Critical illness myopathy is frequent – accompanying neuropathy protracts ICU discharge

Susanne Koch, Simone Spuler, Maria Deja, Jeffrey Bierbrauer, Anna Dimroth, Friedrich Behse, Claudia Spies, Klaus D. Wernecke, Steffen Weber-Carstens

▶ **To cite this version:**

Susanne Koch, Simone Spuler, Maria Deja, Jeffrey Bierbrauer, Anna Dimroth, et al.. Critical illness myopathy is frequent – accompanying neuropathy protracts ICU discharge. Journal of Neurology, Neurosurgery and Psychiatry, 2010, 82 (3), pp.287. 10.1136/jnnp.2009.192997 . hal-00570137

HAL Id: hal-00570137
https://hal.science/hal-00570137

Submitted on 27 Feb 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Critical illness myopathy is frequent – accompanying neuropathy protracts ICU discharge

Susanne Koch[1], Simone Spuler[3], Maria Deja[1], Jeffrey Bierbrauer[1], Anna Dimroth[1], Friedrich Behse[2], Claudia D. Spies[1], Klaus-D. Wernecke[4], Steffen Weber-Carstens[1]

[1]Department of Anesthesiology and Intensive Care Medicine, Campus Virchow-Klinikum and Campus Charité Mitte, Charité-Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany

[2]Department of Neurology, Campus Virchow-Klinikum and Campus Charité Mitte, Charité-Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany

[3]Muscle Research Unit, Experimental and Clinical Research Center, Charité-Universitätsmedizin Berlin, Lindenberger Weg 80, 13125 Berlin, Germany

[4]Institute of Medical Biometry, Charité-Universitätsmedizin Berlin, Charité-Platz 1, 10098 Berlin, Sostana GmbH, Germany

Running head: CIM frequent - CIP protracts discharge

Corresponding author:

Susanne Koch, MD

Dept. of Anesthesiology and Intensive Care Medicine

Charité Universitätsmedizin Berlin, Campus Virchow-Klinikum and Campus Mitte

Augustenburger Platz 1

D-13353 Berlin, Germany

e-mail: susanne.koch@charite.de

Phone: (++49) 30-4505-651055

Fax: (++49) 30-4505-51909

Words: main text 3490, abstract 250

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) ≥ 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)[1] and critical illness polyneuropathy (CIP)[2,3], the primary cause of these Intensive Care Unit (ICU) acquired weaknesses remains unresolved.[4] ICU acquired weakness complicates recovery in critically ill patients and prolongs duration of mechanical ventilation and length of stay in ICU.[5,6] Some authors advise against differentiation of CIM and CIP, as differentiation is complicated and may not result in consequences.[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.[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.[11,12] Authors using this technique of direct muscle stimulation found myopathy to be more frequent in critically ill patients.[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).[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 1 Clinical characteristics of ICU-control, CIM- and CIM/CIP-patients

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

p-value [a] compares all three groups (Kruskal-Wallis-test / Fisher's exact test), whereas p-value[b] (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.

	Nerve	ICU – control (n=13)	CIM (n=16)	CIM/CIP (n=20)	p-value [a]	p-value [b]
neCMAP (mV)	Median	10.1± 4.3 (n=11)	6 ± 4.5 (n=11)	4.5 ± 2.9 (n=15)	0.003	0.51
	Peroneal	5.3 ± 3.7 (n=13)	2.3 ± 3.4 (n=15)	1 ± 1.2 (n=19)	0.003	0.32
	Tibial	11.8 ± 6.1 (n=13)	3.2 ± 4.1 (n=15)	3.7 ± 4.2 (n=13)	0.013	0.16
SNAP (µV)	Median	22.1 ± 7.9 (n=11)	17.3 ± 6.7 (n=11)	15.4 ± 7.6 (n=17)	0.058	0.4
	Sural	6.5 ± 3.4 (n=12)	12.8 ± 21.8 (n=15)	1.5 ± 2 (n=18)	<0.001	<0.001

p-value [a] compares all three groups (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. 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

