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Myofilament Protein Alterations Promote Physical Disability in Aging and Disease

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Abstract

Skeletal muscle contractile function declines with age and age-associated diseases. Although muscle atrophy undoubtedly contributes to this decrease, recent findings suggest that reduced myofilament protein content and function also may participate. Based on these data, we propose that age- and disease-related alterations in myofilament proteins represent one molecular mechanism contributing to the development of physical disability.

Keywords

myosin; actin; muscle; human; fiber; molecular

INTRODUCTION

Aging and chronic disease reduce whole-skeletal muscle performance, which, in turn, decreases the ability to perform everyday tasks such as walking, standing from a seated position, and climbing stairs (21). Decrements in whole-muscle performance lead to disability and increase the risk of falling/fall-related injuries, both of which lead to loss of independence and increased morbidity and mortality. Understanding the physiological mechanisms behind mobility limitations has direct relevance to the development of lifestyle and pharmacologic countermeasures to improve whole-muscle contractile function, allowing older and diseased individuals to maintain functional independence and quality of life.

Physical functional capacity is strongly dependent on skeletal muscle power output (22). Muscle power, calculated as the product of the force-generating capacity and contractile velocity, decreases with age and disease partially because of decreases in muscle quantity or mass (*i.e.*, muscle atrophy). However, muscle atrophy alone does not fully explain losses in whole-muscle performance (21). Whole-muscle functional alterations also may be driven by reduced force generation or contractile speed per muscle size (*i.e.*, muscle quality).

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Reductions in muscle quality may be caused by alterations in myofilament contractile proteins (myosin and actin), which scale up from the molecular to the single fiber and tissue level to impact muscle performance. Unfortunately, whole-muscle performance measures are not necessarily an accurate reflection of myofilament protein content/function because of the intervening effects of numerous physiological systems (*e.g.*, muscle architecture, excitation-contraction coupling, neuromuscular activation of agonist versus antagonist muscles, tendon compliance) to regulate whole-muscle function. Because of this, a reductionist approach is required to evaluate the fundamental structural and contractile properties of the myofilaments. Studies in isolated single muscle fibers offer a rigorous experimental model to examine the effects of age and disease on myofilament proteins at both the molecular and cellular level (5,6,8,13,18,25,31,32).

Our recent work has focused on examining skeletal muscle structure and function at the molecular, cellular (single fiber), and whole-muscle levels in aging and diseased populations ((Miller MS, *et al.*, unpublished manuscript, 2012); (16,17,23, 29,30)). In these studies, we used control groups that were matched for physical activity level with the aged or diseased groups to mitigate any effects of the muscle disuse that accompanies aging and acute/chronic illness. Because of these experimental considerations, we believe that our findings reflect the unique effects of aging and disease. Building off of this work, the current review will focus on the hypothesis that the age- and disease-related changes in contractile protein content, structure, and function at the molecular and cellular level influence whole-muscle performance in ways that lead to physical disability.

MYOFILAMENT PROTEIN CONTENT AND FUNCTION

At its most basic level, muscle contraction is caused by the coordinated interaction of two proteins: myosin and actin. Their prominence in muscle function is mirrored in their quantitative contribution because they comprise nearly two thirds of all myofilament proteins (43% myosin heavy chain (MHC) and 22% actin) and more than one third of all muscle proteins (25% MHC and 13% actin) (34). Myosin and actin are contained within the thick and thin filaments, respectively, which form a highly ordered hexagonal array in the sarcomere. Muscle myosin contains four light chains (MLC) and two heavy chains (MHC), the latter of which separate into two globular heads that protrude from the thick filament backbone and contain the adenosine triphosphate (ATP)- and actinbinding sites necessary to convert chemical energy (ATP) into mechanical work.

