Commentary

Early goal directed mobility in the ICU: 'something in the way you move'

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In the March issue of Critical Care Medicine, Hodgson and colleagues from the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group, published a multicenter pilot randomized controlled trial (RCT) conducted across international ICUs to evaluate the feasibility of implementing early goal directed mobility (EGDM) to achieve active exercises early during the ICU stay using a mobility team (1). Early mobilization of critically ill patients is a candidate intervention to reduce the incidence and severity of ICU acquired weakness (ICUAW) and improve outcomes, including reduced duration of mechanical ventilation, shorter ICU length of stay (LOS), improved long-term functional independence, and possibly reduced mortality (2,3). A total of 391 patients admitted to ICUs in Australia and New Zealand were screened between September 2013 and October 2014, and 50 patients met inclusion criteria for trial enrollment (~13%). Patients were randomly assigned to a program of physiotherapist-directed active physical exercises EGDM beginning on the day of enrolment (intervention, 29 patients) or to standard care with physiotherapy delivered as ordered by the primary care team (control, 21 patients). The primary goal of the study was to test feasibility and separation in a complex intervention delivered early during the ICU stay. The authors found that EGDM could be safely delivered within 3 days after intubation and mechanical ventilation and there was separation in the highest level of activity achieved during the ICU stay and the time spent exercising between the intervention group and controls.

Over the past 10 years, multiple relatively small, single center studies, have attempted to demonstrate (with modest success) that early mobilization and rehabilitation of critically ill patients may help prevent or mitigate the sequelae of bed rest and improve outcomes in critically ill patients (3). In addition, quality improvement projects have demonstrated that early mobilization and rehabilitation is safe and feasible in critically ill patients, with potential benefits including improved physical functioning and decreased duration of mechanical ventilation, intensive care and hospital stay (4-7). The study from the Early Activity and Mobilization Study Investigators extends these observations to an international multicenter level. The cumulative evidence from these multiple studies point to a signal that favors benefit; but whether early mobility improves outcomes by reducing ICU related iatrogenicity (improvement in general medical care), or whether it acts on muscle-specific pathways that prevent, limit or reduce the incidence and/or severity of ICU acquired muscle dysfunction remains to be determined.

There is the potential for direct muscle effect due to mobilization and direct stimulation of muscle signaling associated with activity *vs.* bedrest, although this stimulus may be insufficient to counteract the predominant proteolytic stimuli ramped up in the critically ill patient. Discerning improvements in the process of care from the biological effects of exercise on muscle injury and repair is a challenge. For example, there is little doubt that when sedation is adjusted to facilitate exercise at the highest

level of activity possible, even if sedation practices are not protocolized, the overall result is a reduction in sedation which *per se* improves outcomes (8). In parallel there may also be a direct pharmacologic effect of sedatives on muscle growth and repair capacity, for example, Diazepam inhibits myoblast fusion and expression of muscle specific protein synthesis (9)—although this may have a very minimal effect on muscle loss relative to the impact of prolonged bed rest. Accordingly, limiting or reducing the intensity of 'critical care' may be a desirable outcome (irrespective of its direct effect on muscle specific pathways) and the cumulative contribution(s) afforded by (early) changes in the process of care should not be underestimated or undermined, but need to be understood and quantified so that future interventions can be designed to target specific modifiable factors that impact outcomes in ICU survivors and ICUAW.

It is also important that we be mindful that early mobilization may in fact favour those patients that are destined to do well, irrespective of the time to initiation and dose of therapy (intensity and time of mobility program). Recently, the Canadian Critical Care Trials group published the first phase of the RECOVER program showing the 7-day Functional Independence Measure (FIM) is an independent risk factor for 1-year ICU mortality and a determinant of recovery trajectory in survivors after ICU discharge (10). Importantly, the 7-day FIM was predicted by age and ICU LOS. Four specific disability groups were identified. At one extreme, younger patients with the shortest time on the ventilator (less than 2 weeks) had the best long term outcomes. The patients in this lowest disability group had the lowest Charlson score, rarely required RRT or tracheostomy, were mostly able to walk on day 7 after ICU discharge and had a relatively short median hospital LOS (24 days). Accordingly, they might not benefit from intensive rehabilitation early in their ICU stay because they are likely to do well irrespective of the timing and intensity of an exercise program. At the opposite end of this spectrum of risk for disability, significant impairment was seen in the oldest patients who required mechanical ventilation for more than 2 weeks. Forty percent of these patients died within the first year after ICU discharge and the surviving patients had severe and persistent functional dependency. The rehabilitation potential of this high disability risk group may be so limited that expending large amounts of resources may ultimately not result in a change in outcomes.

