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ORIGINAL ARTICLE

Sharon A. Jubrias · Ib R. Odderson
Peter C. Esselman · Kevin E. Conley

Decline in isokinetic force with age: muscle cross-sectional area and specific force

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Abstract Humans produce less muscle force (*F*) as they age. However, the relationship between decreased force and muscle cross-sectional area (CSA) in older humans is not well documented. We examined changes in *F* and CSA to determine the relative contributions of muscle atrophy and specific force (*F*/CSA) to declining force production in aging humans. The proportions of myosin heavy chain (MHC) isoforms were characterized to assess whether this was related to changes in specific force with age. We measured the peak force of isokinetic knee extension in 57 males and females aged 23–80 years, and used magnetic resonance imaging to determine the contractile area of the quadriceps muscle. Analysis of MHC isoforms taken from biopsies of the vastus lateralis muscle showed no relation to specific force. *F*, CSA, and *F*/CSA decreased with age. Smaller CSA accounted for only about half of the 39% drop in force that occurred between ages 65–80 years. Specific force dropped about 1.5% per year in this age range, for a total decrease of 21%. Thus, quantitative changes in muscle (atrophy) are not sufficient to explain the strength loss associated with aging.

Key words *MVC* maximum voluntary contraction · Myosin heavy chains · Magnetic resonance imaging

Introduction

A decline in physical strength is commonly associated with aging in humans [2, 4]. Decreased force production by muscle underlies this drop in strength, which begins in the sixth decade of life and continues thereafter [21, 24, 36]. Force production is closely related to muscle cross-sectional area (CSA), and muscle atrophy is an important reason for declining force production with age [4]. However, several studies comparing groups of young and old human subjects indicate that the loss in muscle force cannot be entirely explained by this quantitative change in muscle cross-sectional area [5, 18, 25, 27, 36, 39]. This suggests that a change in the capacity to generate force per unit muscle area (force/CSA) contributes to the loss of strength with age. We will refer to the voluntary force produced per unit muscle CSA as specific force.

Estimates of the difference in specific force between young and old subjects range from about 10% [25] to 37% [36], so the loss of force production due to this mechanism may be substantial. It has been suggested that decreases in specific force indicate alterations in fiber recruitment [18], cellular properties such as fiber type [5, 25, 39], or the contractile mechanism [5]. However, loss of specific force with age is not universally observed [13, 14, 18, 25, 38]. Thus neither the extent to which changes in specific force contribute to declining strength nor the mechanisms responsible for altered specific force are clear. One limitation of many studies has been the inability to distinguish contractile CSA from other muscle components which do not generate force but may occupy significant space (e.g., intramuscular fat, connective tissue, etc.) [7]. This methodological problem leads to inaccurate estimates of specific force due to incorrect measures of muscle CSA. In elderly subjects, who tend to have increased intramuscular and subcutaneous fat, this may result in underestimates of specific force [9]. An additional limitation of previous studies is that the majority have compared an older with a younger group of subjects. Although this is sufficient to demonstrate gross differences due to age, it does not reveal the time course or the extent of changes in the elderly.

In this study, we quantify the relative contributions of muscle atrophy and loss of specific force to decreased force production in the elderly. Muscle atrophy represents a quantitative change in muscle, while loss of spe-

S.A. Jubrias (✉) · K.E. Conley
Department of Radiology,
University of Washington Medical Center,
Box 357115, Seattle WA 98195, USA

I.R. Odderson · P.C. Esselman
Department of Rehabilitation,
University of Washington Medical Center,
Box 356490, Seattle WA 98195, USA

cific force suggests the occurance of qualitative changes. Since the separation of contractile from non-contractile tissue area is crucial in the determination of muscle specific force, we used magnetic resonance imaging (MRI) to measure muscle CSA. MRI combined with quantitative morphometric analysis provides a straightforward method for quantifying the contractile CSA of muscle. The use of a regression design allows us to determine not only the existence of decrements, but also the rate of change in force and muscle CSA (and thus specific force) in our elderly subjects. Finally, we analyzed myosin heavy chain (MHC) isoforms (a correlate of fiber types) to determine whether the proportions of MHC change with age and whether this change contributes to strength loss. Our results indicate that there is a reduction in isokinetic specific force with age, that this reduction is a significant factor in the loss of strength in the elderly, and that this decline is not related to changes in muscle fiber type.

