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Sensory – Motor control of ligaments and associated neuromuscular disorders

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Abstract

The ligaments were considered, over several centuries, as the major restraints of the joints, keeping the associated bones in position and preventing instability, e.g. their separation from each other and/or mal-alignment. This project, conducted over 25 years, presents the following hypothesis:

1. Ligaments are also major sensory organs, capable of monitoring relevant kinesthetic and proprioceptive data.
2. Excitatory and inhibitory reflex arcs from sensory organs within the ligaments recruit/de-recruit the musculature to participate in maintaining joint stability as needed by the movement type performed.
3. The synergy of the ligament and associated musculature allocates prominent role for muscles in maintaining joint stability.
4. The viscoelastic properties of ligaments and their classical responses to static and cyclic loads or movements such as creep, tension–relaxation, hysteresis and strain rate dependence decreases their effectiveness as joint restraint and stabilizers and as sensory organs and exposes the joint to injury.
5. Long-term exposure of ligaments to static or cyclic loads/movements in a certain dose-duration paradigms consisting of high loads, long loading duration, high number of load repetitions, high frequency or rate of loading and short rest periods develops acute inflammatory responses which require long rest periods to resolve. These inflammatory responses are associated with a temporary (acute) neuromuscular disorder and during such period high exposure to injury is present.
6. Continued exposure of an inflamed ligament to static or cyclic load may result in a chronic inflammation and the associated chronic neuromuscular disorder known as cumulative trauma disorder (CTD).
7. The knowledge gained from basic and applied research on the sensory – motor function of ligaments can be used as infrastructure for translational research; mostly for the development of “smart orthotic” systems for ligament deficient patients. Three such “smart orthosis”, for the knee and lumbar spine are described.
8. The knowledge gained from the basic and applied research manifests in new physiotherapy modalities for ligament deficient patients.

Ligaments, therefore, are important structures with significant impact on motor control and a strong influence on the quality of movement, safety/stability of the joint and potential disorders that impact the safety and health of workers and athletes.

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1. Historical background

For centuries the role of the ligaments was thought to be that of mechanical structures that maintain the bones asso-

ciated with the joint in a relative position to each other, e.g. prevent the separation of the bones. Over the years additional information was obtained providing more details on the properties of the ligaments, their anatomy and mechanical functions. The collagen fibers of the ligaments were shown to be viscoelastic and the fibers were shown to be at various levels of laxity or tension such that

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elongation created a process of recruitment which increased with length allowing increase in tension (Woo and Buckwalter, 1988; Woo et al., 1980, 1981, 1987). Furthermore, the position, orientation and shape of a specific ligament was shown to also increase and decrease its tension at specific range of motion, providing resistance to joint separation in that range (Renstrom et al., 1986). It was also shown that interaction of several ligaments associated with the same joint provided joint stability for most of the range of motion in several axis, allowed equal pressure distribution of the two cartilage surfaces and kept the surfaces moving on a prescribed track. Such data confirmed the mechanical properties of ligaments as joint stabilizers.

As far back as the early 20th century, Payr (1900) suspected that ligaments may have a neurological function in addition to their mechanical properties. His hypothesis went without experimental proof for nearly 50 years until several anatomical studies demonstrated the existence of mechanoreceptors in ligaments (Gardner, 1944; Wrete, 1949; Freeman and Wyke, 1967a,b; Ekholm et al., 1960; Patridge, 1924).

Together with the earlier demonstration of articular nerves emerging from ligaments (Rudinger, 1857), the possible neurological role of the ligaments as a sensory element was emerging.

2. The ligamento-muscular reflex

At about the same time, in the mid-20th century, groups of Swedish researchers were attempting to demonstrate the possibility of a reflex arc from the knee ligaments to the thigh muscles. Palmer (1938, 1958) developed tension in the knee's medial collateral ligament of humans and was able to see some muscle activity in the semimembranosus, sartorius, and vastus muscles and noted decreasing activity as the transverse tension via a ligature was shifted distally along the ligament. Stener (1959, 1962) and Andersson and Stener (1959), failed to observe the reflex in the anesthetized feline, yet were able to record nerve activity in the articular nerves of the feline and unanaesthetized humans upon ligament loading, but no muscle activity. In patients with ligament rupture, pain sensation and some muscular activity was observed upon stretch of the damaged ligaments. It was assumed that ligament innervation was to deliver pain sensation upon damage.

The conflicting and confusing results from the two groups remained until 1987 when we were able to demonstrate a distinct reflex activity from the anterior cruciate ligament to the hamstrings in the *in vivo* feline and in unanaesthetized humans as shown in Fig. 1a–c (Solomonow et al., 1987). Several groups went on to independently confirm the existence of a reflex arc from various knee ligaments to the leg muscles in humans and animal models (Grabiner and Weiker, 1993; Beard et al., 1994; Raunest et al., 1996; Sjolander, 1989).

As the neurological functions of the knee ligaments and its reflexive activation of the thigh muscles were estab-

lished, several new questions emerged; are all ligaments in the major joints innervated and capable of eliciting a reflex? And what is the biomechanical/physiological function of the reflex arc from the ligaments to the muscles?

Over the following years we have been able to demonstrate that mechanoreceptors exist in the ligaments of the major joints (Guanche et al., 1999; Solomonow et al., 1996; Petrie et al., 1997, 1998) and that a reflex arc could be elicited by either electrically stimulating the articular nerve emerging from the ligaments or applying tension directly to the ligaments. Mechanoreceptors and a reflex arc were demonstrated in the knee, elbow, shoulder, ankle, palmar wrist, and lumbar spine as shown in Figs. 2 and 3 (Solomonow et al., 1996, 1998, 2002; Phillips et al., 1997; Knatt et al., 1995; Guanche et al., 1995; Stubbs et al., 1998). It is, therefore, a fair conclusion that most ligaments are also a sensory organ and a source of reflex arc to relevant muscles.

Several interesting issues were also revealed. All ligaments are innervated with the same four types of afferents; Golgi, Pacinian Corpuscles, Ruffini endings, and bare endings. Furthermore, in some ligaments these afferents are distributed homogeneously throughout the length of the ligament, whereas in other ligaments most afferents are distributed near the two insertions of the ligament to the bone with otherwise poor presences in their mid-substance. For example, afferents are evenly distributed throughout the annular and transverse medial ligaments but near the insertions of the radial posterior and anterior ligaments of the elbow (Petrie et al., 1998).

