

# Implications of Muscle Design on Surgical Reconstruction of Upper Extremities

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**Abstract:** The basic anatomic and physiologic properties of human upper extremity muscles have been elucidated using a novel intraoperative sarcomere length measuring device in conjunction with quantitative anatomic and biomechanic models of these same muscles. We reviewed the genesis of these studies which began with development of the optical tools, validation using animal models, and application to human upper extremity surgery. Human muscles have a remarkable degree of specialization, even among synergists. Mechanical properties of human tendons provide another source of specialization such that the muscle-tendon unit does not simply retain the properties of a muscle plus a tendon. The operating range of different muscles is also a method whereby the balance of the joint can be maintained in the face of altered moment arms and muscle forces. The derivation of these principles is explained along with their importance in surgical tendon transfers where one muscle substitutes function for another.

(*Clin Orthop* 2004;419:267–279)

This article summarizes a series of studies that began in 1981 with the development of a theory of laser light diffraction in skeletal muscle. Although this theory was developed initially to enable basic science studies of single frog muscle cell contraction, it soon was applied to the study of human muscles during hand surgery. To do these surgical studies in a meaningful way, the design of the human upper extremity muscles, joints, and tendons also was studied in detail. Taken together, these anatomic, physiologic, biomechanical, and intraoperative studies have formed the basis for a novel

and objective approach to surgical reconstruction of the upper extremity. In addition, ancillary applications have been initiated that will have impact in pediatric orthopaedic, eye, and plastic surgery.

## THE LASER DIFFRACTION METHOD

In 1980, a group of investigators at the University of California, Davis combined efforts to create a theory describing the interaction between laser light and skeletal muscle.<sup>45</sup> The method exploits the constructive interference that results when laser light strikes the A- and I-bands of striated muscle. The initial purpose of this work was to develop a tool that would allow high-resolution, high-speed studies of single frog muscle cells during contraction. Additionally, a high-speed digital computer system was created to allow real-time acquisition of the diffraction patterns and to control the contracting fiber.<sup>30,33</sup> This interdisciplinary effort culminated in a high-resolution basic science study of the behavior of sarcomere populations along the length of single muscle cells.<sup>14</sup> The technique was tested experimentally in rabbits,<sup>16</sup> and mice,<sup>1</sup> and has been applied to 10 studies of human skeletal muscle during surgical reconstruction procedures that are detailed below. Because the sarcomere is the basic unit of force generation in skeletal muscle, the ability to measure sarcomere length intraoperatively provides the surgeon with an objective tool that can predict the function of muscles during surgical procedures without the need to electrically activate and test the muscles directly.

## HUMAN UPPER EXTREMITY MUSCLES

Several studies were done that improved our understanding of the design of the upper extremity musculoskeletal system. We began by studying the design of the prime wrist movers,<sup>20</sup> and then extended this study to include all of the extrinsic and intrinsic muscles of the hand.<sup>11,25</sup> These studies confirmed that, in the human upper extremity (as in other mammalian systems) skeletal muscles are highly specialized in architectural design.<sup>23</sup> Briefly, skeletal muscle architecture is the most important parameter that can be used to predict muscle functional properties. Muscle force production is proportional to physiologic cross-sectional area and muscle excursion is proportional to muscle fiber length. This result has two implications: (1) all muscles are not interchangeable in the

Received for publication October 25, 2002; revised March 19, 2003, April 28, 2003; accepted October 6, 2003.

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DOI: 10.1097/01.blo.0000118446.74964.03

amount of force they generate or their excursion, and (2) the musculoskeletal system is highly specialized with respect to function at the various joints. Because the two most important muscle functional parameters in tendon transfer are force and excursion, we expressed these parameters in graphic form to emphasize the specialization of the different muscle groups and to facilitate the surgeon's ability to choose muscles for a transfer.<sup>25</sup> For example, the digital extensors can be characterized by their high excursion-low force producing ability, whereas the flexor carpi ulnaris clearly is designed for high force production and low excursion. These results are discussed in detail elsewhere.<sup>23</sup>

Many parameters were measured from each muscle. However, to simplify comparisons between muscles in terms of their architecture, we defined a difference index, ( $\delta_{2-1}$ ) between any pair of muscles 1 and 2, based on the five most different architectural parameters (obtained using the statistical method of discriminant analysis): fiber length, physiologic cross-sectional area, muscle length, fiber length/muscle length ratio, and mass.<sup>18</sup> This index is a modification of the well-known algebraic distance formula which is used to calculate the distance between two points in a plane. Difference indices were calculated for all possible muscle pairs,<sup>23</sup> and can be used to make surgical decisions regarding replacement of one muscle with another.

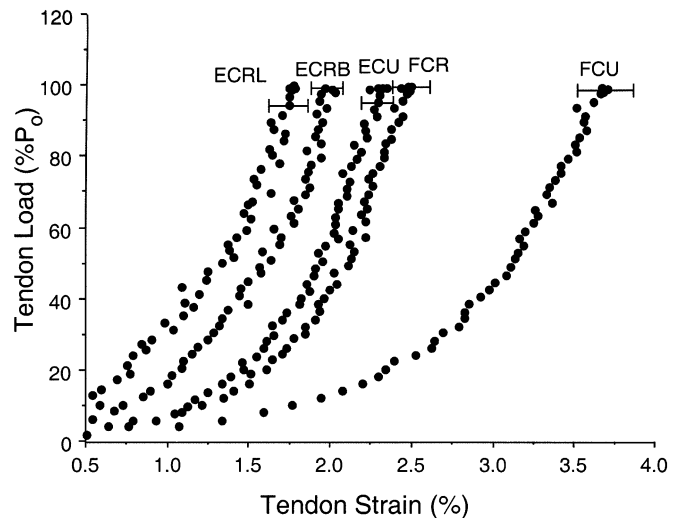
### INFLUENCE OF TENDON COMPLIANCE ON MUSCLE FUNCTION

As these muscle studies were being done several studies were showing that tendon compliance could alter the properties of the muscle-tendon unit compared with muscle properties alone.<sup>9,10,46</sup> Typically, many viewed the function of a tendon from an anatomic point of view as simply providing a connection between muscles and bone. Although this is true, because muscle force generation is length and velocity-dependent, tendon compliance can result in muscle length and velocity changes that affect function. We measured the magnitude of the tendon strain that occurs during contraction of the frog semitendinosus muscle-tendon unit.<sup>19,26</sup> Because the frog muscle-tendon unit can be studied in vitro, we chose it as a simple system to quantify the extent of muscle force modification by tendon compliance. The experimental approach which distinguished our study from a traditional tendon biomechanical study<sup>44</sup> was that we first directly measured maximum muscle contraction force and then loaded tendons to these physiologic force levels. This is in contrast to traditional deformation-to-failure experiments in which loads and strains often exceed physiologic levels. We found that, in frog semitendinosus and gastrocnemius muscles (which vary dramatically in size and shape<sup>19,26,43</sup>), tendon strain under maximum physiologic tension was only 2% to 3%, placing the tendons in the toe region of the classic load-strain curve. Obviously, this is the highly compliant region which will permit muscles to

shorten a great deal at the expense of tendon lengthening and generally is discarded by biomechanists as being irrelevant because most modulus values are reported in the linear region of the stress-strain curve. We extended this frog model result to the human wrist by loading each prime wrist mover tendon to the maximum force which would be produced by its muscle (as predicted from architectural measurements) and measured the resulting strain.<sup>35</sup> Again, the strains were in the range of 2% to 3% (Fig. 1), but the most surprising finding was that tendon compliance actually accentuated muscle architectural properties. This experiment showed that it is inappropriate to assume that muscles simply strain a certain amount during contraction based on general literature values—strain during muscle contraction is unique for each muscle-tendon unit and actually contributes to its design. Therefore, to understand the numerous upper extremity transfers that involve digital tendons, compliance of the digital flexors and extensors must be measured under physiologically relevant loads.

### DESIGN OF ANIMAL AND HUMAN TORQUE MOTORS

Although we attempted to understand architectural and tendon mechanical results in terms of their significance during movement, we suspected that it was not appropriate to simply extrapolate muscle-tendon properties to those of the individual with intact muscle-tendon properties. As a joint rotates, muscle



**FIGURE 1.** Each curve represents the average of five different specimens. Each tendon type strains to a different magnitude with a varying shape in the physiologic force range. Normalization of load to stress does not appreciably diminish the variability among tendons. Standard error of data ( $n = 5$ ) shown near the top of the curve are averaged across the data range and offset for clarity. ECRB, extensor carpi radialis brevis; ECR, extensor carpi radialis longus; ECU, extensor carpi ulnaris; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris

fiber length and muscle moment arm change simultaneously. Therefore, joint moment arm could confound our interpretation of muscle architectural data. For example, a muscle with short fibers and a very small moment arm could provide a larger range of motion (ROM) compared with the same muscle with a large moment arm. Therefore architecture alone cannot provide a complete characterization of the torque motor. We therefore investigated muscle-joint interaction in animal and human systems.

