Incomitant Strabismus

Does Extraocular Muscle Form Denote Function?

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The paradigm that an “underacting” extraocular muscle is always atrophic or hypoplastic and that an overacting extraocular muscle should always be enlarged leads to inconsistencies with clinical observations. These include findings of “overacting” inferior oblique muscles, superior rectus muscle overaction or contracture syndrome, and normal extraocular muscle diameters in patients with apparent superior oblique muscle palsy, among other clinical entities. These inconsistencies can be reconciled if one accepts the possibility that extraocular muscle contractile activity may reflect a change in neural input to an anatomically normal muscle or that muscle contractile activity may be altered by shifts in fiber type and distribution within a normal-sized muscle. This remodeling may result from vergence adaptation or from any change in neural stimulus to the muscle. There is substantial evidence to suggest that both of these theoretical possibilities may likely occur. Arch Ophthalmol. 2010;128(12):1604-1609

Incomitant strabismus is typically described in terms of extraocular muscle (EOM) overaction or underaction. For example, if an eye moves further than normal on a version into the field of action of a given muscle, that muscle is commonly said to “overact.” If there is deficient movement and no restriction limiting the movement, the muscle is said to “underact.” This terminology is descriptive and does not necessarily describe the underlying pathogenesis. For example, changes in the normal anatomical course that a muscle follows—from pulley heterotopia, torsion, orbital anomalies, and/or iatrogenic oblique muscle incarceration—can alter its torque vector and thus alter its function. Similarly, a muscle may appear to underact if its torque vector has been altered by posterior fixation surgery, if muscle slippage or elongated scar formation has occurred after strabismus surgery, or it may result from uncomplicated recession surgery according to the torque vector theory.

If the torque vector of the muscle is not abnormal, alteration of muscle function—an increase or a decrease—would result from a change in the force generated by the muscle, as well as from changes in the torque generated by its antagonist muscle. Denervation of skeletal muscle results in atrophy that is characterized by a smaller than normal cross-sectional area, and greater muscle strength can be associated with hypertrophy (an increase in muscle fiber size) or, to a lesser degree, with hyperplasia (an increase in the number of muscle fibers), both of which result in a larger than normal total cross-sectional area. However, EOMs have a unique response to denervation. They show a pattern of atrophy that differs from that seen in other striated muscles, which indicates some degree of resilience to denervation. The paradigm that a stronger than normal muscle should have an increased cross-sectional area and that a paretic muscle should have a smaller than normal cross-sectional area leads to numerous inconsistencies with respect to clinical observations. For example, some patients with the clinical picture of superior oblique muscle paresis have a normal-sized superior oblique muscle as determined by magnetic resonance imaging. Size of the superior oblique muscle does not correlate with the magnitude of the Biel-
schowsky head tilt phenomenon in patients with superior oblique muscle palsy. Although the con \- 
tralesional superior oblique muscle has been shown to be larger than normal in patients with unilateral superior oblique muscle palsy, I have never seen objective intorsion in the contralateral eye of such patients even when studied prospectively. If enlargement of the contralateral superior oblique muscle indicated that it was stronger than normal, one would expect to see the eye intorted even in the primary position, as contractile force generated by the resting tonus of the muscle should be greater than normal. Finally, the degree of inferior oblique muscle “overaction” in patients with primary inferior oblique muscle “overaction” does not correlate with the size of the “overacting” muscle. Certainly, any attempt to assess EOM size by orbital imaging may potentially be flawed because of artifacts from positioning, technique, or volume averaging. However, the aforementioned studies described rigorous controls to eliminate such errors.

Attempts to reconcile these apparent inconsistencies between clinical observations and muscle size have resulted in various explanations. In some cases, abnormalities of muscle position (eg, pulley displacement or heterotopia) have been observed that are consistent with the clinical observation. For patients with the clinical picture of superior oblique muscle palsy but with normal muscle position and position, Guyton has suggested that strabismus may simply represent the vertical equivalent of horizontal drift that can occur because of vergence adaptation when fusion is lost. However, this explanation begs the question of how to explain the specific incomitance pattern without invoking a weakened superior oblique muscle. Specifically, if there is hypertropia of one eye that increases in adduction and on ipsilateral head tilt and if the muscles and pulleys are in the normal position, there is most likely weakness of the ipsilateral superior oblique muscle regardless of whether it is caused by vergence adaptation.