Materials and methods

Subjects

We tested 57 subjects aged 23–80 years (29 males, 28 females). There were no age-related differences in body weight (males 81.0 ± 2.6 kg, females 63.6 ± 1.6 kg) or height (males 175.3 ± 1.2 cm, females 161.6 ± 0.9 cm). Nine of the women (all aged 65 or older) were receiving hormone replacement therapy (HRT). All subjects were in good health with no orthopedic problems and no history of cardiovascular or neuromuscular disease. The subjects' activity profiles ranged from housework, yardwork, and occasional walks to aerobic activities several times per week. None of the subjects were trained athletes, and none habitually engaged in strength-training exercise. All subjects gave informed consent to participate in the study.

Isokinetic measurements

We used a Cybex 6000 dynamometer (Cybex, Ronkonkoma, N.Y., USA) for isokinetic testing of the right knee extensor muscles. Isokinetic testing is a highly reliable means of testing maximum efforts in young and old subjects [8, 33]. The seat back was set to a 90° angle. Subjects performed four warm-up repetitions followed by three test repetitions at speeds of 60, 120, 180, and 240°/s. The order of testing was randomized, and a 2-min rest period separated exercise at each speed. Subjects were encouraged to exert maximum effort during each testing bout. For each speed, the highest torque value achieved during the test trials was designated the maximum torque. For each individual, we measured the length of the lever arm of the external force (i.e., from the axis of rotation at the knee to the point of application of external resistance on the leg) and calculated force in Newtons by dividing the maximum torque values by this length. The resulting measurement represents the force generated at the leg, which underestimates the actual force of the quadriceps muscles. Although some authors [18, 23] have estimated quadriceps force by accounting for the moment arm at the knee joint itself (axis of rotation to patellar tendon), this measurement overestimates the force of the quadriceps. A true measure of quadriceps muscle force must take into account the fact that the four quadriceps tendons are not parallel for their entire lengths, the differing angles of fiber pennation [16], and that the moment arm of the knee changes as the knee joint angle changes [31]. We chose to use the measurement of leg force for two reasons. First, we wished to report measurements which would be comparable with those in the existing literature, and many studies of in vivo force and cross-sectional area have used a similar technique [5, 22, 25–27, 38, 39]. Second, Klitgaard et al [18] have noted a proportionality between the knee moment arm and the external force lever arm. We thus believe that, although our measurements are not quantitatively accurate, they do accurately reflect differences in muscle force among individuals.

CSA measurements

We measured CSA with MRI of the thigh. Subjects lay supine in a Signa 1.5 Tesla scanner (General Electric Medical Systems, Milwaukie, Wis., USA) while axial images were taken in series from the femoral head to the femoral condyles (15–20 images per subject). Two-dimensional spin echo images were collected with TR/TE = 600/10, 5 mm slice with a 20-mm interslice interval, 256 × 192, and 2 NEX. CSA was determined as follows using standard stereological techniques [37]. Images were magnified to ensure a sufficient sample size for point counting. A grid of equally spaced points was superimposed on the image, with each point representing a quantity of muscle area. The area value of the points was related to the magnification used. We counted the number of points falling on contractile and non-contractile tissues in the quadriceps muscle group, thus eliminating contributions to the muscle CSA by visible fat and other non-contractile connective tissues. The number of points counted was multiplied by the area value of a point to yield the total quadriceps contractile area for each image. The three consecutive images displaying the largest quadriceps areas were averaged, and this value was used as the CSA for that individual. The maximum CSA fell within the middle third of the thigh for all subjects. The distinction between contractile and non-contractile tissues was made visually by an experienced evaluator on the basis of intensity differences. The evaluator was blinded to the age and gender of subjects.