	muscle	healthy volunteers (n=17)	ICU controls (n=13)	CIM (n=16)	CIM/CIP (n=20)	p-value [a]	p-value [b]
dm CMAP (mV) (concentric needle electrode) lower limit =3mV	Tib ant	8 ± 2.1 (n=8)	5.6 ± 1.8 (n=12)	2.2 ± 2.3 (n=15)	1.6 ± 1.9 (n=19)	<0.001	0.008
	Abd poll brev	9.3 ± 2.3 (n=6)	4.3 (n=2)	4.2 (n=2)	2.6 ± 5 (n=10)	0.136	0.006
dm CMAP (mV) (surface electrode) lower limit =0.6mV	Tib ant	2.8 ± 0.4 (n=17)	1.6 ± 0.5 (n=9)	0.3 ± 0.1 (n=9)	0.1 ± 0.1 (n=8)	0.010	0.139
	Abd poll brev	7.1 ± 5.3 (n=12)	4.5 ± 4.1 (n=5)	1.3 ± 1.7 (n=6)	0.7 ± 1.6 (n=6)	0.044	0.134
MFCV (m/s)	Tib ant	-	5.9 ± 1.6 (n=3)	5.2 ± 1.1 (n=8)	4.6 ± 1.1 (n=9)	0.454	0.335
ne/dmCMAP ratio	Tib ant	1.79 ± 1.02 (n=7)	2.2 ± 0.7 (n=9)	13.8 ± 14.6 (n=4)	4.9 ± 3.9 (n=9)	0.018	0.276
MUAP duration (ms)	Tib ant	-	11.2 ± 0.6 (n=8)	9.0 ± 2.6 (n=7)	6.9 ± 1.8 (n=10)	0.001	0.477
	Ext dig com	-	10 ± 1 (n=8)	6.3 ± 3.1 (n=9)	5.6 ± 1.1 (n=12)	0.001	0.246

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 occured 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

Univariate Cox' regression with time dependent covariates	Hazard Ratio[HR]	95%-CI[HR]	p
CIM and CIM/CIP	0.33	0.16 – 0.66	0.001
SOFA	1.05	0.95 – 1.17	0.34
SAPS-II	0.99	0.97 – 1.03	0.85
Multivariate Cox' regression with time dependent covariates (after backward selection)			
CIM and CIM/CIP	0.34	0.16 – 0.72	0.005
SOFA	1.05	0.89 – 1.25	0.5
SAPS-II	0.99	0.95 – 1.04	0.86

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 logisitical 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 $\pm$ 0.9mV, lower limit $\geq$ 3mV, n = 18; Lefaucheur et al., 2006: 9.61 $\pm$ 2.36mV, lower limit $\geq$ 4.88mV, n = 12 AND our data: 8.0 $\pm$ 2.1mV, lower limit $\geq$ 3mV, n = 8), *subdermal electrodes* (Trojaborg et al.,

2001: 4.5 ± 1.7mV, lower limit ≥ 1mV, n = 18), or *surface electrodes* (our data: 2.8 ± 0.4, lower limit ≥ 0.6mV, 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 ± 1,1m/s) are various. Interestingly, patients classified as ICU control showed a reduction of MFCV (5.9 ± 1.6m/s, n = 3) and dmCMAP amplitude (5.6 ± 1.8mV, 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.

Coexistance 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.

Acknowledgment

This study was supported by the Deutsche Forschungsgemeinschaft (KFO 192, WE 4368/ 1-1). Competing Interest: None declared.

The authors want to thank Prof. Dr. Werner Trojaborg for advice and assistance in direct muscle stimulation techniques and quantitative electromyography.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Group and co-owners or contracting owning societies (where published by the BMJ Group on their behalf), and its Licensees to permit this article (if accepted) to be published in Journal of Neurology, Neurosurgery and Psychiatry with practical Neurology and any other BMJ Group products and to exploit all subsidiary rights, as set out in our licence.

References

1 MacFarlane IA, Rosenthal FD. Severe myopathy after status asthmaticus. Lancet 1977;17:615.

2 Mertens-HG: Disseminated neuropathy following coma. On the differentation of so-called toxic polyneuropathy. Nervenarzt 1961;32:71-9.

3 Bolton CF, Gilbert J, Hahn AF, et al. Polyneuropathy in critically ill patients. J Neurol Neurosurg Psychiatry 1984;47:1223-31.

4 Schweickert WD, Hall J. ICU Acquired weakness. Chest 2007;131:1541–9.

5 De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit. JAMA 2002;288:2859–67.

6 Garnacho-Montero J, Madrazo Osuna J, Garcia Garmendia JL, Ortiz-Leyba C, Jimenez-Jimenez FJ, Barrero-Almodovar A, et al. Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients. Intensive Care Med 2001; 27:1288–96.

7 Bednarik J, Lukas Z, Vondracek P. Critical illness polyneuromyopathy: the electrophysiological components of a complex entity. Intensive Care Med 2003;29:1505-14.