Such findings give rise to several suggestions regarding the role of the ligamento-muscular reflex. One possibility suggests that if afferents are distributed only at the bony insertion of the ligaments, where the higher tissue stiffness results in less strain, the excitation threshold of the afferents will be elevated and the reflex will become active only at high strains/tensions. This may be at levels which pose a risk for ligament damage and then the reflexively recruited muscular activity may serve to reduce the strain/stress in the ligament by load sharing. Conversely, if a ligament is evenly distributed with afferents, that may indicate an ongoing service as a sensory organ for detection of angle, position, load, joint velocity, etc., e.g. kinesthetic sensing organ. This may also indicate an ongoing synergistic reflexive activation of muscles during movement.

The absence of Pacinian afferents in the radial collateral ligament of the elbow may emphasize its role as a high threshold strain detector or a nociceptive role where near injurious loads may directly trigger a reflex response from the muscles (Petrie et al., 1998), assisting in preventing injury.

3. Biomechanical functions

The biomechanical function of the reflex initiated by the ligaments was proposed by us to be that of a joint

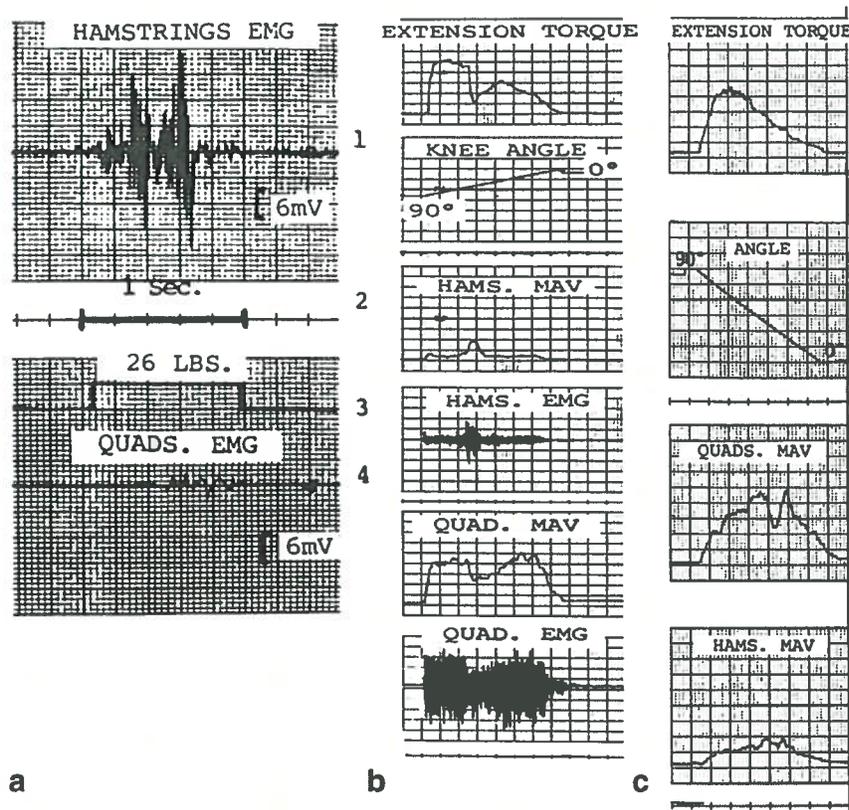


Fig. 1. (a) The substantial increase in EMG activity of the cat's hamstring (Trace 1) over 1 s duration (Trace 2) of direct load application (Trace 3) to the ACL. The quadriceps EMG (Trace 4) exhibits short initial low-level activity and then becomes inhibited for the duration of the ligament's loading. (b) Extension torque, knee angle, hamstring MAV (mean absolute value of the EMG) and EMG, and quadriceps MAV and EMG obtained from a patient with a midsubstance tear of the ACL. Note the large subluxation torque failure near 42°, which appears simultaneously with decrease in quadriceps EMG/MAV and increase in hamstring EMG/MAV, indicating the reflexive attempt of the muscles to correct the instability. (c) Extension torque, knee angle, quadriceps MAV, and hamstring MAV taken from an ACL deficient patient 2 weeks postarthroscopy. Note that the torque does not show any sign of failure, while the reflexive decrease in quadriceps MAV and increase in hamstring MAV do take place near 37° of flexion. The patient had abnormally tight hamstrings. Identical responses were obtained from subjects with hypertrophic knee muscles due to continuous participation in various exercise and sports activity.

stabilizer as well as the source of co-contraction which is so necessary for refined and controlled motion. Hirokawa et al. (1991, 1992) conducted a two stage study to assess the interaction of the thigh muscles, quadriceps and hamstrings, and the relative position of the distal femur and proximal tibia. Sequential X-rays of cadaver knee were taken while loading the quadriceps tendon at different loads and then applying loads to the hamstrings tendon simulating co-contraction, while the quadriceps were fully loaded as shown in Fig. 4. Small metal spheres embedded in the bones, as in the X-ray of Fig. 5a and b, served as markers that were analyzed geometrically. The study shows that anterior translation of the tibia was elicited in the range of motion of 60° flexion to full extension with quadriceps loading as shown in Fig. 6a. As the hamstrings were simultaneously loaded as shown in Fig. 6b, a substantial decrease in the anterior translation of the tibia occurred. It was clear, therefore, that the quadriceps can elicit instability and strain in the ACL due to anterior translation of the proximal tibia from 60° flexion to full

extension, and that the hamstrings can substantially attenuate the anterior translation with just a few percent of co-activation.

We concluded that reflexive activation of the hamstrings as we observed in the feline and humans (Solomonow et al., 1987) could decrease the anterior translation of the tibia and decrease the tension in the ACL. This is specifically applicable for the range of motion from 60 degrees flexion to near full extension. In full extension both quadriceps and hamstrings could stiffen the joint and minimize instability, but without having direct impact on opposing anterior forces as was shown by Markolf et al. (1976, 1978) and Shoemaker and Markolf (1982).

4. Effects of velocity and training

Clear evidence was provided to explain the function of the ligamento-muscular reflex as a synergistic sensory-motor control scheme for maintaining joint stability, decreasing and/or preventing risk of damage to the

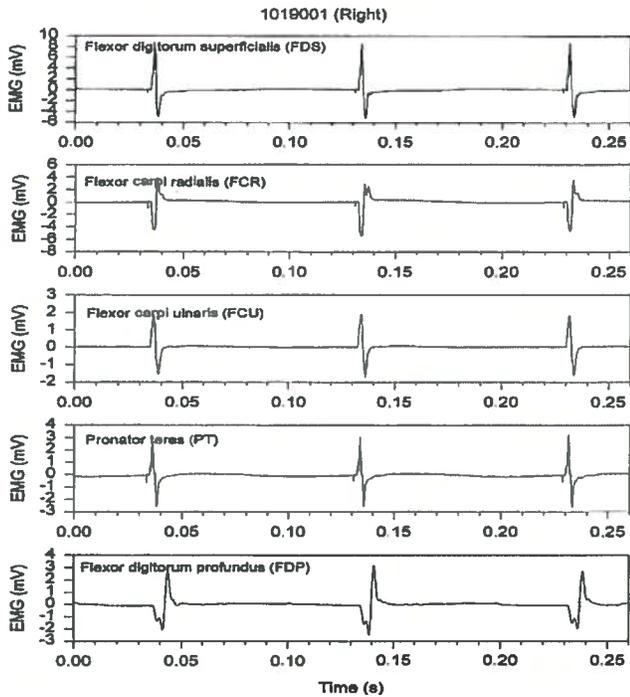


Fig. 2. Typical myoelectric discharge of the flexors digitorum superficialis and profundus, flexors carpi radialis and ulnaris, and the pronator teres in response to stimulation of the median articular nerve to the medial ligaments of the elbow.