MHC analysis

We used the Bergstrom needle biopsy technique [12] to acquire tissue from the mid-thigh level of the right vastus lateralis muscle in 24 subjects aged 65–80. The sample was freeze clamped immediately after collection and stored at –80°F until subsequent analysis. MHC isoforms I, IIa, and IIb (IIx) were separated using the sodium dodecyl sulfate-polyacrylamide gel electrophoresis technique of Talmadge and Roy [34]. Rat diaphragm was run on each gel as the standard. Although there are differences in rat diaphragm and human skeletal muscle MHCs, these differences are consistent and well documented [30]. The gels were imaged using a CCD camera interfaced with a frame-grabber board. The relative proportion of each isoform was quantified using the gel analysis macro in the program "NIH Image".

Statistics

Data on body weight, height, and percentage non-contractile tissue were tested with analysis of variance (ANOVA) and a significance level of $P \leq 0.05$. Averaged data are reported as mean ±SE. All other data were evaluated with regression analysis and a significance level of $P \leq 0.05$. Polynomial equations did not fit the data significantly better than linear equations, so all reported regressions are linear. We used the StatView 512+ statistical program (BrainPower, Calabasa, Calif., USA) for the MacIntosh computer.

Results

Isokinetic force

We first asked whether the isokinetic knee extension force produced by our subjects varied with age. Over the

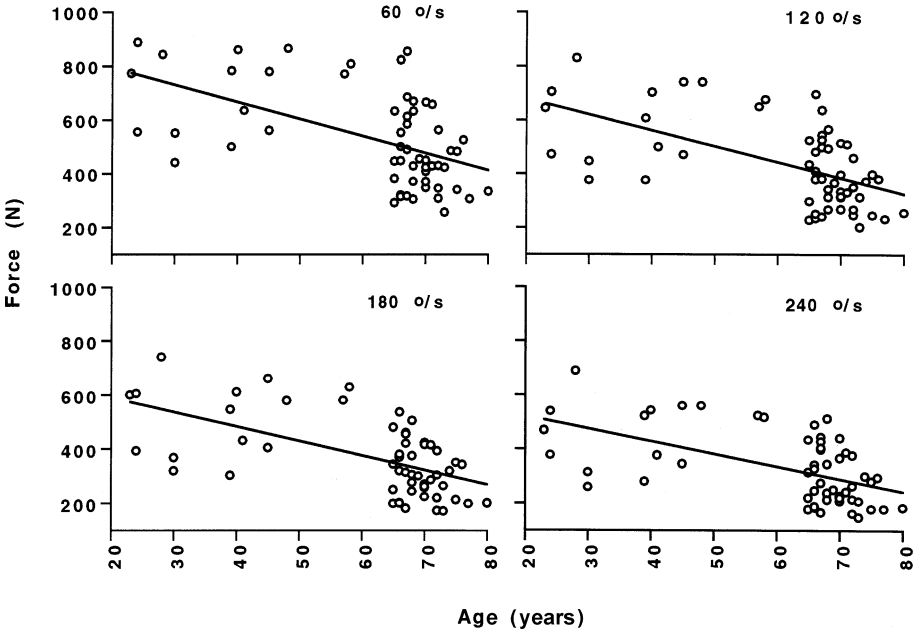

Fig. 1 Relationship between force and age. Data are shown on the same scale for four angular velocities of isokinetic knee extension. The *solid lines* are the linear regressions. All relationships are significant ($P = 0.001$). See Table 1 for r^2 values

Table 1 Force vs age at 4 angular velocities of knee extension (upperpart). Data are fit with linear regression equations. The lowerpart lists the equations for significant regressions and the 95% confidence limits of the slopes

