research Council (MRC) scale. MRC scores were summated and divided by the number of muscle groups tested to obtain an average MRC score. ICU-AW was defined an average MRC score <4.3

Clinical data collection
The following clinical characteristics were collected: age, gender, admission type, presence of sepsis⁵⁹, severe sepsis⁷⁹, septic shock⁷ during admission, Acute Physiology and Chronic Health Evaluation IV (APACHE IV) score and the maximal total Sequential Organ Failure
Assessment (SOFA) score during admission. In addition, we collected: presence of risk factors for polyneuropathy (like diabetes mellitus, alcohol abuse or chemotherapy), presence of a pre-existing polyneuropathy, days with mechanical ventilation and ICU length of stay.

**Sample size estimation**

Sample size was based on an assumed sensitivity of 90% of one electrophysiological parameter. Subsequent calculation showed a sample size of 70 patients to be sufficient (2-sided, alpha: 0.05, expected proportion: 0.90, confidence interval: 0.10, population prevalence 50%).

**Analysis plan**

Feasibility of the different recordings was analyzed in all included patients (intention-to-diagnose population). Feasibility was expressed as the percentage of recordings that were both possible to perform and had sufficient technical quality.

Diagnostic accuracy was subsequently investigated for recordings with acceptable feasibility (defined as a feasibility of ≥75%) using two approaches. First, sensitivity and specificity, positive and negative predictive values were calculated based on cut-off values obtained from healthy controls. Amplitudes were considered abnormal when below the 2.5th percentile; durations were abnormal when above the 97.5th percentile (cut-off values shown in table 3).

Also, we assessed diagnostic accuracy using cut-off values from critically ill patients with and without ICU-AW. First, we assessed discriminative power of feasible parameters using receiver operating characteristic (ROC) curves displayed with area under the curve (AUC with 95% CI). We defined discriminative power of AUC values between 0.90-1 as excellent, between 0.80-0.90 as good, between 0.70-0.80 as fair, between 0.60-0.70 as poor and <0.60 as failed. Only for parameters with excellent or good discriminative power, optimal cut-off values were calculated as the point with maximal distance from the reference line of the ROC curve. Sensitivity and specificity, positive and negative predictive values based on these optimal cut-off values were calculated for parameters separately and combined.

Mean values are presented with standard deviation (±SD), median values with interquartile range (IQR) and proportions with percentages and total numbers. Differences between proportions were assessed using Fisher’s exact test. Differences between normally distributed variables were assessed using Welch’s t-test; differences between non-normally distributed continuous variables were assessed using Wilcoxon rank-sum test.

**RESULTS**

Enrollment of patients was started in January 2011 and was prematurely ended in July 2013 due to slow recruitment. Forty patients were included, see study flowchart in figure 1. Patient and admission characteristics are displayed in table 1.

**Feasibility of electrophysiological recordings**

Feasibility of electrophysiological recordings is displayed in table 2. Feasibility of ulnar motor and sensory and peroneal motor recordings was acceptable. Sural nerve recordings and myography had low feasibility. Discomfort was recorded in 3 patients.
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>demographics</th>
<th>ICU-AW (N:17)</th>
<th>no ICU-AW (N:18)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>males, n (%)</td>
<td>12 (71)</td>
<td>11 (61)</td>
<td>1.00</td>
</tr>
<tr>
<td>age, median year (IQR)</td>
<td>62 (52-73)</td>
<td>56 (46-60)</td>
<td>0.18</td>
</tr>
<tr>
<td>neurological co-morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>risk factor for polyneuropathy, n (%)</td>
<td>4 (24)</td>
<td>5 (27)</td>
<td>1.00</td>
</tr>
<tr>
<td>pre-existing polyneuropathy, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>admission characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>admission type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>medical, n (%)</td>
<td>6 (35)</td>
<td>12 (67)</td>
<td>0.10</td>
</tr>
<tr>
<td>surgical elective, n (%)</td>
<td>5 (30)</td>
<td>1 (6)</td>
<td></td>
</tr>
<tr>
<td>surgical emergency, n (%)</td>
<td>6 (35)</td>
<td>5 (27)</td>
<td></td>
</tr>
<tr>
<td>APACHE IV score, median (IQR)</td>
<td>103 (81-115)</td>
<td>71 (57-93)</td>
<td>0.02</td>
</tr>
<tr>
<td>maximal SOFA score during admission, median (IQR)</td>
<td>16 (16-20)</td>
<td>10 (9-12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>sepsis during admission, n (%)</td>
<td>17 (100)</td>
<td>16 (89)</td>
<td>0.49</td>
</tr>
<tr>
<td>severe sepsis during admission, n (%)</td>
<td>17 (100)</td>
<td>14 (78)</td>
<td>0.13</td>
</tr>
<tr>
<td>septic shock during admission, n (%)</td>
<td>15 (88)</td>
<td>8 (44)</td>
<td>0.02</td>
</tr>
<tr>
<td>LOS ICU, median days (IQR)</td>
<td>20 (15-29)</td>
<td>11 (8-16)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>days with mechanical ventilation, median (IQR)</td>
<td>13 (10-21)</td>
<td>9 (7-13)</td>
<td>0.03</td>
</tr>
<tr>
<td>days from admission until first reliable muscle strength assessment, median (IQR)</td>
<td>10 (8-16)</td>
<td>10 (8-16)</td>
<td>0.55</td>
</tr>
<tr>
<td>average MRC score, median (IQR)</td>
<td>1.5 (1.1-2.7)</td>
<td>5 (4.6-5)</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

