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Variability in muscle fibre areas in whole human quadriceps muscle: effects of increasing age

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INTRODUCTION

With increasing age, the volume of human skeletal muscle is gradually reduced (Allen, Andersen & Langham, 1960; Tzankoff & Norris, 1977; Grimby, Danneskiold-Samsøe, Hvid & Saltin, 1982), leading to a decline in motor function (Grimby & Saltin, 1983; Vandervoort, Hayes & Belanger, 1986). Our knowledge of the cause of this ageing atrophy has increased through enzyme histochemical preparation of muscle biopsies and quantitative assessment of the sizes of the different fibre types. It is generally agreed that the size of Type 2 (fast-twitch) fibres is considerably reduced with increasing age, while the size of Type 1 (slow-twitch) fibres remains more or less unaffected (Tomlinson, Walton & Rebiez, 1969; Jennekens, Tomlinson & Walton, 1971; Tomonaga, 1977; Larsson, Grimby & Karlsson, 1978; Scelsi, Marchetti & Poggi, 1980; Aniansson, Grimby, Hedberg & Krotkiewski, 1981; Grimby *et al.* 1982; Lindboe & Torvik, 1982; Nygaard & Sanchez, 1982; Aniansson, Hedberg, Henning & Grimby, 1986; Essén-Gustavsson & Borges, 1986; Poggi, Marchetti & Scelsi, 1987).

However, because of the nature of the biopsy techniques, only a very small part of whole human muscles can be investigated. Our knowledge of the composition of individual human muscles at different ages and the variability between individuals is therefore limited. Consequently, several fundamental questions about the relationship between structure and function of the human muscle remain unanswered and our understanding of the mechanisms underlying the normal development and ageing of human muscle is incomplete.

The development of new equipment, i.e. large cryomicrotomes, and modified morphometric procedures now enable us to prepare and to analyse cross-sections of *whole* human muscles from autopsies (Lexell, Henriksson-Larsén & Sjöström, 1983*a*). Extensive studies of the vastus lateralis muscle from previously physically healthy men, 15 to 83 years of age, have then revealed a complex distribution of the different fibre types (Lexell *et al.* 1983*a*; Lexell, Downham & Sjöström, 1984; Lexell & Taylor, 1989) and considerable changes throughout the whole fibre population with increasing age (Lexell, Henriksson-Larsén, Winblad & Sjöström, 1983*b*; Lexell, Downham & Sjöström, 1986; Lexell, Taylor & Sjöström, 1988).

To elucidate further the relationship between structure and function of human muscle at different ages, we have continued our morphometrical analysis of *whole* human muscles from autopsies, and this study examines in detail the sizes of the different fibre types at different ages and the variability within individual muscles and between individuals. Cross-sections of the vastus lateralis muscle from 20 men between 19 and 84 years were prepared and the cross-sectional areas of 375 Type 1 and Type 2 fibres were measured in five different regions throughout each muscle.

MATERIALS AND METHODS

Muscle and subjects

The vastus lateralis muscle from the right leg of 20 previously physically healthy normally active men were extirpated less than three days *post mortem*. Each man had suffered a sudden accidental death. None had a history of neuromuscular disease, nor was there evidence of pathological abnormalities at the *post-mortem* examination. Ethical consent was obtained from the Swedish National Board of Health and Welfare. The 20 men were divided into two age groups: there were 8 and 12 men in each age group, mean age 27 years (age range 19–35 years) and 77 years (69–84 years), respectively.

Preparative procedure

A slice about 10 mm thick was cut from each muscle approximately 200 mm from its origin (half way between the origin and the insertion), frozen in liquid nitrogen and embedded in carboxymethyl cellulose (CMC). Thin cross-sections (15 μm) were prepared and were stained for myofibrillar adenosine triphosphatase (mATPase) at pH 10·4 to visualise Type 1 (lightly stained) and Type 2 (heavily stained) fibres (Lexell *et al.* 1983*a*).

Sampling and measuring procedure

Measurements of the muscle fibre cross-sectional area (CSA) were made from photographs (magnification $\times 120$) using a planimetry system which included a digitising tablet connected to a micro-computer (ABC 800, Luxor AB, Sweden) and a standard morphometric programme. Measurements were made in those parts of the muscle cross-section where the quality was ideal and permitted reliable identification of the fibre types. No measurements were made in parts with artefacts, e.g. ice-crystal damage and fibres with fuzzy cell borders, or in parts where fibres had a tendency to have been longitudinally sectioned.