The interaction of myosin and actin has important consequences for single-fiber force and contractile velocity, the determinants of power (force $\times$ velocity). To better understand the role of myofilaments in determining muscle force production and contractile velocity, it is necessary to describe the underlying mechanical determinants of these two characteristics. The half-sarcomere is an important reference frame to understand force production because each half-sarcomere must produce identical forces during an isometric contraction because unbalanced forces will cause changes in sarcomere length. As the forces must be balanced in each half-sarcomere along the entire length of the myofibril, the half-sarcomere force (F_{hs}) is equivalent to the myofibril force (F_{iso}). The amount of force generated in a half-sarcomere during Ca^{2+} activation is calculated by multiplying two values: 1) the number of strongly

bound myosin-actin cross-bridges in that halfsarcomere and 2) the force generated per cross-bridge (19). To calculate the first value, we assume a two-state model where myosin is either strongly bound to actin in a force-producing state (cross-bridge) or in a detached non-force-producing state. Using this model, the total time required for a complete attached-detached cycle (cycle time or t_{cycle}) consists of the time when myosin is strongly bound to actin (t_{on}) and the time when myosin is detached from actin (t_{off}) (Fig. 1A). In addition, the fraction of time that a cross-bridge is formed is equal to the t_{on} divided by t_{cycle} and is called the myosin duty ratio ($t_{\text{on}}/(t_{\text{on}} + t_{\text{off}})$). As the number of crossbridges formed in a half-sarcomere is equivalent to the total population of available myosin heads (N) multiplied by the fraction of time a cross-bridge is formed, the equation to calculate this value is $N(t_{\text{on}}/(t_{\text{on}} + t_{\text{off}}))$. To calculate the second value required to estimate force production, we assume that the cross-bridge behaves as a Hookian spring, where force is equal to the deflection of the spring (d) multiplied by the spring stiffness (k). In other words, the force generated per cross-bridge (F_{uni}) is proportional to the unitary displacement generated by the myosin power stroke (d_{uni}) multiplied by the elastic stiffness of the cross-bridge (k_{stiff}). Altogether, these relationships result in the equation for myofibril isometric force shown in Figure 1B (19), which can be scaled up to the single-fiber level by multiplying the force produced per half-sarcomere (F_{hs}) by the number of parallel myofibrils in a single fiber.

Contractile velocity also depends on cross-bridge kinetics; more specifically, it is proportional to d_{uni} divided by t_{on} (Fig. 1B). Accordingly, single-fiber velocity has been shown to decrease with longer t_{on} (*i.e.*, longer, strongly bound cross-bridges (20)). In addition, recent evidence also indicates that single-fiber velocity is decreased with a longer t_{off} (*i.e.*, reduced myosin attachment rate (20)) (Fig. 1B). Although this result is controversial, single-myosin molecule and ensemble experiments, in combination with modeling, suggest that velocity is related to myosin attachment rate (11,33). A potential mechanism to explain this relationship is that a longer t_{off} would reduce the myosin duty ratio ($t_{\text{on}}/(t_{\text{on}} + t_{\text{off}})$), which would decrease the number of cross-bridges and reduce the internal force experienced by each cross-bridge, causing an increase in t_{on} and a slowing of contractile velocity (33). Notably, contractile velocity should be related positively to d_{uni} (larger displacement produces faster velocity); however, d_{uni} does not seem to change over a range of contractile velocities in muscle fibers (20). These relationships allow the cross-bridge kinetic and structural properties (molecular level) to be related to the single-fiber properties (cellular level) of force and velocity.

The potential effect of aging and/or disease to alter the quantity or kinetic properties of individual myosins on the force-producing ability of a population of myosin is illustrated in Figure 2. Assuming the duty ratio of an individual myosin is 20%, or t_{on} is 20% of t_{cycle} , five myosin heads are required to have one strongly bound myosin at any point in time (Fig. 2A). If a “normal” half-sarcomere is made up of 10 myosin heads, at any moment in time, two myosin heads would be strongly bound to actin and the “normal” half-sarcomere would produce an average isometric force of two myosin heads (Fig. 2A). This also can be calculated using the isometric force equation (Fig. 1B), where $F_{\text{iso}} = F_{\text{hs}} = (t_{\text{on}}/[t_{\text{on}} + t_{\text{off}}]) \times N \times F_{\text{uni}} = 0.2 \times 10 \times F_{\text{uni}} = 2 \times F_{\text{uni}}$. Reducing N from 10 to 8 myosin heads (20% reduction) would reduce the average half-sarcomere force by 20% to 1.6 myosin heads (Fig.