8 Hermans G, Wilmer A, Meersseman W, et al. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. Am J Respir Crit Care Med 2007;175:480–9.

9 Tepper M, Rakic S, Haas JA, et al. Incidence and onset of critical illness polyneuropathy in patients with septic shock. Neth J Med 2000;56:211-4.

10 Tennilä A, Salmi T, Pettilä V, et al. Early signs of critical illness polyneuropathy in ICU patients with systemic inflammatory response syndrome or sepsis. Intensive Care Med 2000;August:1-5.

11 Trojaborg W, Weimer LF, Hays AP. Electrophysiologic studies in critical illness associated weakness: myopathy or neuropathy – a reappraisal. Clin Neurophysiol 2001;112:1586-93.

12 Lefaucheur JP, Nordine T, Rodrigues P, et al. Origin of ICU acquired paresis determined by direct muscle stimulation. J Neurol Neurosurg Psychiatry 2006;77:500-6.

13 Rich MM, Bird ShJ, Raps EC, et al. Direct muscle stimulation in acute quadriplegic myopathy. Muscle Nerve 1997,20:665-73.

14 Allen DC, Arunachalam R, Mills KR. Critical illness myopathy: Further evidence from muscle-fiber excitability studies of an acquired channelopathy. Muscle Nerve 2008;37:14-22.

15 Weber-Carstens S, Koch S, Spuler S, et al. Non-excitable muscle membrane predicts ICU-acquired paresis in mechanically ventilated, sedated patients. Crit Care Med 2009;37(9):2632-7

16 Rich MM, Bird ShJ, Raps EC, McCluskey LF, Teener JW. Direct muscle stimulation in acute quadriplegic myopathy. Muscle and Nerv 1997, 20: 665 673

17 Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS-II) based on a European/North American multicenter study. JAMA 1993;270:2957-63.

18 Deja M, Hommel M, Weber-Carstens S, et al. Evidence-based therapy of severe acute respiratory distress syndrome: an algorithm-guided approach. J Int Med Res 2008;36:211-21.

19 Dellinger RP, Carlet JM, Masur H, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32:858-73.

20 Vincent JL, Moreno R, Takala J, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the european society of intensive care medicine. Intensive Care Med 1996;22:707–10.

21 Ramsay MA, Savege TM, Simpson BR, et al. Controlled sedation with Alphaxalone - alphadolone. Br Med J 1974;2:656-9.

22 British Medical Research Council. Aids to the examination of the peripheral nervous system. Memorandum No. 45, London: Her Majesty's Stationary Office, 1976.

23 Trojaborg W. Quantitative electromyography in polymyositis: a reappraisal. Muscle Nerve 1990;13:964-71.

24 Buchthal F, Kamieniecka Z. The diagnostic yield of quantified electromyography and quantified muscle biopsy in neuromuscular disorders. Muscle Nerve 1982;24:801-7.

25 Rosenfalck P, Rosenfalck A. Electromyography, sensory and motor conduction: findings in normal subjects. Laboratory of clinical neurophysiology, Copenhagen: Rigshospitalet, 1975:1-49.

26 Leven B, Fasshauer K. Lesions of the peripheral nerves in Wilson's disease. Electrodiagnostic findings. Fortschr Neurol Psychiatr Grenzgeb. 1978;46:202-6.

27 Troni W, Cantello R, Rainero I: Conduction velocity along human muscle fibers in situ. Neurology 1983;33:1453-9.

28 Zwarts MJ. Evaluation of the estimation of muscle fiber conduction velocity. Surface versus needle method. Electroencephalogr Clin Neurophysiol 1989;73:544-8.

29 Rich MM, Tenner JW, Raps EC, et al. Muscle is electrically inexcitable in acute quadriplegic myopathy. Neurology 1996;46:731-6.

30 Z'Graggen WJ, Lin CSY, Howard RS, Beale RJ, Bostock H. Nerve excitalility changes in critical illness polyneuropathy. Brain 2006; 129: 2461-70

31 Zochodne DW, Bolton CF, Wells GA, et al. Critical illness polyneuropathy. A complication of sepsis and multiple organ failure. Brain 1987;110:819–42.

32 Latronico N, Bertolini G, Guarneri B, et al. Simplified electrophysiological evaluation of peripheral nerves in critically ill patients: the Italian multi centre CRMYNE study. Crit Care 2007;11(1):R11.

