Intensive care unit-acquired weakness: early diagnosis, symptomatology and prognosis
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SUMMARY
In this thesis three aspects of Intensive Care Unit – acquired weakness (ICU-AW) were investigated: an 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. Here, the results from the studies on these three aspects are summarized.

Part I bundles studies investigating an early diagnosis of ICU-AW. Chapter 2 describes clinical examination using manual muscle strength assessment, the current diagnostic method according to expert consensus. To reliably perform muscle strength assessment an awake and attentive patient is needed. However, early after ICU admission many patients are sedated or suffer from delirium and this makes muscle strength assessment impossible or unreliable, thereby causing a diagnostic delay. This delay is unwanted because important prognostic information is withheld from families and physicians. Also, early initiation of future treatments may be more effective as abnormalities in the early stages of ICU-AW can still be reversible.

Three different diagnostic methods were investigated. In chapter 3 a prediction model was developed based on previously identified risk factors for ICU-AW. Patients who were mechanically ventilated for two or more days were included in this prospective cohort study. Development of ICU-AW was assessed with manual strength assessment when patients were awake and attentive. A literature review was done to determine all previously identified risk factors. Risk factors were translated into clinically usable predictors. Predictors were exclusively based on information available in the first two days of ICU admission so to enable early prediction. The best discriminating predictors were selected from the pool of predictors using a bootstrapped backward selection process followed by additional selection based on model fit. The highest lactate level and aminoglycoside treatment in the first two days after ICU admission and age were selected for the prediction model. After internal validation, the prediction model showed fair diagnostic accuracy. Diagnostic accuracy of our prediction model was better than previously proposed scoring systems. External validation is needed.

In chapter 4 the diagnostic accuracy of neurofilaments levels in plasma, a biomarker for axonal damage, was investigated. All non-elective and non-neurological admissions were prospectively included at ICU admission. Plasma was collected daily for the entire admission and neurofilament levels were measured using ELISA. Development of ICU-AW was assessed with manual strength assessment when patients were awake and attentive. Peak neurofilament levels during admission were higher in patients with ICU-AW. However, in most patients, neurofilament levels did not peak before muscle strength assessment became possible. The highest neurofilament levels before muscle strength assessment was possible could not discriminate between ICU-AW and no ICU-AW. Therefore, neurofilaments are probably not useful to establish an early diagnosis of ICU-AW.

In chapter 5 feasibility and diagnostic accuracy of early electrophysiological recordings were investigated. Patients mechanically ventilated for two days and sedated at the time of enrollment were prospectively included. Nerve conduction studies of the ulnar, peroneal and sural nerve were performed and, when coagulation disorders were absent, needle myography of the dorsal interossei I/II, deltoid and tibialis anterior muscles. Development of ICU-AW was assessed with manual strength assessment when patients were awake and attentive. Feasibility
was low for myography, mostly because of coagulation disorders, and for nerve conduction
studies of the sural nerve, mostly because of insufficient technical quality. For nerve conduction
studies of the ulnar and peroneal nerve acceptable feasibility was found. However, diagnostic
accuracy was low when based on cut-off values from healthy controls. When based on cut-off
values that were obtained by comparing patients with and without ICU-AW, good diagnostic
accuracy was found for the compound muscle action potential (CMAP) of the peroneal nerve
and for the sensory action potential (SNAP) of the ulnar nerve. These cut-off values should be
established in a new and larger study.

**Part II** bundles studies investigating non-motor signs and symptoms of ICU-AW. **Chapters 6**
and 7 focus on autonomic dysfunction. Conventional autonomic function tests are difficult
or impossible to perform in critically ill patients. As an alternative, heart rate variability has
been used as a relatively simple method to assess autonomic function in critically ill patients.
In chapter 6, we investigated safety and feasibility of two other simple methods to measure
autonomic function, i.e. the skin wrinkle test and the cold face test, in critically ill patients
together with heart rate variability. The skin wrinkle test and cold face test were both safe
and feasible but not as practical as measuring heart rate variability. Therefore, in chapter 7,
we assessed heart rate variability longitudinally in a prospectively collected cohort of non-
elective and non-neurological ICU admissions. Development of ICU-AW was assessed with
manual strength assessment when patients were awake and attentive. Heart rate variability was
abnormal in patients with ICU-AW but also in patients without ICU-AW. Moreover, heart rate
variability was influenced by several confounders, like heart rate or norepinephrine dosage at
the moment of measurement. Other autonomic function test should be used to further explore
if autonomic dysfunction truly occurs in patients with ICU-AW and if autonomic dysfunction is
associated with ICU-AW.

In chapter 8, we investigated the occurrence of small nerve fiber damage in patients
with ICU-AW. Some patients with ICU-AW develop sensory symptoms, which may be related
to large sensory nerve fiber dysfunction but could also result from small nerve damage. In a
 prospectively collected pilot cohort of ten patients with ICU-AW, intra-epidermal nerve fiber
density was measured in skin biopsies taken at least 20 days after onset of critical illness. All
patients had abnormally reduced intra-epidermal nerve fiber densities. This finding needs
replication in a larger cohort of patients, including also patients without ICU-AW.

**Part III** contains chapter 9 in which we studied the impact of ICU-AW on mortality and physical
functioning at six months after ICU discharge. Previous studies have suggested that ICU-AW
is associated with long-term mortality and morbidity and failed to include proper controls
or control for the influence of confounders. Patients mechanically ventilated for two days or
more were prospectively included and, when patients were awake and attentive, development
of ICU-AW was assessed with manual strength assessment. Physical functioning was assessed
using the physical functioning domain score of the Short-Form Health Survey (SF-36). ICU-AW
was independently associated with increased post-ICU mortality and a clinically relevant
reduction in physical functioning in survivors at six months after ICU discharge.