Velocity	Ages 23–80		Ages 23–57		Ages 65–80	
	r^2	P	r^2	P	r^2	P
60°/s	0.29	0.001	0.04	0.47	0.08	0.08
120°/s	0.32	0.001	0.03	0.53	0.12	0.03
180°/s	0.34	0.001	0.03	0.53	0.11	0.04
240°/s	0.30	0.001	0.03	0.54	0.10	0.04

Ages 23–80, 60°/s y = –6.348x + 920.617, –9.009 to –3.687
120°/s y = –5.891x + 796.891, –8.2 to –3.581
180°/s y = –5.365x + 699.209, –7.377 to –3.353
240°/s y = –4.64x + 614.926, –6.557 to –2.723

Ages 65–80, 120°/s: y=–11.547x+1181.296, –21.553 to –1.542
180°/s: y=–8.942x+937.783, –17.184 to –0.663
240°/s: y=–8.681x+888.586, –16.92 to –0.443

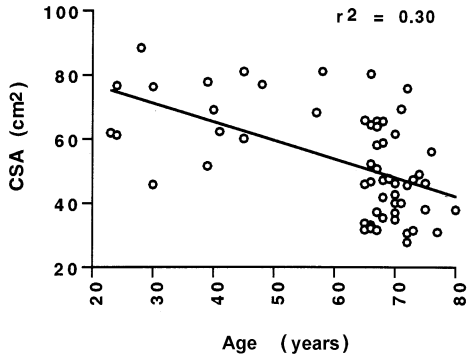

Fig. 2 Relationship between quadriceps muscle cross-sectional area (*CSA*) and age

full age range of our subjects (23–80 years), force decreased significantly with age at all speeds tested (Fig. 1, Table 1). Linear regression equations fit these data as well as higher order equations. Since muscle force is maintained into the sixth decade [21, 24, 36], the linearity of our data may result from the fact that we have few data points representing ages 50–65 years. Subjects showed no loss of force between the ages of 23–57 years (Table 1). In contrast, when we examined subjects aged 65–80 years, regression analysis shows that force at the three highest test velocities (120, 180, and 240°/s) dropped at an average of 10 N/year. This resulted in a 39% decline in force from 65 to 80 years. Force at 60°/s dropped by 31%, but this was not statistically significant.

For this age range (65–80), we saw no differences in the decline in force between men and women or between women with and without HRT. We therefore analyzed these data as one group. One study has shown that women not using HRT begin to lose muscle force at the onset of menopause, or about 10 years earlier than men or women on HRT [27]. It is possible that the variance of our data prevented the detection of actual differences among these groups, or of differences existing prior to age 65.

CSA

Our data illustrate the importance of excluding noncontractile tissues (intramuscular fat and connective tissue) from the determination of muscle CSA. When expressed as a fraction of the total "muscle" CSA, subjects aged 65–80 years had more than twice the amount of intramuscular noncontractile tissue as subjects aged 23–57 (0.17 ± 0.007 and 0.07 ± 0.006, respectively ($F_{(1,53)} = 49.8$, $P = 0.0001$)). There was no difference between males and females.