33 Rich MM, Pinter MJ. Crucial role of sodium channel fast inactivation in muscle fibre inexcitability in a rat model of critical illness myopathy. J Physiol 2003;547:555–66.

34 Filatov GN, Rich MM. Hyperpolarized shifts in the voltage dependence of fast inactivation of Na_v 1,4 und Na_v 1,5 in a rat model of critical illness myopathy. J Physiol 2004;559:813-20.

35 Haeseler G, Foadi N, Wiegand E, et al. Endotoxin reduces availability of voltage-gated human skeletal muscle sodium channels at depolarized membrane potentials. Crit Care Med 2008;36:1239-47.5

36 Cunningham JN, Carter NM, Rector FC, et al. Resting transmembrane potential difference of skeletal muscle in normal subjects and severely ill patients. J Clin Invest 1971;50:49-59.

37 Guarneri B, Bertolini G, Latronico N. Long-term outcome in patients with critical illness myopathy or neuropathy: The Italian multicentre CRIMYNE study. J Neurol Neurosurg Psychiatr 2008;79:838–41.

38 Latronico N. Neuromuscular alterations in the critically ill patient: critical illness myopathy, critical illness neuropathy, or both. Intensive Care Med 2003;29:1411–3.

39 Guth L, Kemerer VF, Samaras TA, et al. The roles of disuse and loss of neurotrophic function in denervation atrophy of skeletal muscle. Exp Neurol 1981;73:20-36.

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 $\geq$ 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.

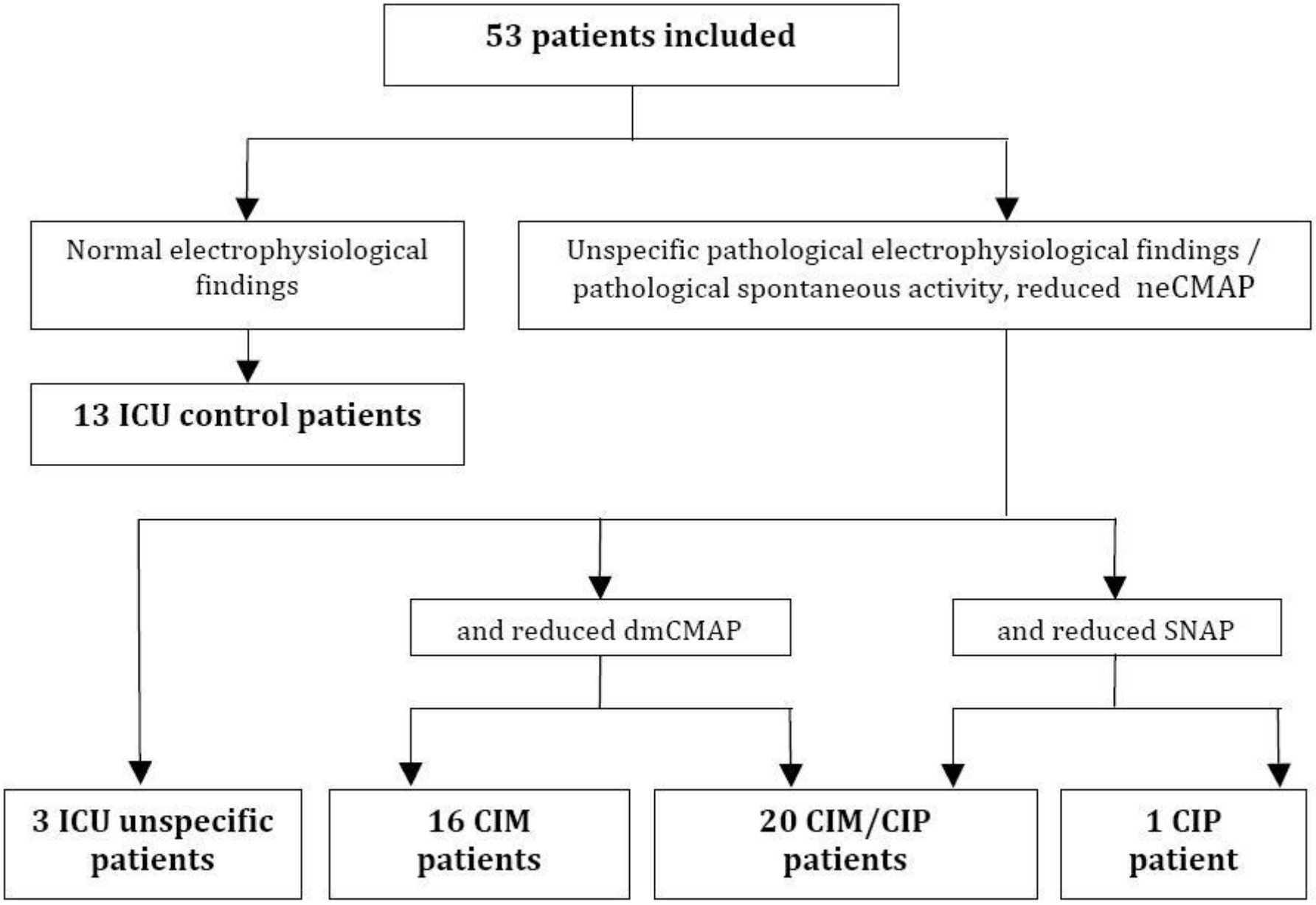
53 patients included
Normal electrophysiological findings
Unspecific pathological electrophysiological findings / pathological spontaneous activity, reduced neCMAP
13 ICU control patients
and reduced dmCMAP
and reduced SNAP
3 ICU unspecific patients
16 CIM patients
20 CIM/CIP patients
1 CIP patient

