Intensive care unit-acquired weakness: early diagnosis, symptomatology and prognosis
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In this thesis three aspects of Intensive Care Unit – acquired weakness (ICU-AW) were investigated: early diagnosis of ICU-AW, non-motor signs and symptoms of ICU-AW and long-term impact of ICU-AW on mortality and physical functioning. In this chapter, the results from the studies on these three aspects are discussed and put into a broader perspective. Finally, an overview of current and future treatment strategies is given.

**EARLY ICU-ACQUIRED WEAKNESS DIAGNOSIS**

Diagnosing ICU-AW early after ICU admission may have several advantages. Accurate and important prognostic information is available early for patients, families and physicians. Early tracheostomy for the expected long duration of mechanical ventilation in patients with ICU-AW may be performed. Early rather than late tracheostomy may reduce the duration of mechanical ventilation and length of stay in the ICU. Abnormalities of muscle and nerve early during development of ICU-AW may be still reversible because these are caused by functional and not structural problems. Treating ICU-AW at this early stage may therefore be more effective. None of these potential advantages have been investigated and therefore it is important to test whether an early ICU-AW diagnosis really confers benefit to patients compared to the conventional and delayed approach. Ideally, this should be investigated using a diagnostic randomized clinical trial (RCT). In diagnostic RCTs, diagnostic strategies are compared by investigating effects of interventions, which are started based on the results of either diagnostic strategy. Only a few therapeutic studies in ICU-AW have been performed and no high quality evidence is available supporting any intervention. Therefore a diagnostic RCT is currently premature. Conversely, the ability to perform therapeutic studies will also depend on the availability of accurate (early) diagnostic methods.

Three diagnostic methods for an early ICU-AW diagnosis have been explored in this thesis: i.e. a clinical prediction model for ICU-AW (chapter 3), plasma neurofilament levels as a potential biomarker for ICU-AW (chapter 4) and electroneurography and electromyography (EMG) recordings as a diagnostic test for ICU-AW (chapter 5).

We constructed a prediction model using the highest lactate level, treatment with any aminoglycoside in the first two days of ICU admission and age (chapter 3). These predictors had the best discriminative performance for ICU-AW. Diagnostic accuracy of the prediction model was fair and performed better that the Acute Physiology and Chronic Health Evaluation (APACHE) IV score and Sequential Organ Failure Assessment (SOFA) score, two widely used ICU scoring systems for severity of illness and presence of organ failure that may also be used for prediction of ICU-AW. The model is therefore promising but needs validation in an external population. Plasma levels of neurofilaments, which are markers of axonal damage, were higher in patients with ICU-AW but levels did not peak before manual muscle strength assessment became possible and are therefore not a useful diagnostic biomarker (chapter 4). Of the different EMG recordings, we found good diagnostic accuracy for the peroneal compound motor action potential (CMAP) amplitudes and ulnar sensory nerve action potential (SNAP) amplitudes (chapter 5). Diagnostic accuracy of peroneal CMAP and sural SNAP amplitudes was only graded as good when based on cut-off values from critically ill patients with and without...
ICU-AW. The sample size was too small to determine externally valid ICU-based cut-off values and these should be established in a larger study.

When we compare our results to other studies, some interesting points can be mentioned. No other prediction models have been specifically developed for ICU-AW. Non-specific models that have been used to predict ICU-AW are the APACHE II score combined with the presence of systemic inflammatory response syndrome (SIRS) although diagnostic accuracy was not reported.7 In our study, the APACHE IV score had poor diagnostic accuracy (chapter 3). The maximal SOFA score or number of days with SIRS until 7 days after ICU admission may also be used to predict ICU-AW with fair diagnostic accuracy, but this does not allow for prediction early after admission.8 Diagnostic accuracy of other biomarkers has not been investigated. Creatine kinase (CK) has been measured in non-diagnostic studies and is probably not useful.9 One study assessing electrophysiological recordings showed good diagnostic accuracy for direct muscle stimulation (DMS) when assessed longitudinally.10 Diagnostic accuracy of DMS when assessed at one time point early after ICU admission is unknown. The validity of DMS has been questioned and DMS is technically more demanding than conventional EMG recordings11,12 Also in that study, diagnostic accuracy of peroneal CMAP and sural SNAP amplitudes was poor but these analyses were based on cut-off values from healthy controls.10

