The Journal of Physiology

JOURNAL CLUB

Age-dependent effects of bed rest in human skeletal muscle: exercise to the rescue

Jose B. N. Moreira[1], Martin Wohlwend[1], Ingrid Åmellem[1] and Paulo R. Jannig[2]
[1] *KG Jebsen Center for Exercise in Medicine, Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway*
[2] *School of Physical Education and Sport, University of Sao Paulo, Sao Paulo, Brazil*
Email: jose.moreira@ntnu.no

In recent past, the prescription of bed rest was common practice in medical care, being indicated to patients with a wide range of health conditions. Despite lack of empirical evidence, it was believed that reducing metabolic demand could facilitate recovery by favouring delivery of oxygen and metabolic resources to the malfunctioning body site/organ. However, overwhelming evidence from clinical trials proved the contrary by showing that even short periods of bed rest can lead to serious complications including loss of cardiovascular and muscle function, both associated with poor outcomes (Creditor, 1993). Deterioration of skeletal muscle capacity (i.e. loss of muscle mass and strength) is one of the first manifestations and is particularly worrying in older individuals, who are more prone to hospitalization and less physically active than the young. It therefore becomes important to understand whether the effects of bed rest differ between young and older individuals, so that therapeutic strategies can be tailored to each particular age group. Although it is assumed that older individuals experience exacerbated muscle loss after bed rest, the study by Tanner *et al.* (2015) in *The Journal of Physiology* reports the first direct comparison between age groups. The authors aimed to verify age-dependent differences in muscle loss, protein synthesis and catabolic signalling in response to a 5 day bed rest protocol, and potential rescue by a rehabilitation programme. Well-controlled protocols complemented by molecular analyses make the study attractive, but some limitations deserve attention.

Young (18–35 years old) and older (60–75 years) adults of both sexes and matched for baseline characteristics were recruited and underwent five continuous days of bed rest, in a protocol designed to simulate hospitalization procedures. This strategy brings the protocol closer to a clinical scenario; however, the good health status of participants impedes full extrapolation of the findings, mainly because hospitalized patients have additional health complications that may influence skeletal muscle response. On the other hand, a healthy cohort excludes the interference of confounding factors contributing to muscle loss. X-ray absorptiometry revealed significant loss of leg lean mass and 16% reduction in knee extensor strength in older volunteers after bed rest, while young participants displayed preserved values. Muscle protein synthesis after amino acid ingestion was disrupted after bed rest only in older subjects. This is consistent with results on skeletal muscle mass and strength, and helps explain the different response between groups. Although the young cohort appeared to be protected in this short bed rest protocol when compared to the older group, several studies employing longer resting periods demonstrated skeletal muscle loss in young adults (LeBlanc *et al.* 1992). Overall, these findings indicate that the time course of muscle disuse is delayed in younger individuals.

In a second arm of the study, the authors aimed to investigate the effects of a rehabilitation programme starting after bed rest. High-intensity eccentric exercise sessions followed by protein supplementation were performed every other day under supervision. In follow-up examinations after rehabilitation, muscle mass returned to pre-bed rest levels in older individuals and was increased above baseline in the young cohort. This might be explained by the fact that the latter did not experience muscle loss after bed rest and not necessarily by different responses in young and older groups to the rehabilitation programme. Isometric strength post-rehabilitation returned to baseline in both groups. Although the authors interpret the observed muscle recovery as an effect of the exercise programme, this conclusion would have been further supported by including a control group not receiving the exercise intervention after bed rest. This comparison would account for the effects of muscle reloading ('reambulation'), when individuals return to spontaneous ambulatory activity. In fact, muscle recovery after 4 months of bed rest was observed in young subjects within 8 weeks of reambulation, without exercise training (LeBlanc *et al.* 1992). However, since older adults have an impaired ability to regain muscle tissue after disuse (Suetta *et al.* 2013), the interpretation by Tanner *et al.* is certainly plausible. However, direct evidence will be required to allow for a robust conclusion regarding the effects of exercise.

A particular strength of the study is the evaluation of intracellular signalling. While extensive evidence in animal models of muscle unloading is available, human data are scarce, making this study an important contribution to the literature. To gain insights on key molecules involved in protein turnover, Tanner *et al.* evaluated several targets in vastus lateralis biopsies collected before and after bed rest and rehabilitation. Their data demonstrate for the first time that increases in MAFBX expression and LC3II/I ratios, well accepted markers of protein degradation, are more pronounced in older compared with young volunteers after bed rest. While nutrient-induced protein synthesis was blunted only in older participants post-bed rest, mTORC1 signalling displayed a similar response between groups, suggesting that the time span between mTORC1 signalling and manifestations in protein synthesis is shorter in older adults. Therefore the accelerated muscle loss observed in the older group probably resulted from a combination of reduced nutrient-induced protein synthesis and increased protein degradation.