In each of the muscle cross-sections, five regions were selected, and each region was classified as lying superficially (S), i.e. close to the skin, or deeply (D), i.e. towards the bone. In each region, a fibre of a given type was selected haphazardly and measured, and the nearest 74 fibres of the same type were measured. This process was repeated for the other fibre type, and a total of 375 fibres of each type was measured within every muscle cross-section.

Description of the data

For each of the five regions in the muscle cross-sections, the mean, the standard deviation (S.D.) and the range of the CSA (μm^2) of the 75 Type 1 and 75 Type 2 fibres were obtained. The mean and S.D. for the whole muscle cross-sections were calculated using all the data of each type of the 375 fibres. Finally, the difference between the mean CSA of Type 2 and Type 1 fibres, i.e. Type 2 minus Type 1, for each region and for each muscle cross-section was calculated.

Statistical analysis

A t test, an F test and an analysis of variance were used throughout. The t statistic was calculated to test the difference between the mean Type 1 and the mean Type 2 fibre CSA for each region and for each muscle cross-section and the difference between young and old individuals. The F statistic was calculated on the basis of the ratio of

Table 1. *Estimates of mean muscle fibre cross-sectional area (CSA) in whole cross-sections of vastus lateralis muscle from 20 men*

Individual and age (years)		Muscle fibre CSA (μm^2)					
		Type 1 fibres			Type 2 fibres		
		Mean	S.D.	Range	Mean	S.D.	Range
1	19	4129	1181	1407–7325	4112	909	1020–7587
2	20	4257	1320	1084–8009	4985	928	2927–11776
3	26	3823	1198	1219–8496	4655	1252	1839–9234
4	27	3341	822	836–9386	3261	924	338–7148
5	29	4060	1573	1155–9457	4621	1129	1453–8774
6	30	3501	763	1354–8417	3373	535	1189–5780
7	31	3446	1135	992–10750	3697	1163	1235–7168
8	35	4286	1168	1445–9027	4206	819	1986–9378
Means (S.D.):							
	27	3855	1145		4113	957	
	(5)	(382)	(259)		(629)	(227)	
9	68	2484	740	980–4719	1417	567	279–3733
10	70	3666	1091	1222–7300	3011	989	702–6096
11	71	4463	1726	690–11658	3516	1386	622–8488
12	72	3314	931	651–6973	2703	854	395–5227
13	73	4620	1437	1416–10090	3640	1021	827–6913
14	75	2891	823	897–5199	2026	695	246–5059
15	79	2714	717	411–5654	1861	720	188–4967
16	80	3489	1015	1166–7894	2634	1307	467–15399
17	81	2739	677	1091–5521	1869	603	195–5119
18	82	4475	1676	344–9098	3561	1348	773–8394
19	84	3948	1557	743–15657	3086	998	279–6133
20	86	4509	1192	373–9107	3033	915	837–6102
Means:							
	77	3609	1132		2696	950	
	(6)	(790)	(383)		(748)	(283)	

A total of 375 fibres of each type was measured within every muscle cross-section. The mean, S.D. and range for each individual were calculated from all the data of each type of the 375 fibres.

the variance of the CSA of Type 1 and Type 2 fibres for each region and for each muscle cross-section. The analysis of variance was used to test the mean CSA of Type 1 and Type 2 fibres for homogeneity between the five regions.

RESULTS

General morphology

Fibres in all 20 muscle cross-sections were tightly packed in well-preserved fascicles. With very few exceptions, the shape and size of fibres in muscle cross-sections from the young individuals appeared normal. Fibres in muscle cross-sections from the old individuals showed different structural 'abnormalities' ranging from clearly seen differences in size to variations in shape. Small and sometimes angulated fibres, both isolated ones and groups of various sizes of these fibres could also be seen, as well as large hypertrophied fibres of both types. Changes were, in general, most prominent in muscle cross-sections from individuals above 79 years of age where they occurred on average in two thirds of all fascicles; in muscle cross-sections from the 69–74 years old individuals changes were seen in one third of all the fascicles.