### MECHANISM OF TORQUE GENERATION

Unfortunately, a review of the literature revealed a paucity of information on the mechanism of torque generation. We therefore developed a frog muscle-joint model which enabled a detailed description of the interaction between muscles and joints (Fig. 2).<sup>17</sup> The frog was chosen because it was the only species for which the actual sarcomere length-tension relationship was directly known.<sup>8</sup> In our experimental study, we found that the optimal joint angle (where torque was maximum) was neither the joint angle at which muscle force was maximum

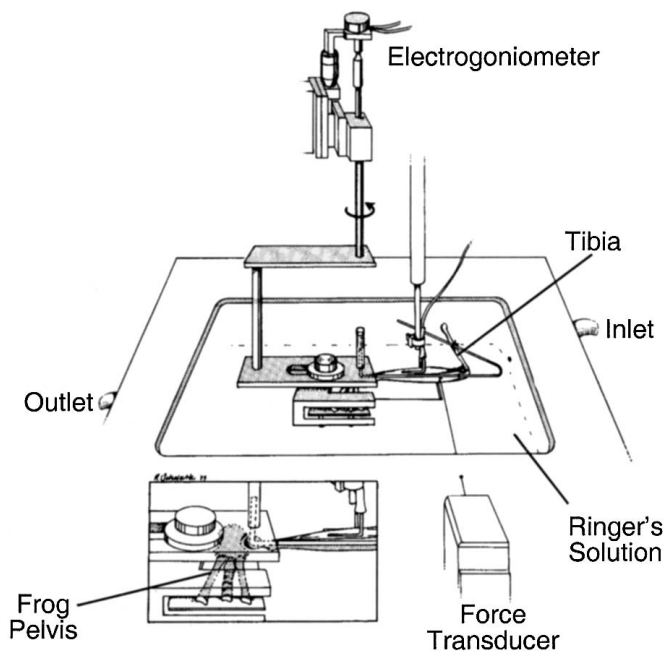
nor the angle at which moment arm was maximum.<sup>17</sup> In other words, torque resulted from the interaction between muscle and joint properties and not either property alone.<sup>31</sup> This result suggested that the design of the musculoskeletal system was much more elegant than previously supposed. It became clear that knowledge of muscle and joint properties was essential for correct understanding of any joint torque data whether obtained during isometric contraction or normal gait. These results had profound implications in orthopaedics and rehabilitation where clinical evaluation of strength and ROM routinely are used to assess muscular sufficiency. This study was among the first which suggested the central importance of muscle fiber length in determining the nature of the torque generating system.

### LASER DIFFRACTION DEVICE

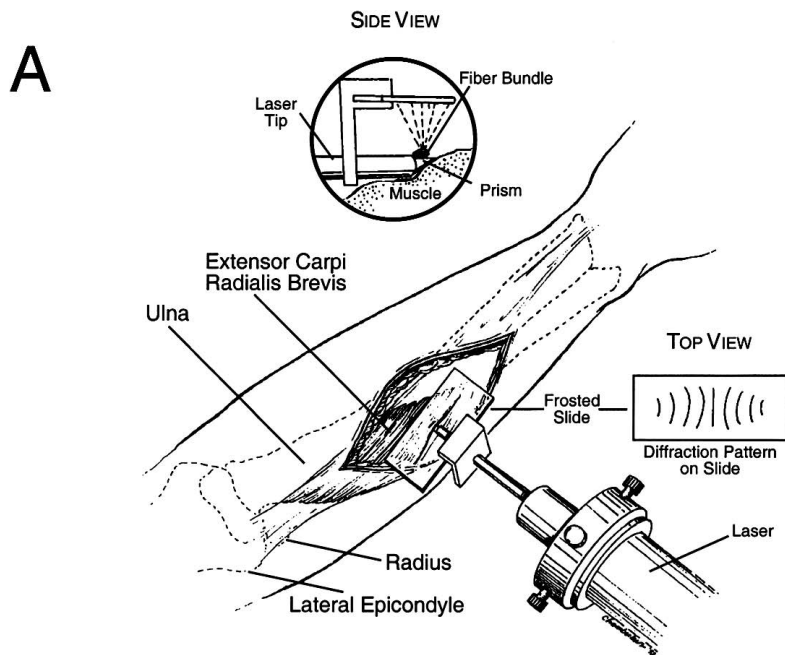
With support from the Department of Veterans Affairs and the National Institutes of Health, we developed a prototype for use in upper extremity surgery. Our device was a modification of that originally described by Lieber and Baskin<sup>15</sup> consisting of a 5-mW helium-neon laser beam aligned with a specially-designed prism such that the beam projected normal to one prism face and is reflected 90°, exiting the other prism face (Fig. 3A). The device was calibrated using diffraction gratings of 2.50- $\mu\text{m}$  and 3.33- $\mu\text{m}$  grating spacings placed at the location of the muscle fiber bundle directly on the prism. In practice, repeated measurement of diffraction order spacing results in sarcomere length variability of  $0.10 \mu\text{m} \pm 0.21$ . We also created a laser device with an electronic photodetector interfaced to a computer obviating the need for any calculations by the surgeon. A battery-powered version of this device was developed (Myogenesis, Inc, La Jolla, CA) which readily permits rapid and accurate intraoperative sarcomere length measurements (Fig. 3B).

### TORQUE GENERATION IN THE NORMAL HUMAN WRIST

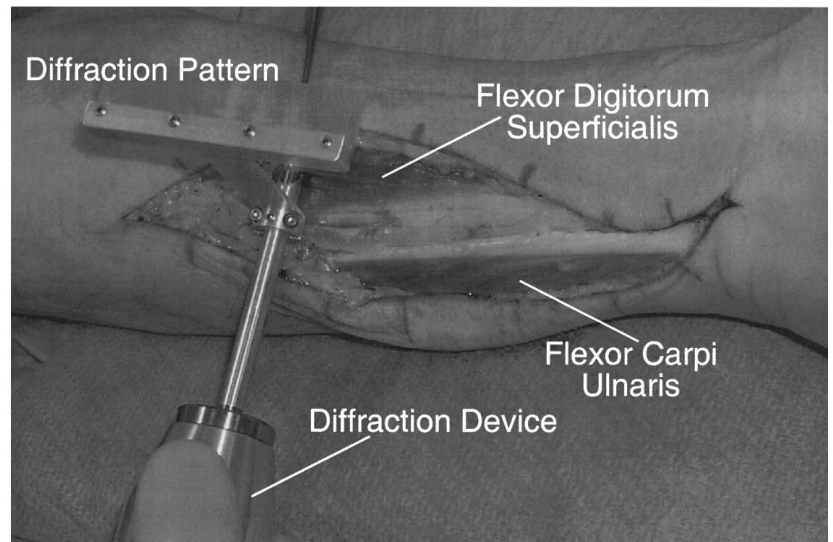
We were excited to do analogous studies in human upper extremities. In March 1993, we were successful in measuring the first intraoperative laser diffraction patterns in living human muscle during surgery.<sup>4,28</sup> To calibrate human sarcomeres in terms of their filament length changes, we also did quantitative electron microscopy on the human extensor carpi radialis brevis muscle to enable force prediction from sarcomere lengths alone.<sup>28</sup> We then measured, in five patients, the sarcomere length change as the wrist was rotated from full flexion to full extension. The results surprised us in that, sarcomere length varied from approximately 3.7  $\mu\text{m}$  in full flexion to approximately 2.5  $\mu\text{m}$  in full extension. This means that the extensor carpi radialis brevis would produce almost no force with the wrist flexed and maximal force with the wrist extended based on differences in filament overlap as a function of joint angle. This result contradicted the status quo and even



**FIGURE 2.** The frog bone-muscle complex is secured to the rotating arm of the jig. Stimulating electrodes flank the semitendinosus muscle. Joint angle is changed by rotating the arm, and joint angle is read directly from a goniometer. The femur and tibia are stabilized throughout the experiment. Modified with permission from Mai MT, Lieber, RL: A model of semitendinosus muscle sarcomere length, knee and hip joint interaction in the frog hindlimb. (Reprinted with permission from Mai MT, Lieber RL: A model of semitendinosus muscle sarcomere length, knee and hip joint interaction in the frog hindlimb. *J Biomech* 23:271–279, 1990.