Several other methods might have early diagnostic potential. Abnormalities on muscle ultrasound have been found in ICU-AW and their diagnostic accuracy should be investigated.13 Ultrasound can also be used to assess peripheral nerves but this has not been investigated in ICU-AW.14 Another possibility is non-volitional strength measurements, where a nerve is stimulated and the subsequent force produced by the innervated muscles is recorded. Decreased force has been found in long-term critically ill patients but experience with this technique is limited to a few centers.17 Nerve and muscle excitability studies have shown abnormalities in patients with ICU-AW.18,19 Decreased nerve and muscle excitability is one of the first signs of ICU-AW and is thought to precede development of structural damage.4 Excitability studies, like threshold tracking or muscle velocity recovery cycles, may therefore be an interesting diagnostic option, although technically complex to perform. Finally, other plasma biomarkers may be investigated like carbonic anhydrase III, which is a marker for skeletal muscle damage.20 Muscle and skin biopsies are probably not useful for an early diagnosis because they are invasive and still normal during the early stages of ICU-AW.15,16

Based on the small number of available studies, a recommendation on which diagnostic method to use in the clinic for an early diagnosis of ICU-AW cannot be made. Even if several methods would be available, the choice for which diagnostic method to use will depend on the intended purpose in daily care. For example, when used for starting early rehabilitation, which may reduce ICU-AW6, sensitivity should be high and specificity is less relevant, due to the low risk nature of the intervention.21 Also, diagnostic tests may be combined in a triage flowchart.22 First, a simple test identifies high-risk patients. Next, a more accurate but less easy test is performed only in high-risk patients. A prediction model, identifying patients at high risk for developing ICU-AW, who are then examined with EMG, may be an interesting approach.
Non-motor signs and symptoms of ICU-acquired weakness

Paresis is the hallmark symptom of ICU-AW. Paresis may be the result of an underlying myopathy, i.e. critical illness myopathy (CIM), an underlying polyneuropathy, i.e. critical illness polyneuropathy (CIP) or an underlying combined neuromyopathy, called critical illness neuromyopathy (CINM). Detailed studies on the incidence of any of these disorders underlying ICU-AW are lacking but it is thought that CINM occurs most. As a consequence, symptoms in patients with ICU-AW may not be confined to motor symptoms alone but may also arise because of dysfunction of other parts of the peripheral nervous system.

We found that nearly all patients with ICU-AW have autonomic dysfunction, when assessed using heart rate variability (HRV; chapter 7). However, we found that patients without ICU-AW also frequently had autonomic dysfunction and that the presence of ICU-AW was not associated with HRV indices. Because HRV was influenced by confounders, like the heart rate or norepinephrine dose at time of assessment, a reliable conclusion on the relation between ICU-AW and autonomic dysfunction cannot be drawn from this study (chapter 7).

Some other studies also show that the autonomic nervous system is involved in patients with ICU-AW. Abnormal sympathetic skin responses were found of 5 patients with CIP. Axonal degeneration of the vagal nerve and sympathetic chain has been found post-mortem in one patient with CIP, although without overt clinical signs of autonomic dysfunction. In these studies, findings were not compared to ICU patients without ICU-AW. This is of importance as in the general ICU population, autonomic dysfunction is frequently found and associated with increased mortality. Besides originating in the peripheral nervous system, autonomic dysfunction may also be explained by changes in the autonomic centers in the brain and at the level of the effector organs. Thus, autonomic dysfunction may not be specifically related to ICU-AW.

To draw reliable conclusions on the relation between ICU-AW and autonomic dysfunction, further studies are needed. From our study (chapter 7) we conclude that, in the ICU, assessments other than heart rate variability should be used. Conventional autonomic function tests, like the valsalva maneuver or tilt-table testing, are not suitable in the ICU, as they need patient cooperation. The cold-face test and skin wrinkle test may be options, although confounders for these measurements in critically ill patients have not been investigated (chapter 6). Functional assessments may be supplemented by comprehensive post-mortem studies of the central and peripheral autonomic nervous system to better understand the underlying pathophysiology.

In our pilot study of 10 patients with ICU-AW, we found evidence of small nerve fiber damage in skin biopsies in all patients (chapter 8). This suggests that besides muscle, large motor and sensory fibers, small nerve fibers can also be involved in ICU-AW although we studied a subgroup of ICU-AW patients with a protracted course in the ICU and did not include a control group of ICU patients without ICU-AW.

Small nerve fiber damage in ICU-AW has not been investigated by others. In a cohort of 14 critically ill neurosurgical patients in coma, small nerve fiber damage was found all patients and occurred with or without electrophysiological signs of a large fiber neuropathy. Because of severe central nervous system damage at the moment of skin biopsy, strength and sensory
examinations could only be performed reliably at follow-up (ranging between 8-13 months after ICU discharge) in six patients who survived. Of these patients, three patients had symptoms suggestive of a small fiber neuropathy, like burning pain. Motor examinations revealed a spastic hemiparesis in two patients and normal findings in one. The specific cohort of neurosurgical patients and the long duration between biopsy and clinical assessment makes it difficult to extrapolate these findings to other critically ill patients.