There may be plausible biological explanations underscoring the disability and rehabilitation potential in different patients that may significantly impact the choice, timing and intensity of therapeutic strategies. The accompanying manuscript to the phase one of the RECOVER study from the MEND-ICU group, found that there is a 'disconnect' between recovery of muscle mass and strength in some patients. Moreover, those patients who developed persistent muscle atrophy even at 6 months post ICU discharge had a decrease in muscle progenitor cell number suggesting an underlying limited ability to regenerate new muscle tissue. In this context, the risk of persistent disability may be understood and the impact of EGDM on those individuals with an intermediate risk of disability gains clear and testable biological importance. For these individuals who (I) are older (reduced reparative reserves) but were ventilated for less than 2 weeks (limited injury); or (II) are younger (retained reparative reserves) but were ventilated for longer than 2 weeks (significant injury) they may still retain sufficient recovery potential to justify intensification of rehabilitation in an effort to preserve or recover muscle function. Early and intense exercise may be able to influence the hypertrophic response specifically, even if the hyperplastic response (regeneration) is compromised. The caveat here is—if muscle progenitor cells are intact—otherwise, lesser improvement in muscle mass may be expected from an early and intense exercise/rehabilitation program and would rely upon hypertrophy of existing myofibers.

Although it has been postulated, there is currently little data to suggest early mobility actually changes muscle structure and contractility by either inhibiting muscle breakdown (proteolysis) or enhancing muscle re-growth (hypertrophy and/or regeneration). However, other important functional roles of muscles may be affected by early mobility. A tantalizing glimpse in the potential role of early mobilization on glycemic control, for example, points to other metabolic effects of physical activity. Hyperglycemia has been associated with poor outcomes, including increased infectious complications (11), ICUAW, and mortality (12,13). Moreover, persistent hyperglycemia reduces substrate oxidation and impairs metabolic switching of human myotubes impairing muscle recovery (14). In diabetics, hyperglycemia is associated with muscle weakness, and exercise is known to reduce hyperglycemia and enhance muscle mitochondrial capacity (15,16). Targeting hyperglycemia pharmacologically alone however, has not resulted in improved outcomes in the critically ill (17). Although high-dose insulin has an anabolic effect in experimental conditions, at doses necessary to achieve

normoglycemia insulin appears to have no discernible impact on skeletal muscle degradation or recovery (18); future methodologically more robust studies are needed however to corroborate this finding. Early mobilization in combination with insulin however, has been reported to improve glycemic control and ICUAW, although this was in a secondary analysis (19). As muscle is a key metabolic tissue, achieving the benefits of euglycemia by increasing muscle glucose uptake may help to prevent neuromuscular complications of critical illness (20).

As we move forward towards trying to understand and develop interventions that may improve outcomes in survivors of critical illness we will have to understand and be able to discern the effects of process and biology on outcomes. Once we overcome the limitations of administering a protocolized mobility program, for example, by standardization of "usual care" in the control arm, Hodgson *et al.* clearly demonstrate that we will be able to deliver the intervention on a large randomized multicenter setting, but from a biological perspective will we want to? The authors postulate a sample size of greater than 500 patients would be required to adequately power a study to determine differences between the groups for either functional recovery or hospital LOS. Given these outcomes are likely to be already significantly different for those patients that are actually willing and able to be recruited in the study early (~13% of patients), are these the patients we want to focus our rehabilitation efforts on? Alternatively, we should set our sights on improving outcomes in those individuals who have a high risk of doing poorly but may have significant rehabilitation potential.

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Footnote

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