ICU-AW: Intensive Care Unit – acquired weakness; LOS ICU: length of stay in the intensive care unit; APACHE IV: Acute Physiology and Chronic Health Evaluation IV score; SOFA: Sequential Organ Failure Assessment; MRC: Medical Research Council; IQR: interquartile range; n.a.: not applicable

Table 2. Feasibility of electrophysiological recordings. Feasibility was assessed by registering why a recording could not be performed and by assessing technical quality. Recordings that were both possible and had sufficient technical quality were defined as feasible (see text for more details). Each recording was performed in 40 patients (intention-to-diagnose population).

<table>
<thead>
<tr>
<th></th>
<th>Not possible</th>
<th>Insufficient technical quality</th>
<th>Feasible</th>
</tr>
</thead>
<tbody>
<tr>
<td>ulnar motor, n (%)</td>
<td>0 (-)</td>
<td>2 (5)</td>
<td>38 (95)</td>
</tr>
<tr>
<td>ulnar sensory, n (%)</td>
<td>3 (7)</td>
<td>5 (13)</td>
<td>32 (80)</td>
</tr>
<tr>
<td>peroneal EDB, n (%)</td>
<td>3 (7)</td>
<td>2 (5)</td>
<td>35 (88)</td>
</tr>
<tr>
<td>peroneal TA, n (%)</td>
<td>3 (7)</td>
<td>5 (13)</td>
<td>32 (80)</td>
</tr>
<tr>
<td>sural, n (%)</td>
<td>9 (22)</td>
<td>17 (43)</td>
<td>14 (35)</td>
</tr>
<tr>
<td>myography*, n (%)</td>
<td>21* (52)</td>
<td>5 (13)</td>
<td>14 (35)</td>
</tr>
</tbody>
</table>

*: defined as feasible when at least one of three muscles could be examined reliably
*: 17 measurements not possible because of coagulation problems
EDB: extensor digitorum brevis; TA: tibialis anterior
Figure 1. Flow chart
RASS: Richmond Agitation Sedation Scale; OHCA: out-of-hospital cardiac arrest; mRankin: modified Rankin score; NMD: neuromuscular disorder

Electrophysiological parameters in patients with and patients without ICU-AW
Muscle strength could not be assessed in five patients because they died before awakening (figure 1). Electrophysiological recordings were done on day 4 (median; IQR: 3-6). Muscle strength could be assessed at day 10 (median; IQR: 8-16; table 1). Two recordings were initially postponed because medication induced neuromuscular blockage was found. Figure 2 displays distributions of the electrophysiological parameters for patients with and without ICU-AW. Abnormal spontaneous activity in either the dorsal interossei I/II, deltoid or TA muscles was found in 1 of 4 patients with ICU-AW compared to 3 of 8 patients without ICU-AW (p: 1.00).

