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Mechanisms of sarcopenia: motor unit remodelling and muscle fibre type shifts with ageing

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Ageing causes myriad complications, including weakness and detrimental muscle quality changes. These symptoms can gradually become worse, culminating into sarcopenia, which is characterized by a loss of skeletal muscle size and function. In a study recently published in *The Journal of Physiology*, Piasecki *et al.* (2018) investigated four groups (young non-sarcopenic, old non-sarcopenic, pre-sarcopenic, and sarcopenic old men) to elucidate the interaction between motor unit characteristics (i.e. number and size estimates) of the tibialis anterior (TA) and vastus lateralis (VL) with ageing and sarcopenic status. The investigators reinforced that as men age, muscle mass and motor units decrease, with existing motor units expanding their range of innervation to compensate for those lost. The novel finding of the current study was the determination of an inflection point, where motor unit size did not increase, but rather decreased in sarcopenic older men. Therefore, sarcopenia is also characterized by an attenuation of motor unit growth that would compensate for lost skeletal muscle innervation with increased age.

The investigation by Piasecki *et al.* (2018) had the advantage of a large subject population that was also stratified by sarcopenic status. Additionally, they used more sensitive measures via intramuscular electromyogram (EMG) in both the TA *and* the VL compared to previous literature that utilized surface EMG and/or only observed the TA. Regardless, the study did not determine the participants' muscle fibre type. They contend that the low force produced in their exercise protocol implied that slow-twitch (type I) muscles were primarily activated via Henneman's Size Principle (i.e. motor units are recruited smallest to largest under load), and thus any changes in EMG are due to type I fibre activity. Nevertheless, muscle fibres are not dichotomous, but exist on a spectrum of physiological characteristics.

Until the mid-1980s, human muscle fibre types were determined through histochemical analysis, differentiating between slow- and fast-twitch fibres via ATPase activity. Conversely, modern methodologies have since isolated individual fibres to elucidate enzymatic and contractile properties at the single-fibre level (Murach *et al.* 2016). Myosin heavy chain (MyHC) isoforms dictate muscle fibre type characteristics and can be identified in single muscle fibres via sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). MyHC types exist on a continuum from slow-oxidative (MyHC I), to fast, oxidative-glycolytic (MyHC IIa), and fast-glycolytic (MyHC IIx), with hybrids expressing multiple phenotypes between the 'pure' isoforms. Previous rodent models show that ageing results in the loss of fast-twitch motor units and fast-twitch muscle fibre atrophy; this leads to an increased proportion of type I fibres as slow motor units begin to reinnervate fast-twitch fibres (Macaluso & De Vito, 2004). While this has not been empirically shown in human studies yet, few investigations have utilized single fibre SDS-PAGE to analyse fibre type shifts in elderly populations, potentially clouding the accuracy of their determination. Notably, an investigation by Andersen *et al.* (1999) using SDS-PAGE showed that a group of very old men and women (~88 years) had a MyHC profile that indicated an inordinately higher percentage of hybrid MyHC isoforms (~51% total hybrids *vs.* ~20% in younger individuals). Specifically, the MyHC IIa/IIx isoform was expressed to a high degree, which is typically seen in instances of chronic bed rest or spinal cord injury. The inconsistencies between methodologies (ATPase histochemistry *vs.* single fibre SDS-PAGE) in the literature should be considered when determining fibre type in populations with higher percentages of hybrid MyHC isoforms.

While ageing causes the proportion of MyHC I fibres to increase, a definitive shift from fast to slow is not empirically supported. Ageing typically comes with other cofactors, including decreased physical activity, which is implicated in a slow-to-fast MyHC expression shift (such as with bed rest and/or spinal cord injury). Denervation of muscle fibres clearly occurs with age (Spendiff *et al.* 2016), but it is difficult to predict the life span of a denervated fibre because it is impossible to follow a single fibre's characteristics (i.e. MyHC type) *in vivo* in humans. It is possible that these denervated fibres would shift to fast isoforms and degrade. Conversely, another possibility is that these new age-related fast-twitch fibres are reinnervated by slow-twitch motor units, creating the appearance that ageing results in a slow phenotypic shift (Hepple & Rice, 2016). There is also evidence that the fast-twitch fibres that survive age-related motor unit loss become 'elite' as a compensatory mechanism. Grosicki *et al.* (2016) found that the MyHC IIa fibres from very old men and women (average age 89 ± 1 years) showed significantly higher normalized power (a measure accounting for size, strength and speed) compared to 20-year-old's fibres. Therefore, it would be pragmatic to elucidate the changes in fibre type between different stages of sarcopenia with varied physical activity levels. Ultimately, the shift in MyHC fibre type proportion with ageing does not happen in isolation, and thus the confluence of other stimuli (or lack thereof) must be considered before assuming the fibre profile of subjects across varying ages and sarcopenic status.

Piasecki *et al.* (2018) found that muscle mass loss related to ageing is not directly proportional to declining motor unit numbers. As age and atrophy continue to compound, a critical inflection point is reached and existing motor units no longer increase as a compensatory mechanism. Future research should build on this investigation to parse out how motor unit loss, fibre type shifts, and sarcopenic status intertwine to form a macroscopic view of ageing. Through the sensitivity of MyHC fibre type analysis, science will reveal the true mechanisms underlying sarcopenia and its deleterious effects on older populations. As we understand more about how ageing impacts on our physiology, we can develop more advanced and educated methods to delay, or even prevent, loss in muscle mass and function with ageing.

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