Aging of Human Muscle: Understanding Sarcopenia at the Single Muscle Cell Level

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KEYWORDS

- Aging • Sarcopenia • Skeletal muscle fiber
- Muscle atrophy • Contractility

Sarcopenia (*sarx* = flesh and *penia* = loss), the loss of muscle mass, has become a major subject of scientific research as well as a public health problem of significant dimensions. Although an operational definition that is universally acceptable is not available, researchers agree that the incidence of sarcopenia increases with advanced adult age in both sexes but particularly in men. Further, preliminary studies suggest that the costs associated with sarcopenia in the United States may exceed $20 billion.[1] Thus, understanding sarcopenia and developing therapeutic and rehabilitative interventions to slow down its progress or partially reverse its effects is an important scientific and health care policy goal.

The loss of muscle mass seen in older men and women has significant physiologic, functional, and health consequences. Muscle weakness, a decrease in muscle power, a reduction in walking ability, and an increase in hospitalizations are all associated with sarcopenia.[2] Of importance is that several additional physiologic changes are associated with aging and sarcopenia influencing muscle function, even though these changes do not occur inside the muscle fibers and are not known to alter the basic structure and function of myofilament proteins. Examples of these changes are an increased accumulation of adipose tissue around and between muscle fibers and a decrease in the anabolic influence of the endocrine system. Further examples are

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age-related changes in the nervous system such as the loss of motor neurons, the remodeling of motor units through collateral reinnervation, and the impairment of neuromuscular activation manifested as a decreased maximal firing rate of motor units.

The study of skeletal muscle function in humans (patients or healthy volunteers) has advanced significantly in the last 3 decades. However, many of tests of skeletal muscle function, particularly those used in the clinical environment, reflect the integrated actions of several physiologic systems. Although the integrated response measured as muscle strength or power is of clinical interest, the specific contribution of each of the systems is very difficult to isolate using these tests. For example, in vivo measurements of muscle strength and power reflect the integrated action of muscle fibers, tendons, the neuromuscular junctions, peripheral axons, and the activating central nervous system. Clinical testing protocols may identify the presence of weakness and dysfunction, but cannot identify the specific level at which the impairment is happening and cannot explain the underlying cellular mechanism.

The first experiments with normal single human muscle fibers were published in 1975.[3] Since that time several researchers have used various experimental techniques to isolate and activate segments of single human muscle fibers obtained with the percutaneous muscle biopsy needle (**Fig. 1**). These techniques have been applied to research in healthy volunteers, elite athletes, patients with various diseases of the neuromuscular system, and patients with spinal cord injuries, among others. The first application of this technique to the aging (sarcopenia) problem was published in 1997.[4] This approach allows the investigator to examine the performance of the actin-myosin cross-bridges and muscle regulatory proteins in the absence of the influence of the nervous or endocrine systems. Further, because the technique includes the biochemical identification of the type of myosin heavy chain expressed in individual fibers, it is possible to study muscle-fiber physiology without the confounding effect of the heterogeneity of fiber type that is typical of the intact human neuromuscular system. Fibers are made permeable and then segments are activated maximally with high calcium concentrations. Due to the permeability of fibers, there is no (or very little) sarcolemma or sarcoplasmic reticulum that could interfere with the movements of calcium ion. Thus, the level of activation (or voluntary drive) is eliminated as a confounder. Finally, the absence of the tendon and mechanical leverage system permits the measurement of force generation directly from the fiber and its myofilament structure and not at a distance from the site of force generation.

The single muscle fiber technique allows the measurement and/or calculation of several important morphologic/physiologic, mechanical (**Fig. 2**), and biochemical variables (**Table 1**).

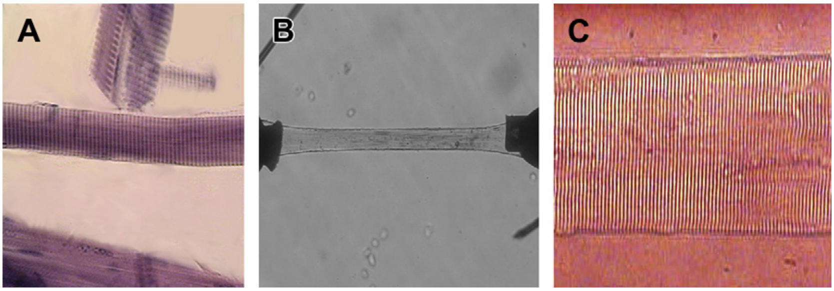

Fig. 1. (*A*) Dissected single human muscle fiber, (*B*) human muscle fiber attached to force transducer and servomotor, and (*C*) preserved sarcomere pattern at higher magnification.