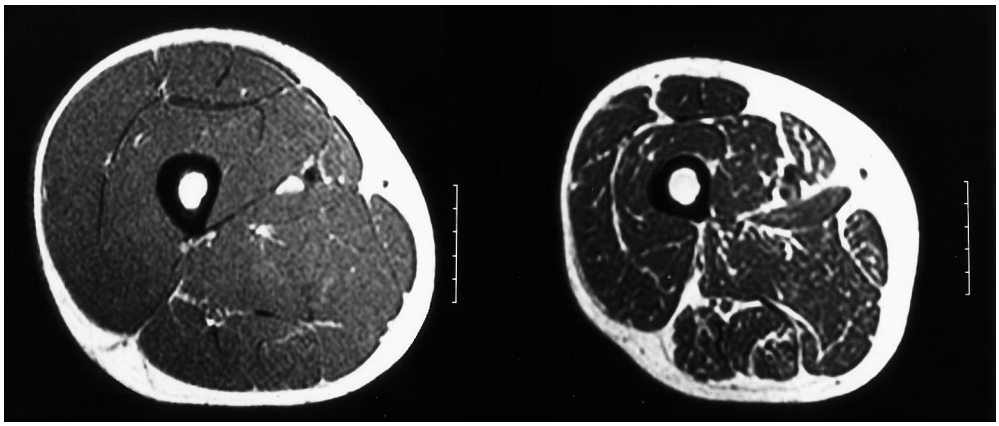

Fig. 3 Cross-sectional magnetic resonance images of the mid thighs from 24 year old (*left*) and 65 year old (*right*) subjects with the same body mass. Scale increments are 1 cm

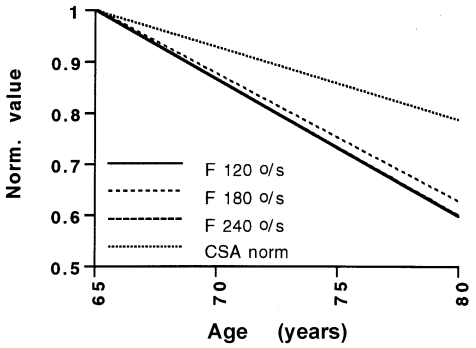

Fig. 4 Relationship between CSA or force (*F*) and age. The *y-axis* shows normalized values based on linear regression equations for ages 65–80 yrs

To examine the role of CSA in the decline of force, we measured the changes in muscle size with age. Quadriceps CSA decreased linearly with age ($r^2 = 0.30$, $P \leq 0.0001$, Fig. 2), although this linear fit may also be related to the small number of subjects aged 50–65. MRI images of the thigh (Fig. 3) illustrate the trend toward smaller muscle CSA, greater infiltration by fat, and a thicker layer of subcutaneous adipose tissue in older subjects. We used two approaches to evaluate whether this drop in muscle CSA accounted for the decline in force seen in our older subjects. First, we plotted the declines of CSA and force from 65–80 years (Fig. 4). The decrease in CSA should match that of force if reduced CSA were to account fully for lower force production. However, force dropped by 39% while CSA declined by only 21%. The change in muscle CSA thus accounted for only about half of the change seen in force production. In our second approach, we sought to confirm these mismatched changes in force and CSA by examining muscle specific force in subjects aged 65–80 years. If muscle atrophy alone underlies the force decrement, then F/CSA (specific force) should remain constant. However, if specific force decreases then muscle atrophy cannot be the sole mechanism responsible for the loss of force production with age. Regression analysis revealed that specific force declined significantly at the three highest angular velocities (120, 180, and 240 /s) in subjects aged 65–80 years (Fig. 5, Table 2). Similar to the pattern seen for force, there was no change at the slowest speed (60°/s). The average drop in specific force between these ages was 1.5 N/cm^2, or 21%. The rates of decline in specific force are similar for these three angular velocities (Fig. 5). In contrast, younger subjects (23–57 years) showed no such decrement in specific force (Table 2). The 21% decrease in specific force accounts for just over half of the 40% drop in force production by subjects older than 65. Thus, muscle atrophy accounts for only about half of the decline in force with age.

