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*Preliminary report*

# In Graves' disease, increased muscle tension and reduced elasticity of affected muscles is primarily caused by active muscle contraction

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ABSTRACT. In three patients with Graves' disease of recent onset, length-tension diagrams were made during surgery for squint under eyedrop anesthesia, while the other eye looked ahead, into the field of action, or out of the field of action of the muscle that was measured. The affected muscles were found to be very stiff when the other eye looked straight ahead. Unexpectedly, the affected muscle did not shorten any further (one case) or only 6-7 mm (two cases) when the other eye looked into the field of action of the muscle, whereas it lengthened 9-10 mm when the other eye looked out of the field of action of the muscle. This means that the raised muscle tension and reduced elasticity of affected muscles in these cases of Graves' disease of recent onset are caused by active muscle contraction. It has been found previously that hyperthyroidism, induced in rats, casues transitions from slower to faster myosin-heavy chain (MHC) types. The findings seem compatible with a transition of slow into fast muscle fiber types in Graves' disease.

*Key words:* Graves' disease; length-tension measurements



## INTRODUCTION

The cause of Graves' disease is unknown. It is generally agreed that, after a long period of muscle thickening, fibrosis of the affected muscles occurs, but how this end stage is reached, has remained elusive. We have made intraoperative, continuous-registration, length-tension diagrams of detached eye muscles in two patients with Graves' disease of recent onset, during surgery for squint under eye drop anesthesia.

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## CASE REPORTS

*Case 1.* In this 50-year-old female, 16 months before admission a proptosis of the left eye occurred, without sensations of burning or tearing. A CT-scan was made, and a thick medial rectus muscle on the left side was found. In a second CT-scan two months later, thickened medial, superior and inferior rectus muscles were seen on the left side, and a diagnosis of Graves' ophthalmopathy was made. Eight months before admission, corticosteroids and radiation of the left orbit (20 Gy) were administered, without success.

The patient had a small diffuse struma. Thyroid function was normal: free thyroxin: 9.8 ng/l, free tri-iodine-thyronine: 4.1 ng/l, TSH (basal): 0.4 mU/l, microsomal antibodies: 39 kU/l, antibodies against thyroglobulin: not demonstrable, TSH-receptor antibodies: 3.8 U/l, free T4: 15 pmol/l, T3: 1.6 nmol/l, iodine phase 2/24 hours: 16/55% of administered dosis. Protein-bound $^{123}I$ in 24-hour serum: 0.214%/l. After intravenous administration of 200 $\mu$g TRH, the TSH level was 0.37, 3.06 and 1.31 mU/l, after 0, 25 and 60 minutes, respectively. The angles of convergent squint were +10 deg, +7 deg and +4 deg, when the right eye was pointed 20 deg to the left, straight ahead, or 20 deg to the right, respectively. No cyclotropia was present. Intra-ocular pressure rose from 17.5 to 23 mm Hg on upgaze, and from 22.5 to 39 mm Hg on left gaze.

Because of decreasing visual acuity (0.2, partly caused by keratitis sicca but an afferent pupillary defect was present) and concentric visual field restriction in the left eye, decompression surgery was performed elsewhere, four months before admission. The left ethmoid was opened to accommodate part of the content of the left orbit, including part of the left medial rectus muscle. In addition, the medial orbital floor and the medial wall of the sphenoid were opened. After surgery, the protrusion of the left eye was reduced from 5 to 1 mm, as compared to the right eye, but the convergent squint had increased. The patient was admitted to this hospital.

On admission, the angles of convergent squint were +23 deg, +18 deg and +13 deg, when the right eye was pointed 25 deg to the left, straight ahead, or 25 deg to the right, respectively. The surgery for squint consisted of a recession of the insertion of the medial rectus muscle by cutting it off the globe and suturing it back onto the globe 6 mm behind the old insertion. In addition, the lateral rectus muscle was shortened by a 6 mm resection. The patient was operated under local anesthesia, *i.e.*, only anesthetic eyedrops were used. After surgery, the angles of squint were +2 deg, −3 deg and −10 deg, respectively. In other words, she now had a divergent squint when looking towards the right.