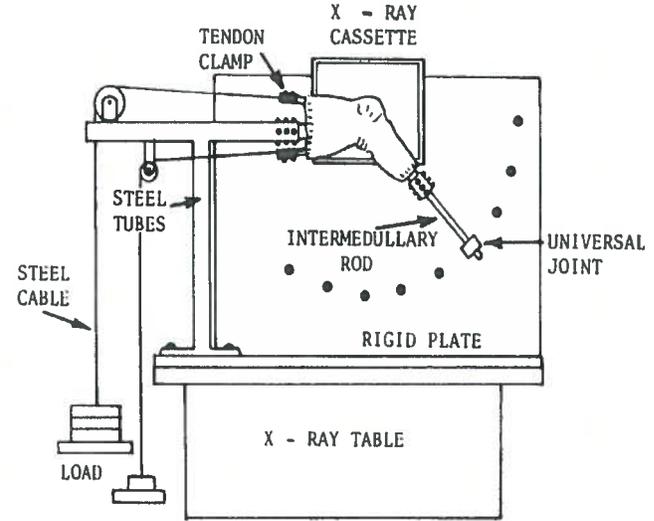


Fig. 4. Experimental apparatus constructed to fix the cadaver knee while permitting loading of the quadriceps and hamstring tendons and change in joint angle.

ligament via co-activation. In addition, one of the roles of ongoing co-activation during various types of joint movement was determined to be preserving joint stability in addition to allowing for joint acceleration, dynamic braking and smooth, controlled motion as shown in Fig. 7a

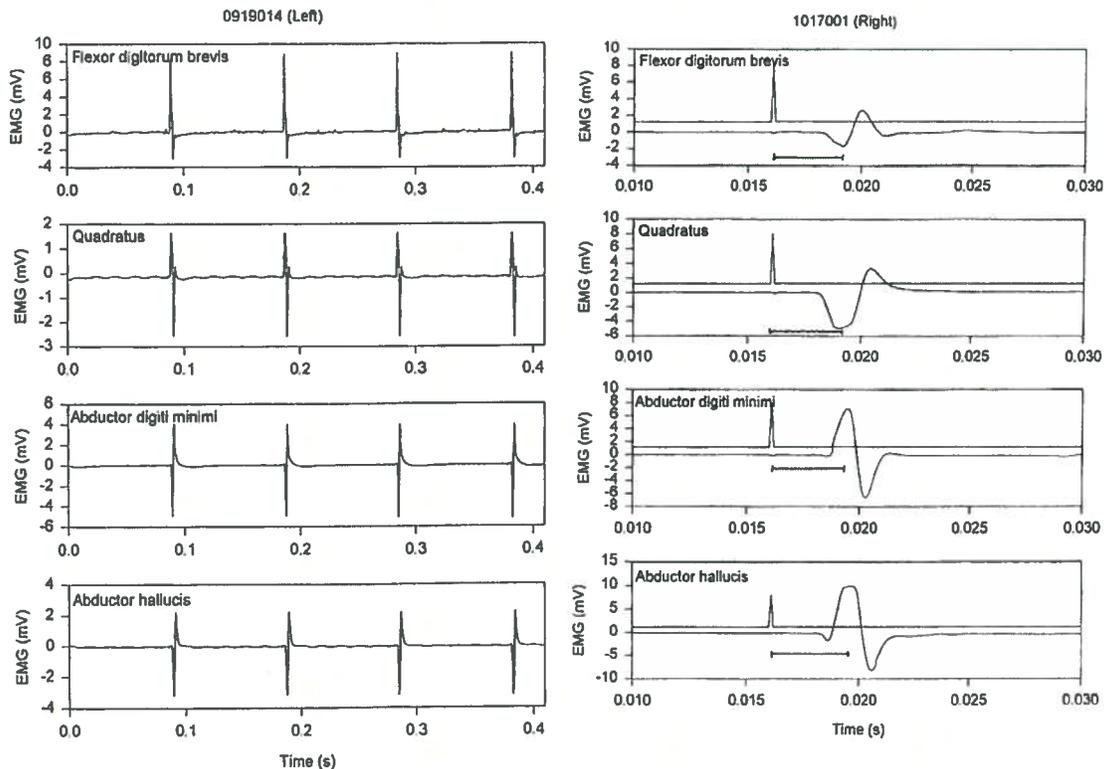


Fig. 3. (a) A typical EMG response of the four intrinsic foot muscles (FDB, Q, ADM, and AH) to a stimulus train of 10 pps. (b) A typical EMG response to one pulse showing the calculated time delay from the peak of the stimulus artifact to the peak of the resulting EMG.