B



**FIGURE 3.** A, The He-Ne laser is inserted under a muscle bundle for direct sarcomere length measurement. Second order diffraction spacing was measured manually using calipers. The inset shows a transverse view of the illuminating prism placed beneath a muscle fiber bundle. B, Intraoperative diffraction was done on a patient receiving lengthening of the flexor digitorum superficialis tendon. The diffraction pattern is clearly seen on the screen as a row of lines.

most physiology texts that assumed muscles generate maximum force in the joint midrange. We then followed up this study with a combination of *in vitro* biomechanics of wrist motors to quantify moment arms<sup>36</sup> and a model of all five prime movers of the wrist along with their specific tendon properties.<sup>35</sup> Using a geometric model of muscle force generation<sup>1</sup> and a computer model of muscle-tendon interaction,<sup>19</sup> we simulated the isometric torque profile of the prime wrist movers as a function of flexion-extension and radial and ulnar deviation. Two major results emerged. First, the human torque

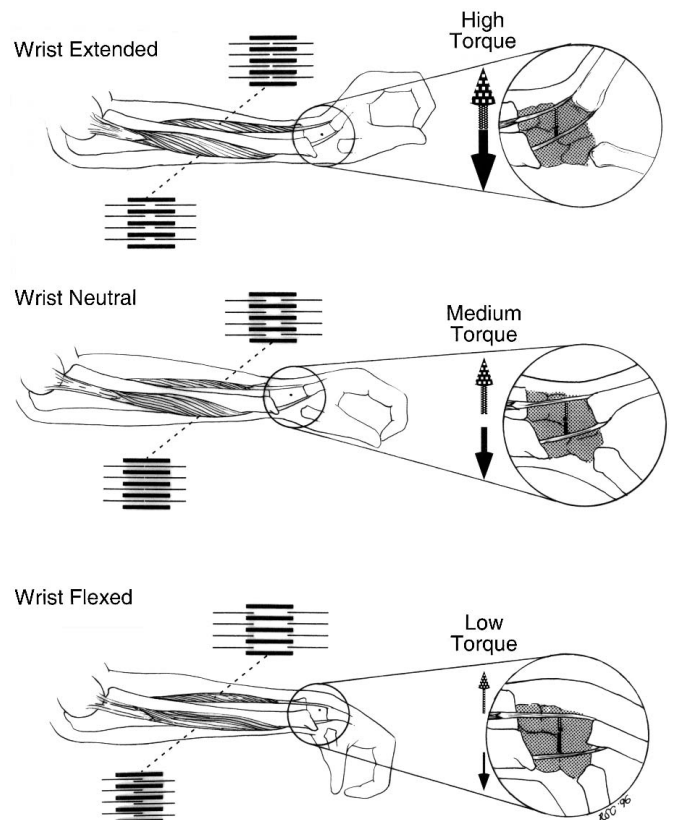
motors were highly specialized similar to that observed for frogs. For the wrist extensor muscles, optimal muscle force was generated near full wrist extension whereas the maximum moment arm was observed closer to the neutral joint angle. The muscle-joint relationship was even more interesting for the wrist flexors where, as the wrist flexed, muscle force decreased while wrist moment arm increased. The net result was that wrist flexion torque was predicted to be relatively constant throughout the normal ROM despite the fact that the flexors, as muscles, are much stronger than the extensors.

The second major finding of the study was that the wrist flexors and extensors operate on different regions of the sarcomere length-tension curve. Although the extensors operate primarily on the descending limb, as mentioned above, the wrist flexors operate primarily on the ascending limb. Functionally, this means that the wrist extensors generate approximately 50% maximum force with the wrist flexed and generate maximum force as the wrist reaches full extension. The wrist flexors also generate approximately 50% maximum force in flexion and maximal force in extension. However, the two functional groups accomplish this in different ways—the flexors increase in length as the wrist extends, getting stronger because sarcomere length is approaching optimum from the shorter lengths, whereas the extensors get stronger as the wrist extends because sarcomere length is decreasing toward the optimum from longer lengths (Fig. 4). The implications for tendon transfer are profound. If muscles do have different sarcomere length operating ranges, then transfers should be inserted such that the normal range is restored. Each muscle ought to be reattached so that it operates over its normal sarcomere length range. This is possible using a combination of theoretical data and an intraoperative sarcomere length measurement device.

### MODEL VALIDATION

To test the model created for the wrist, we tested its predictions in two situations. We compared the sarcomere length changes during wrist extension between the extensor carpi radialis brevis and extensor carpi radialis longus. Based on the relatively short extensor carpi radialis brevis fiber length and large extensor carpi radialis brevis moment arm, the extensor carpi radialis brevis was predicted to change sarcomere length at a rate of 2.57 times that of the extensor carpi radialis longus. The actual experimentally measured ratio was 2.45,<sup>27</sup> impressively close to the predicted value (Fig. 5A). This experiment also revealed another underlying design principle of the muscular system: synergistic muscles often have very disparate architectural designs. The benefit of this disparity is that a wider range of tasks can be done by two disparate muscles than by one equivalent muscle of equal mass.<sup>27</sup> The underlying explanations for the much greater sarcomere length change of the extensor carpi radialis brevis compared with the extensor carpi radialis longus were the shorter fibers and larger moment arm of the extensor carpi radialis brevis compared with the extensor carpi radialis longus (Fig. 5B).

In a second test of the model, the flexor carpi ulnaris muscle was transferred into the extensor carpi radialis longus tendon in six patients with radial nerve palsy<sup>21</sup> and sarcomere length was measured and predicted before and after the surgical transfer (Fig. 6). Correlation between experiment and theory was excellent as shown by the closeness of experimental data and predicted line. Although these data cannot be extrapolated to other muscles, they illustrate our extensive experience with intraoperative measurement, biomechanical mod-

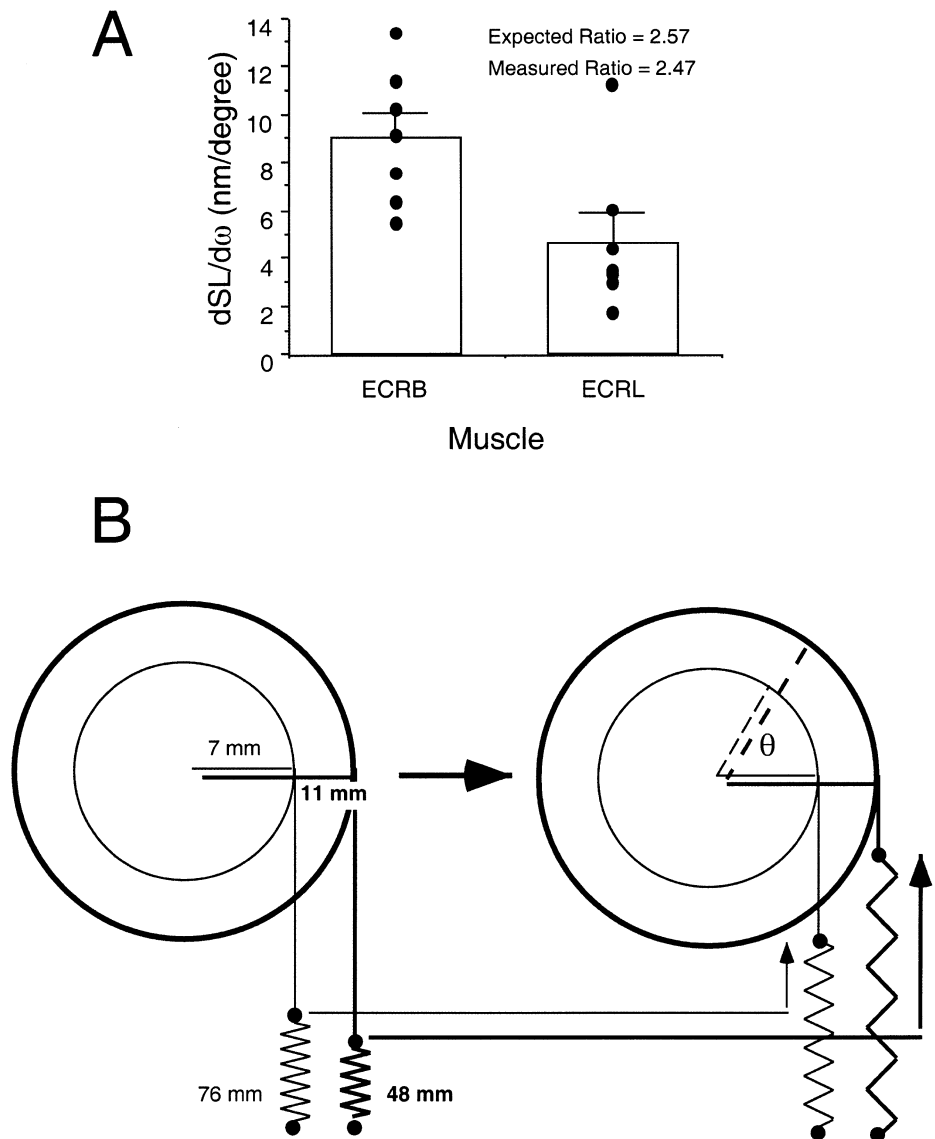


**FIGURE 4.** Maximum muscle force occurs with the wrist fully extended for the flexors and extensors as shown by schematic sarcomeres at optimal overlap. As the wrist is flexed, flexor moment arm (solid vertical line in inset) increases whereas extensor moment arm (dashed vertical line in inset) decreases. Since muscle strength decreases because of decreasing sarcomere overlap, flexor torque (solid arrow) decreases as does extensor torque (dotted arrow). The net result is a torque balance throughout the ROM. This schematic is based on the data published by Loren et al,<sup>36</sup> and modified by Lieber and Fridén<sup>22</sup> (Reprinted with permission from Lieber RL, Friden J: Musculoskeletal balance of the human wrist elucidated using intraoperative laser diffraction. *J Electromyogr Kinesiol* 8:93–100, 1998.)