These apparent inconsistencies can be reconciled by accepting one or both of the following premises: (1) that form does not always denote function (eg, a muscle may be weaker or stronger than normal without having the expected change in cross-sectional area) and/or (2) that innervation to muscles for the same task may not always be consistent depending on adaptations that have occurred in the neural control mechanism. To determine if these premises are plausible, a review of basic muscle physiologic function is in order.

FORM AND FUNCTION

The torque that an EOM exerts on the globe is a function of its force times its lever arm. The introduction gave examples of clinical situations in which the torque vector of an EOM may be altered, thus affecting the lever arm.

The total force that a muscle can generate is the sum of its elastic force and its contractile force. Elastic force of a muscle is a function of the number of sarcomeres in series (end to end) and the amount of stretch. The length-tension curve for elastic force rises steeply as the muscle is stretched beyond its slack length. A contractured muscle has fewer sarcomeres end to end, and a lengthened muscle has more. The length-tension curve for elastic force is the same shape for normal, contractured, and lengthened muscles, with the latter 2 merely being shifted to the left and right of the curve, respectively, for a normal muscle. Sarcomere size can vary within a muscle fiber, and muscle fibers typically do not extend the entire length of a muscle. Therefore, although sarcomere remodeling is thought to occur only at the ends of muscle fibers, it can occur anywhere along the length of a muscle. A muscle may undergo substantial change in its elastic force due to contracture or lengthening without any change in cross-sectional area, as the addition or loss of sarcomeres occurs only in series. A change in elastic force need not have a corresponding change in contractile force.

Contractile force is the increase in force of a muscle that results from the chemical interaction between actin and myosin filaments and causes shortening of sarcomeres. It is the increase in force that results from active contraction of a muscle. The relationship between sarcomere length and contractile force is more complicated than that for elastic force because it is also a function of the velocity of contraction under isotonic conditions (Figure 1). At low velocities, the length-tension curve more closely approximates the curve for isometric conditions. At high velocities, the length-tension curve is
much flatter, and sarcomere length has substantially less effect. For an isometric contraction, the length–contractile force curve approximates the curve for low velocity of an isotonic contraction, as shown in Figure 1, with the force being maximum at approximately the resting length of the muscle. **Figure 2** compares the length-tension curves for contractile force under isometric conditions vs isotonic conditions at high velocity. The total force, which is the sum of the elastic and contractile forces, has a biphasic length-tension curve under isotonic conditions. Under isometric conditions, the total force (elastic plus contractile) for high-velocity movements, which is probably most relevant for versions, does not show the biphasic curve that is characteristic under isometric conditions (**Figure 3**).

Before discussing factors that influence the contractile force of EOMs, it is important to know that EOMs are fundamentally distinct from other skeletal muscles and that rules governing other skeletal muscles do not necessarily apply to EOMs. In addition, there is substantial variability in the properties of EOMs between species. Consequently, any studies performed on skeletal muscles or EOMs of other species may not be applicable to human EOMs. This problem is compounded by the fact that one cannot easily perform in vivo studies about many of the physiologic properties of human EOMs because only the anterior-most aspect of the EOM and tendon is accessible during strabismus surgery. The entire orbital layer lies posterior to the pulley and cannot be seen with routine surgical approaches. Nevertheless, extrapolation from animal studies and studies of human skeletal muscle should be useful at least for determining what is feasible with respect to human physiologic EOM.