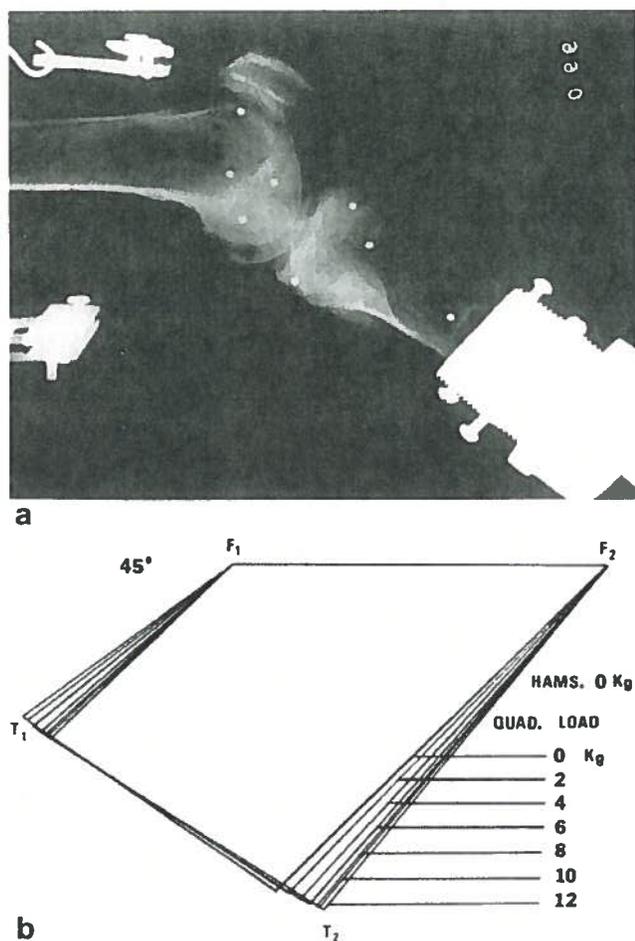


Fig. 5. (a) Typical radiograph of a cadaveric knee positioned at 45° of knee flexion. Note the four metal spheres in the femur and the four metal spheres in the tibia. (b) Seven sequential quadrangles generated from loading the cadaveric knee (set at 45° of flexion) from passive (no load) up to 12 kg load in the quadriceps tendon. Note the deformation of the quadrangle of the passive state in the anterior direction as the load is increased, pointing out the anterior displacement of the tibia. F_1 , F_2 , T_1 , and T_2 correspond to points on the femur and tibia (see Fig. 3).

and b (Hagood et al., 1990; Solomonow et al., 1986, 1988, 1989; Baratta et al., 1988). While co-contraction allows for a measure of joint stability throughout normal motion, the triggering of the ligamento-muscular reflex can provide a fast dose of increase in joint stability when unexpected movement occurs, eliciting sudden increase in ligament tension. It is a protective reflex. We also demonstrated as seen in Fig. 8, that in athletes; jumping activity can decrease the hamstrings coactivation but that could be reversed by three weeks of hamstring retraining (Baratta et al., 1988).

Any protective reflex responding to a potentially damaging or risky stimulus must be a fast-acting one and generate forces in the appropriate muscles. Review of the studies we conducted on the ligamento-muscular reflexes in the elbow, knee, shoulder, ankle, and spine reveal a response time (or latency) ranging from 2.5 to 5 ms (see Fig. 3b for example).

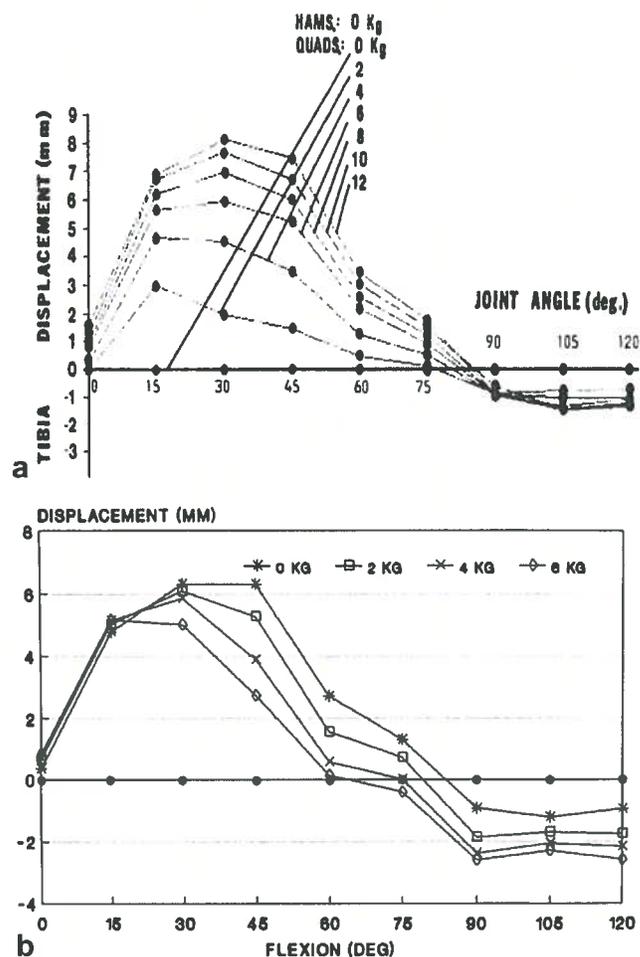


Fig. 6. (a) Anterior-posterior displacement of the tibia versus joint angle for various load levels in the quadriceps. The horizontal axis displays the data of the passive knee (no load). Positive displacement indicates anterior shift, while negative displacement indicates posterior shift. (b) Mean tibia displacement versus joint angle for constant 12 kg quadriceps load and simultaneous hamstrings loads of several magnitudes. Note decrease in anterior translation of the tibia as hamstrings load increases.

Considering the length of the nerves from the spine to the respective joints, a conduction velocity of 120 ms (for large afferents such as Golgi and Pacinian, Mountcastle, 1974) and a 0.5 ms for synaptic transmission, only a monosynaptic or bisynaptic reflex could be assumed. This may emphasize the importance of this reflex as a fast-acting, protective reflex, preventing damage to the ligament and potential risk to the joints.

So far it was shown that the ligaments of the major joints and the lumbar spine are equipped with sensory organs; that there are two patterns of the sensory organ distribution along the ligament with functional neurological implications; that a reflex arc exists from the sensory receptors to muscles associated with the respective joint and that the function of the muscular activation and co-activation is to unload the ligament from overload and prevent potential injury or damage.