2B), showing that a simple loss of myosin will proportionally reduce force production. In another scenario, where t_{on} is increased by 25%, only four myosin heads are required to have at least one strongly bound myosin at any time and the average half-sarcomere force would be increased by 25% to 2.5 myosin heads (Fig. 2C), showing how a slowing of cross-bridge detachment can increase force production. Notably, the aforementioned functional consequences of myosin loss (Fig. 2B) can be counteracted, in terms of half-sarcomere force production, by a longer t_{on} because fewer heads are needed to maintain a “normal” force production of two myosin heads (Fig. 2D). However, as t_{on} is inversely related to contractile velocity (Fig. 1), a longer t_{on} would result in a slower contractile velocity, showing how alterations in molecular properties can have reciprocal effects on contractile properties. Alternatively, a 25% increase in F_{uni} would result in a 25% increase in half-sarcomere force production as each myosin head would be producing more force. As aging and disease may affect one or multiple molecular properties, understanding these relationships is important to evaluating the potential effects on single-fiber force production that lead to alterations in whole-muscle performance.

Many of the cellular functional properties relate to the content and functionality of the myosin molecule. The most prominent determinant of muscle performance (maximum shortening velocity and power output) is the type of MHC isoform that is expressed in each muscle fiber. Human skeletal muscle fibers have three different types of MHC isoforms (I, IIA, or IIX), whereas other lower order vertebrates have an additional MHC (MHC IIB). The ATPase rate, or the rate at which myosin progresses through a complete attached-detached cycle (t_{cycle}), is $I < IIA < IIX < IIB$, leading to contractions that are slow in MHC I, fast in MHC IIA, and very fast in MHC IIX and IIB fibers. Individual fibers can contain a mixture of MHC isoforms, resulting in six different fiber types found in human skeletal muscle (I, IIA, IIX, I/IIA, IIA/IIX, and I/IIA/IIX). The two MLC isoforms, the regulatory and essential, stabilize myosin's lever arm and play a modulatory role in the production of force and velocity. For instance, phosphorylation of the regulatory MLC moves the myosin head away from the thick filament and increases its likelihood of actin binding, effectively decreasing t_{off} (24). There are two regulatory (MLC2s, MLC2f) and three essential (MLC1s, MLC1f, MLC3f) isoforms that typically are found in slow-twitch (s or MHC I) and fast-twitch (f or MHC II) fibers, although various combinations of these isoforms are found. The relative proportion of MLCs expressed in individual human fibers does not seem to affect cross-bridge kinetics (17), although it may regulate function in the fastest fibers in lower order mammals (12). On this background, we will now discuss how aging and disease might alter skeletal muscle performance by modulating these molecular functional properties.

AGING MODIFIES MYOFILAMENT PROTEIN FUNCTION, NOT CONTENT

Whole-muscle power output (force $\times$ velocity) decreases with age (21). A significant portion of the age-related decrease in muscle force production is undoubtedly caused by the concomitant reduction of muscle mass, although alterations in the intrinsic functionality (*i.e.*, function per unit size) of muscle also occurs (21). In keeping with this notion, our data from young (21 to 35 yr old) and older (65 to 75 yr old) men and women that were matched for physical activity level show that reduced whole-muscle power output with age cannot be fully explained by muscle atrophy (Miller MS, *et al.*, unpublished manuscript, 2012).

Specifically, after adjusting for muscle size, aging reduced knee extensor isokinetic power production, yet isometric torque remained unchanged with age, in agreement with results from other researchers (3). Additional work from our laboratory has uncovered a potential molecular basis for age-related adaptations in static and dynamic whole-muscle contractile performance.