The contractile properties of muscles can be characterized by more than just their maximum strength of contraction. They also include their velocity, fatigability, and twitch vs nontwitch status, all of which are determined by fiber type. Some muscle fiber types are fast and some are slow, some maintain maximum contraction and some fatigue easily, and some exert a stronger maximum contraction than others. In general, EOMs show high-velocity and low-tension contractions compared with other striated muscles. Contractile force of a striated muscle is generally proportional to its physiologic cross-sectional area (PCSA), and velocity is proportional to fiber length, if all other variables are unchanged. As PCSA increases, the maximum force it can generate typically increases. Exceptions to this occur in certain pathologic states. There can be a substantial increase of PCSA in Graves orbitopathy, accompanied by a large increase in elastic force, yet contractile force may be decreased because muscle contraction is impeded by the presence of glycosaminoglycans. In myasthenia gravis, contractile force may be similarly substantially decreased, yet there may be no change in PCSA, and an EOM weakened by botulinum toxin A does not show the same pattern of atrophy seen with other skeletal muscles. Therefore, form does not always denote function. As muscle fibers elongate due to the addition of sarcomeres in series, there is no increase in contractile force so long as the length of individual sarcomeres stays constant, and sarcomere remodeling reportedly maintains that constancy. However, there is an increase in velocity. The possibility that a shift in the distribution of fiber type within an EOM can occur and affect contractile properties deserves exploration.

There are many different but overlapping classifications of skeletal muscles. Various fiber types have different metabolic activity. Some fibers demonstrate fast contractions but low fatigue resistance, others are fast but fatigable, and...
some are fast but fatigue resistant, and still others are slow but fatigue resistant.  

Skeletal muscle is one of the most adaptable tissues in the body. It can change its architecture, fiber type and distribution, tendon length, fiber diameter, myosin heavy-chain profile, fiber length, and mitochondrial distribution, among others.  

Extraocular muscles show substantially more plasticity than most other skeletal muscles. According to McLoon et al., the complex structural differences of adult EOMs may have physiologic and pathophysiologic significance. These differences vary over the length of a given muscle (eg, at the tendon end or not), and the proportional length and position of individual myofibers within an individual EOM can be important.  

Extraocular muscles have 2 basic fibers. The first is similar to twitch fibers of other skeletal muscles and is a singly innervated fiber, and the second is similar to slow fibers of other skeletal muscles and is a multiply innervated fiber, of which there are 2 subtypes. It is believed that singly innervated fibers are involved in larger movements, such as saccades and versions in general, and that multiply innervated fibers are involved in smaller movements to saccades and versions in general, and involved in larger movements, such as drial distribution, among others.  

EOMs show substantial plasticity and pathophysiologic adaptation. These differences vary over the length of a given muscle (eg, at the tendon end or not), and the proportional length and position of individual myofibers within an individual EOM can be important.  

ALTERATION IN INNERVATION  

Most explanations for EOM overaction or underaction focus on structural changes in the muscle rather than on a change in innervation to the muscle, with a few notable exceptions.  

In common clinical situations, a muscle may show an abnormal increase in contractile force due to excessive innervation. Several examples of this include accommodative esotropia when hyperopia is not corrected, secondary deviation that occurs when there is fixation duress to the fixing eye due to paresis or restriction, or esotropia that occurs in accommodative effort syndrome. It may be relevant that a monkey line prone to strabismus shows altered motor neuron discharge rates in general. Classic teaching of skeletal muscle physiology is that strength cannot be solely attributed to muscular factors but can also be neural. A large muscle that is activated to only a small extent will generate a weaker force than a small muscle that is fully activated.  

This raises the question of whether EOM overaction or underaction (mimicking paresis) can result from a change in innervation to an anatomically normal muscle. Results of experiments involving human skeletal muscle training suggest that this neural adaptation is possible. Moritani and deVries had human participants perform unilateral isometric elbow flexion exercises. They initially saw a 25% increase in strength of the exercised bicep. However, the contralateral unexercised bicep showed a 15% increase in strength. Using electromyography, the authors determined that 80% of the initial increase in strength resulted from enhanced neural stimulation and only 20% from a change in muscle structure after 2 weeks. This increase in neural stimulation occurred in the exercised and unexercised arms. After 8 weeks, most of the strength in the exercised arm resulted from hypertrophy.  