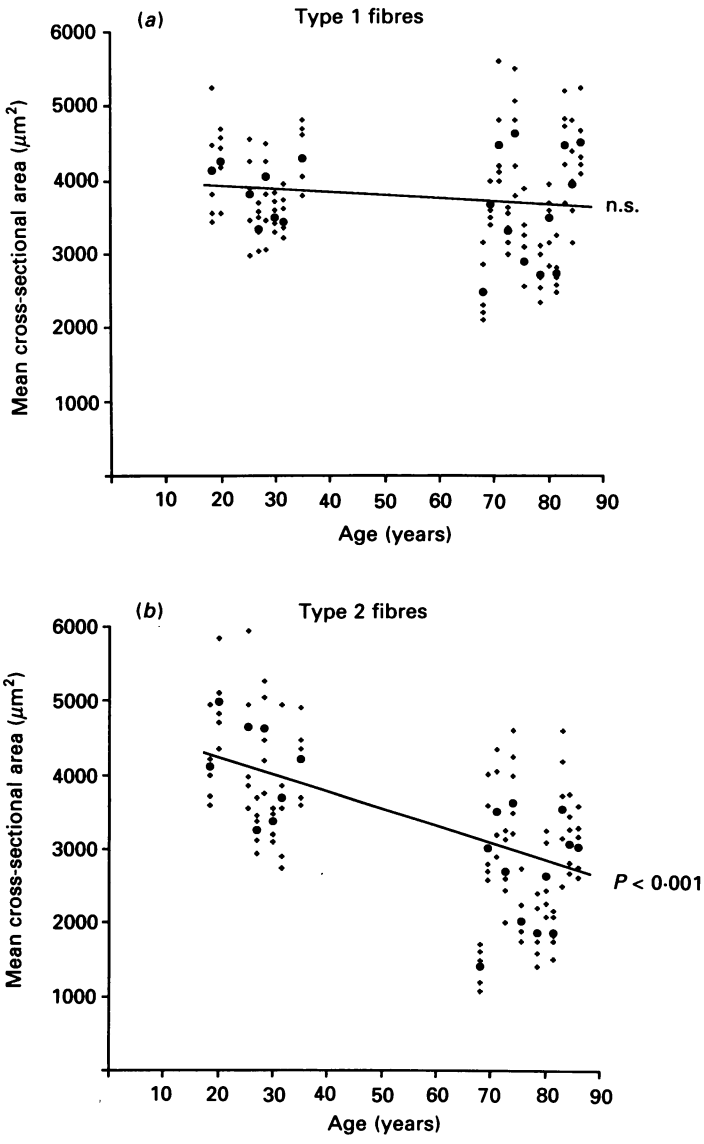

Fig. 1 (*a–b*). The mean cross-sectional area (CSA) (μm^2) of (*a*) Type 1 fibres and (*b*) Type 2 fibres for five regions (+) together with the mean values (●) for whole cross-sections of the vastus lateralis muscle from 20 men. The regression lines and the significance levels give the relationship between the mean Type 1 and Type 2 fibre CSA (●) and age.

Overall variation between and within the muscle cross-sections

Data on the mean, S.D. and range of the CSA of Type 1 and Type 2 fibres for each muscle cross-section are given in Table 1, with the means for the two age groups.

For Type 1 fibres, both the smallest and the largest mean CSA value for a muscle cross-section are found in the old age group. For Type 2 fibres, the largest value is found in the young age group and the smallest value in the old. The ratio between the smallest and the largest mean CSA value for the young individuals is 1·28 for Type 1

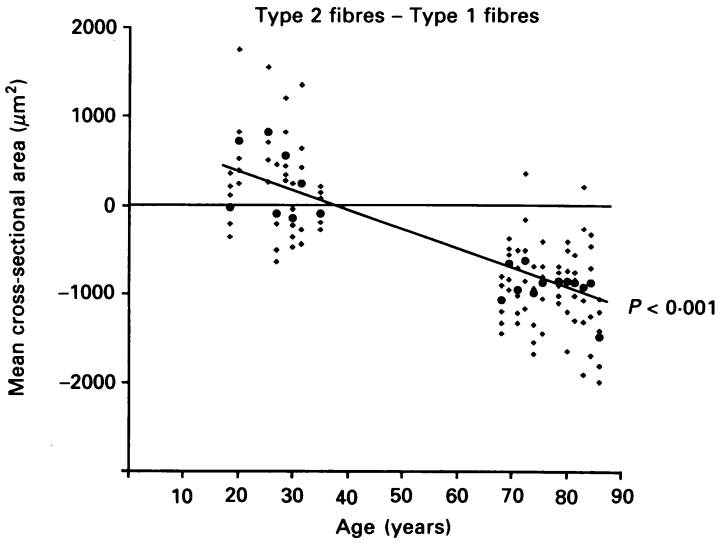

Fig. 2. The difference between the mean cross-sectional area (CSA) (μm^2) of Type 2 and Type 1 fibres [Type 2 – Type 1] for five regions (+) together with the mean (●) difference for whole cross-sections of the vastus lateralis muscle from 20 men. The regression line and the significance level give the relationship between the mean differences (●) and age.