Previous results from human single fibers suggested that aging decreased cross-bridge kinetics (5,18). However, our recent study is the first to perform measurements that allow for calculation of cross-bridge kinetic parameters and identification of specific steps in the cross-bridge cycle that are altered with aging. Our results showed a slowing of cross-bridge kinetics, manifested as a longer t_{on} and a reduced rate of myosin force production or, in other words, the rate of myosin transition between the weakly and strongly bound states (Miller MS, *et al.*, unpublished manuscript, 2012). This slowing of cross-bridge kinetics can alter contractile performance at the molecular, cellular, and whole-muscle level. At the molecular level, the slower kinetics with age leads to higher myofilament stiffness. Greater myofilament stiffness would yield more effective transmission of the force developed at the cross-bridge level, effectively increasing k_{stiff} that would increase F_{uni} and, in turn, increase single-fiber isometric tension (Fig. 2E). This hypothetical framework is supported by a correlation analysis showing that both slowed cross-bridge kinetics and indices of myofilament stiffness are positively associated with single-fiber isometric tension (Miller MS, *et al.*, unpublished manuscript, 2012). In fact, we found that isometric tension actually was increased slightly in older versus young adults. Maintenance of single-fiber isometric force production likely carries over to the whole-muscle level, where, as previously mentioned, we found no age-related decrease in isometric torque per unit muscle size. In this context, reduced cross-bridge kinetics with age can be seen as having a beneficial effect to maintain isometric contractile function at the cellular and whole-muscle level.

There is, however, a downside to these adaptations, as they may impair dynamic contractile function. As strongly bound cross-bridges remain bound to actin longer (*i.e.*, increased t_{on}) and detached from actin longer (*i.e.*, longer t_{off} because of reduced rate of myosin force production) should decrease single-fiber contractile velocity (11,20,33), the slower cross-bridge kinetics should effectively decrease single-fiber power output. In support of this hypothesis, several human studies have found decreased unloaded shortening velocity with age (5,6,18). These decrements at the cellular level would be expected to contribute to reduced whole-muscle power output (Fig. 3). Data from our studies provide circumstantial evidence to support a link between these age-related molecular level modifications and changes in whole-muscle function. We found that slowed cross-bridge kinetics in MHC IIA fibers in young and older adults correlated with both reduced whole-muscle power output during isokinetic evaluations and peak aerobic capacity (peak $\dot{V}O_2$). As whole-muscle power output strongly predicts physical disability in the elderly (22), these results suggest that modifications in cross-bridge kinetics may be a molecular mechanism that contributes to age-related disability.

Our study found decreased phosphorylation of the fast isoform of the regulatory MLC (MLC-2f) with age (Miller MS, *et al.*, unpublished manuscript, 2012). This provides a potential mechanism for the age-related slowing of cross-bridge kinetics. Decreasing

MLC-2f phosphorylation in single fibers confines the myosin heads near the thick filament and increases t_{off} (24), which would be expected based on our findings of a reduced rate of myosin force production with age. As the MLC-2f isoform is present in MHC I and IIA human skeletal fibers (16), its decreased phosphorylation could explain the reduced rate of myosin force production in both fiber types — the most prominent alteration in cross-bridge kinetics with age. Practically, because MHC I and IIA are the two most prominent MHCs in human muscle, such alterations would be expected to have broad functional implications.

In contrast to these myofilament functional properties, our study found no alterations in myofilament protein content or isoform expression with age that might contribute to the cellular or whole-muscle contractile phenotypes that we observed. Previous studies had found a loss of myosin protein content in single muscle fibers from older adults (5) and suggested that these changes contribute to the loss of single-fiber tension commonly found with age (5,18). However, our current and past (28) studies, as well as work from other laboratories (31), have found no such age-related change in myosin or actin protein content with age. In addition, we found an increase in isometric tension with age, which agrees with a recent longitudinal study that found a strong trend ($P = 0.07$) toward an increase with age (8) and a cross-sectional study that found an increase in men with age (31). Regarding isoform expression, whole-muscle power also can be decreased by a shift to slower MHC isoforms. However, we found no age-related shift in MHC isoform expression in tissue homogenates (Miller MS, *et al.*, unpublished manuscript, 2012), in agreement with most human aging studies (2). As myofilament protein content, isoform expression, and single-fiber isometric tension are altered by physical activity level (5,6), our careful matching of young and older groups for physical activity level should yield results that reflect the effects of aging and are independent of muscle disuse. Collectively, these findings suggest that aging does not affect the expression of myofilament proteins in ways that would alter muscle contractile function at the cellular or whole-muscle levels.