EOM PLASTICITY  

As already stated, EOMs demonstrate a large amount of plasticity. They show a wide range of response to disease, and alteration in the neuronal discharge rate may change muscle fiber type composition. Extraocular muscle myofiber contraction speed and fatigue resistance have correlates in fiber structure (eg, myosin heavy-chain isoform, sarcoplasmic reticulum calcium pump, and sarcoplasmic reticulum elements).  

Fatigue resistance is directly related to dependence on glycolytic or oxidative enzymes, mitochondrial content, and structure of myofibers. In theory, changes in any of these factors can alter contractile properties without necessarily inducing a corresponding change in cross-sectional area.  

FACTORS THAT CAN CAUSE MUSCLES TO CHANGE  

In his elegant theory about vergence adaptation, Guyton focused primarily on causes of changes in muscle length due to sarcomere addition or loss. Because these changes are primarily related to EOM length, they would mostly influence elastic force of the muscle. This would affect the resting length of the muscle but not its contractile force. As Guyton hypothesized, it would explain the changes that occur in strabismus over time, particularly in the primary position. It less comprehensively explains apparent muscle overaction or paresis. I believe that his ideas are wholly compatible with the theory that I am setting forth, which deals with other forms of remodeling that can affect EOM contractile activity, specifically changes in distribution of myofibril type and changes in innervation. Guyton believed that chronic vergence stimulation was the main factor causing EOMs to lengthen or shorten due to vergence adaptation. For many years, it was thought that there was a common final neural pathway to the EOMs and that the activ-
ity of any single motor unit correlated with eye position and not the type of movement needed to get there. More recently, studies have confirmed that the neural organization governing multiply innervated fibers and singly innervated fibers in fact differ, and this would suggest that versions and vergences are innervated differently. Irrespective of whether it is primarily vergence stimulation or any stimulation that causes EOM remodeling, numerous changes are known to occur in EOMs secondary to stimulation.

In general, long-term electrical stimulation of skeletal muscles causes fast fibers to become slow. This is a true conversion of individual fibers and not a loss of fast fibers by dropout. However, some of these experiments on denervated muscles are not replicated in normally innervated muscles. All stimulation of human and animal EOMs shows an increase in endurance; however, some experiments show strengthening in humans but weakening in animals. This makes it hard to extrapolate from one species to another. These differences may be a result of species variations or of experimental design. However, muscle fiber transformation can occur given appropriate stimuli.

COMMENT

In many cases, EOM form may denote function. A muscle that is atrophied will have a smaller than normal PCSA and will clinically manifest weak contractile force. A muscle that has a larger than normal PCSA from hypertrophy or hyperplasia may manifest “overaction” clinically. However, relying on the paradigm that an underacting muscle is always atrophied and that an enlarged muscle will always manifest “overaction” is probably an oversimplification.

Our knowledge of the nature of sarcomere remodeling in human EOMs is based on a valid hypothesis; however, knowledge is limited about how sarcomere length and number are regulated in human EOMs. Scott suggested that gain or loss of sarcomeres in human EOMs is for the purpose of maintaining optimal length. In his experiments, muscles were maintained in positions of constant stretch or shortening by suturing the globes to the orbital wall. The EOMs were not recessed or resected. Other studies have shown complex and varied forms of sarcomere remodeling after EOM recession or resection in the operated on muscle and in its antagonist. However, these studies were conducted in rats and rabbits, and human EOMs are known to differ in many respects from EOMs of other species. One cannot definitively extend conclusions from studies of EOMs in nonprimates to humans. In addition to muscle length and load, various types of stimuli may affect sarcomere remodeling. Whether this is largely influenced by vergence stimuli, as suggested by Guyton, or by other forms of neural stimuli needs to be elucidated. In addition, little is known about factors that affect EOM plasticity with respect to muscle fiber type and distribution. Similarly, not much is known about causes of long-term change in resting innervational tone to EOMs. Future studies should shed more light on this complex subject. Although much more needs to be learned, changes in muscle fiber type and distribution or changes in innervation to EOMs may alter their clinical function without affecting PCSA. Substantial evidence suggests that both of these theoretical possibilities may likely occur.

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