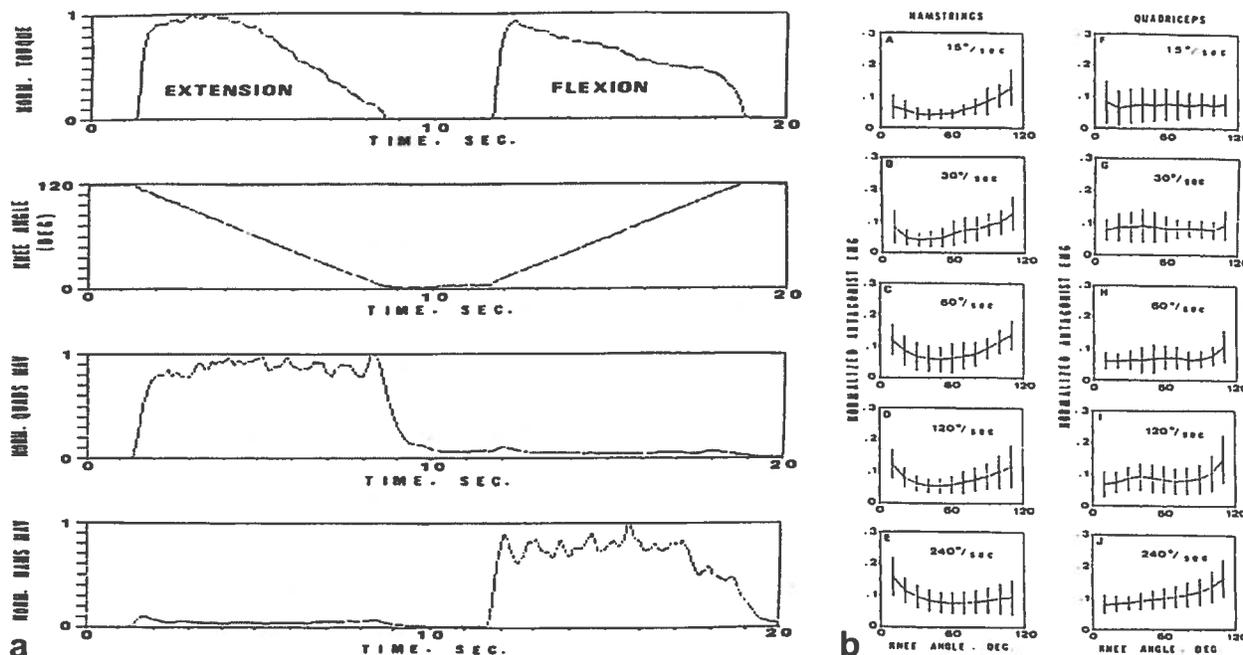


Fig. 7. (a) Typical recording of actual trial from one subject at isokinetic knee velocity of 15 degree/s. Traces show (from top to bottom) extension and flexion normalized torque, knee angle, normalized quadriceps MAV of its EMG during extension and flexion, and the hamstrings normalized MAV of its EMG during extension and flexion. Note that the quadriceps MAV during extension and the hamstrings MAV during flexion were nearly constant (despite the typical fluctuations at maximal force levels) throughout extension and flexion. (b) The antagonist coactivation patterns of the hamstrings (left column) and quadriceps (right column) are shown for increasing joint velocity as normalized antagonist EMG (MAV) versus knee angle. The plots are based on the data pooled from all subjects. The vertical bars indicate the standard deviation for each angle and the curve connects the mean value of the MAV value throughout the range of motion. Note the increase in hamstrings coactivation with increasing velocity just before full extension and decreasing coactivation at the initiation of the motion.

5. Neuromuscular neutral zones

Viscoelastic tissues, such as ligaments, have classical responses to elongation and tension which includes hysteresis and elongation rate dependence (Solomonow, 2004). Ligaments can display large elongations and relatively low associated tension when stretched slow. Fast rates of stretch, however, develop very high tensions that can result in severe damage (known as sprain) or rupture at relatively short elongations. Furthermore, when subjected to a stretch and release cycle, the length versus tension trajectory during the stretch is different than the trajectory during the release, e.g. hysteresis. These two mechanical factors are expected to have a substantial impact on the sensory-motor functions of the ligaments as expressed by the ligamento-muscular reflex.

The above issues were studied and reported in two reports (Eversull et al., 2001; Solomonow et al., 2001). We found that during a single sinusoidal stretch-release cycle of the supraspinous ligament, the reflex was initiated only after a certain length and tension were developed. The length-tension range prior to the triggering of the reflex was properly designated as a "neutral zone" indicating that small perturbation (1–2 mm) in the ligament length around its resting length are probably inconsequential for joint stability and do not require co-committant muscular activation (see Fig. 9).

During the relaxation phase, the reflex disappeared at a different length and different associated tension, much larger than the length and tension thresholds observed during the stretch phase as seen in Fig. 9.

During the stretch phase, past the activation threshold of the ligamento-muscular reflex, the EMG gradually increased to the peak and then gradually decreased during the relaxation phase. It was clear that increasing length and tension in the ligament required an increase in muscular force in order to sustain joint stability. This emphasized the synergistic relationships of ligaments and muscles in maintaining that stability.

From Fig. 9, one can also see that as the frequency of the sinusoidal cycle increased from 0.1 Hz to 1.0 Hz, the length and tension thresholds of the reflex decreased (e.g. reflex was triggered earlier) during the stretch phase. During the relaxation phase, the length and tension thresholds increased (e.g. the reflex terminated earlier). Furthermore, as the stretch-release cycle frequency increased, the peak to peak EMG and its corresponding mean absolute value (MAV) increased as seen in Fig. 10, indicating that fast elongations of ligaments require much larger con-committant muscle force to maintain stability and minimize the potential risk of rupture. For fast ligament elongation, therefore, higher stiffness from the muscles protect the ligament from development of high tension and strain and potential rupture.

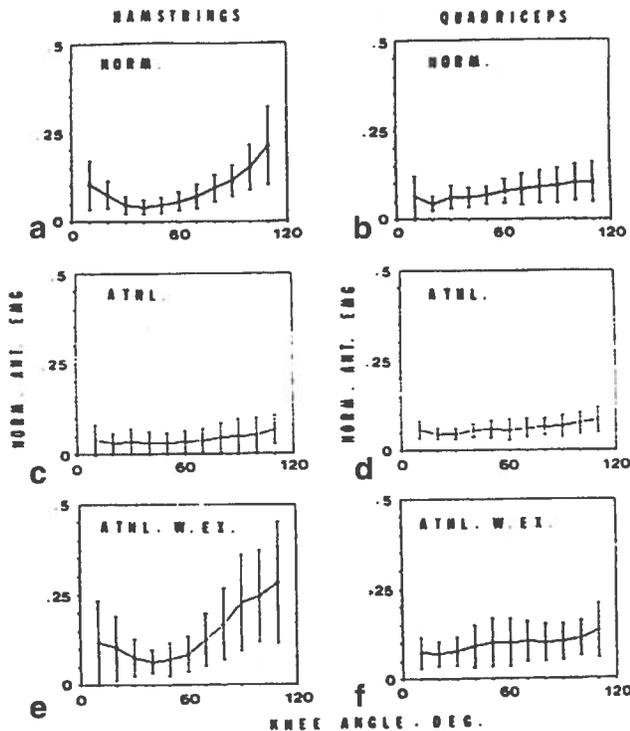


Fig. 8. The average normalized antagonist MAV versus knee angle for the hamstrings (a) and quadriceps (b) of normal subjects compared with the hamstrings and quadriceps MAV versus knee angle of verified athletes (c and d) and athletes who routinely exercise their hamstrings (e and f). The athletes had hypertrophied quadriceps, which resulted in inhibition of the hamstrings motor drive (EMG) when extension movement was performed (see c versus a and e). Quadriceps coactivation patterns of normal subject group and athletes were nearly identical. The vertical bars at each data point represent the standard deviation from the mean of all subjects tested in that category.