Figure 1

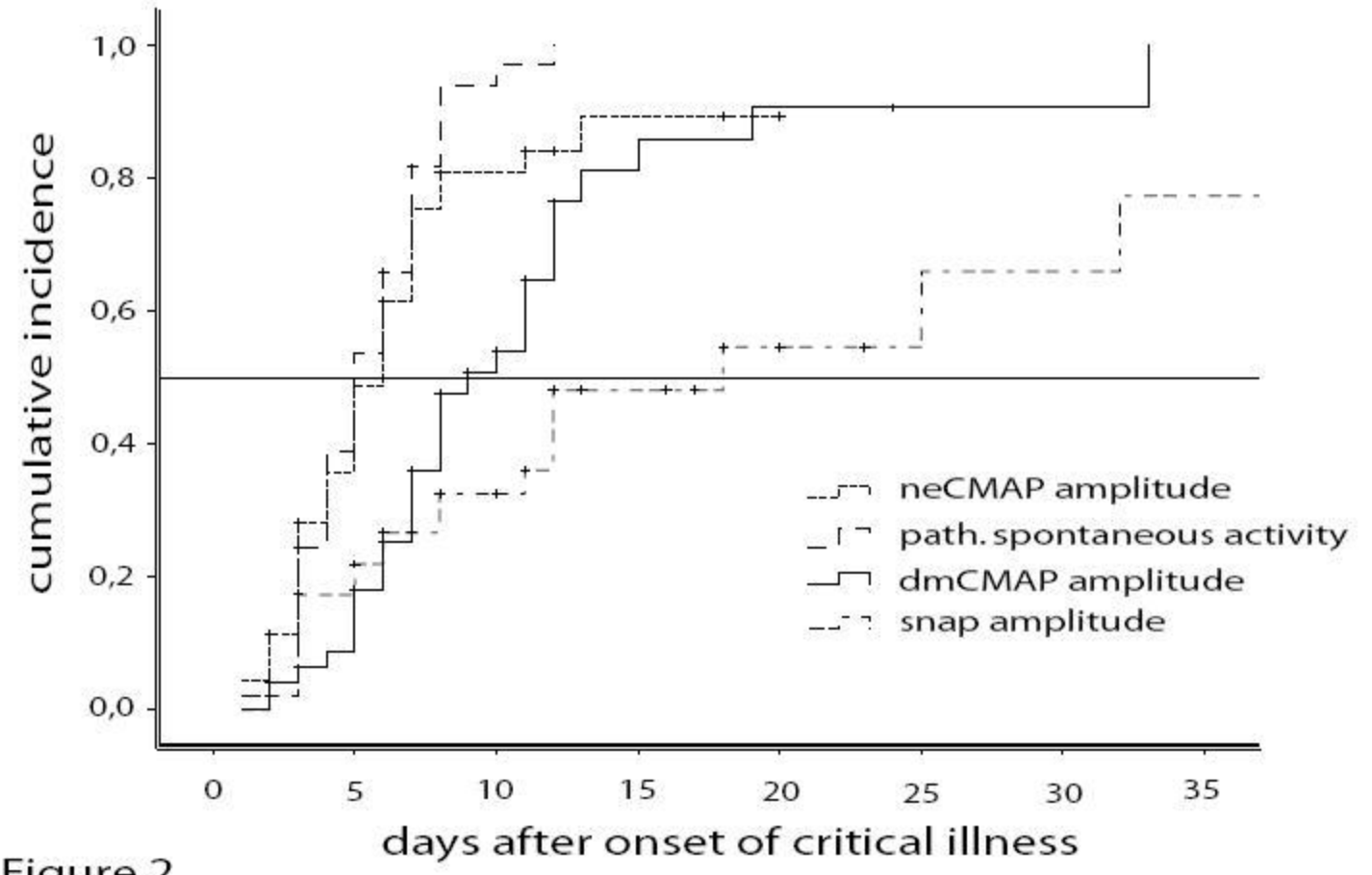
1,0
0,8
0,6
0,4
0,2
0,0
cumulative incidence
0
5
10
15
20
25
30
35
days after onset of critical illness
neCMAP amplitude
path. spontaneous activity
dmCMAP amplitude
snap amplitude