Diagnostic accuracy of feasible electrophysiological parameters
Table 3 displays sensitivity and specificity for feasible electrophysiological parameters based on cut-off values from healthy controls. All parameters had either low sensitivity or low specificity. Figure 3 displays the ROC curves, based on critically ill patients with and without ICU-AW in this study. Good discriminative power was found for EDB peroneal CMAP amplitude (AUC: 0.80 95% CI: 0.64-0.96). The ulnar SNAP amplitude had excellent discriminative power (AUC: 0.93 95% CI: 0.84-1.0). All other parameters had fair, poor or non-significant discriminative power. Table 4 displays optimal cut-off values for EDB peroneal CMAP amplitude and ulnar SNAP amplitude calculated from the ROC curves. Based on these cut-off values, both the ulnar SNAP amplitude and EDB peroneal CMAP amplitude showed good sensitivity and specificity, either alone or when combined (table 4).
Figure 2. Differences in electrophysiological parameters between patients with or without Intensive Care Unit – acquired weakness.

Patients with Intensive Care Unit – acquired weakness (ICU-AW) are shown in black; patients without ICU-AW are shown in grey. Solid lines represent median values per group. Differences between groups are analyzed using the Wilcoxon rank-sum test, presented with p-value. The number of patients available for each parameter is shown in grey at top of each graph. Dotted lines represent cut-off values from healthy controls (see table 3). Amplitudes are abnormal when below the cut-off value; durations are abnormal when above the cut-off value.

Intensive Care Unit – acquired weakness; UN: ulnar nerve; CMAP: compound muscle action potential; SNAP: sensory nerve action potential; PN: peroneal nerve; EDB: extensor digitorum brevis; TA: tibialis anterior; SN: sural nerve
Table 3. Diagnostic accuracy of feasible electrophysiological parameters based on cut-off values from healthy controls for Intensive Care Unit – acquired weakness. Sensitivity and specificity, positive and negative predictive values (presented with 95% confidence interval) for electrophysiological parameters with a feasibility of ≥75 %. Amplitudes were considered abnormal when below 2.5th percentile of local reference values obtained from healthy controls; durations were abnormal when above 97.5th percentile.20 For the number of patients available for each parameter, see figure 2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>cut-off value</th>
<th>sensitivity</th>
<th>specificity</th>
<th>positive predictive value</th>
<th>negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ulnar CMAP amplitude</td>
<td>&lt;6.2 mV</td>
<td>100% (71-100)</td>
<td>0% (0-27)</td>
<td>48% (31-66)</td>
<td>n.a.</td>
</tr>
<tr>
<td>duration</td>
<td>&gt;6.0 ms</td>
<td>31% (11-59)</td>
<td>88% (64-99)</td>
<td>71% (29-96)</td>
<td>58% (37-77)</td>
</tr>
<tr>
<td>ulnar SNAP amplitude</td>
<td>&lt;8.2 μV</td>
<td>36% (13-65)</td>
<td>100% (68-100)</td>
<td>100% (35-100)</td>
<td>61% (39-80)</td>
</tr>
<tr>
<td>EDB peroneal CMAP amplitude</td>
<td>&lt;1.4 mV</td>
<td>100% (70-100)</td>
<td>31% (11-59)</td>
<td>58% (37-77)</td>
<td>100% (36-100)</td>
</tr>
<tr>
<td>duration</td>
<td>&gt;8.0 ms</td>
<td>17% (2-48)</td>
<td>100% (70-100)</td>
<td>100% (9-100)</td>
<td>60% (39-79)</td>
</tr>
<tr>
<td>TA peroneal CMAP amplitude</td>
<td>&lt;2.4 mV</td>
<td>100% (68-100)</td>
<td>36% (13-65)</td>
<td>61% (39-80)</td>
<td>100% (36-100)</td>
</tr>
<tr>
<td>duration</td>
<td>&gt;8.8 ms</td>
<td>54% (25-81)</td>
<td>25% (5-57)</td>
<td>44% (20-70)</td>
<td>33% (7-70)</td>
</tr>
</tbody>
</table>

CMAP: compound muscle action potential; SNAP: sensory nerve action potential; EDB: extensor digitorum brevis; TA: tibialis anterior, n.a.: not applicable