MHC isoforms

We examined whether the decline in specific force with age is related to changes in the content of specific fiber types (see Discussion). We identified relative proportions of muscle fiber types based on analysis of MHC isoforms in 24 subjects aged 65–80 years. The percentages of MHC isoforms in a sample correspond closely with fiber type percentages based on histochemical determination of myofibrillar actomyosin adenosine triphosphatase (ATPase) rates [1, 35], and MHC composition is the major determinant of a fiber's mATPase reaction [19]. On average, the vastus lateralis muscle was composed of similar fractions of MHC type I and type IIa isoforms (44% and 39%, respectively) (Table 3), and the type IIb isoform accounted for a smaller fraction of the total (17%). However, the averaged data mask a strikingly wide range of MHC compositions in our subjects. For example, the ranges for MHC types I and IIa content were 22–69% and 25–58% respectively, and MHC type IIb content ranged from 3–32% (Table 3). Although the fraction of MHC type IIb declined with age ($r^2 = 0.23$, $P = 0.02$), there was no similar change in the fraction of other MHC isoforms. MHC composition was not related to specific force at most angular velocities, but an inverse correlation was found between MHC type I content and specific force at 120°/s ($r^2 = 0.17$, $P = 0.04$). Thus it appears that we cannot account for the decline in specific

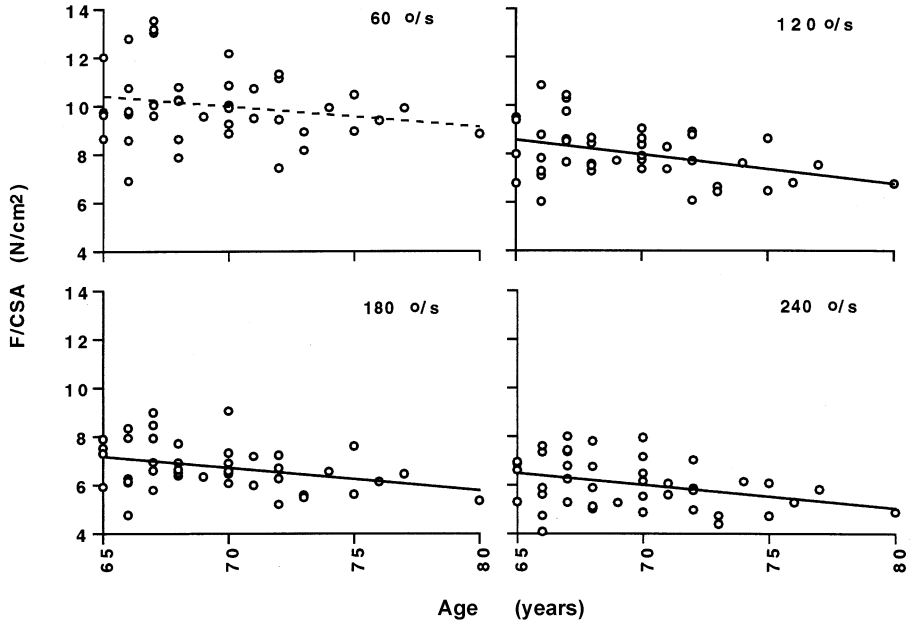

Fig. 5 Relationship between specific force (F/CSA) and age at different angular velocities. Data are shown on the same scale for four angular velocities of isokinetic knee extension. *Lines* are the linear regressions, *solid lines* indicate significant relationships ($P < 0.05$), the relationship shown by the *dashed line* is not significant. See Table 2 for r^2 values

Table 2 The relationships between specific force (force/cross-sectional area) and age at four angular velocities of knee extension. The *upperpart* shows r^2 and P for these relationships. Data are fit with linear regression equations. The lower part shows the equations for significant regressions and the 95% confidence limits of the slopes

Velocity	Ages 23–57		Ages 65–80	
	r^2	P	r^2	P
60°/sec	0.01	0.78	0.04	0.19
120°/s	0.01	0.78	0.15	0.01
180°/s	0.01	0.77	0.11	0.03
240°/s	0.01	0.68	0.11	0.03

Ages 65–80, 120°/s: y=–0.121x+16.472, –0.214 to –0.029
180°/s: y=–0.092x+13.144, –0.174 to –0.01
240°/s: y=–0.096x+12.713, –0.182 to –0.011

Table 3 Myosin heavy chain (MHC) isoforms of elderly muscle (ages 65–80)

Type	Mean[a]	SE	Range
MHC I	0.44	0.02	0.22–0.69
MHC IIa	0.39	0.02	0.25–0.58
MHC IIb	0.17	0.02	0.03–0.32

[a] Data are expressed as a fraction of the total

force after 65 years of age on the basis of the MHC composition of the vastus lateralis.