The study is associative by necessity and extrapolation of causal mechanisms is derived from studies in rodents. In this regard, the so-called 'atrogenes' *MAFBX* and *MURF1* attract special attention because mice lacking these factors display attenuated muscle atrophy upon catabolic stimuli or ageing (Hwee *et al.* 2014), raising the hypothesis that inhibiting

© 2016 The Authors. The Journal of Physiology © 2016 The Physiological Society DOI: 10.1113/JP271758

atrogenes could be a therapeutic option for muscle atrophy. An alternative interpretation argues that atrogenes and the ubiquitin–proteasome system (UPS) are activated to remove damaged proteins that accumulate as toxic aggregates in atrophying muscle. In fact, mice lacking MURF1 lose less muscle mass upon ageing, but display poorer muscle function than wild-type (Hwee *et al.* 2014). This is consistent with the notion that UPS is activated as a consequence of muscle damage, and blocking this activation results in accumulation of dysfunctional proteins. The same applies to autophagy, whose excess or deficiency leads to muscle atrophy. In addition, increased LC3II/I ratio could indicate either autophagic induction or autophagic flux blockage. The LC3II/I ratio was increased even further after rehabilitation, probably due to augmented muscle demand imposed by exercise, a known inducer of autophagic flux. Therefore, anti-atrophy therapeutics could aim to target molecular triggers of protein damage rather than the recycling machineries activated as a consequence. In this sense, unbiased genome/proteome-wide screenings are valuable to identify mechanisms displaying early activation in atrophying states and molecules recruited by exercise, as those could guide future steps of drug discovery. Although previous studies performed such screenings, most data remain largely associative, which impedes the distinction between cause and consequence.

In summary, Tanner *et al.* provide the first head-to-head comparison of bed rest effects between age groups and demonstrate that older individuals are more susceptible to muscle loss than the young. While exercise-based rehabilitation seems to re-establish muscle strength in both groups, further studies are needed to verify to what extent exercise training is additive to simply returning to normal daily activities. Their molecular analyses suggest that findings previously reported in rodents are conserved in humans. Better understanding of the molecules responsible for the early onset of disuse-induced muscle loss in the elderly is needed, so that protective mechanisms lost upon ageing can be reconstructed in the form of therapeutic agents. Considering the debilitating effects of bed rest in muscle function of hospitalized patients (particularly at old age), anti-atrophy therapies are expected with great anticipation.

References

Creditor MC (1993). Hazards of hospitalization of the elderly. *Ann Intern Med* **118**, 219–223.

Hwee DT, Baehr LM, Philp A, Baar K & Bodine SC (2014). Maintenance of muscle mass and load-induced growth in Muscle RING Finger 1 null mice with age. *Aging Cell* **13**, 92–101.

LeBlanc AD, Schneider VS, Evans HJ, Pientok C, Rowe R & Spector E (1992). Regional changes in muscle mass following 17 weeks of bed rest. *J Appl Physiol (1985)* **73**, 2172–2178.

Suetta C, Frandsen U, Mackey AL, Jensen L, Hvid LG, Bayer ML, Petersson SJ, Schroder HD, Andersen JL, Aagaard P, Schjerling P & Kjaer M (2013). Ageing is associated with diminished muscle re-growth and myogenic precursor cell expansion early after immobility-induced atrophy in human skeletal muscle. *J Physiol* **591**, 3789–3804.

Tanner RE, Brunker LB, Agergaard J, Barrows KM, Briggs RA, Kwon OS, Young LM, Hopkins PN, Volpi E, Marcus RL, LaStayo PC & Drummond MJ (2015). Age-related differences in lean mass, protein synthesis and skeletal muscle markers of proteolysis after bed rest and exercise rehabilitation. *J Physiol* **593**, 4259–4273.

Additional information

Competing interests

None declared.

Funding

J.B.N.M. and I.Å. are supported by the Norwegian Health Association and the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology (NTNU). P.R.J. holds a scholarship from the São Paulo Research Foundation (FAPESP).

© 2016 The Authors. The Journal of Physiology © 2016 The Physiological Society