Table 4. Diagnostic accuracy of feasible electrophysiological parameters using ICU-based cut-off values for Intensive Care Unit – acquired weakness. Sensitivity and specificity, positive and negative predictive values (presented with 95% confidence interval) for feasible electrophysiological parameters with good or excellent discriminative power (i.e. area under the receiver operating characteristic (ROC) curve ≥0.80; see figure 3). From the ROC curves shown in figure 3, the optimal cut-off value (i.e. ICU-based cut-off value) is calculated as the point with maximal distance from the reference line. The final row shows diagnostic accuracy of combined abnormal ulnar SNAP amplitude and EDB peroneal CMAP amplitude. For the number of patients available for each parameter, see figure 2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ICU-based cut-off value</th>
<th>sensitivity</th>
<th>specificity</th>
<th>positive predictive value</th>
<th>negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ulnar SNAP amplitude</td>
<td>&lt;17.6 μV</td>
<td>100% (68-100)</td>
<td>79% (49-95)</td>
<td>82% (57-96)</td>
<td>100% (62-100)</td>
</tr>
<tr>
<td>EDB peroneal CMAP amplitude</td>
<td>&lt;0.43 mV</td>
<td>80% (52-96)</td>
<td>75% (48-93)</td>
<td>75% (48-93)</td>
<td>80% (52-96)</td>
</tr>
<tr>
<td>ulnar SNAP and EDB peroneal CMAP amplitude abnormal</td>
<td>n.a.</td>
<td>77% (46-95)</td>
<td>100% (70-100)</td>
<td>100% (59-100)</td>
<td>83% (59-96)</td>
</tr>
</tbody>
</table>

CMAP: compound muscle action potential; SNAP: sensory nerve action potential; EDB: extensor digitorum brevis; TA: tibialis anterior, n.a.: not applicable
Figure 3. Discriminative power of feasible electrophysiological parameters for Intensive Care Unit – acquired weakness

Receiver operating characteristic (ROC) curves with area under the curve (AUC with 95% confidence interval) for feasible electrophysiological parameters. For the number of patients available for each parameter, see figure 2.

AUC: area under the curve; CI: confidence interval; UN: ulnar nerve; CMAP: compound muscle action potential; PN: peroneal nerve; EDB: extensor digitorum brevis; TA: tibialis anterior; SNAP: sensory nerve action potential
DISCUSSION
Nerve conduction studies of the ulnar and peroneal nerve have acceptable feasibility when assessed in non-awake critically ill patients. Sensory recordings of the sural nerve and myography had low feasibility. Based on cut-off values from healthy controls, diagnostic accuracy for ICU-AW of feasible electrophysiological parameters was low. However, when using cut-off values from critically ill patients with and without ICU-AW, the EDB peroneal CMAP amplitude and ulnar SNAP amplitude were found to have good diagnostic accuracy.

Feasibility of early electrophysiological recordings for an early ICU-AW diagnosis
This is the first study that evaluated feasibility of electrophysiological recordings assessed by a single examiner in non-awake critically ill patients. The most important reason for preventing the different NCS was insufficient technical quality of the recordings. Often this was caused by electrical interference of renal-replacement devices or cardiac assist devices. Coagulation disorders prevented myography in approximately 50 % of attempted recordings. We are aware that coagulation disorders are not an absolute contraindication for myography but the risk/benefit ratio of performing myography in patients with coagulation disorders should be weighted. In our opinion, the added benefit of establishing an early ICU-AW diagnosis does not outweigh the risk of myography in critically ill patients with coagulation problems, especially since therapeutic consequences are not yet available.

Validity of cut-off values from healthy controls for electrophysiological parameters
Unexpectedly, we found that all feasible parameters had either low sensitivity or low specificity, when based on reference values obtained from healthy controls. Almost all patients, with or without ICU-AW, had abnormal CMAP amplitudes. Several explanations are possible. First, abnormal CMAP amplitudes may be the result of a subclinical, i.e. without causing weakness, reduction in muscle and/or nerve excitability which has been described in critically ill patients. Second, CMAP amplitudes may appear lower because of tissue edema. Third, abnormal CMAP amplitudes may be the result of muscle atrophy, which develops early in many critically ill patients. The reduction in muscle mass seen with atrophy does not necessarily cause weakness. Finally, it may be that during the interval between electrophysiological recordings and muscle strength assessment, the patient recovered. Quick recovery of reduced CMAP amplitudes has been reported when the underlying illness subsides and may be attributed to a restoration of sodium channel function in structurally intact muscles and/or nerves.