Small nerve fiber involvement in ICU-AW may explain sensory symptoms, like pain and decreased sensation, seen in some patients. Existing studies on sensory symptoms in ICU-AW are small. Therefore, more detailed information on the incidence, characteristics and impact of sensory symptoms in patients with ICU-AW is needed. Small nerve fiber involvement in ICU-AW may also partly explain autonomic dysfunction. Within the ICU-AW spectrum, it is unknown if small nerve fiber damage occurs as part of a mixed large and small fiber polyneuropathy, seen in CIP or CINM, or in isolation, as part of pure small fiber neuropathy together with CIM. In the before mentioned cohort study of critically ill neurosurgical patients, suggestions for both possibilities were found. In this study, two patients with small nerve fiber damage had normal EMG findings suggesting that small fiber damage may also occur without ICU-AW. A large study incorporating detailed clinical examinations of muscle strength and sensation, electrophysiological recordings, skin and muscle biopsies in patients with and without ICU-AW may provide a full overview of the neuromuscular abnormalities in the ICU-AW spectrum.

LONG-TERM IMPACT OF ICU-AW

During ICU admission, ICU-AW is associated with various adverse outcomes: increased duration of mechanical ventilation, increased length of stay in the ICU and increased ICU-mortality. After ICU discharge, we found that ICU-AW is independently associated with increased mortality up to 6 months after ICU discharge (chapter 9). Most deaths occurred during hospital admission. After hospital discharge, mortality did not differ between patients with or without ICU-AW, although this finding may be the result of a small sample size.

Increased in-hospital mortality in patients with ICU-AW has also been reported by others. Mortality after hospital discharge has not been investigated before. Increased mortality in patients with ICU-AW may be explained in part by the underlying severity of illness. However, in our and other studies, an effect of ICU-AW independent of severity of illness was observed. ICU-AW specific explanations for an increase in mortality have been sparsely studied. One study reported infections to be the cause of death in 61% of patients with ICU-AW. More research is needed on the causes of death to learn whether they can be prevented. Possible other ICU-AW specific explanations for mortality may be the risk of thrombo-embolic events caused by decreased ambulation. A potential confounding factor may be that patients with ICU-AW are often severely ill patients who die more often due to restrictions in care. This self-fulfilling prophecy needs to be addressed in future studies.

We found lower physical functioning scores in survivors with ICU-AW (chapter 9). More importantly we found that ICU-AW was associated with clinically relevant lower physical functioning scores, when corrected for possible confounders (chapter 9). Previous studies
have also reported poor physical functioning in survivors with ICU-AW but because proper control groups were not studied or effects of confounders were not corrected for, the magnitude of the attributable effect was not known.

The underlying mechanisms leading to long-term decreased physical functioning in ICU-AW have not been investigated. Patients with CIP or CINM have slower or incomplete recovery compared to patients with CIM. This could be because of the slow and sometimes incomplete process of axonal regeneration. However, physical impairments can continue after weakness has resolved. This may be explained by reduced muscle endurance, when muscle quantity and quality have returned to normal. Furthermore, ICU-AW and other factors that influence long-term outcome, like ICU-acquired delirium, frequently co-occur in patients and may thus constitute a “double hit” for the surviving patient. Future long-term outcome studies should investigate these factors together with ICU-AW. Moreover, these long-term effects do not only affect patients; also among caregivers increased incidence of post-traumatic stress disorders and depression have been reported.

ICU-AW may have significant economic consequences. No studies have investigated this directly so the impact can only be estimated. In the Netherlands, an ICU admission day costs approximately €1.200 more than a hospital admission day. For an average critically ill patient admitted with sepsis, the costs for increased length of stay in the ICU, attributable to ICU-AW, can be estimated at €6.000 per admission. Longer duration of hospital admission in patients with ICU-AW also increases expenditures. During the five years after ICU discharge, one study found that health care use is increased in critical illness survivors. This study also found that, in a population that was working before ICU admission, 77% of the survivors had returned to work, five years after ICU discharge.

**THERAPY FOR ICU-AW**

Improvements in early diagnostic methods and understanding of the impact of ICU-AW should provide the tools to enroll patients at the appropriate time in clinical trials testing the effect of interventions on outcomes relevant to patients with ICU-AW. Three preventive interventions for ICU-AW have been investigated. The grade of evidence supporting an effect on ICU-AW for any of the investigated interventions is moderate at best and therefore none can currently be recommend for standard clinical care.

