Acute Quadriplegic Myopathy and myosin loss in ICU patients: Underlying mechanisms, improved diagnostics and a specific intervention strategy

L. Larsson,[1,3] J. Ochala,[1] V. Banduseela,[1] A-M. Gustafsson,[1] P. Radell,[2] L.I. Eriksson[2] and B. Dworkin,[1]
[1]Department of Clinical Neurophysiology, Uppsala University, Sweden, [2]Dept of Anaesthesia and Intensive Care, Karolinska Institute, Sweden and [3]Department of Neuroscience and Center for Development and Health Genetics, Penn State University, Pennsylvania, U.S.A. (Introduced by G.S. Lynch)

Severe muscle wasting and impaired muscle function accompany critical illness in intensive care unit (ICU) patients with negative consequences for recovery from primary disease and weaning from the respirator. While ICU outcome has traditionally focused simply on survival, modern critical care also addresses post-ICU complications and quality of life. Several recent studies show unambiguously that neuromuscular dysfunction, resulting in muscle wasting and weakness, is the most persistent and debilitating of problems for survivors from the ICU for as long as two years after hospital discharge (Herridge *et al*., 2003; Cheung *et al*., 2006). There is accordingly a significant need for more research focused on the mechanisms underlying the muscle wasting and weakness in ICU patients. Primary disease, sepsis and multiorgan failure undoubtedly contribute to the impaired muscle function, but there is heterogeneity of underlying disease and pharmacological treatment among patients with similar outcomes. Thus, it is highly likely that the common components of ICU treatment *per se*, such as bed rest, muscle unloading, mechanical ventilation, neuromuscular block, and corticosteroids are directly involved in the progressive impairment of muscle function during long-term ICU treatment.

Acute Quadriplegic Myopathy (AQM) is considered a consequence of modern treatment in anesthesiology and intensive care. The first AQM case report was published three decades ago by MacFarlane and Rosenthal (1977). Patients with AQM are characterized by weakness/paralysis and preferential myosin losses in spinal nerve innervated muscles with craniofacial muscles being spared or less affected, and intact cognitive and sensory function. Prognosis is typically good if the patient survives the primary disease, but full or near full recovery may take as long as 10-12 months. Besides AQM, this disease has been given a number of different descriptive titles, such as critical illness myopathy, thick filament myosin myopathy, acute myopathy in severe asthma, and myopathy of intensive care. While AQM was initially thought to be a rare event, we now know that neuromuscular dysfunction is found in up to 30% of the general ICU population and 70-80% of certain sub-groups. This potentially lethal condition prolongs the recovery of critical care patients, thereby increasing the median ICU treatment costs three-fold per patient. Additional substantial costs are associated with the subsequent extended rehabilitation requirements and drastically impaired quality of life.

The understanding of basic mechanisms underlying AQM in the clinical setting is poor, in part due to the fact that the generalized muscle weakness is complicated by different underlying disease, polypharmacy, age, gender, and collection of muscle samples several weeks after admission to the ICU. There is, accordingly, compelling need for experimental animal models mimicking the ICU conditions. In an attempt to mimic the ICU condition, we have used novel large (porcine) and small (rodent) experimental ICU models in time resolved studies (hours to 3 weeks) in parallel with clinical studies in ICU patients. Specific interest is focused on regulation of myofibrillar protein synthesis and degradation at the gene level, protein expression at the muscle fibre level, and regulation of muscle contraction at the single muscle fibre level. In addition, different methods for improving monitoring and diagnosis are presently being evaluated in the clinical studies and specific intervention strategies are tested in the rodent ICU model. Preliminary results demonstrate specific pathways controlling protein synthesis/degradation and a positive effect of mechanical loading on muscle structure and function has been observed in pharmacologically paralysed limb muscles.

Cheung, A.M., Tansey, C.M., Tomlinson, G., Diaz-Granados, N., Matte, A., Barr, A., Mehta, S., Mazer, C.D., Guest, C.B., Stewart, T.E., Al-Saidi, F., Cooper, A.B., Cook, D., Slutsky, A.S. & Herridge, M.S. (2006). *American Journal of Respiratory and Critical Care Medicine*, **174**, 538-544.

Herridge, M.S., Cheung, A.M., Tansey, C.M., Matte-Martyn, A., Diaz-Granados, N., Al-Saidi, F., Cooper, A.B., Guest, C.B., Mazer, C.D., Mehta, S., Stewart, T.E., Barr, A., Cook, D. & Slutsky, A.S. (2003). *New England Journal of Medicine*, **348**, 683-693.

MacFarlane, I.A. & Rosenthal, F.D. (1977). *Lancet*, **2**, 615.

Supported by the Swedish Research Council and the Association Française contre les Myopathies.