Effects of Unloading in Old Versus Young Humans

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The loss of muscle mass with aging (ie, sarcopenia and the concomitant decline in muscle strength) is associated with increased disability and mortality.[1,2] In addition, elderly individuals are more prone to periods of bed rest because of a higher degree of comorbidity and hospitalization,[2] which per se result in a rapid and accelerated loss of skeletal muscle mass.[3,4]

Despite this, very little is known about the physiological consequences of unloading on muscle mass and neuromuscular function in the elderly, while even less is known about the regenerative capacity of skeletal muscle in the elderly human being. Furthermore, although it is evident that aging leads to a multitude of changes in the neuromuscular system that are similar to those evoked by unloading,[5] the lack of research into the effect of unloading in elderly humans makes it difficult to ascertain what effects are attributed to a decreased physical activity per se and which to the aging process.

In the present study, concurrent data were obtained on the change in muscle contractile function, muscle size, central activation, and muscle architecture induced by unloading and retraining in old vs young human individuals, respectively.[6] It was the purpose to address the effect of aging on the magnitude of acute muscle disuse atrophy and the adaptive plasticity of subsequent exercise rehabilitation. By assessing these changes, we also aimed to study the potential interaction between changes in muscle contractile properties, specific force, and

muscle mass characteristics after immobilization, and further to examine the regenerative capacity of old men (OM) compared to young men (YM).[6]

Immobilization was accomplished by 2 weeks of randomized unilateral whole-leg casting, using a light-weight fiber cast applied from just above the malleolus to just below the groin. Normal range of motion was obtainable at the knee joint. The retraining protocol was accomplished by 4 weeks of surveyed and supervised unilateral strength training on the immobilized leg, with three sessions each week. To induce a sufficient response in the thigh musculature, the training intensity was three to four sets x 12 reps in week 1 (15 repetition maximum [RM]), 5 sets x 10 reps in weeks 2 and 3 (12 RM), and 4 x 10 reps in week 4 (12 RM). Training load was adjusted on a weekly basis by the use of 5-RM tests.

In brief, both young and old subjects experienced decreases in maximal muscle strength, resting twitch peak torque, and twitch rate of force development, quadriceps muscle volume, muscle fiber pennation angle, and specific force after 2 weeks of unilateral lower limb immobilization (P=<0.05).[6] The decline in quadriceps volume (OM: -5.3%, YM: -8.9%) and muscle fiber pennation angle (OM: -6.5%, YM: -9.3%) was smaller in old compared to young (P=<0.05). In contrast, only old men experienced a decrease in quadriceps activation (OM: -9.9%, P=<0.05; YM: -1.0%, ns [ns=not significant]).[6] In addition, re-training induced smaller gains in quadriceps volume in old compared to young (OM: +3.8%, YM: +8.2 %, P=<0.05), and muscle fiber pennation angle increased in young only (YM: +12.0%, P=<0.05).[6]

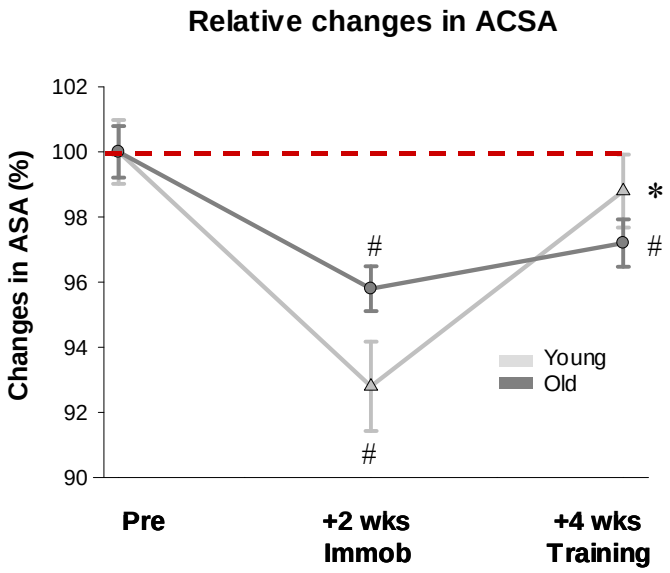

Fig. Changes in anatomical cross-sectional area prior to immobization (pre), after 2 weeks of immobilization , and after 4 weeks of retraining.[6]

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In conclusion**,** the main and novel findings were that young subjects showed a greater magnitude of muscle atrophy and more marked changes in muscle fiber pennation angle after immobilization compared to old subjects, old subjects demonstrated a diminished capacity to restore muscle size and muscle architecture during subsequent retraining, and immobilization led to reduced muscle activation in old but not young subjects. Thus, the present data suggest that the adaptive plasticity in skeletal muscle mass and central nervous system function associated with unloading and subsequent remobilization, respectively, may differ substantially between old and young individuals.