The measurement procedure has been described elsewhere[1, 2]. In short, a length and tension measuring device[3] was fixed during surgery rigidly above the head of the patient. It consisted of a 2 mm hardened steel shaft, suspended by precision micro ballbearings and equipped with a shaft-position encoder and an eddy-current motor. The torque generated by the eddy-current motor in the shaft and the position of the shaft were assessed electronically. The frame on which it was mounted consisted of 30 mm steel posts fixing the railing of the operating table, a 20 mm steel transverse bar above the chest of the patient, a 20 mm steel bar that could be clamped tight in any position rectangular to the transverse bar. The head of the patient was fixed on the circular cushion of the steel head support of the operating table. A 4.0 silk suture was passed through the muscle to be measured and wrapped around the shaft with a tight knot. The position of that part of the shaft and the suture were kept in line with the muscle to be measured. The torque generated in the shaft was slowly (taking more than 45 s either way) increased and decreased, exterting a pull that varied between 0 and 40 g.

Calibration of the length-tension measuring device was as described previously[1]. The starting friction of the shaft, caused by the precision micro ballbearings was less than 1 gram · mm. The patient gave oral informed consent.

The lateral rectus had almost normal length-tension characteristics, although the muscle was stiffer than normal. The medial rectus muscle was very stiff when the right eye looked straight ahead. Unexpectedly, the medial rectus did not shorten any further when the right eye looked far to the right, whereas it lengthened more than 10 mm when the right eye looked far to the left. Pulling the medial rectus muscle was painful from approximately 15 g onward, only when the patient looked to the left with the right eye. Pulling the muscle was not painful when the patient looked straight ahead or to the right. In other patients, pain was never experienced during pulling with a force varying between 0 and 40 g.

*Case 2.* Length-tension registrations were made of an inferior rectus in a second case of Graves' disease of recent onset: a middle-aged man with exophthalmos of one year's duration, retraction of the upper eyelids, marked restriction of elevation in both eyes and thickened inferior recti in a CT-scan.

*Case 3.* A 50-year-old female had Graves' disease of six months' duration. She underwent a strumec-

tomy five months before admission.

The inferior rectus in Case 2 and the medial rectus in Case 3 both shortened 6-7 mm but lengthened approximately 9 mm from primary-position length. Spring constants were between 1 and 2.6 g/deg.

## DISCUSSION

The finding of a very stiff muscle when the other eye looked ahead, little additional contraction when the other eye looked into the field of action of the muscle, but considerable relaxation when the other eye looked out of the field of action of the muscle, indicates that innervation to the affected muscle was high when the other eye looked ahead, and that the increased muscle tension and reduced elasticity of the affected muscle was caused by active muscle contraction, not by fibrosis. It has been found previously that hyperthyroidism, induced in rats, causes a transition to faster myosin-heavy-chain (MHC) types[4, 5]. In human skeletal muscles, MHC types are expressed successively during embryonal, neonatal and juvenile development; in other words, as new MHC types arrive, previous MHC types, like embryonal and neonatal MHC, disappear. In human eye muscles, however, almost all MHC types coexist[5]: they contain fast and slow, but also embryonal and neonatal MHC. The fact that hyperthyroidism causes a transition to faster MHC types in rats raises the following provoking questions: Was the increased level of contraction and hypertrophy of the affected muscles in our patients with Graves' disease of recent onset caused by a transition from slow to fast muscle fiber types? Is it possible that this elevated level of contraction had secondarily caused the hypertrophy of the muscle?

We have previously made length-tension registrations in patients with Graves' disease during general anesthesia for squint surgery[2]. In those patients we found no contraction of the affected eye muscle after administration of succinylcholine chloride, which normally causes an intense contraction of eye muscles by stimulating the slow-tonic multiply innervated muscle fibers[2]. The lack of contraction could be interpreted as a loss of slow fibers, which would be compatible with a transition from slow to faster fiber types.

The innervation of the slow-tonic multiply innervated muscle fibers is likely to be almost continuous, to abate only in extreme gaze out of the field of action to the muscle[6]. It seems conceivable that the fibers that underwent a transition to a faster type contract powerfully when stimulated by this continuous-type innervation. One would then expect saccadic peak velocity to increase. This has indeed been found: Kirsch *et al.*[7] found saccadic peak velocities of 800 to 900 deg/s in Graves' disease of recent onset, in one patient more than 1000 deg/s.

Our findings must be interpreted with great care, however, because several phenomena remain unexplained in our speculation. The ocular symptoms may occur years after the onset of hyperthyroidism but also before its onset. Moreover, eye muscle thickening never regresses fully when the thyroid status of the patients is normalized. Finally, it should be noted that the levator muscle mainly has singly-innervated slow muscle fibers (global layer, red type) and no multiply-innervated fibers. Hence, only a transformation of singly-innervated slow fibers could be postulated, if our hypothesis is extended to the phenomenon of eyelid retraction.

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