HEART FAILURE ALTERS MYOFILAMENT PROTEIN CONTENT AND FUNCTION

Aging is associated with an increased prevalence of acute and chronic diseases, which, in turn, increases the risk for developing disability. The presence of disease could alter an individual's trajectory toward disability in a number of ways. One is through a direct effect of the disease or its sequelae on myofilament protein content and function. Presumably, the effects of any disease process would be superimposed on the aforementioned effects of aging. However, this simplistic notion may not be the case. Because many chronic diseases develop over time (*e.g.*, cardiovascular disease), they could modify normal age-related changes in myofilament proteins either directly or indirectly. In the case of direct modification, a disease such as peripheral arterial disease, which reduces blood flow to skeletal muscle, could modify myofilament protein content and/or function. Conversely, chronic cardiovascular disease could alter myofilament proteins via the often accompanying state of chronic inflammation. The type of disease, its etiology, and its temporal context all could affect how the disease process interacts with normal age-related changes in myofilament protein content and function to produce the final phenotype. Recent work from

our laboratories in patients with chronic heart failure (HF) demonstrates alterations in both myofilament protein content and function that may contribute to muscle contractile dysfunction and disability.

HF is the final common pathway for many chronic cardiac diseases. Exercise intolerance, manifesting as breathlessness and muscle fatigue, is the cardinal symptom of HF and undoubtedly contributes to the high rates of self-reported disability in these patients. Historically, reduced functional capacity was attributable to central hemodynamic factors, which is logical, considering that cardiac dysfunction is at the root of the disease. However, research during the past three decades has led to the consensus that alterations in the physiology of the skeletal musculature contribute to exercise limitation (4), most notably, atrophy, weakness, and reduced endurance. Whereas most of this research has focused on alterations in muscle oxidative and vascular function, there is evidence for a role of muscle contractile function as a determinant of physical work capacity, whether defined by classical laboratory-based assessments, such as peak oxygen consumption (peak $\dot{V}O_2$ (10,30)), or in laboratory-based assessments of performance of activities of daily living (23). The cellular/molecular basis for such decrements in whole-muscle contractile function, however, is unclear.

Recent studies have shown that human HF is characterized by a loss of myofilament protein content. Both animal models (32) and human studies (27) have observed a reduction in the contractile protein myosin at the whole-muscle and singlecell level per unit protein content or cell volume. This phenotype has been observed in other preclinical models of disease (1,9) and patient populations (5,13), suggesting that it may be linked mechanistically to some factor common to acute/chronic illness (*e.g.*, inflammation). Regardless of the mechanism, loss of myosin would be expected to reduce contractile force (Fig. 2B), and studies in single muscle fibers generally supported this assertion (5,13). Accordingly, decreased whole-muscle contractile function per unit size in HF patients (10,30) may be explained partially by the loss of myosin protein content (27). To test this notion, we evaluated single-muscle fiber myosin protein content and function in HF patients and healthy controls matched for age and habitual activity levels. Quite surprisingly, although HF patients were found to have reduced single-fiber myosin content compared with controls, from both biochemical and mechanical measurements, single-fiber isometric tension generally did not differ between groups (16,17). Any decrements in single-fiber tension that were observed were disproportionately smaller than the respective myosin loss (*e.g.*, MHC I fibers (17)) and were completely obviated when studied under conditions that were closer to those *in vivo* (higher temperature and phosphate level) (16). This dissociation between myosin protein content and single-fiber function was explained by a reduction in myosin-actin cross-bridge kinetics in HF patients, manifested as an increase in t_{on} (16,17). Because single-fiber tension is proportional to the fraction of the cycle time that myosin is bound to actin, an increase in t_{on} in HF patients (16) effectively compensated for reduced myosin protein content (reduced N), leading to no net reduction in isometric tension (Fig. 2D). In other words, alterations in the functional properties of the myofilament proteins compensated for their quantitative loss to yield no change in isometric tension in single fibers.