eling, and developing tests required to validate the biomechanical models. The lines shown in Figures 6A and 6B are not curve fits. Rather, they are independent sarcomere length predictions made from architectural, biomechanical, and kinematic measurements of muscles, joints, and tendons.<sup>36</sup> Thus, the agreement between experiment and theory is even more impressive.

### SARCOMERE LENGTH

To emphasize the importance of sarcomere length in a transferred muscle, we also simulated the tendon transfer of the flexor carpi ulnaris to extensor carpi radialis longus (Fig. 6C) because we had complete data on both of these prime wrist



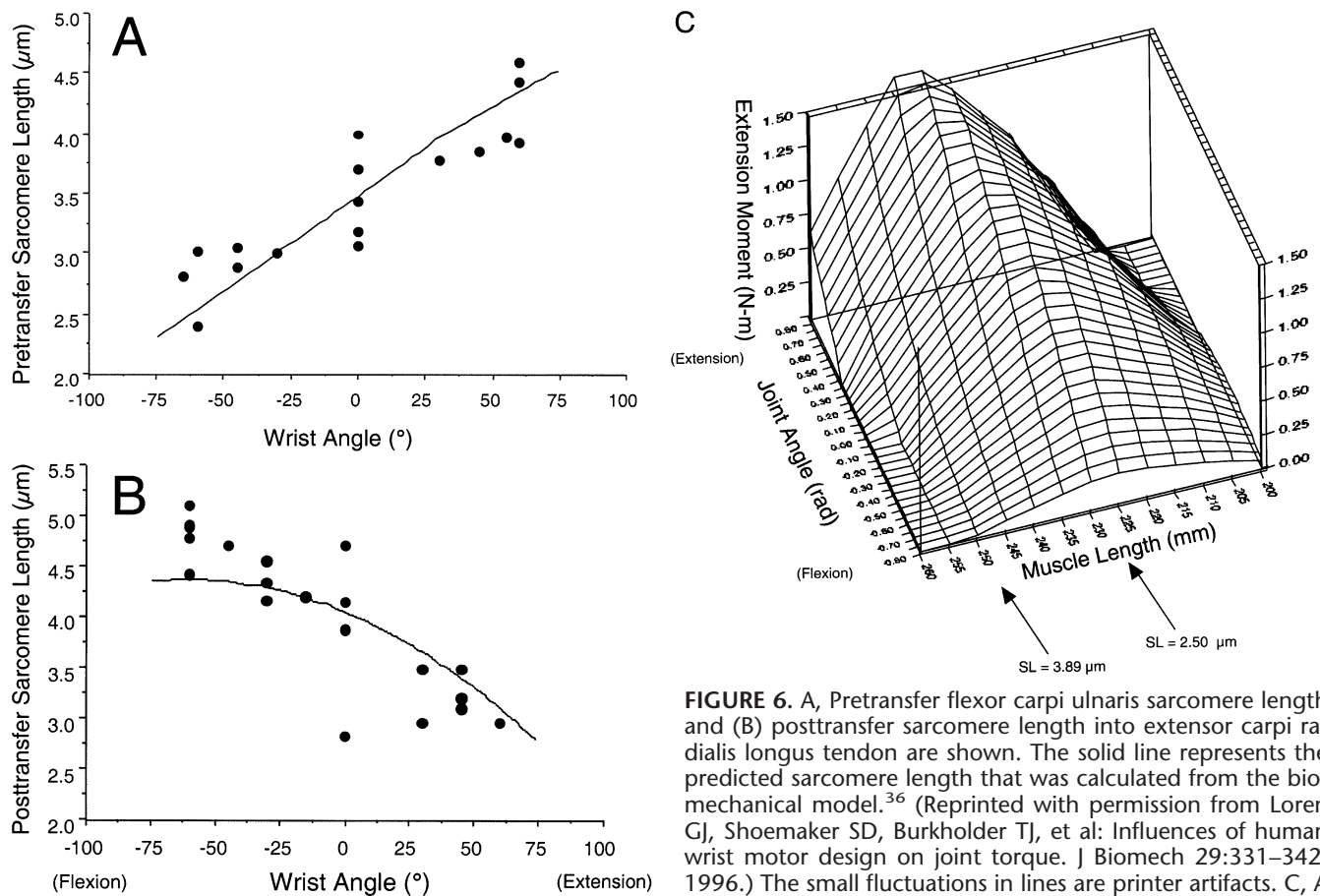
**FIGURE 5.** A, Values are calculated as sarcomere length change per degree of joint extension and plotted as positive values for convenience. B, The extensor carpi radialis brevis (bold print, thick lines) with its shorter fibers and longer moment arm changes sarcomere length approximately 2.5 times as much as the extensor carpi radialis longus with its longer fibers and smaller moment arm (as shown in part A).

movers and the intraoperative sarcomere length data presented above (Fig. 6). After the transfer, the flexor carpi ulnaris muscle-tendon unit acts through the extensor carpi radialis longus moment arm.<sup>21</sup> Now, as a wrist extensor, the flexor carpi ulnaris operates through a moment arm which is greatest in extension and which is larger than the original flexor carpi ulnaris moment arm. If the flexor carpi ulnaris is inserted in a slack position (sarcomere length = 2.1  $\mu\text{m}$  at neutral wrist rotation) we predicted a flexor carpi ulnaris-extensor carpi radialis longus motor that operates primarily on the ascending limb of the sarcomere length tension curve with peak muscle force in wrist flexion and consequently a markedly compromised joint. However, tenorrhaphy of the flexor carpi ulnaris-extensor carpi radialis longus tendon under tension (sarcomere length = 3.0  $\mu\text{m}$  at neutral) may more accurately replicate the

predicted extensor carpi radialis longus sarcomere operating range on the plateau and approximate the extensor torque profile. Such sarcomere length manipulation by intraoperative laser diffraction during tendon transfer, combined with realistic theoretical models, may optimize the magnitude of the torque and thus improve patient function. Sarcomere length may be a critical variable in achieving desirable outcome after transfer.

### SARCOMERE LENGTH AS A PREDICTOR OF FUNCTION

Because skeletal muscles are composed of hundreds of thousands of sarcomeres arranged in series and in parallel, it is possible that regional variations in sarcomere length may be so great as to render localized measurements useless. We therefore were concerned about the extent to which intraoperative



**FIGURE 6.** A, Pretransfer flexor carpi ulnaris sarcomere length and (B) posttransfer sarcomere length into extensor carpi radialis longus tendon are shown. The solid line represents the predicted sarcomere length that was calculated from the biomechanical model.<sup>36</sup> (Reprinted with permission from Loren GJ, Shoemaker SD, Burkholder TJ, et al: Influences of human wrist motor design on joint torque. *J Biomech* 29:331–342, 1996.) The small fluctuations in lines are printer artifacts. C, A graphic representation of the three-dimensional surface representing wrist extension moment (N·m), wrist angle (radians [rad]), and the length of muscle at time of transfer (mm) are shown.