Figure 2

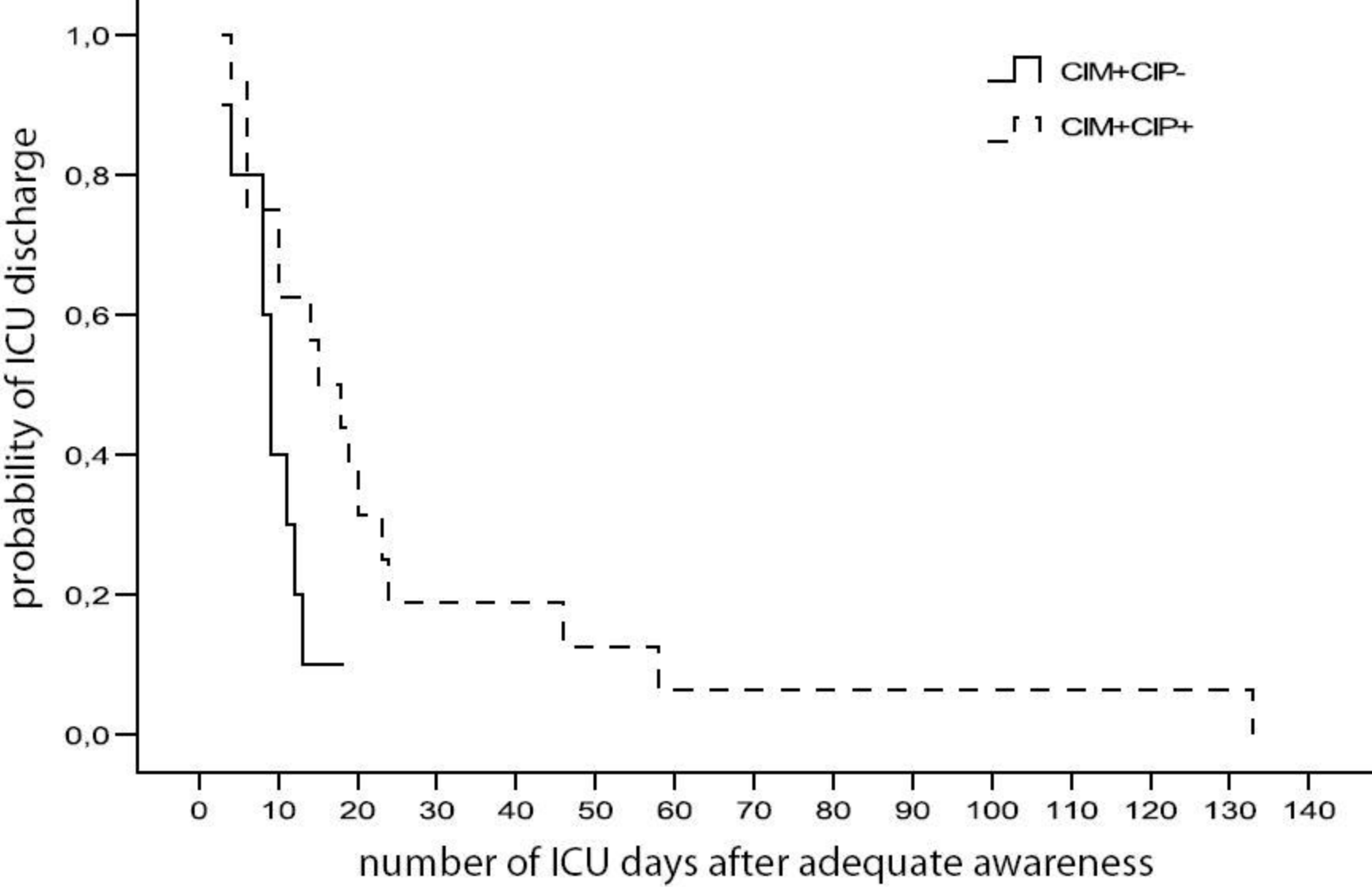
1,0
0,8
0,6
0,4
0,2
0,0
probability of ICU discharge
CIM+CIP-
CIM+CIP+
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
number of ICU days after adequate awareness