These molecular adaptations, however, may not be functionally benign. Although reductions in cross-bridge kinetics compensated for myosin protein depletion to yield no loss of single-fiber isometric contractile function, they could impair dynamic contractile function. As previously detailed for aging, the most likely scenario for this occurring is through decreased contractile velocity, which, in turn, would reduce muscle power output. The basis for this assertion is in the correlations between reduced cross-bridge kinetics and both whole muscle power output and peak $\dot{V}O_2$ (Miller MS, *et al.*, unpublished manuscript, 2012). The interpretation of these correlations, with the assumption of the primacy of myofilament properties as determinants of whole-muscle contraction, is that reductions in cross-bridge kinetics provide functional limitations on whole-muscle performance. Data to support this notion, however, are limited. Work from our laboratory has shown that 4 months of resistance exercise training increased myosin-actin cross-bridge kinetics in HF patients, and these changes were accompanied by improved whole-muscle function (29) and, in turn, performance in activities of daily life (23). In other words, improvements in cross-bridge kinetic function were accompanied by reduced physical disability in HF patients. Neither of these findings is sufficient to determine a direct causal link between variation in molecular myofilament function and whole-muscle function. Indeed, because of the limitations imposed by human clinical studies, particularly in diseased patients, demonstration of a causative link between variation in cross-bridge kinetics and whole-muscle dynamic contractile performance/functional disability will likely require the use of animal models. Nonetheless, our results are the first demonstration of a link between molecular functional indices and whole-muscle/body functional measures in humans. In this context, they highlight molecular adaptations in muscle that may predispose to reduced muscle contractile function and physical disability (Fig. 3). Parenthetically, we should not dismiss the loss of myofilament protein content and myosin, in particular, as functionally benign either because recent computational modeling from our laboratories suggests that certain patterns of myosin loss from the sarcomere might provoke a slowing of myosin-actin cross-bridge kinetics (Tanner BCW, *et al.*, unpublished observations, 2012). In this context, the nature and causes of variation in both the quantity and functionality of myofilament proteins in acute and chronic disease deserve further study as potential molecular mediators of physical disability.

ROLE OF MUSCLE DISUSE IN MYOFILAMENT ADAPTATIONS

A major caveat when studying skeletal muscle adaptations to aging or disease is the intervening effect of muscle disuse, which can have profound effects on myofilament protein expression, structure, and function (7). The potential modifying effects of muscle use are highlighted most clearly in HF, the most glaring example being variation in MHC isoform expression. A shift in skeletal muscle MHC isoform expression toward a more fast-twitch phenotype has long been held as one of the cornerstones of the myopathy of HF and is thought to be one factor contributing to reduced functional capacity (14). This shift in MHC isoforms, however, may be explained by the physical inactivity that characterizes the HF syndrome (26) because a similar slow to fast-twitch phenotype shift is a well-founded adaptation to muscle disuse. In support of this notion, work from our laboratory and others, where healthy controls were recruited to match HF patients for activity levels (17) or peak

$\dot{V}O_2$ (15), has shown no alterations in MHC isoform expression with HF. The failure to consider muscle disuse as a modulating effect may have complicated assessments of myofilament protein function in HF. In previous studies that did not control for physical activity level, a pronounced reduction in single-muscle fiber tension was found in HF patients (–33% in MHC I and IIA fibers (25)). In contrast, our studies, which carefully selected controls to match HF patients for muscle use and confirmed similar activity levels with accelerometry, found minimal or no differences in single-fiber tension (16,17). This is similar to our findings in young and older groups with similar physical activity levels because there was no difference in MHC isoform expression, MHC content, and an increase in single-fiber tension with age, in contrast to previous aging studies that displayed a slow to fast-twitch phenotype shift, decreased MHC content, and reduced single-fiber tension (5,18). In these instances, failure to consider the modulating role of muscle use has led to incorrect assignment of these myofilament phenotypes as unique manifestations of the disease state or aging. This is not a trivial distinction because many disease states can be untreatable, whereas muscle disuse is eminently addressable with exercise paradigms. Aside from the practical consequences of such distinctions, the possibility that even modest amounts of activity may have effects on myofilament protein expression and function suggests that careful consideration should be made of suitable control population to match aged or diseased, aged populations.