A relatively large sarcomere length (SL) change (approximately 50%) corresponds to a relatively small muscle length change (approximately 10%) because the flexor carpi ulnaris muscle has very short fibers arranged along the muscle length. (Reprinted with permission from Lieber RL, Fridén J: Intraoperative measurement and biomechanical modeling of the flexor carpi ulnaris-to-extensor carpi radialis longus tendon transfer. *J Biomech Eng* 119:386–391, 1997.)

measurements from one region of a large muscle were representative of the entire muscle. Because it was not possible to sample widely across human muscles intraoperatively because of limited exposure, detailed spatial studies of sarcomere length distribution in cadaveric muscles and then physiologic studies in large canine muscles were done.<sup>13,34</sup> In cadaveric specimens, sarcomere length and fiber length measurements were obtained from nine regions of the flexor carpi ulnaris muscle and the pronator teres muscle from two specimens. The flexor carpi ulnaris was chosen because of its relatively simple architectural design of short fibers arranged essentially in parallel along the muscle length<sup>20</sup> and its relatively single plane action along the wrist flexion and ulnar deviation plane. The pronator teres was chosen because of its obviously complex architecture that probably results from its multiple axes of action in elbow flexion and forearm pronation.<sup>25</sup> Because the majority of our experience is with upper extremity muscles, we

thought that these two muscles would represent the range of complexity observed among all human muscles. Sarcomere length and fiber length were measured in nine regions of each muscle: the proximal, middle, and distal regions at each of three levels: superficial, middle, and deep. In each location, two measurements were made (n = 72, nine locations x two measurements per location x two specimens per muscle x two muscles) and the data were analyzed by three-way analysis of variance (ANOVA) with repeated measures. Significant fiber length variation was observed between muscles ( $P < 0.0001$ ) and in the pronator teres muscle ( $P < 0.01$ ) but not in the flexor carpi ulnaris muscle ( $P > 0.4$ ). However, despite this large fiber length variability, no significant sarcomere length difference was seen between muscles ( $P > 0.35$ ) or between locations in either muscle ( $P > 0.4$  for flexor carpi ulnaris,  $P > 0.6$  for pronator teres). These data reinforce the concept that skeletal muscle has a profound ability to regulate sarcomere num-

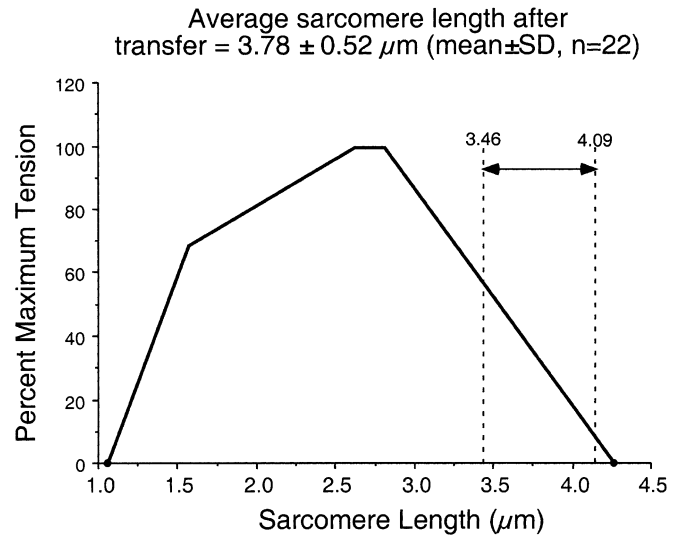
ber in response to various length changes to establish a certain sarcomere length. This result also indicates that sarcomere length is a stable variable throughout a muscle and supports its utility as a functionally relevant variable used intraoperatively.

In a physiologic study, the large canine flexor muscle mass was activated by electrical stimulation of the muscles near their motor point at the medial epicondyle.<sup>32</sup> Sarcomere length was measured across a range of muscle lengths and then regressed on maximum tetanic tension. There was a highly significant linear correlation between sarcomere length measured in the distal musculature (as is done intraoperatively) and muscle tension measured physiologically ( $r^2 = 0.86$ ;  $P < 0.01$ ) showing that a sarcomere length measurement made in this fashion can accurately predict function. This is critical should intraoperative measurements be used in surgical reconstruction procedures because the objective is to influence function.

### PASSIVE TENSION WAS A POOR PREDICTOR OF OPTIMAL MUSCLE LENGTH

Laser diffraction was used to study surgical correction of tennis elbow,<sup>4</sup> and tendon transfers needed secondary to radial nerve palsy or spinal cord injury.<sup>21,27,29</sup> The response has been enthusiastic. Surgeons are beginning to ask sophisticated questions regarding the optimal methods needed for transferring and lengthening muscle-tendon units. We think that laser diffraction technology has the potential to revolutionize the effectiveness of this type of surgery.

Although sarcomere length is an excellent predictor of muscle function, many surgeons rely on the feel or passive tension of the muscle during surgery to set the appropriate length. However, it is clear that measurement of passive tension for prediction of optimal length is inadequate. In a descriptive study, we found that, on average, hand surgeons tended to stretch muscle well beyond optimal.<sup>5</sup> Sarcomere length was measured intraoperatively during 22 tendon transfers about the wrist, most involving the flexor carpi ulnaris. Muscle tension during transfer was chosen based on traditional guidelines suggested for optimal function. Using these criteria, it was determined that sarcomere lengths were consistently much longer than optimal length, even to the point of resulting in zero active tension generation. Average sarcomere length after transfer was  $3.78 \pm 0.52 \mu\text{m}$  (mean  $\pm$  SD,  $n = 22$ ) which was significantly greater than optimal sarcomere length ( $2.8 \mu\text{m}$ ) in human skeletal muscle ( $P < 0.0001$ ) and the 99% confidence interval spanned from  $3.46 \mu\text{m}$  to  $4.09 \mu\text{m}$  (Fig. 7). Based on the average  $3.78\text{-}\mu\text{m}$  sarcomere length, muscles were predicted to generate only 28% of maximum force. The reasons muscles were stretched to such an extent seemed to be attributable to the fact that passive tension in upper extremity flexors only becomes significant at relatively long lengths. We suggest that the use of passive tension as the major factor in intraoperative decision-making results in overstretch of the



**FIGURE 7.** Sarcomere length-tension relationship for human skeletal muscles is shown as a solid line. The dashed vertical lines represent the 99% confidence interval for the average posttransfer sarcomere lengths.

muscle-tendon unit and accompanying low active force generation.

This collection of studies is the most objective evidence suggesting that it is impossible to assume a priori that a particular joint angle corresponds to optimal muscle length as has been claimed.<sup>42</sup> Therefore, the surgeon has no guidance with respect to the length at which the muscle should be set. The only way to set the muscle to its appropriate length is to know the normal sarcomere length operating range and set the muscle to that sarcomere length during the procedure. Yet without new basic science information, such precise decisions are impossible.

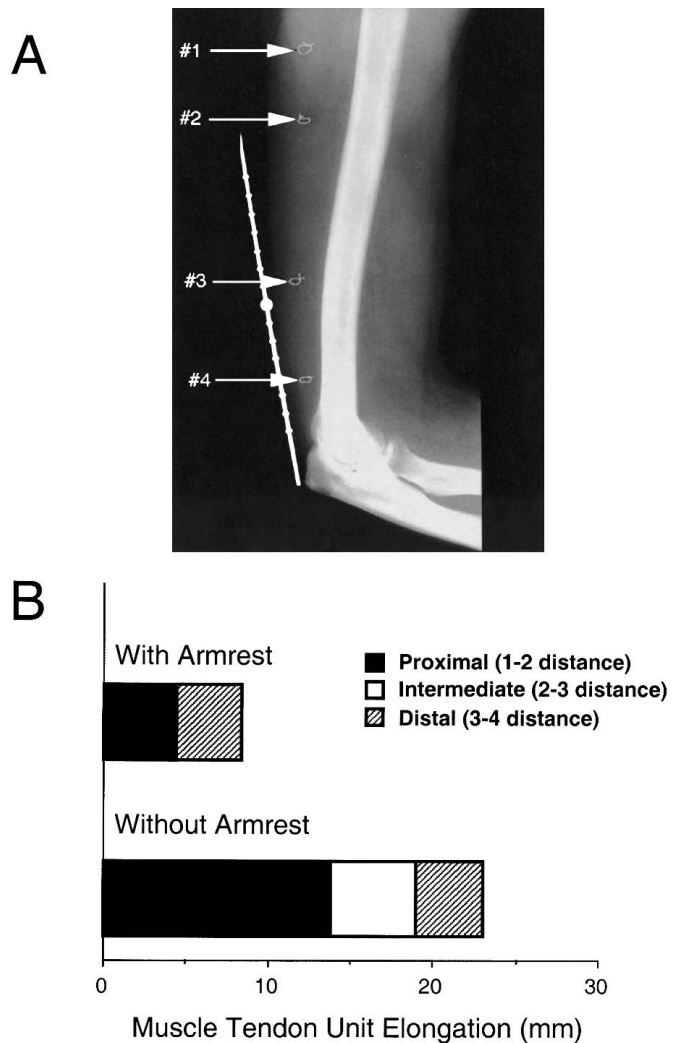
### RECONSTRUCTIVE TETRAPLEGIA SURGERY AND REHABILITATION PROCEDURES

The ultimate goal of our research is to improve the treatment of patients with musculoskeletal diseases. One early example of this is the combined anatomic and biomechanical study of the brachioradialis muscle as a donor in restoration of hand function after spinal cord injury.<sup>2</sup> After defining the brachioradialis architecture we documented that the brachioradialis muscle is strongly tethered to surrounding structures in the forearm and releases, as much as 9 cm proximal from the insertion, provided only minimal mobility. As the release progressed toward the elbow, large increases in mobility were measured that enabled us to recommend an average release distance of 15 cm to provide sufficient mobility for the brachioradialis to replace, for example, thumb flexion or wrist extension, without risking injury to the radial nerve. Another example revolves around the debate that surgeons who treat