The present data thus indicate that aging affects the response to short-term immobilization and the regenerative capacity of human skeletal muscle. In the present study, young subjects demonstrated a greater reduction and subsequent increase in muscle mass because of

immobilization and retraining, respectively, compared to old subjects. Conversely, it seemed neural function was more affected in old subjects, who showed a larger decline in neuromuscular activation than young subjects. Together these findings put forward that old individuals apparently are more affected with respect to neural function, whereas young individuals are more affected in terms of muscle size. Furthermore, the present data indicate that aging is accompanied by an impaired ability to recover from disuse muscle atrophy. Consequently, old individuals may need longer time to recover from periods of disuse compared to young individuals.

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Q & A

Q: Thank you for the interesting study. Were the elderly and the young controlled for diet?

Dr Suetta: No, we did not control for diet.

Q: Did you measure any inflammatory cytokines or inflammatory markers and the effect of immobilization on them?

Dr Suetta: We have blood samples, and we have taken muscle biopsies as well. However, we do not have the data yet on cytokines or inflammatory response, but it is definitely something we will look into. That possibly explains some of the differences between our findings, that maybe bed rest increases inflammatory response to a greater degree than just unloading one limb.

Q: I think the issue about recovery in these older folks is really important. I was intrigued by the primary data that you showed from the explosive force production protocol. One of the things that was obviously different between the young and the old is that the original tracings from the old individual had a periodicity to them; so, there was an oscillatory characteristic to it that looked like the first inflection, which was most reproducible at about 80 or 100 milliseconds if I read it correctly, suggesting maybe a spinal reflex inhibition.

Do you see inhibitory effects on the EMGs [electromyograms]? Is this a neural component to the difference between the two age groups?

Dr Suetta: Yes, it seems like this is the case.

Q: I thought the satellite cell data was very intriguing. The thing that makes me wonder, and I do not know if anybody has ever done this, if you take satellite cells from these older individuals and grow them in culture, do they have a different replicative capacity? Can you see that they either develop less rapidly when you switch serum or that they replicate poorly, or that they do not form myofibrils as well? This is a very interesting finding.

Dr Suetta: I was waiting for that question. Irina Conboy's group from UC Berkely has done many of those studies in mice [Conboy IM et al: *Nature* 2005;433:760-764], and I was fortunate enough to be at Berkeley University last spring, where we came to talk and decided to see if the satellite cells are reacting the same way in humans. We took some biopsies from old and young, and cultured them just as they previously did in mice.

It seems like if you culture the satellite cells from old humans in their old serum, they do not grow very well. However, if they are cultured in young sera, they grow very well [Carlson et al: *EMBO Mole Med* 2009;1:381-391], which means that there is definitely something in the systemic environment that activates them.

Q: Well, that is even more fantastic. Are you in the process of trying to identify that substance?

Dr Suetta: Irina Conboy group has shown is that it seems like the Notch and TGF-β control each other [Carlson ME et al: *Nature* 2008;454:528-532]. What they find in mice is that Notch is lowered and TGF-β is increased. What we recently published together is that the same pattern is seen in human muscle tissue [Carlson et al: *EMBO Mole Med* 2009;1:381-391]. What is even more interesting is that this difference actually is bonded with the resistance training. So, resistance training is very potent in many ways.

Q: The satellite cells, as I understand it, are really two types of satellite cells now with some of the newer staining techniques, one of which seems to be a little more potent than the other. How did you stain for your satellite cells? And which of the two types? The one sort of looks like a true muscle, as I understand it, and the other one is sort of a questionable muscle? I am not very good at it, but clearly they are becoming different.

Dr Suetta: It is kind of new for me, too. In Copenhagen we stain with NCAM or Pax7. Right now we are trying to compare the two stainings, but with these methods, we are not able to distinguish between the satellite cells.

Q: If you are suggesting that there is a neural component that is going awry because of immobilization, then do you really believe that giving them protein, like Dr Paddon-Jones has suggested, over this period of time would actually help correct for loss of strength or loss of power in the muscle? Or is there something else we need to be looking at?

Dr Suetta: That is a very good question. My opinion is that we need to provide patients with a protein supplement to counteract a decrease in muscle mass, because the size of a given muscle mass is strongly correlated to the force it can produce. However, despite

similar decreases in maximal muscle strength in young and old individuals after the immobilization period, the old individuals experienced a larger decrease in qualitative muscle strength (rate of force development), which indicates that a neural component definitely exists and is very important for muscle function. To my point of view, the neural component is not affected by dietary supplementation, but needs to be maintained with exercise.

Q: Is anyone exploring that right now to see if there are things that could be done to help?

Dr Suetta: It is quite simple. Several studies have shown, including some of our own [Suetta C et al: *J Appl Physiol* 2004;97:1954-1961] that resistance training during a hospitalization can counteract a decrease in both muscle mass and muscle function.

Q: I am intrigued as to why sarcopenia occurs, and I know very little about it. If you take a cross section of a muscle and measure the number of muscle fibers between a young and an old person, are they the same number but thinner in the older person? Or do you see a reduced number of muscle fibers per unit area?

Dr Suetta: Very classical studies from Sweden that are done on cadavers very clearly show that you lose both muscle size and a huge amount of muscle fibers with age. You do not do that with disuse. It is very different pathways that govern it.