Effect of subnutrition on normalized muscle force and relaxation rate in human subjects using voluntary contractions

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(Received 29 June/17 October 1988; accepted 25 October 1988)

SUMMARY
1. Muscle weakness and wasting are well-known consequences of subnutrition, but there have been no published comparisons of these variables in a single muscle or muscle group. We report voluntary force measurements of adductor pollicis muscle in 11 subnourished patients normalized for their cross-sectional areas. We also report normalized relaxation rates of these contractions and the results are compared with those obtained in 40 healthy normally nourished subjects.

2. Normalized muscle force was no different in the subnourished group. However, relaxation rate was significantly slower than in the control group.

Key words: muscle function, normalized force, normalized relaxation rate, subnutrition.

INTRODUCTION
Muscle wasting during periods of undernutrition is well recognized [1], but recently specific functional changes (abnormal force-frequency relationship, slow relaxation rate and increased fatiguability during a 30 s stimulated tetanus) have been described in the adductor pollicis muscles of patients who were chronically subnourished secondary to a variety of gastrointestinal disorders [2]. Subsequently, similar changes were described in obese patients after 2 weeks of a 1674 kJ diet followed by 2 weeks fasting [3], and it was claimed that the changes in muscle function were more sensitive indicators of nutritional status than standard assessment techniques. In the same study it was reported that these changes were reversed after 2 weeks refeeding [3], and this finding was confirmed in six severe anorexia nervosa patients [4]. On refeeding, the anorexic patients also showed improvement in maximal voluntary contractions (MVC) and maximal stimulated forces. In a subsequent study [5] improvement in muscle function with improved nutritional status was demonstrated without any significant change in muscle bulk as assessed by arm muscle area. This observation, and the speed of the observed changes, suggests that improvements in muscle function may precede recovery of bulk and therefore lead one to expect a different relationship between force and cross-sectional area (CSA) in normally nourished and in subnourished subjects. However, to date no direct comparison of these two variables for a single muscle or muscle group appears to have been attempted in subnourished patients.

We have therefore measured MVC and CSA of adductor pollicis of 11 subnourished patients and compared the results with those obtained from 40 normally nourished healthy subjects. We have also measured normalized relaxation rates after a brief MVC and fatigue during a MVC sustained for 30 s.

METHODS
Subjects
Forty normally nourished healthy subjects (age range 17–53 years, mean 28 years, 21 male, 19 female) were selected from staff and students at University College London to give as wide a range as possible for height and frame size. Results for 20 of these subjects have been presented in a preliminary communication [6].

Eleven patients who were known to be chronically less than 90% of ideal body weight for height and frame size were tested (age range 19–54 years, mean 29 years, six

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Potentiometer A

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Fig. 1. (a) Apparatus for estimating CSA of adductor pollicis. Hand thickness was measured by the difference between the outputs of potentiometers A and B, and distance from the starting point (see the text) by the output of potentiometer C. The resulting X–Y plot is shown in (b). (b) Profile of the hand as measured by the apparatus shown in (a). The area above the broken line is taken to represent the CSA of adductor pollicis. The area below the broken line represents skin and subcutaneous fat.

males, five females). Eight of these had Crohn's disease, one had ulcerative colitis, one short-bowel syndrome and one pulmonary tuberculosis. At the time of testing their percentage ideal body weights ranged from 76.4 to 89% (mean 83.5%). Two of these patients were on steroids at the time they were tested. Patients with specific muscle diseases, osteomalacia or thyroid disease were excluded.

All subjects gave informed consent verbally and the project received approval from the ethical committees at University College London, Hastings Health Authority and Guy's Hospital.

Force measurement

MVC of the adductor pollicis was measured using a strain gauge bridge circuit. The gauge was mounted in the centre of a small brass plate which was seated in a brass cylinder. A rod, which opposed thumb adduction at the base of the proximal phalanx, ran down inside the cylinder and depressed the plate when force was applied. The system was insensitive to sideways forces applied to the cylinder. The other end of the cylinder was applied to a ballbearing mounted in a Perspex hand splint so as to lie between the index and middle fingers. The splint inhibited flexion of the fingers about the metacarpo-phalangeal joints. Contribution to the recorded force from the flexor muscles of the fingers was thus reduced though not completely eliminated. The point of opposition of adduction of the thumb was chosen because it is close to the attachment of the adductor pollicis muscle and because it is proximal to the attachments of the flexor muscles of the thumb. The force measured was therefore largely due to activity of adductor pollicis and a contribution from first dorsal interosseous.