Discussion

The primary focus of this study was to determine the relationship between muscle force and CSA in elderly humans. This is important because if loss of force is due primarily to muscle atrophy, then the problem is essentially one of quantitative changes in muscle and may be significantly affected by exercise training. However, the finding of a progressive decrement in muscle specific force in older subjects would suggest qualitative changes which may be less amenable to exercise intervention. To address these issues, we first used a wide age range of subjects to confirm previous reports of decreased force and CSA in the elderly. We then determined the relative contributions of muscle atrophy and loss of specific force to changes in force production in subjects 65–80 years of age. In older subjects, knee extensor isokinetic force decreased with age at the three fastest angular velocities tested. Only about half of this decline resulted from smaller muscle CSA. The specific force in these subjects decreased at the rate of about 1.5% per year. Thus, the common observation of declining force production appearing in the sixth decade of life [21, 24, 36] is due in equal parts to reduced muscle CSA and specific force.

The processes which result in reduced specific force with age are not clear. One factor related to specific force in the elderly is their level of physical activity. Klitgaard et al. [18] found that sedentary elderly subjects showed a decline in specific force, but elderly subjects with a long and recent history of strength or endurance training had specific forces equal to those of the young. This result suggests that the drop in specific force often seen with aging may be related to the relative physical inactivity of the elderly. Thus, differences in the populations studied may explain the disparate reports on specific force and aging found in the literature. However, this is difficult to determine since the current level and history of physical activity of subjects in these studies are rarely quantified. Our subjects were classified as physically active, but not trained athletes, although we did not examine their history of participation in physical activities. We thus exam-

ined a population not studied by Klitgaard et al. [18]. Our finding of reduced specific force in physically active older subjects, coupled with Klitgaard's similar finding in a sedentary group, suggests that a protective effect of exercise may only appear when exercise is performed at a high intensity. Although we found a significant correlation between specific force and age, only a small portion of the variance in specific force was explained (average $r^2 = 0.11$, Table 2) by age. Klitgaard's results [18] suggest that history of physical activity may also account for a portion of the variance, and this possibility should be examined in future studies.

Several mechanisms for an age-related reduction in specific force have been proposed, including smaller type II muscle fiber CSA [5, 25, 39], a change in the contractile apparatus [5], and alteration of recruitment or neuronal patterns [18]. We asked whether changes in MHC isoform content (used as a correlate of fiber type) were related to the altered specific force in our subjects. We found that the proportion of MHC type IIb isoform declined with age, but neither the fraction of this isoform nor the other fast MHC isoforms correlated with specific force in our subjects. MHC type I content accounted for a small fraction of the variance in specific force at 120°/s, but no systematic relation between MHC isoform content and specific force was apparent in our data. Other reports also have found no relationship between specific force and MHC or fiber type in young and old subjects [18, 29, 32]. The lack of relationship between myosin isoforms and specific force in our subjects makes it unlikely that the decline in specific force seen with age is based on a change in fiber types. This conclusion is supported by the observation in mice that changes in the proportions of native myosins are not responsible for age-related reductions in specific force [28]. It should also be noted that in vitro studies indicate that slow and fast myosins produce approximately equal forces [30]. Therefore, a selective loss of fast rather than slow isoforms should have no influence on specific force.