SUMMARY/CONCLUSIONS

Aging and its attendant chronic disease are associated with increased physical disability because, in part, of lower extremity skeletal muscle contractile dysfunction. Loss of skeletal muscle mass undoubtedly contributes to this impairment, but contractile dysfunction is disproportionately greater than decrements in size. We propose that alterations in the quantity and functional quality of skeletal muscle myofilament proteins contribute to lower extremity skeletal muscle dysfunction with aging and chronic disease (Fig. 3) and that resistance exercise training can partially correct these deficits. In support of this proposition, we have shown that chronic disease in older adults is associated with reductions in myosin protein content and that both aging and chronic disease are associated with reduced myosin-actin cross-bridge function (Miller MS, *et al.*, unpublished manuscript, 2012; (17)). Experimental control for physical activity levels obviated aging-or HF-related muscle disuse as a potential mediator. The relevance of these cellular and molecular adaptations to physical function is suggested by their associations with diminished whole-muscle contractile performance (Miller MS, *et al.*, unpublished manuscript, 2012; (27)). In addition, we have shown that myosin-actin cross-bridge defects observed in chronic disease can be remediated by resistance exercise training (29), suggesting the importance of including this exercise modality in rehabilitative approaches. Collectively, these data suggest that alterations in skeletal muscle myofibrillar protein content and/or function may contribute to the development of physical disability with aging and chronic disease and the potential remediative effects of resistive-type training to correct impairments in myosin-actin cross-bridge kinetics.

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Figure 1.

Schematic diagram and equations depicting the relationships between the individual myosin and multiple myosin (myofibril) levels. A. Schematic diagram showing the properties for an individual myosin based on a two-state model, meaning myosin is either strongly bound to actin in a force-producing state (*on*) or in a detached non-force-producing state (*off*). t_{cycle} , time required for a complete attached-detached cycle; t_{on} , time when myosin is strongly bound to actin; t_{off} , time when myosin is detached from actin; F_{uni} , unitary force generated per strongly bound myosin (cross-bridge). B. Myofibril isometric force (F_{iso}), which is the same as the isometric force generated by the half-sarcomere (F_{hs}), is equal to the fraction of time that myosin is bound to actin ($t_{on}/(t_{on} + t_{off})$) multiplied by the total population of available myosin heads per half-sarcomere (N) and F_{uni} . Contractile velocity is proportional to the unitary displacement of myosin (d_{uni}) divided by t_{on} and inversely proportional to t_{off} , although the relationship to t_{off} remains controversial.

Figure 2.

Schematic diagram indicating the effect of molecular alterations of individual myosin on the force-producing ability of a population of myosin. A. A “normal” half-sarcomere contains 10 myosin heads with a 20% duty ratio (myosin attachment time, or t_{on} , is 20% of a complete attached-detached cycle, t_{cycle}) and produces two myosin heads of force. B. Reducing the total population of available myosin heads per half-sarcomere (N) by 20% decreases force production. C. Increasing t_{on} by 25% with no change in t_{off} increases force production by 25%. D. Decreasing N by 20% and increasing t_{on} by 33% counteract one another and result in a “normal” force production. E. Increasing unitary force generated per cross-bridge, or F_{uni} , increases force production by 25%. Dashed vertical lines in (C) and (D) indicate “normal” t_{on} , and dashed horizontal lines in (E) indicate “normal” F_{uni} .

Figure 3.

Schematic diagram showing the effects of aging and heart failure at the molecular, cellular (single fiber), and whole-skeletal muscle levels. The *bold* text indicates similar changes in both aging and heart failure, showing that aging and disease decrease myosin-actin cross-bridge cycling rates, leading to decreased whole-muscle power output presumably through decreased single-fiber contractile velocity. The main difference between the two groups is that myosin content was unchanged with age but was decreased in heart failure. *Not measured in our studies.