fibres and 1·53 for Type 2 fibres, and for the old 1·86 for Type 1 fibres and 2·57 for Type 2 fibres.

The S.D. of the mean CSA value for muscle cross-sections from the young individuals varies from 763 to 1573 for Type 1 fibres and 535 to 1252 for Type 2 fibres, with mean values of 1145 and 957, respectively. For muscle cross-sections from the old individuals, the variation in S.D. of the mean CSA value for Type 1 fibres is 677 to 1726 and for Type 2 fibres 567 to 1386, with mean values of 1132 and 950, respectively.

For the young individuals, the difference between the smallest and the largest single fibre CSA value for a muscle cross-section varies by a factor of 4 to 21, with mean values of 7·8 and 7·3 for Type 1 and Type 2 fibres. For the old individuals, the difference varies by a factor of 4·8 to 33·0, with a mean value of 12·4 for Type 1 fibres and 17·0 for Type 2 fibres.

Variation between and within the regions

The mean CSA of Type 1 and Type 2 fibres for the five regions in each of the muscle cross-sections from the young and the old individuals are presented in Figure 1 (*a*, *b*).

There is a highly significant ($P < 0.001$) variation in the mean CSA of both Type 1 and Type 2 fibres within all 20 muscle cross-sections, i.e. the hypothesis of homogeneity between the five regions can be rejected at the 0·1% significance level. However, the variation within a muscle cross-section is considerably different between the individuals, see for example the 29 and 30 years old individuals, and the 70 and 73 years old individuals in Figure 1 (*a*), which are the two most extreme cases in each age-group.

For the young individuals, the variance of the mean CSA of Type 1 fibres is significantly ($P < 0.05$) larger than that of Type 2 fibres in 35 out of 40 regions (87·5%). For the old individuals, the variance of the mean CSA of Type 1 fibres is significantly ($P < 0.05$) larger than that of Type 2 fibres in only 24 out of 60 regions (40%).