Our subjects demonstrated a drop in specific force at the faster speeds (120, 180, 240°/s), but not at the slowest speed (60°/s) tested. This observation agrees generally with that of Overend et al [25], who have reported that, compared with 25 year-olds, 70 year-old subjects have lower specific force with isokinetic testing (120°/s) but not with isometric (0°/s) testing. They proposed that a loss of specific force at higher speeds may be due to atrophy of type II muscle fibers. If this hypothesis is correct, then the decrement in specific force with age should increase with faster speeds of movement in isokinetic testing. In our subjects, the rate of decline in specific force with age was similar at 120°/s and above, indicating that the loss of specific force is not speed dependent for this range. Although we did observe a decrease in the proportion of MHC type IIb isoform with age, this isoform was not related to specific force at any test speed. Several studies have demonstrated a slowing of muscle twitch properties with age which may result from a decreasing proportion of type II fibers [9, 24]. It can be argued that this may influence the ability to generate force at higher limb speeds. Although we have no data on the twitch properties of these muscles, we found no relation between force and MHC isoforms at any speed tested. Thus, the appearance of decrements in specific force at faster, but not slower, speeds is not explained by changes in muscle fiber type.

Although changes in muscle fiber type do not appear to affect specific force, studies of elderly humans and animals have demonstrated alterations in muscle cell function which could affect force production. For fast fibers, Delbono [10] has shown a reduction in calcium release by the sarcoplasmic reticulum (SR) in humans, and the specific activity of the SR calcium pump is depressed in the rat [20]. Single fibers from old mice show a right shift of the force-pCa curve, indicating a decreased sensitivity to calcium [3]. Consistent with this, these fibers generate lower specific force than young fibers when stimulated with submaximal levels of calcium [3], although specific force is not different with maximal activation. Phillips et al. [28] have reported lower specific force in isolated mouse muscle, and attribute this to a proportional shift of crossbridges to the low-force state. There is thus a reasonable body of evidence that there are alterations at the level of the muscle fiber which may result in lower specific force.

On the other hand, there are also significant neurological changes which could lead to a depression of force production in vivo in the absence of problems at the cell level. Aging is associated with a reduction in the number of motor units after the age of about 60 years, an effect which could lead to reduced muscle force in vivo [6, 11, 15, 32]. In addition, the average size of remaining motor units increases, and it is thought that this occurs through the reinnervation of at least some of the muscle fibers which lost their original motor neuron [15, 32]. Thus, loss of motor units should only affect force production to the extent that reinnervation of muscle fibers is incomplete [32]. The decrease in motor units is associated with muscle atrophy and loss of fibers [11] and should manifest itself as a decrease in muscle CSA. This suggests that the reduction in motor units would affect muscle force, but not necessarily muscle specific force.

There are, however, other neural changes which would be likely to reduce specific force in vivo. For example, inability to recruit all motor units on demand would lead to lower force/CSA. Although we did not test our subjects for their ability to recruit fully their quadriceps during isokinetic testing, several studies report no deficiency in their elderly subjects' muscle recruitment [11, 26, 36]. Maximum muscle force is attained through two mechanisms: recruitment of all motor units, and maximal firing frequencies (discharge rates) of the motor neurons. Older humans exhibit lower discharge rates than younger subjects [15, 17]. It is possible that these lower discharge rates are offset by the higher relaxation rates found in older muscle, such that comparable force is attained at lower frequencies. However, the absence of

such a relationship could lead to reduced force production by muscles in which all motor units are recruited.

Our data allow us to draw few conclusions about the mechanisms underlying the reduction of specific force in our subjects. It does not appear that changes in MHC isoforms are responsible for this drop, but we cannot speak to other alterations at the cellular or neurological levels. Further experiments are needed to distinguish the contributions of neural and muscle cell changes to the decline of specific force with age.

In conclusion, our major objective was to determine the relative contributions of muscle atrophy and declining specific force to decreased force production in aging muscle. Smaller contractile CSA (atrophy) and loss of specific force each explained roughly half of the change in force in our older subjects. Thus, the loss of force in these subjects was due to both quantitative and qualitative changes. Since specific force was not related to MHC isoforms, it is likely that changes in muscle recruitment, contractile apparatus function, or excitation-contraction coupling are responsible for alterations in specific force.

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