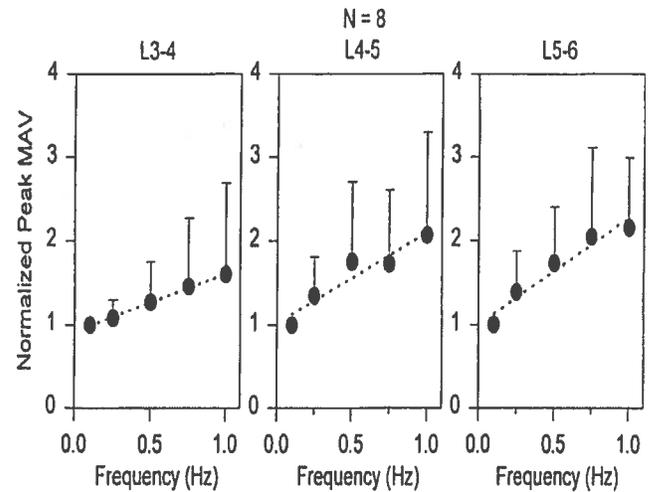


Fig. 10. The mean (\pm SD) of the peak MAV of the EMG is shown as a function of frequency, demonstrating that progressively stronger muscle contraction was associated with increasing cycle frequency.

Finally, when the ligament was exposed to continuous sinusoidal stretch-relaxation cycling, the reflex trigger thresholds increased and the termination threshold increased as well. The peak EMG amplitude decreased. In essence, prolonged exposure of ligaments to cycling stretch results in laxity and hysteresis accompanied with substantial decrease in the duration and magnitude of the reflexively activated muscular forces, exposing the ligament to increasing potential risk for injury. This was the early sign that prolonged cycling activity of ligaments is associated with risk of injury and/or a neuromuscular disorder, which will be fully addressed later.

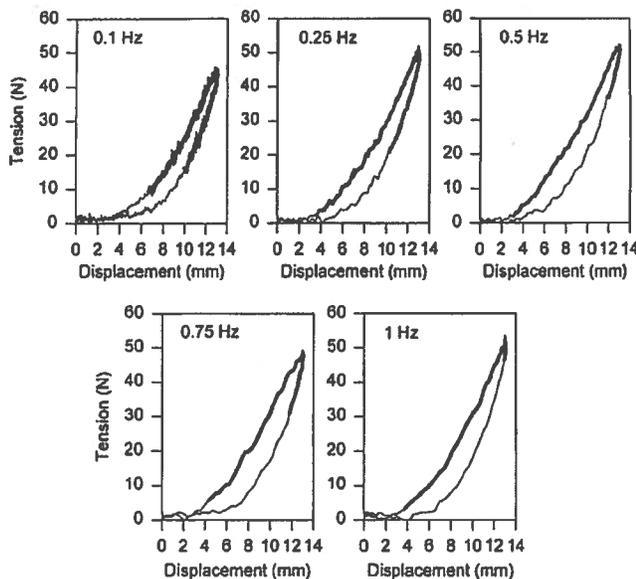


Fig. 9. Typical hysteresis curves where the tension versus displacement of a single cycle at each of the frequencies employed is shown; the period where the EMG was recorded from its initiation in the stretch phase to its termination in the release phase is designated in boldface on the curve.

6. Ligaments and the flexion-relaxation phenomena

Assessment of spinal function, as it relates to the lumbar region, in flexion-extension requires knowledge and ability to document the flexion-relaxation phenomena. This phenomena consists of active EMG recorded from the paraspinal muscles as anterior flexion begins. The EMG amplitude gradually decreases as flexion progresses and reaches a complete silence at or near 45–50° flexion. The EMG silence persists through deep flexion and the initial range of extension. At mid-extension the EMG reappears and increases up to full extension (Ahern et al., 1988; Allen, 1948). The current understanding is that the upper body mass, when subjected to the effect of gravity, as it moves into flexion, requires counter resistance from the paraspinal muscles to prevent free collapse forward. As flexion progresses, the posterior ligaments (supraspinous, interspinous, posterior longitudinal, and dorsolumbar fascia) elongate and develop tension. At some angle, in mid-flexion, the tension developed in the posterior ligaments exceeds the required counter force, allowing the muscles to relax. Further flexion is associated with contraction of abdominal muscles to overcome the increasing forces in

the posterior ligaments. Overall, the process is a load-sharing phenomena between posterior muscles, posterior ligaments, and abdominal muscles.

Since during flexion the posterior ligaments stretch, one would expect that the mechano-receptors within these tissues will be stimulated and trigger paraspinal muscles contraction to reduce the load in the ligaments. In fact, the opposite occurs; increased stretch in the ligaments during deeper flexion is associated with EMG silence. This immediately points out that perhaps the inhibitory component of the ligamento-muscular reflex is active in the flexion-relaxation process.

We conducted a series of experiments to assess the role and function of the ligamento-muscular reflex in the flexion-relaxation phenomena (Olson et al., 2004, in press, submitted for publication). In order to offset the effect of gravity, the same subject group was assessed while performing flexion-extension from erect posture and from the supine position (e.g. sit-ups). The results demonstrated that in the sit-up position, the flexion-relaxation in the paraspinal muscles disappeared and a similar pattern of activity (initial EMG activity and silence about the $\pm 90^\circ$) was observed in the abdominal muscles. The conceptual conclusions point out the demand for dealing with the internal moments (generated by body mass and its orientation to the gravity vector) dictates the pattern of muscular activity in strength, timing and which muscles. From the reflexive standpoint, this is the first indication that the ligamento-muscular reflex is substantially modulated by the spinal and possible higher sensory and motor neurons of different systems (proprioceptive, vestibular, etc.) to yield excitatory or inhibitory responses. The mechanical requirements to execute the intended movement, therefore, are governing the ligamento-muscular reflex response pattern.

In the latest report (Olson et al., submitted for publication), passive flexion extension was executed with the aide of an active dynamometer. The dynamometer supported the body mass throughout the movement. Surprisingly, muscular activity was not observed in any of the anterior or posterior muscles. The results support the assertion made in the previous paragraph, e.g. there was no need to support internal or external moments (since the dynamometer took care of all movements), and the reflex did not trigger any muscular activity.

A tentative, and very fascinating, conclusion is that the ligamento-muscular reflex is much more complex than a hard-wired neurological process which triggers or suppresses muscles responses upon stretch of the ligaments. The reflex is governed by a complex neural network taking into account joint stability, internal mass and its implication in light of movement velocity and acceleration, orientation to gravity, etc.

Evidently, much is left to study on the interactions of the various components and internal or external factors associated with the ligamento-muscular reflex. It is not a simple reflex by any stretch of the imagination.