Figure 3

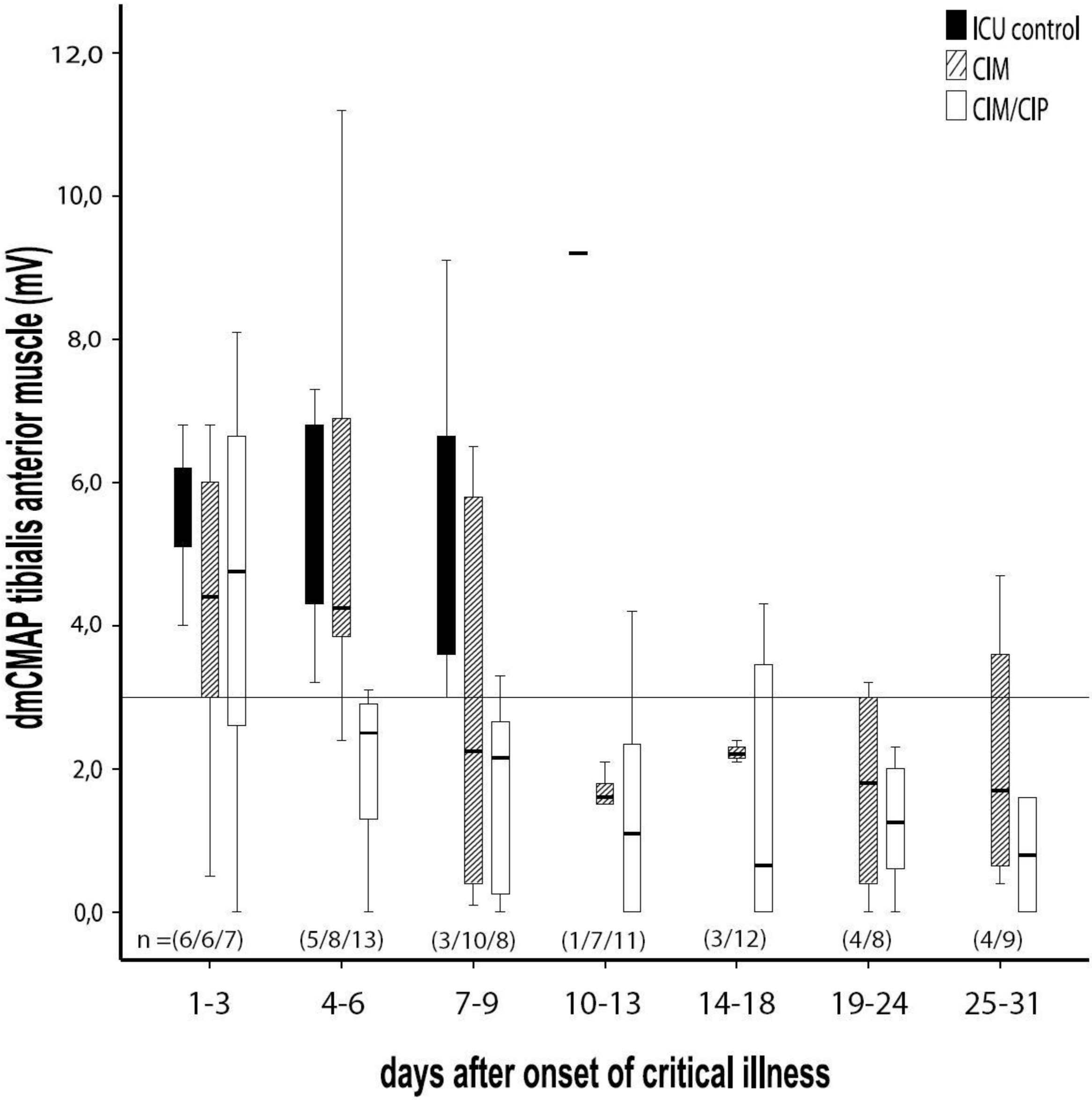
ICU control
CIM
CIM/CIP
dmCMAP tibialis anterior muscle (mV)
12,0
10,0
8,0
6,0
4,0
2,0
0,0
n =(6/6/7)
(5/8/13)
(3/10/8)
(1/7/11)
(3/12)
(4/8)
(4/9)
1-3
4-6
7-9
10-13
14-18
19-24
25-31
days after onset of critical illness