patients with tetraplegia have regarding whether the posterior deltoid muscle is an architecturally suitable donor for replacement of elbow extension in C6 spinal cord injury. To address that question, we developed a novel high pressure formaldehyde perfusion technique and studied the deltoid and triceps muscle architecture and mechanics in 10 cadaveric specimens.<sup>6</sup> We found that the physiologic cross-sectional area of the posterior deltoid was predicted to provide only approximately 20% of the maximum isometric tension of the combined heads of the deltoid and triceps and that the long fibers of the posterior deltoid (almost twice as long as the average length of deltoid and triceps muscle fibers) render it a very forgiving transfer because of its tremendous excursion. As a logical consequence to an earlier observation that high passive tension may elongate the repair sites in the posterior deltoid-to-triceps tendon transfer, stainless steel sutures were inserted into the donor muscle, graft, and tendon insertion sites (Fig. 8A).<sup>3</sup> The distances between the various markers then were measured radiologically during a 2-year period. Significant tendon elongation of  $23 \pm 3.7$  mm ( $n = 8$ ) was observed in patients receiving traditional postoperative care (Fig. 8B). Therefore a special armrest was developed that was applied the first postoperative day. The armrest was designed to maintain the elbow in  $20^\circ$  flexion and to prevent shoulder adduction. The addition of this armrest to the traditional postoperative protocol resulted in a dramatic decrease of tendon elongation to only  $8.4 \pm 3.0$  mm ( $n = 5$ ,  $P < 0.05$ ) and improved elbow extension function (Fig. 8B). Although such studies are not exhaustive, they do illustrate the power of understanding and applying muscle design and function to surgical reconstruction.

**PASSIVE MECHANICAL PROPERTIES**

Based on intraoperative measurements, it was obvious that the passive properties of human muscles dominated the surgeon’s decision-making process. It also was obvious that these properties were highly variable among muscles and yet there were no data available from which to understand these properties. Therefore, the single muscle cell technology that we had used approximately 20 years earlier<sup>14,30</sup> was used to begin to understand the mechanical properties of human muscle cells (Fig. 9).<sup>2</sup> In the initial study of 13 experiments on 55 muscle fibers from five different muscles, single cells were slowly elongated while measuring force and sarcomere length. Average peak stress was  $44 \pm 10$  kPa which was only approximately 25% of that observed previously in frog skeletal muscle.<sup>39</sup> In addition, we observed tremendous variability among fibers for reasons that are unclear but were not attributable to fiber type (as determined on myosin heavy chain polyacrylamide gels) or storage length. We hypothesize that these fibers are different, in part, because of different titin isoforms expressed in them, and the molecular biologic expertise to test this hypothesis has been developed.<sup>37</sup> The mechanical

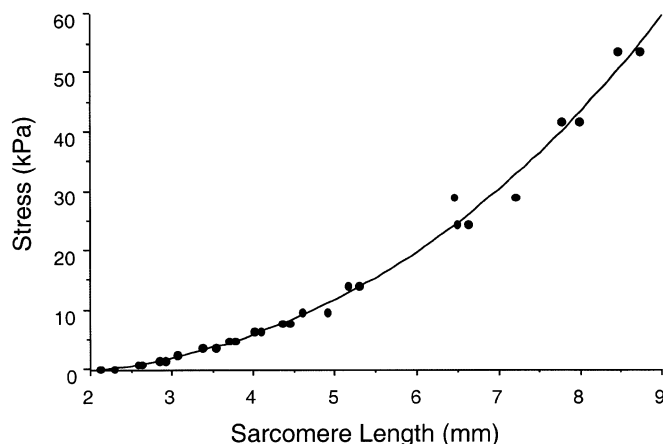


**FIGURE 8.** A, A lateral radiograph of the deltoid-to-triceps tendon transfer was obtained after surgical placement of stainless steel markers. The distances between the markers are denoted as proximal (#1–#2), distal (#3–#4), and intermediate (#2–#3) in illustration (B). The calibration ruler is shown to the left in the picture. B, The postoperative repair regimen included a custom armrest (upper panel) or traditional rehabilitation (lower panel). With the armrest, less elongation occurs which we think increases function.

properties of single cells from spastic skeletal muscles have been tested and it was found that resting sarcomere length is shorter whereas fiber stiffness is higher in these muscles.<sup>7</sup> There is increasing evidence that the mechanical basis of passive tension in skeletal muscle is not only connective tissue or sarcolemma as stated, but the giant intramuscular protein known as titin.<sup>41</sup>

**PRELIMINARY CLONES OF HUMAN UPPER EXTREMITY TITIN**

Titin is a difficult protein to clone and sequence. First, it is the largest protein discovered to date (approximately 3



**FIGURE 9.** Sarcomere length from a single cell was measured from the first and second order diffraction peak, yielding two sarcomere lengths per stress value (seen as two symbols at each stress level). Three important parameters obtained from these data are resting sarcomere length (2.077  $\mu\text{m}$ ), peak stress (53.57 kPa), and modulus (164.4 kPa). (The experiment was done on one fiber from a human digital extensor muscle in a patient receiving an ulnar osteotomy unrelated to the muscle). Curve fit from equation:

$$\sigma = \frac{E_0}{\alpha} (e^{\alpha \epsilon_s} - 1)$$

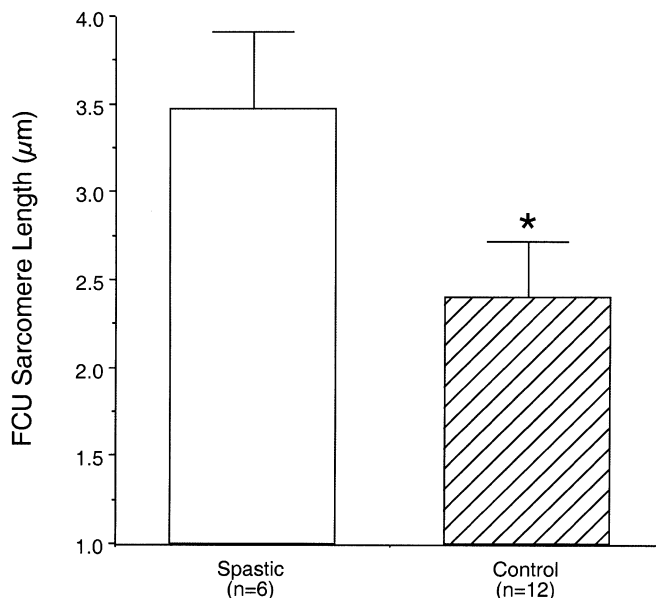
where  $\sigma$  represents passive fiber stress,  $\alpha$  is an empirical constant,  $E_0$  is the initial elastic modulus and  $\epsilon_s$  is sarcomere strain.<sup>38</sup> Values for  $\alpha$  and  $E_0$  then are obtained by linear regression by plotting natural log of stress versus strain. These two parameters interact to produce a value for muscle stiffness and can be used to solve for muscle resting length, the sarcomere length corresponding to zero tension. Data were fit to the exponential relationship shown above yielding the relationship  $s = 1.5 \cdot e^{1.29 \epsilon_s} - 1$ , yielding constants of 1.5 and 1.29 for  $E_0$  and  $\alpha$  respectively ( $r^2 = 0.94$ ,  $P < 0.001$ ).