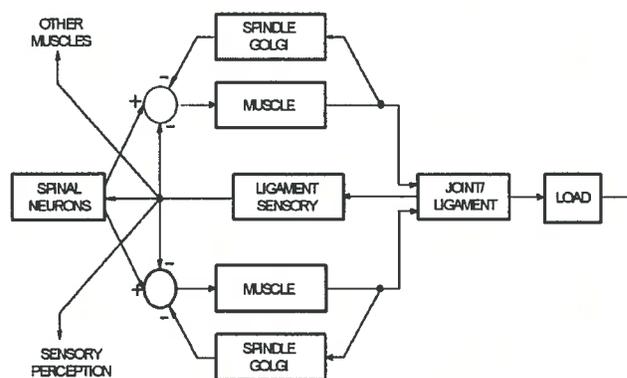


Fig. 11. A control diagram of the forward and feedback components of a joint including the muscles, ligaments, and spinal projections.

From the system viewpoint, one can draw the simplified diagram of Fig. 11 representing the interaction of ligaments and the motor control of a joint.

Reconsidering the mechanical properties of the ligaments; e.g. creep, tension-relaxation, hysteresis, etc. one can predict from the control diagram of Fig. 11 that several types of neuromuscular disorders can develop with time when performing occupational and sports activities. Similarly, an injury or rupture of a ligament could be assessed as a cause for a neuromuscular syndrome.

7. Clinical implications

Indeed, in the early 1980s, a large number of patients with anterior cruciate ligament (ACL) rupture underwent a surgical repair with a synthetic or autograft from part of the patellar tendon. In both cases, the initial results were encouraging, demonstrating a measure of restored stability in the knee. Overtime, however, it was observed that the implanted ligament became lax; that the quadriceps tended to atrophy in many patients; that muscular desynchronization due to the rupture could be restored with physical therapy, and that with time, the patients developed osteoarthritic knees. Overall, conflicting and misunderstood responses were accumulating, indicating that ACL injury is not an isolated deficit but most likely a complex syndrome.

With the help of Fig. 11, one can attempt to gain insight to the logical chain of events that were observed clinically.

1. Rupture of the ACL, even if repaired surgically, can leave a sensory perceptible (kinesthetic) deficit since the afferents in the ligaments are not functioning (ruptured or surgically removed). Indeed, Skinner and Barrack (1991) demonstrated that patients with ACL rupture demonstrated deficiency in kinesthetic perception; e.g. perception of the knee angle was deficient. Such a sensory deficit can be a harbinger of additional damage/injury to the knee when going up or down stairs, playing sports and performing occupational activities. Indeed,

many ACL deficient patients of that time were reporting with secondary knee injury incurred during demanding daily activity.

2. Quadriceps atrophy was commonly observed in ACL deficient patients. The natural response of orthopaedic surgeons and physical therapists was to subject the patient to a quadriceps strengthening program for several weeks to reverse the degeneration. Often, the patients with the now more powerful quadriceps were subjected to additional injury or increased episodes of instability.

A part of the syndrome, quadriceps muscles at their normal strength can generate forces that increase anterior tibial translation and with the absence of an ACL also cause an anterior knee subluxation (Hirokawa et al., 1991, 1992). It seems that while the ligamento-muscular reflex in normal subjects excites the hamstrings in the range of motion from 60° flexion to full extension, it also inhibits the quadriceps muscles from exerting very large forces, preventing subluxation. The concept of muscular inhibition attracted little attention in the motor control field, but its implications are highly significant for joint stability. The quadriceps is apparently inhibited, in the normal subject, from generating its true maximal forces such that knee stability and overloaded ACL are prevented. In the ACL deficient patient the inhibition is substantially larger since the sensory ACL function is missing. In such conditions, even moderate quadriceps force in the range of 65° to full extension can subluxate the tibia. The weighted control of the ACL reflex seems to inhibit the quadriceps as necessary for the performance of the movement at hand. With its absence, however, deep inhibition occurs, probably via spinal networks. One can conclude that in addition to the excitatory reflex from ligaments to muscles, there is also an inhibitory ligamento-muscular reflex and that was shown in human subjects by Dyhre-Poulsen and Krogsgaard (2000), Solomonow and Krogsgaard (2001), Williams and Brance (2004), and Voigt et al. (1998). The overall objective of the inhibitory and excitatory ligamento-muscular reflex is to provide a stable and safe joint motion.

The quadriceps strengthening program implemented in the period prior to 1987 was a contraindication as it increased the risk of subluxation and the potential of new injury. In our report of 1987 (Solomonow et al., 1987), we concluded that hamstring strengthening is most beneficial in the early phase of ACL deficient patients rehabilitation, as it will increase the co-contraction level from the hamstrings, improve knee stability and allow increased force production from the quadriceps later on (Solomonow et al., 1989).

3. Muscular balance of the hamstrings and quadriceps, agonist and its antagonist, is therefore, one of the most important aspects in maintaining knee stability and preservation of the healthy, functional ACL. One important component in balancing an antagonist muscle

pair of a joint is the sensory role of ligaments via their inputs to the spinal motor units in an excitatory and/or inhibitory mode. Indeed several groups managed to demonstrate that with an appropriate physical therapy program, advocating muscle re-education, ACL deficient patients could be successfully rehabilitated with conservative treatment (Giove et al., 1983; Steiner et al., 1986).

4. The implications of muscular imbalance or synchronization on the gait of patients with ACL damage was repeatedly reported in the literature (Hasan et al., 1991; Sinkjaer and Arendt-Nielsen, 1991), and increased quadriceps activity was observed in our research with normal subjects whose ACL was statically stretched and developed creep (Chu et al., 2003; Sbriccoli et al., 2005).

In such circumstances, the ACL was intact, yet the laxity developed due to the creep prevented the mechanoreceptor within the ligament from properly firing at the appropriate threshold and inhibiting the quadriceps during maximal voluntary extension. It seems that rupture of the ACL, for example, can increase the inhibition imposed on a muscle, whereas stretched or lax ACL decreases the inhibition. The exact neural mechanism of the two phenomena may need further study, yet it is clear that the sensory-motor functions of the ligament plays a major role in both phenomena.

8. Neuromuscular disorders associated with ligaments

So far, neuro-muscular disorders associated with a complete rupture of a ligament: e.g. desynchronization of agonist – antagonist activity, changes in the natural inhibition of muscles, muscular atrophy, deficient kinesthetic perception and deficient gait were delineated.

In recent years we embarked on the assessment of neuromuscular disorders associated with an intact ligament, yet subjected to continuous activity such as found in many occupational and athletic environments. Indeed, in the occupational field, non-specific low back disorders/pain is one of the most common medical problems and is a costly problem from the standpoint of the loss of work, medical treatment, and cost to government and industry, etc. The diagnosis and treatment of such non-specific low back disorder or as it is also known as Cumulative Trauma Disorder (CTD) are poorly developed and/or understood (NAS, 2001).

The epidemiology, however, clearly establishes the relationship between static and repetitive (cyclic) work activities and CTD. Biomechanical or physiological validation of the epidemiology is lacking especially experimental validation.