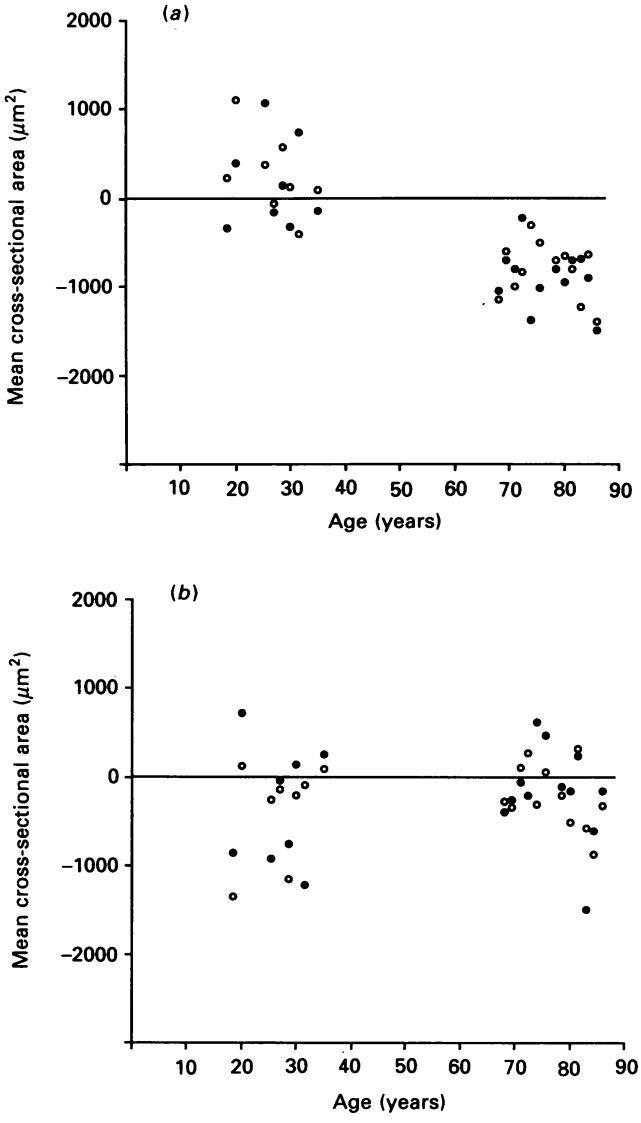

Fig. 3(*a–b*). (*a*) The difference between the mean cross-sectional area (CSA) (μm^2) of Type 2 fibres and Type 1 fibres in superficial regions (○) [Type 2 (S) – Type 1 (S)] and in deep regions (●) [Type 2 (D) – Type 1 (D)], and (*b*) the difference between the mean cross-sectional area (CSA) (μm^2) in superficial and in deep regions for Type 1 fibres (○) [Type 1 (S) – Type 1 (D)] and Type 2 fibres (●) [Type 2 (S) – Type 2 (D)], for whole cross-sections of the vastus lateralis muscle from 20 men.

For both the young and the old age groups there is a significant ($P < 0{\cdot}05$), positive, correlation between the mean CSA of Type 1 and Type 2 fibres. Analysing each individual separately, there is a significant ($P < 0{\cdot}05$), positive, correlation between the mean CSA of Type 1 and Type 2 fibres in the sampled regions from 4 of the 8 young individuals (50%) and in 3 of the 12 old individuals (25%).

Differences between the fibre types

In Figure 1(*a*, *b*) the relationships between age and the mean CSA of Type 1 and Type 2 fibres for each muscle cross-section are presented. For Type 1 fibres, there is no

significant relationship between the mean CSA and age. For Type 2 fibres, there is a strong relationship with increasing age: the mean CSA of Type 2 fibres is significantly ($P < 0.001$) smaller in muscle cross-sections from the old individuals.

The difference between the mean CSA of Type 2 and Type 1 fibres, i.e. Type 2 minus Type 1, for each region and for each muscle cross-section, is presented in Figure 2. A positive value indicates that the mean Type 2 fibre CSA is larger than the mean Type 1 fibre CSA in that region or muscle cross-section. For the young individuals all values lie around the zero line or above the line; there is a positive value in 27 out of 40 regions (68%). For the old individuals, there is a positive value in only 2 out of 60 regions (3%). There is also a strong relationship with increasing age; the mean difference between Type 2 and Type 1 fibres for a muscle cross-section is significantly ($P < 0.001$) smaller in the old individuals. The difference between the mean Type 2 and Type 1 fibre CSA ranges from -630 to $+1750$ in regions from the young individuals, and from -1990 to $+360$ in regions from the old individuals.

Difference between superficial and deep regions

To investigate the variation of the fibre CSA with depth, the mean CSA of Type 1 and Type 2 fibres in all superficial and in all deep regions were compared.

Firstly, the difference between the mean CSA of Type 2 and Type 1 fibres in superficial regions (Type 2_S minus Type 1_S) and in deep regions (Type 2_D minus Type 1_D) are compared for each individual (Fig. 3*a*). There is no significant difference for either age group. Secondly, the difference between the mean Type 1 fibre CSA in superficial and in deep regions (Type 1_S minus Type 1_D) and the difference between the mean Type 2 fibre CSA in superficial and in deep regions (Type 2_S minus Type 2_D) are compared for each individual (Fig. 3*b*). For both the young and the old individuals, no significant difference in CSA with depth either for Type 1 or for Type 2 fibres is found, when treated separately. When the mean CSA values for both Type 1 and Type 2 fibres from all the superficial regions of the young individuals are combined, and then compared with the summarised mean CSA values for both fibre types from all the deep regions of the same muscle cross-section (S_1 plus S_2 vs. D_1 plus D_2), a significant ($P < 0.05$) difference is found, i.e. the combined mean fibre CSA is larger in the deep regions than superficially. For the old age group, no significant difference between the combined data from superficial and deep regions is found.

DISCUSSION

The possibility of preparing cross-sections of *whole* human muscles has allowed detailed determination of the fine architecture of individual muscles at different ages and thereby revealed considerable alterations throughout the fibre population as part of the normal development and ageing processes. The present results on the muscle fibre CSA at different ages, and the variability within individual muscles and between individuals, are no exception and correspond well with previous patterns of changes.

