

Institutionen för Fysiologi och Farmakologi
Sektionen för Anestesi och Intensivvård

Muscle function in the critically ill – clinical and experimental investigations

AKADEMISK AVHANDLING

som för avläggande av doktorsexamen i medicinsk vetenskap vid
Karolinska Institutet offentligen försvaras i Nanna Svartz
föreläsningssal, Karolinska Universitetssjukhuset Solna

Fredagen den 9 september 2011 kl 09.00

av

Karsten Ahlbeck

Leg. Läkare

Huvudhandledare:

Docent Peter Radell
Karolinska Institutet
Institutionen för Fysiologi och Farmakologi

Handledare:

Professor Lars I Eriksson
Karolinska institutet
Institutionen för Fysiologi och Farmakologi

Docent Tor Ansved
Karolinska Institutet
Institutionen för Neurovetenskap

Fakultetsopponent:

Professor Klaus Olkkola
Kliniken för anestesiologi, intensivvård, akutvård
och smärtbehandling
Åbo Universitet och
Åbo Universitetscentralsjukhus
Finland

Betygsnämnd:

Docent Anna Krook
Karolinska Institutet
Institutionen för Fysiologi och Farmakologi

Docent Lars Hyllienmark
Karolinska Institutet
Institutionen för Neurovetenskap

Universitetslektor Sören Berg
Institutionen för Medicin och Hälsa
Hälsouniversitetet Linköping

ABSTRACT

It is common that critically ill patients develop muscle weakness in the intensive care unit (ICU), not only delaying mobilisation and increasing the risk of co-morbidities, but also prolonging rehabilitation after hospital care. The aim of this thesis was to describe the diagnosis, time course and possible risk factors for this weakness.

When specific diseases such as CNS lesions, intoxication or other nerve and muscle disorders have been excluded in the ICU, a "critical illness polyneuropathy and myopathy" (CIPNM) should be considered. The pathology behind this entity is unclear; among possible etiologic factors sepsis, corticosteroids and neuromuscular blocking agents (NMBAs) have been suggested.

CIPNM consists of a nerve pathology (neuropathy) and/or a muscle pathology (myopathy) and is diagnosed by a clinical assessment in combination with neurophysiological examination. The latter can be cumbersome due to the challenging environment in the ICU and is in itself not a definitive method of differentiating between a polyneuropathy and a myopathy.

We demonstrate a rapid method of electrophoresis, using an ultra-thin gel to evaluate the myosin to actin (M/A) ratio as a means of diagnosing critical illness myopathy (CIM). Using this diagnostic tool, there was a significant difference in M/A ratio between the patients having CIM, a control group, and patients having axonal neuropathies.

To evaluate the prevalence of CIPNM and the temporal pattern of its two major components critical illness polyneuropathy (CIP) and CIM, a prospective study was conducted including ICU patients who had been mechanically ventilated for at least 72 hours. The eventual prevalence of CIPNM was investigated, including neurophysiological and clinical examination. Muscle biopsies were obtained, in order to study the myosin to actin ratio and mitochondrial function. All septic patients, who were also receiving corticosteroid treatment, had a CIPNM diagnosis, whereas none of the non-septic patients fulfilled the necessary criteria. As a marker of oxidative stress, mitochondrial superoxide dismutase was increased in all patients, with a marked elevation in the CIPNM group.

To examine possible predisposing risk factors and mechanisms behind CIPNM in an experimental porcine ICU model over 5 days, groups were separated by interventions including corticosteroids, NMBAs and endotoxin, during mechanical ventilation. No group had a pathologic M/A ratio. All groups had significant changes in compound muscle action potential amplitude, including the inactivity/mechanical ventilation only group. The groups including corticosteroid treatment, endotoxin and the combination of all interventions had decreased muscle specific force and mitochondrial complex I activity, which were not seen in the mechanical ventilation group.

In conclusion, this thesis demonstrates an alternative method of diagnosing a critical illness myopathy, which could prove to be both time-efficient and reliable. In ICU patients there was a high prevalence of CIPNM in patients mechanically ventilated for more than 72 hours. An experimental model showed both decreased specific muscle force and mitochondrial complex I activity in intervention groups receiving corticosteroids, endotoxin or a combination, for both respiratory and non-respiratory muscles.

Key words: myopathy, polyneuropathy, critical illness, myosin to actin ratio, single muscle fibre force, mitochondrial dysfunction