Diagnostic accuracy of electrophysiological recordings
When using cut-off values from critically ill patients with and without ICU-AW, the EDB peroneal CMAP amplitude and ulnar SNAP amplitude had good diagnostic accuracy. The EDB peroneal CMAP amplitude for an early diagnosis of ICU-acquired neuromuscular disorders has been advocated previously. Because muscle strength was not assessed in this study, diagnostic accuracy for ICU-AW is not known. Weber Carstens et al reported a sensitivity of 92 % but low specificity of 44 % for the EDB peroneal CMAP amplitude based on cut-off values from healthy
controls. This was similar to what we found when using cut-off values from healthy controls. ICU-based cut-off values were not investigated by Weber-Carstens et al.

In contrast to our findings, they reported low diagnostic utility for SNAP amplitudes, but this may again be explained by the use of healthy control based cut-off values. The ICU-based cut-off value for the ulnar SNAP amplitude we found in critically ill patients was higher than the standard cut-off value in healthy controls. The external validity of this finding therefore seems low.

The other electrophysiological recordings measured in our study were either not feasible or had low diagnostic accuracy. In particular, we found that abnormal spontaneous activity, with an earlier reported sensitivity of 48% and specificity of 93%, was not feasible. Peroneal CMAP duration, reported to be increased in when a myopathy underlies ICU-AW, had poor discriminative power.

We did not directly compare feasibility and diagnostic accuracy of conventional electrophysiological recordings to DMS. DMS was proposed as the best electrophysiological recording for an early diagnosis of ICU-AW by Weber-Carstens et al. However, DMS has several limitations. CMAPs are obtained by stimulating the muscle directly using a monopolar needle inserted in the muscle and recording the subsequent response using a monopolar needle inserted more distally. The technique of DMS is only semi-quantitative, related to changes in placement of the recording electrode and the entire muscle may not be stimulated. DMS is technically more demanding than conventional electrophysiological recordings and therefore less practical. Moreover, because DMS requires insertion of monopolar needles, we speculate that the feasibility of DMS in the ICU is low if coagulation disorders are taken into account. Patients with coagulation disorders were excluded by Weber-Carstens et al. The reported high diagnostic accuracy of DMS was based on sequential measurements; abnormal DMS results could be found at the initial early assessment but also during follow-up. Abnormal DMS results developed at day 7.5 (median) after ICU admission. Thus, diagnostic accuracy of an early single DMS recording is unknown and we speculate that it will be lower than for sequential recordings.

Limitations

Our study has several limitations. Very few patients met our inclusion criteria leading to a slow recruitment rate and therefore premature ending of this study without reaching the calculated sample size. Patients in our ICU were often already awake on the second day of admission and could therefore not be included in this study. We speculate that this is because of the reduced use of sedation, which can improve outcome. As a consequence, the included patients, still needing sedation, were often severely ill, as evidenced by very high APACHE IV and maximal SOFA scores. Also, our sample size is insufficient to set new ICU-based cut-off values and the reported values should be interpreted cautiously. Feasibility was assessed in a single center and for one examiner. Finally, our goal was to diagnose ICU-AW and therefore we did not perform all the necessary diagnostics to differentiate between the underlying disorders causing ICU-AW. Consequently, we cannot attribute our findings to the presence of either critical illness myopathy (CIM), critical illness polyneuropathy (CIP) or critical illness neuromyopathy (CINM) specifically.
CONCLUSION

Feasibility of ulnar and peroneal motor recordings and ulnar sensory recordings is acceptable. However, diagnostic accuracy based on cut-off values is low from healthy controls. When using cut-off values from critically ill patients with or without ICU-AW, the EDB peroneal CMAP amplitude and ulnar SNAP amplitude had good diagnostic accuracy. This suggests that cut-off values based on healthy controls are not valid for an early ICU-AW diagnosis and specific ICU-based cut-off values need to be established.

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CONFLICTS OF INTEREST

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