There are well-known problems associated with the measurement of muscle fibre areas, so we have kept to the same precautions as in previous studies (Lexell & Taylor, 1989). The choice of individuals is equally important, as the muscle fibre area can be affected by the subject's nutritional status, level of physical activity, state of health, etc. (Lindboe & Platou, 1982; Lindboe & Torvik, 1982). All the 20 individuals were, as in our previous studies, healthy and 'normally' active until their sudden death, and no one with an ongoing or previous history of systemic disease was included. By that, we believe the demonstrated range of CSA values within and between the muscle cross-

sections, and the differences between the muscle fibre types reflects reality, i.e. the situation in the *living* human muscle of *healthy* young and old men in Sweden.

The most noticeable – and previously also the only clearly documented – age-related morphological finding is the significant reduction in the size of Type 2 fibres. In this study, the mean CSA of Type 2 fibres was on average nearly 35% smaller ($P < 0.001$) in old muscles. The effect of age on the size of Type 1 fibres is also known to be much smaller. Here, there was no significant effect of age on the mean CSA of Type 1 fibres, and from Table 1 it can be calculated that the mean CSA of Type 1 fibres was on average only just over 6% smaller in old muscles.

Previous studies of whole muscles have, above all, revealed a considerable inter- and intramuscular heterogeneity at all ages (Lexell *et al.* 1983*a*, *b*, 1986, 1988). In this study, the mean CSA of both fibre types varied similarly *between* the individuals in both age groups, but the variation was markedly larger in the old age group, particularly for Type 2 fibres.

There was also a highly significant ($P < 0.001$) variation in the mean CSA of both fibre types *within* every muscle cross-section. This may, at least partly, explain the large discrepancies between studies based on single biopsies, both with respect to the reported age-related reduction in the size of Type 2 fibres (5–40%), and why it has been speculated that the size of Type 1 fibres may even increase with advancing age.

There were also very close points of similarity between previously found changes in the distribution of different fibre types with increasing age, and the alterations in the distribution of the fibre CSA demonstrated here. In muscles from young men, the proportion of different fibre types varies systematically: Type 2 fibres predominate superficially and Type 1 fibres in deep regions (Lexell *et al.* 1983*a*) and Type 2 fibres are much more common on the boundary of fascicles than internally (Lexell *et al.* 1984). In old muscles, the pattern is changed towards a more homogeneous distribution of the fibre types, both with regard to the region of the muscle (Lexell *et al.* 1983*b*) and within individual fascicles (Lexell *et al.* 1986). Here, the fibre CSA also varied in young muscles as a function of depth – fibres in the deep regions of the muscle were significantly larger than superficially – while in old muscles there was no significant systematic difference between superficial and deep regions.

Another consistent difference between the two age groups was the increased range of fibre CSA within old muscles, also expressed as the ratio between the largest and the smallest single fibre CSA value. This was mainly caused by the increased occurrence of both hypotrophied and atrophied fibres, and hypertrophied fibres. The occurrence of hypertrophied fibres, and very large fibres, particularly of Type 1, was most likely the result of a compensatory response due to the reduction in the total number of fibres with increasing age. The CSA of Type 1 fibres, but not Type 2 fibres, is known to be inversely related to the total number of fibres: a muscle with few fibres has in general large Type 1 fibres while a muscle with many fibres has small Type 1 fibres (Lexell *et al.* 1988).

Despite the increased range in fibre CSA, the variability within old muscles, expressed as the mean S.D. and the S.D. of the means, was more or less unaffected compared to young muscles. The number of hypotrophied and atrophied, and hypertrophied fibres was therefore small compared to the whole fibre population. It also implies that the reduction in CSA of Type 2 fibres was fairly uniform throughout the muscle cross-sections, with no more discernible effect in any particular part of the muscle. This is further supported by the data in Figure 2: the CSA of Type 2 fibres in old muscles was larger than the Type 1 fibre CSA in only 3% of all the regions, compared to 68% in young muscles.