Each subject's hand and forearm were warmed in hot water (40°C) for 5 min and they were then asked to perform nine 2 s MVCs, within a period of about 3 min. Twenty of the control subjects and nine of the subnourished were then asked to perform an MVC sustained for 30 s.

The subjects were allowed to watch the screen of the Nicolet 3091 portable oscilloscope on which data were collected, and encouraged verbally. Results from subjects tested during our preliminary study [6] were obtained using a different transducer [7]. The results obtained from the two transducers were directly comparable after appropriate calibration.

Measurements for the subnourished patients were made at the bedside but data could also be transferred for analysis on to the Nicolet 4094 oscilloscope or on to a personal computer. Maximal relaxation rate (MRR) was measured using a differentiating program available on this oscilloscope or Nicolet PC31 computer, program and normalized by the maximum force exerted [8] and had the units s⁻¹ (equivalent to percentage force loss in 10 ms).

CSA

The apparatus for measuring CSA is shown in Fig. 1(a). The profile of the hand was measured with the thumb fully abducted. The plane of the measurement bisected the angle between the metacarpal bones of the thumb and index finger up to the point between the bases of these bones. The thickness of the hand along this plane was measured by the difference in the outputs of two linear potentiometers, the shafts of which were held by springs against the two surfaces of the hand. The potentiometers were held in a light frame which could be moved over the hand while its position was monitored by a third potentiometer. This apparatus was also used in the preliminary study [6]. An X–Y plot of thickness against distance moved thus represents a profile of the hand (Fig. 1b). Three profiles were obtained for each subject, the
subject being asked to remove the hand from the apparatus between each measurement. These profiles were integrated after allowing for skin thickness (Fig. 1b). An anatomical dissection of a cadaver hand through this plane confirmed that the results of these measurements should approximate to the CSA of adductor pollicis together with part of first dorsal interosseous.

The area measurement could be made at the bedside using Gaussian quadrature integration but specimen records were kept for transfer either to the Nicolet 4094, which has an integration program, or on to a personal computer. Areas could be measured on computer using an extended Nicolet PC31 program.

RESULTS

Force/CSA

The coefficient of variation for the force measurements on each subject was 5% or less for the control group and for all but one of the subnourished group. The mean coefficient of variation for the area measurements on any one subject was 5.1% in both groups.

We have found the area measured by this method to be well correlated ($r=0.937$) with measurements of muscle CSA obtained from computer-assisted tomography (CAT) and n.m.r. images through the same plane (Fig. 2). The estimated CSA obtained from our hand profiles appears to underestimate the actual muscle CSA by approximately 40%. This is partly because some of the muscle is proximal to the bases of the metacarpal bones and is therefore not included in our CSA measurements. There is also a small compressing effect of the springs holding the potentiometers against the two surfaces of the hand. This underestimate does not affect our conclusions which are based on comparing relationships between force and CSA and not on the absolute value of their ratio.

The results of force and CSA measurements for the 40 normal subjects and the 11 subnourished patients are shown in Fig. 3. The regression line and 95% confidence limits for the control observations are shown. The regression line passes through the origin within the confidence limits and it can be seen that all but two of the observations from the subnourished patients are evenly scattered about it. These two observations are discussed below.

Force/height

Fig. 4 shows force plotted against height for 20 of the controls (with the regression line for these observations) and the 11 subnourished patients. It can be seen that the subnourished patients are generally weaker relative to their height than the controls. The significant correlation between force and height seen in the control group ($r=0.73$) is absent in the subnourished group. This is partly because of the smaller range of heights, but is probably mostly because of the variable degree of subnutrition in this group.

MRR

MRR was measured for 28 of the control group and eight of the subnourished patients. The mean coefficient of variation for measurements of relaxation rate on control and subnourished subjects was 13.7%. The normalized MRR in the control group was $6.8 \pm 0.216$ s$^{-1}$ (mean $\pm$ sem, range 4.9–9.4 s$^{-1}$). In the subnourished patients the value was $5.2 \pm 0.336$ s$^{-1}$ (range 4.0–6.7 s$^{-1}$). Thus relaxation was significantly slower in this group ($P<0.001$).
DISCUSSION

quadriceps muscle group and height of normal subjects \( (*, n = 20) \) and subnourished patients \( (\triangle, n = 11) \). The unbroken line is the regression line for the normal subjects.