MDa) which means that the primary sequence is more than 225,000 amino acids long. The titin molecule also is a modular protein composed of hundreds of repeating units that makes identification of unique regions problematic. However, the major elastic region of the titin molecule, known as the PEVK region (named for the component amino acids), is fairly unique and has been shown to differ in size between stiff heart muscle and compliant soleus muscle.<sup>12</sup> The cloning strategy we have used is to download and identify consensus regions of the compliant PEVK regions from human muscles. Using such homology searches, we identified a few unique regions of the extremely long PEVK region in human upper extremity titin. Then, we developed polymerase chain reaction (PCR) primers to these regions to enable selective amplification of small pieces of the PEVK region that range from 250 to 7000 bp in length. Although we developed the approach using small muscle biopsies, we are able to extract RNA and do the identical analysis on isolated single muscle cells. Initially, we

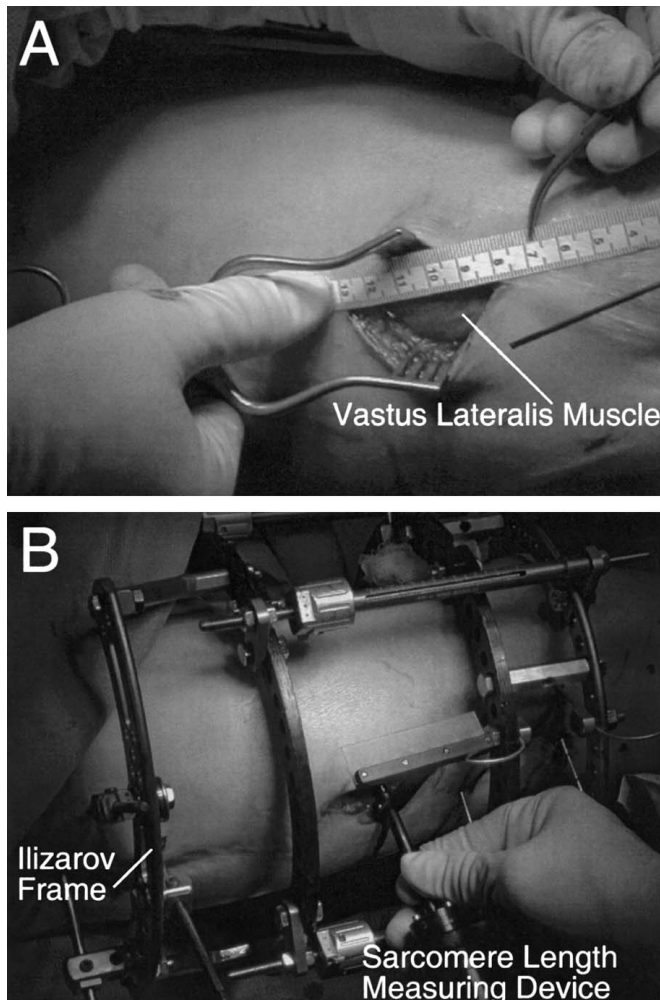
documented the differences in titin transcript composition in stiff cardiac muscle compared with compliant soleus muscle.

## SPASTIC MUSCLES

Throughout the course of the intraoperative studies, we were fascinated with the prospect of understanding the structure and function of spastic skeletal muscle. The muscle that we had the most access to was the flexor carpi ulnaris. We measured sarcomere length from patients with severely spastic wrist flexion contractures ( $n = 6$ ) and patients with radial nerve injury ( $n = 12$ ) who served as control subjects in the sense that these muscles were not spastic.<sup>24</sup> It was surprising that spastic flexor carpi ulnaris muscles had extremely long sarcomere lengths with the wrist fully flexed compared with the flexor carpi ulnaris muscles of patients with radial nerve injury (Fig. 10). Initially, we thought that this indicated that spastic muscles had a decreased sarcomere number attributable to the central nervous system lesion. However, this was not the case. We determined this because, in three of the patients with spastic wrist flexion contractures, the slope of the flexor carpi ulnaris sarcomere length-joint angle relationship was measured and found to be, essentially, normal ( $0.017 \pm 0.005 \mu\text{m}/^\circ$ ,  $n = 3$ ) suggesting that serial sarcomere number (and therefore muscle fiber length) was unchanged despite the dramatic absolute sarcomere length change. We cannot fully explain these results,



**FIGURE 10.** The flexor carpi ulnaris (FCU) sarcomere length was measured with the wrist fully flexed in patients with spastic wrist flexion contractures (open bar) or in patients without spastic muscles who serve as controls (hatched bar). The data represent mean  $\pm$  SEM for each group. Sarcomere lengths were significantly different, as seen by one-way ANOVA ( $*P < 0.001$ ).

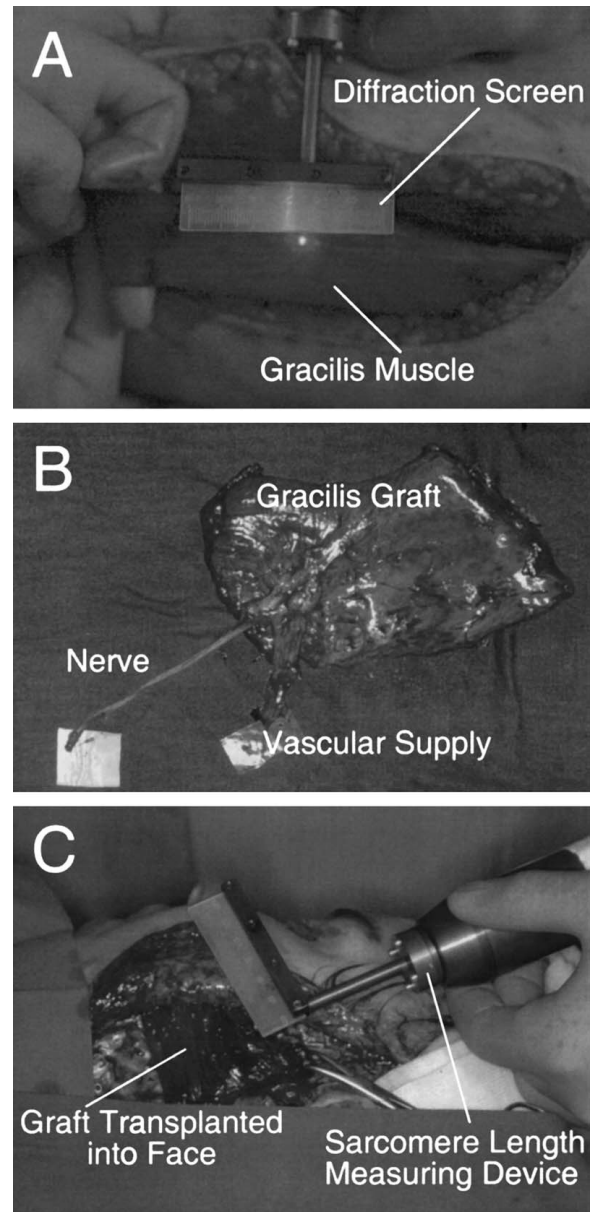


**FIGURE 11.** A, The vastus lateralis muscle was isolated before sarcomere length measurement and Ilizarov frame placement. B, Laser diffraction of the distal aspect of the vastus lateralis was done after placement of the Ilizarov distraction frame. (Photographs courtesy of Dr. Jennette Boakes, Shiner’s Hospital, Sacramento, CA.)

but they indicate that spasticity results in a major alteration of normal muscle-joint anatomic relationships. Such an alteration appears unprecedented in either the literature regarding muscle plasticity or neuromuscular disease. As most clinicians already appreciate, spasticity is a novel mode of skeletal muscle adaptation. We hypothesize that the results are explained either by the inability of muscle fibers to add serial sarcomeres in response to growth or the selective loss of flexor carpi ulnaris muscle length secondary to the central nervous system lesion.

**FUTURE APPLICATIONS**

These studies showed the evolution and refinement of our understanding of normal musculoskeletal design. The basic science tool of laser diffraction was applied to the field of



**FIGURE 12.** A, Laser diffraction was done of the gracilis muscle graft before removal from the leg. Sarcomere length was first measured to establish its normal operating range. B, A free muscle graft was removed from the leg and trimmed to the correct length. The motor nerve and vascular supply are indicated. Sarcomere lengths can be determined from excised graft and before removal with normal innervation and perfusion. C, Laser diffraction was done of the transplanted gracilis muscle that was used to replace the frontal muscle area and was reset to proper sarcomere length.

hand surgery and, based on this initial success, collaborations with other institutions and other subspecialties were developed. We are collaborating with the Shriners’ Hospital in Sacramento (Dr. Jennette Boakes) and Texas Scottish Rite Hospi-

tal in Dallas (Drs. John Birch and Michael Samchukov) to improve understanding of the acute and chronic muscular changes that occur during limb-lengthening procedures (Fig. 11). We also are doing a National Institutes of Health-funded project at Children's Hospital in San Diego (Dr. Hank Chambers) to distinguish between two commonly-used methods to correct equinus deformity in children afflicted with cerebral palsy. Finally, we will be studying muscles involved in maxillofacial surgery at Sahlgrenska Hospital in Göteborg, Sweden (Drs. Hans Mark, Jonas Lundberg, and Peter Tarnow) where sarcomere length in the gracilis muscle is first measured (Fig. 12A), the free gracilis muscle flap is removed from the leg (Fig. 12B) and transplanted into the jaw and reinnervated with the facial nerve to correct for the lost frontal muscle (Fig. 12C). Although the use of intraoperative laser diffraction is confined to these specialized areas of research, it is not inconceivable that improvements in technology and understanding of human muscle function may render application of this device more common in the future.