Most of the findings in the old muscles can be explained by a systematic adjustment of Type 2 fibre properties in smaller parts of the muscle, leading to an increased variability locally. The variance of the CSA of Type 1 fibres was significantly ($P < 0{\cdot}05$) larger than for Type 2 fibres in almost all regions (87·5%) of young muscles, but in old muscles this difference only remained in 40% of the regions. Furthermore, in 4 of 8 young muscles, there was a significant, positive, correlation between the mean CSA of Type 1 and Type 2 fibres in a region: if a fibre of a given type was small, the other fibre type was also small, and *vice versa*. This correlation was partly lost and only existed in 3 of 12 old muscles.

What then is the cause of all these changes and the much greater effect on the CSA of Type 2 fibres? Hypotrophy and atrophy of Type 2 fibres is one of the most common abnormalities described in muscle pathology. It occurs when muscle strength is impaired secondary to extrinsic problems, particularly if the neural input to the muscle is reduced or lost, as when the motor neurons in the spinal cord or the peripheral nerve axons are affected (Dubowitz, 1985). Even though more and more evidence suggests that part of the fibre population undergoes a denervation and reinnervation process with increasing age (for references, see Lexell *et al.* 1988), it can only partly, and indirectly, explain the age-related alterations in fibre CSA, such as the compensatory hypertrophy of Type 1 fibres and the atrophy of Type 2 fibres.

A selective reduction in the size of Type 2 fibres is very common due to inactivity and immobilisation. Furthermore, it is known that this type-specific hypotrophy is reversed more or less completely with physical activity and muscle training, even above the age of 80 years (Grimby, 1988). Therefore, we believe that many of the changes in Type 2 fibre CSA in the present study are also the result of a change in the physical activity pattern. In all our previous studies where we have found a systematic variation in different fibre properties, the primary conjecture has been that it is an indication of the functional differences between the various parts of the muscle (Lexell *et al.* 1983; Sjöström, Downham & Lexell, 1986; Lexell & Taylor, 1989). Different parts of the muscle are used during different phases of movement. The functional demands over a long period therefore differ and fibres develop different properties (Saltin & Gollnick, 1983). As the movement of ageing individuals is, in general, more restricted, the functional demands on the fibre population with respect to force, velocity and duration are also changed or decreased, resulting in a more homogeneous dispersion of fibre properties (Lexell *et al.* 1983*b*, 1986). By analogy with these studies, the more non-systematic distribution of the fibre CSA in old muscles presented here may, then, be the result of a slow adaptation of the fibre population due to the changes in physical activity pattern.

Thus, the collected evidence suggests a combination of a progressive neurogenic process and a change in functional demands as major contributors to the ageing atrophy and decline in motor function with increasing age; even though it is beyond the scope of this study, it should be mentioned that identical ideas have been persuasively put forward also for the ageing mammalian muscle (see for example, Boreham *et al.* 1988). However, longitudinal studies are required to elucidate further the relative importance of these factors. Also, other muscles in the human body – with other functions – may be affected differently with increasing age, so until further data are available, the results and inferences should be limited to the male vastus lateralis muscle.

SUMMARY

Cross-sections of whole vastus lateralis muscle from 20 men, 19 to 84 years of age, were prepared, and the cross-sectional area (μm^2) of 375 Type 1 and 375 Type 2 fibres was measured in five different regions throughout each muscle. In muscles from the old individuals, the mean CSA of Type 2 fibres was on average nearly 35% smaller ($P < 0.001$) while the mean CSA of Type 1 fibres was on average just over 6% smaller (NS) than in muscles from the young individuals. There was a highly significant ($P < 0.001$) variation in the mean CSA of both fibre types within all muscles. In the old muscles, there was no significant difference in mean fibre CSA between deep and superficial parts while in the young muscles the mean fibre CSA was significantly ($P < 0.05$) larger in deep regions than superficially. The range of the fibre CSA was larger in the old muscles with an increased number of both hypotrophied and atrophied fibres as well as large, sometimes very large, fibres. The standard deviation of the fibre CSA of Type 2 fibres was significantly ($P < 0.001$) larger than for Type 1 fibres in 60% of the regions of the old muscles compared to 12.5% of the regions of the young muscles, but the standard deviation for the whole muscles was more or less unaffected with increasing age. In the old age group, there were fewer muscles and regions with a correlation between the CSA of Type 1 and Type 2 fibres than in the young age group. In conclusion the age-related changes in the mean fibre CSA, and in the pattern of variation in fibre CSA throughout the muscle and in small sample regions, suggest a combination of a progressive denervation process and an altered physical activity level as the two major mechanisms underlying the effects of normal development and ageing on the human vastus lateralis muscle.

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