Fatigue

There was no significant difference between the 20 control subjects and nine subnourished patients. The mean fall of force for all subjects and patients was 25% ± 12% (mean ± SEM).

Force/CSA

Although measurement of isometric force from the adductor pollicis muscle is a well-established research and clinical technique [9, 10], we believe this is the first attempt to correlate force measurements from this muscle with CSA. This information is essential to compare voluntary activity in a muscle between subjects and good correlations have previously been obtained with the quadriceps muscle group [11–13]. However, this group contains multipennate muscles, which makes the comparison of force/CSA measurements with other muscles difficult. It also obscures the interpretation of data when changes in muscle bulk have occurred because increase in muscle bulk of a mature muscle, due to hypertrophy, leads to a change in the angle of pennation of the fibres and therefore the effective lever ratio [14]. It seems likely that loss of muscle secondary to subnutrition or ageing would have a similar effect. Adductor pollicis is a more easily parallel-fibred muscle (S. A. Bruce, D. Newton & R. C. Woledge, unpublished work). Our modification of the technique for force measurement minimizes the differences in lever ratio between individuals because the point of opposition of the force at the base of the proximal phalanx of the thumb is closer to the attachment of the muscle than the more conventional interphalangeal joint [10]. These factors contribute to the better correlation between force and CSA achieved by our technique than those published for quadriceps [11–13]. The forces observed in this study are higher than have been previously reported for adductor pollicis partly because the lever ratio is small but also because there is some contribution from long flexor muscles of the fingers and because very strong subjects were deliberately selected for the control group.

Muscle function and nutritional status

Our results confirm that subnourished subjects are weak relative to their height, which was chosen as an indicator of body build, but show that the weakness is generally in proportion to muscle bulk. Observations from two of our patients with Crohn's disease fell outside the 95% confidence limits for the control observations (Fig. 3). One of these patients was on long-term steroids; the other had a history of alcohol abuse. Both steroid therapy [15] and alcohol [16] are known to cause myopathies which might have affected the results, although there was no clinical evidence of specific muscle disease in either patient. The coefficient of variation of the force observations from the second of these two patients was 8.4%, suggesting that her contractions may not have been maximal. Even including these two observations the subnourished group did not significantly differ from the controls \( (P = 0.2) \). This suggests that the most important effect of subnutrition on muscle is loss of bulk consequent on its homeostatic function as a store of protein [1]. The difficulties in interpreting earlier studies of muscle function and nutritional status have recently been reviewed [17]. Since that review, further studies [5, 18] have reported slow relaxation rates in adductor pollicis muscle-stimulated contractions tested in subnourished surgical patients, confirming that this is the most consistently abnormal normalized muscle variable in subnourished patients. Reported changes in the force–frequency relationship [2–5, 18] are probably largely explained by the prolonging of relaxation [17]. Our finding that relaxation rate measured in voluntary contractions is also demonstrably slower in subnourished patients should make the test more widely available and more readily tolerated.

The MRR of our control subjects was slower by approximately 25%, than that previously published for stimulated relaxation rates [17]. A large part of this difference is probably due to asynchronous activation of motor units during voluntary contraction. A numerical simulation of this asynchrony was carried out using a differentiated force record from one of our control subjects. The record was averaged in a moving window of 80 ms width. This depressed the peak value of fall of force by 27, suggesting that this explanation is likely to be correct.

Our results suggest that force generated during MVC is unlikely to be a useful measurement in the diagnosis or follow-up of subnourished patients as the major change is on muscle bulk which is non-specific. This is in contrast to the indirect inference, from results of submaximal stimulated contractions, in the work cited above that subnutrition has a specific effect on the ability of muscle
protein to develop force, perhaps through changes in
calcium kinetics [19]. However, relaxation rate may well
be a useful additional test in demonstrating marginal sub-
nutrition and in assessing the efficacy of re-feeding
regimens in subnourished patients.

ACKNOWLEDGMENTS

This project is funded by South-East Thames Regional
Health Authority (Locally Organized Research Scheme).
We are most grateful to Dr G. Sladen for his encourage-
ment and for enabling us to study his patients, and to Dr
M. Wilson for writing the extension to the PC31 com-
puter program.

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