Figure 4a

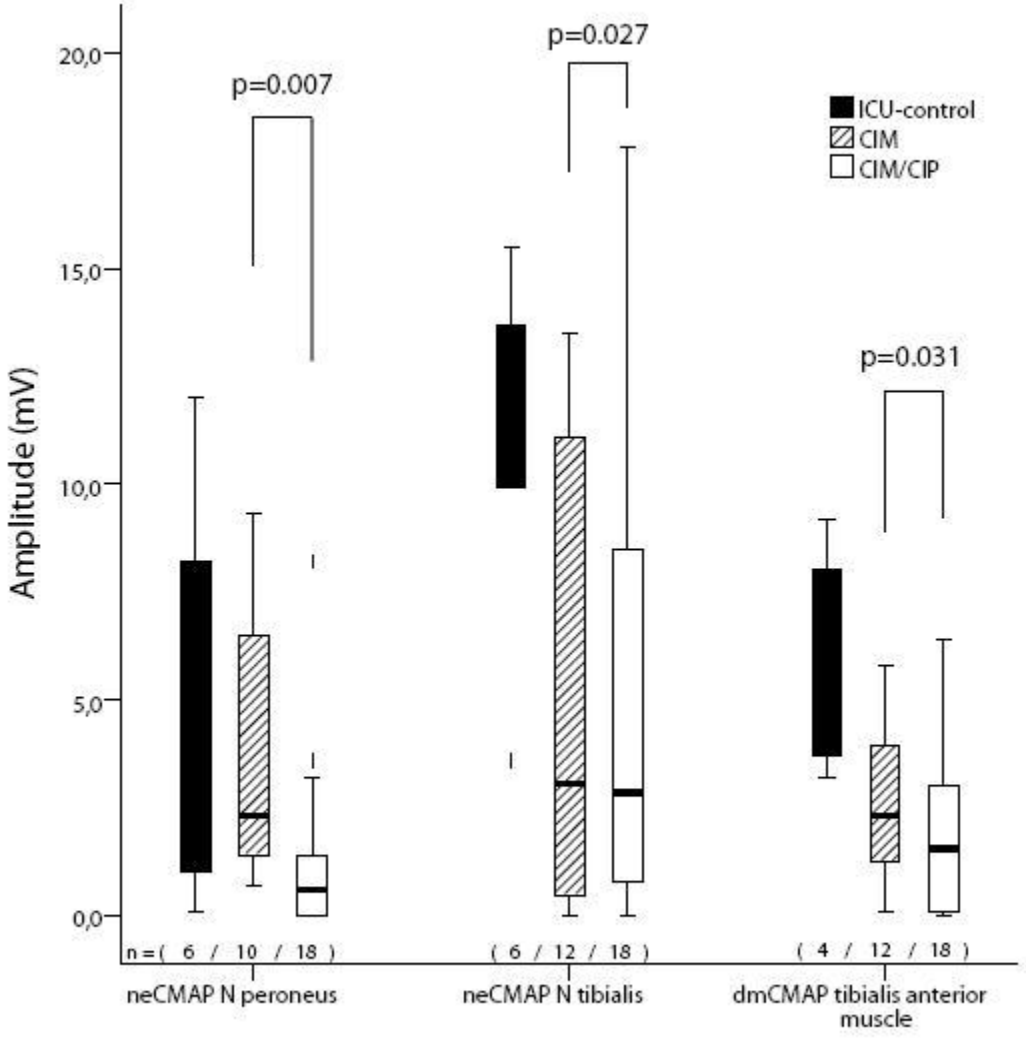
p=0.007
p=0.027
p=0.031
ICU-control
CIM
CIM/CIP
Amplitude (mV)
20,0
15,0
10,0
5,0
0,0
n = (6 / 10 / 18)
(6 / 12 / 18)
(4 / 12 / 18)
neCMAP N peroneus
neCMAP N tibialis
dmCMAP tibialis anterior muscle

Figure 4b