In the general ICU population, an early intensive rehabilitation program combined with daily interruption of sedation was safe and improved functional outcome; ICU-AW was not the primary outcome of this RCT. In patients in whom muscle strength could be assessed, the number of patients with ICU-AW at hospital discharge in intervention group was lower than in the control group (16/41 in the intervention group vs. 26/41 in the control group; relative risk 0.62 95% CI 0.39 to 0.96). In the full intention-to-treat analysis the effect was not statistically significant. A possible limitation of intensive rehabilitation may be that not all patients with

*: based on the predicted difference in length of stay for patients with or without ICU-AW (confounders: age 60, unplanned admission and sepsis, APACHE IV score 75, maximal SOFA score 10). Absolute predicted difference is 15 vs. 10 days. Population from chapter 3.
ICU-AW possess rehabilitation potential. For example, with widespread axonal degeneration of peripheral nerves, active rehabilitation may not be possible. Also, excessive exercise may impede recovery, as has been described in some other neuromuscular disorders. A new and larger RCT is needed to test the effect of an early intensive rehabilitation program not only on prevention of ICU-AW but also on the course of ICU-AW. Using the differences observed in the intention-to-treat population for a power calculation, 120 patients per experimental arm need to be included.

In strict glucose control (SGC), glucose levels are strictly kept between standardized levels, thereby avoiding the detrimental effects of hypo- and hyperglycemia. A meta-analysis of two RCTs found that implementation of SGC was associated with a decrease in ICU-AW. In these RCTs, ICU-AW was not diagnosed with muscle strength assessment but using abnormal spontaneous activity on needle myography. Therefore, the exact effect of strict glycemic control on the clinically relevant outcome of muscle strength is unknown. The safety of SGC in critically ill patients has been questioned and nowadays careful regulation of glucose is advised but at higher levels than the original two RCTs.

Electrical muscle stimulation (EMS) is a technique in which muscle contractions are evoked using transcutaneous electrical stimulation. It potentially enables training of muscles in patients who cannot contribute actively themselves. EMS may prevent decrease in muscle strength and mass in critically ill patients, although conflicting results from small and heterogeneous studies were found in a systematic review. In a subgroup of severely ill patients, who have the highest risk of developing ICU-AW, no effect on muscle mass was observed. This could be explained because inexcitability, a part of ICU-AW pathophysiology, may render the muscle partially insensitive to EMS. If this limitation is confirmed in larger studies, EMS may not be a relevant preventive option for ICU-AW.

NEW THERAPEUTIC OPTIONS

New therapeutic options may come from pharmacological interventions. Administration of immunoglobulin reduced electrophysiological abnormalities in animals but a clinical RCT did not find an effect. Systemic inflammation is probably the main risk factor for development of ICU-AW, but our understanding of the exact underlying pathophysiology is poor. As a consequence, a plethora of different drugs have been investigated in ICU-AW animals models, like melatonin, oxytocin, levetiracetam, indomethacin and leupeptin. Without a proper understanding of how and why these drugs exactly work in ICU-AW, translation of these results to clinical studies is premature. Furthermore, none of the existing animal studies investigated muscle strength, although this is the hallmark symptom in patients. A new animal model is therefore the first crucial step.

Current care practices need to be critically evaluated to identify iatrogenic causes for ICU-AW. Feeding strategies may influence development of ICU-AW. Delayed parenteral feeding, compared to early full parenteral feeding, reduced the incidence of ICU-AW in one RCT. Impaired autophagy in muscle, a process of removal of damaged cellular parts through lysosomes, was found in the early full parenteral feeding arm and the authors speculated that this mechanism impairs muscle function and leads to ICU-AW. Medication, like corticosteroids,
neuromuscular blocking agents and aminoglycosides, may also play a role in development of ICU-AW, although the strengths of these associations are conflicting.\textsuperscript{57–59} This may be because all these drugs have been studied individually, while in critically ill patients these medications are frequently co-administered. When combined, side effects of individual drugs may be enhanced. For example, aminoglycosides potentiate the effects of rocuronium on the neuromuscular junction.\textsuperscript{60} Another explanation may be that studies looked at use or dosage of medications without investigating serum levels. Pharmacokinetics can vary widely between critically ill patients and therefore use or dosage may be an inadequate representation of actual exposure.\textsuperscript{61}

**CONCLUSION**

To decrease the burden of ICU-AW, several steps are needed. A clinically relevant animal model is needed to increase knowledge on pathophysiology and provide targets for possible interventions. Concurrently, diagnostic studies need to further investigate existing methods for an early ICU-AW diagnosis and identify new strategies. Particularly, external validity of the prediction model as well as ICU-based cut-off values for conventional EMG recordings need to be prospectively investigated. The added clinical benefit of an early ICU-AW strategy should be investigated, when therapeutic options supported by high-grade evidence are available. Large observational cohort studies should be undertaken to study determinants for long-term physical functional outcome and mortality, the incidence and impact of non-motor signs and symptoms and to identify additional risk factors and possible iatrogenic causes for ICU-AW.

**REFERENCES**

General Discussion


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