#### ACKNOWLEDGEMENTS

We thank Dr. Ronald J. Baskin (University of California, Davis) who conceived some of the original laser diffraction experiments and supported their development and Dr. Michael J. Botte (Scripps Clinic and V.A. Medical Center, San Diego) for support during this study. We also thank Drs. Arvid Ejeskär, Alastair Rothwell, Vincent R. Hentz, and Michael Keith for fruitful discussions and helpful input over the years.

#### REFERENCES

- Burkholder TJ, Fingado B, Baron S, et al. Relationship between muscle fiber types and sizes and muscle architectural properties in the mouse hindlimb. *J Morphol*. 1994;221:177-190.
- Fridén J, Albrecht D, Lieber RL. Biomechanical analysis of the brachioradialis as a donor in tendon transfer. *Clin Orthop*. 2001;383:152-161.
- Fridén J, Ejeskär A, Dahlgren A, et al. Protection of the deltoid-to-triceps tendon transfer repair sites. *J Hand Surg*. 2000;25A:144-149.
- Fridén J, Lieber RL. Physiological consequences of surgical lengthening of extensor carpi radialis brevis muscle-tendon junction for tennis elbow. *J Hand Surg*. 1994;19A:269-274.
- Fridén J, Lieber RL. Evidence for muscle attachment at relatively long lengths in tendon transfer surgery. *J Hand Surg*. 1998;23A:105-110.
- Fridén J, Lieber RL. Quantitative evaluation of the posterior deltoid to triceps tendon transfer based on muscle architectural properties. *J Hand Surg*. 2001;26A:147-155.
- Fridén J, Lieber RL. Spastic muscle cells are shorter and stiffer than normal cells. *Muscle Nerve*. 2003;27:157-164.
- Gordon AM, Huxley AF, Julian FJ. The variation in isometric tension with sarcomere length in vertebrate muscle fibres. *J Physiol (Lond)*. 1966;184:170-192.
- Griffiths RI. Shortening of muscle fibres during stretch of the active cat medial gastrocnemius muscle: The role of tendon compliance. *J Physiol (Lond)*. 1991;436:219-236.
- Hoffer JA, Caputi AA, Pose IE, et al. Roles of muscle activity and load on the relationship between muscle spindle length and whole muscle length in the freely walking cat. *Prog Brain Res*. 1989;80:75-85.
- Jacobson MD, Raab R, Fazeli BM, et al. Architectural design of the human intrinsic hand muscles. *J Hand Surg*. 1992;17A:804-809.
- Labeit S, Kolmerer B. Titins: Giant proteins in charge of muscle ultrastructure and elasticity. *Science*. 1995;270:293-296.
- Lieber RL, Amiel D, Kaufman KR, et al. Relationship between joint motion and flexor tendon force in the canine forelimb. *J Hand Surg*. 1996;21A:957-962.
- Lieber RL, Baskin RJ. Intersarcomere dynamics of single muscle fibers during fixed-end tetani. *J Gen Physiol*. 1983;82:347-364.
- Lieber RL, Baskin RJ: Surgical myometer method. US Patent 4 570 641, February 18, 1986.
- Lieber RL, Blevins FT. Skeletal muscle architecture of the rabbit hindlimb: Functional implications of muscle design. *J Morphol*. 1989;199:93-101.
- Lieber RL, Boakes JL. Sarcomere length and joint kinematics during torque production in frog hindlimb. *Am J Physiol*. 1988;254:C759-C768.
- Lieber RL, Brown CC. Quantitative method for comparison of skeletal muscle architectural properties. *J Biomech*. 1992;25:557-560.
- Lieber RL, Brown CG, Trestik CL. Model of muscle-tendon interaction during frog semitendinosus fixed-end contractions. *J Biomech*. 1992;25:421-428.
- Lieber RL, Fazeli BM, Botte MJ. Architecture of selected wrist flexor and extensor muscles. *J Hand Surg*. 1990;15A:244-250.
- Lieber RL, Fridén J. Intraoperative measurement and biomechanical modeling of the flexor carpi ulnaris-to-extensor carpi radialis longus tendon transfer. *J Biomech Eng*. 1997;119:386-391.
- Lieber RL, Fridén J. Musculoskeletal balance of the human wrist elucidated using intraoperative laser diffraction. *J Electromyogr Kinesiol*. 1998;8:93-100.
- Lieber RL, Fridén J. Functional and clinical significance of skeletal muscle architecture. *Muscle Nerve*. 2000;23:1647-1666.
- Lieber RL, Fridén J. Spasticity causes a fundamental rearrangement of muscle-joint interaction. *Muscle Nerve*. 2002;25:265-270.
- Lieber RL, Jacobson MD, Fazeli BM, et al. Architecture of selected muscles of the arm and forearm: Anatomy and implications for tendon transfer. *J Hand Surg*. 1992;17A:787-798.
- Lieber RL, Leonard ME, Brown CG, et al. Frog semitendinosus tendon load-strain and stress-strain properties during passive loading. *Am J Physiol*. 1991;261:C86-C92.
- Lieber RL, Ljung BO, Fridén J. Intraoperative sarcomere measurements reveal differential design of long and short wrist extensors. *J Exp Biol*. 1997;200:19-25.
- Lieber RL, Loren GJ, Fridén J. In vivo measurement of human wrist extensor muscle sarcomere length changes. *J Neurophysiol*. 1994;71:874-881.
- Lieber RL, Pontén E, Burkholder TJ, et al. Sarcomere length changes after flexor carpi ulnaris to extensor digitorum communis tendon transfer. *J Hand Surg*. 1996;21A:612-618.
- Lieber RL, Roos KP, Lubell BA, et al. High speed digital data acquisition of sarcomere length from isolated skeletal and cardiac muscle cells. *IEEE Trans Biomed Eng*. 1983;30:50-57.
- Lieber RL, Shoemaker SD. Muscle, joint, and tendon contributions to the torque profile of frog hip joint. *Am J Physiol*. 1992;263:R586-R590.
- Lieber RL, Silva MJ, Massie J, et al. Wrist and digital joint motions generate unique flexor tendon forces and excursions in the canine forelimb. *Trans Orthop Res Soc*. 1998;44:609.
- Lieber RL, Yeh Y, Baskin RJ. Sarcomere length determination using laser diffraction: Effect of beam and fiber diameter. *Biophys J*. 1984;45:1007-1016.
- Ljung BO, Fridén J, Lieber RL. Sarcomere length varies with wrist ulnar deviation but not forearm pronation in the extensor carpi radialis brevis muscle. *J Biomech*. 1999;32:199-202.
- Loren GJ, Lieber RL. Tendon biomechanical properties enhance human wrist muscle specialization. *J Biomech*. 1995;28:791-799.
- Loren GJ, Shoemaker SD, Burkholder TJ, et al. Influences of human wrist motor design on joint torque. *J Biomech*. 1996;29:331-342.
- Lutz GJ, Razzaghi S, Lieber RL. Cloning and characterization of the S1 domain of four myosin isoforms from functionally divergent fiber types in adult Rana pipiens skeletal muscle. *Gene*. 2000;250:97-107.
- Magid A, Law DJ. Myofibrils bear most of the resting tension in frog skeletal muscle. *Science*. 1985;230:1280-1282.
- Magid A, Reedy MK. X-ray diffraction observations of chemically skinned frog skeletal muscle processed by an improved method. *Biophys J*. 1980;30:27-40.

40. Mai MT, Lieber RL. A model of semitendinosus muscle sarcomere length, knee and hip joint interaction in the frog hindlimb. *J Biomech*. 1990;23:271–279.
41. Patel TJ, Lieber RL. Force transmission in skeletal muscle: From actomyosin to external tendons. *Exerc Sport Sci Rev*. 1997;25:321–363.
42. Simon SR, Ryan AW. Biomechanical/Neurophysiologic Factors, Related to Surgical Correction of Equinus Deformity. In Sussman MD (ed). *The Diplegic Child*. Rosemont, IL: American Academy of Orthopaedic Surgeons; 1992:365–381.
43. Trestik CL, Lieber RL. Relationship between Achilles tendon mechanical properties and gastrocnemius muscle function. *J Biomech Eng*. 1993;115:225–230.
44. Woo SLY, Gomez MA, Amiel D, et al. The effects of exercise on the biomechanical and biochemical properties of swine digital flexor tendons. *J Biomech Eng*. 1981;103:51–56.
45. Yeh Y, Baskin RJ, Lieber RL, et al. Theory of light diffraction by single skeletal muscle fibers. *Biophys J*. 1980;29:509–522.
46. Zajac FE. Muscle and tendon: Properties, models, scaling, and application to biomechanics and motor control. *Crit Rev Biomed Eng*. 1989;17:359–411.