A set of experiments imposing alternating periods of static and/or cyclic load on the lumbar supraspinous ligaments yielded a wealth of new information (Claude et al., 2003; Courville et al., 2005; Gedalia et al., 1999; Solomo-

now et al., 1999; Jackson et al., 2001; LaBry et al., 2004; Lu et al., 2004; Navar et al., in press; Sbriccoli et al., 2004a,b, 2005, in press; Solomonow et al., 2003a,b,c; Williams et al., 2000):

A. Substantial creep developed in the ligament within six periods of 10 min of load spaced by 10 min of rest. A continuous rest period of up to 7–8 h after the six work and rest sessions are not sufficient for the ligament to recover its original length and stress-strain condition. As seen in Fig. 12, the work periods display gradual decrease of reflexive EMG, spasms and cumulative creep. The long rest periods is characterized with initial hyperexcitability in muscle activity and very long recovery of the creep towards the return of the ligament to its original resting length and normal length–tension relationship. Several important issues should be addressed:

- As the creep causes laxity in the ligament, the thresholds at which the ligamento-muscular reflex is triggered as well as kinesthetic perception change. The feedback signal (see Fig. 11), therefore, is corrupted and results in false perception and lower level activation of the muscles.
- False kinesthetic or proprioceptive perception introduces errors in the precision of movements and may result in an accident or injury.
- The decrease in muscular activity elicited by the ligamentous reflex also decreases the normal stiffness and stability of the lumbar spine, exposing it to increasing risk of injury.

- The long recovery period (over 24 h) required to restore normal ligament operation renders the lumbar spine to prolonged function with decreased protective capacity and increased exposure to injury.

Therefore, an acute or transient neuromuscular disorder exists after a moderate work period during which an increased exposure to injury is present due to ligament laxity, reduced muscular activity and false sensory perception. The origin of this acute/transient disorder is in the creep/laxity of the ligament and its sensory-motor (neuromuscular) implications are due to the corrupt feedback signals from the sensory receptors within the ligaments.

B. It was also shown that several loading components have a critical impact on the development of an acute inflammation in the ligament.

- Decreasing the rest period between each 10 min work session from 10 min to 5 min.
- Increasing the number of repetitions from six to nine sessions.
- Increasing the load from low or moderate to high load within the physiological range.
- Increasing the work/load duration to sustained periods over 30 min.

All of the above factors elicit an acute inflammation in the ligament (Solomonow et al., 2003a). The neuromuscular component of the acute inflammation phase, observed 2–3 h after the load/rest session is a significant hyperexcitability of the musculature lasting for several hours. Since workers are required to return the work the next day, the

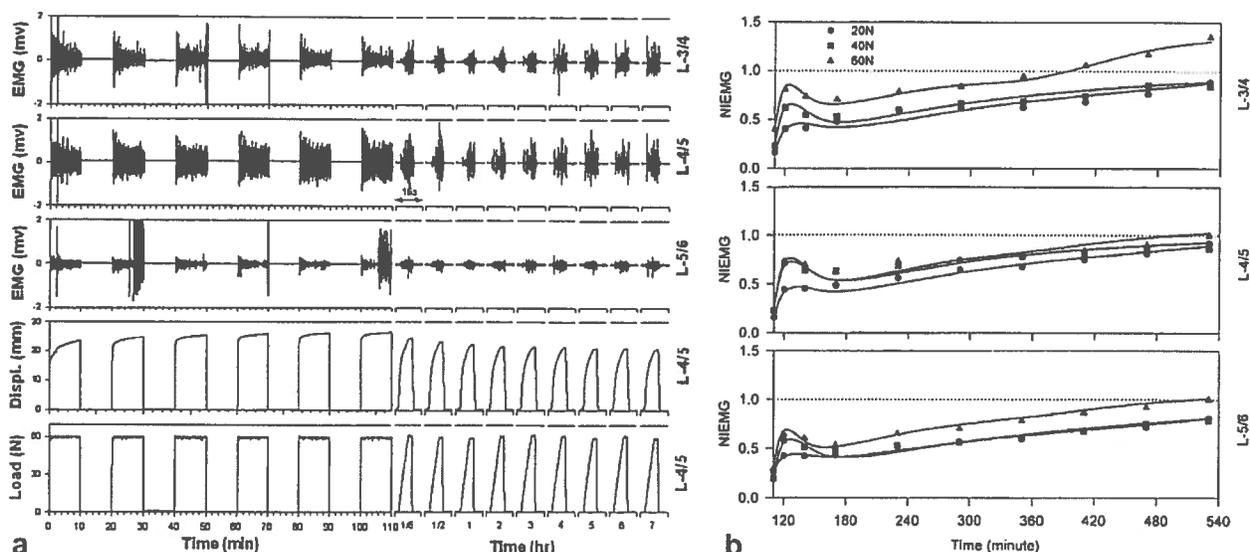


Fig. 12. (a) A typical recording of EMG from the L-3/4, L-4/5, and L-5/6 level (top three rows) as well as lumbar displacement and static load (bottom) recorded from one preparation subjected to a 60-N load. Note the large-amplitude spasms that are superimposed on the gradually decreasing EMG during different 10-minute static load periods. The time axis marked in units of hr. indicates the 7 h recovery period during which short samples of 12 s loading was applied to assess recovery of creep and EMG. (b) The mean NIEMG data and the developed models for the 7 h recovery period are shown superimposed for 20-, 40-, and 60-N loads. Note that the EMG for the 60-N load exceeds unity, indicating hyperexcitability development.

acute inflammation does not have sufficient rest period to heal the damage (micro-ruptures in the collagen fibers), the tissue is exposed to additional stretching and damage, and with continued exposure, develops chronic inflammation. In Fig. 13, samples of ligaments with inflammatory symptoms as evidenced by wide spread of neutrophils is compared to a control sample with few spontaneous neutrophils. The presence of neutrophils infusion in the ligament was always associated with a delayed hyperexcitability.

Chronic inflammation is not a medically treatable injury, is degenerative (results in conversion of ligament fibers to fibrous tissue) and is associated with pain, loss of muscular force (weakness), reduced range of motion of

a joint and muscle spasms (Leadbetter, 1990). CTD is an overuse injury where the ligamentous tissues become chronically inflamed resulting in permanent disability (Leadbetter, 1990; Solomonow et al., 2003a).

Additional important observations were made. The work to rest ratio of 1:1 was observed to be a good rule to follow in order to prevent or attenuate the development of acute inflammation. This ratio, however, remained limited to durations of work and load up to 30 min (e.g. 10 min work: 10 min rest, 20 min work: 20 min rest, and 30 min work: 30 min rest). Tests at 60 min work and 60 min rest resulted in acute inflammation. Long work periods cannot be implemented without avoiding damage even if equal duration rest is allowed.

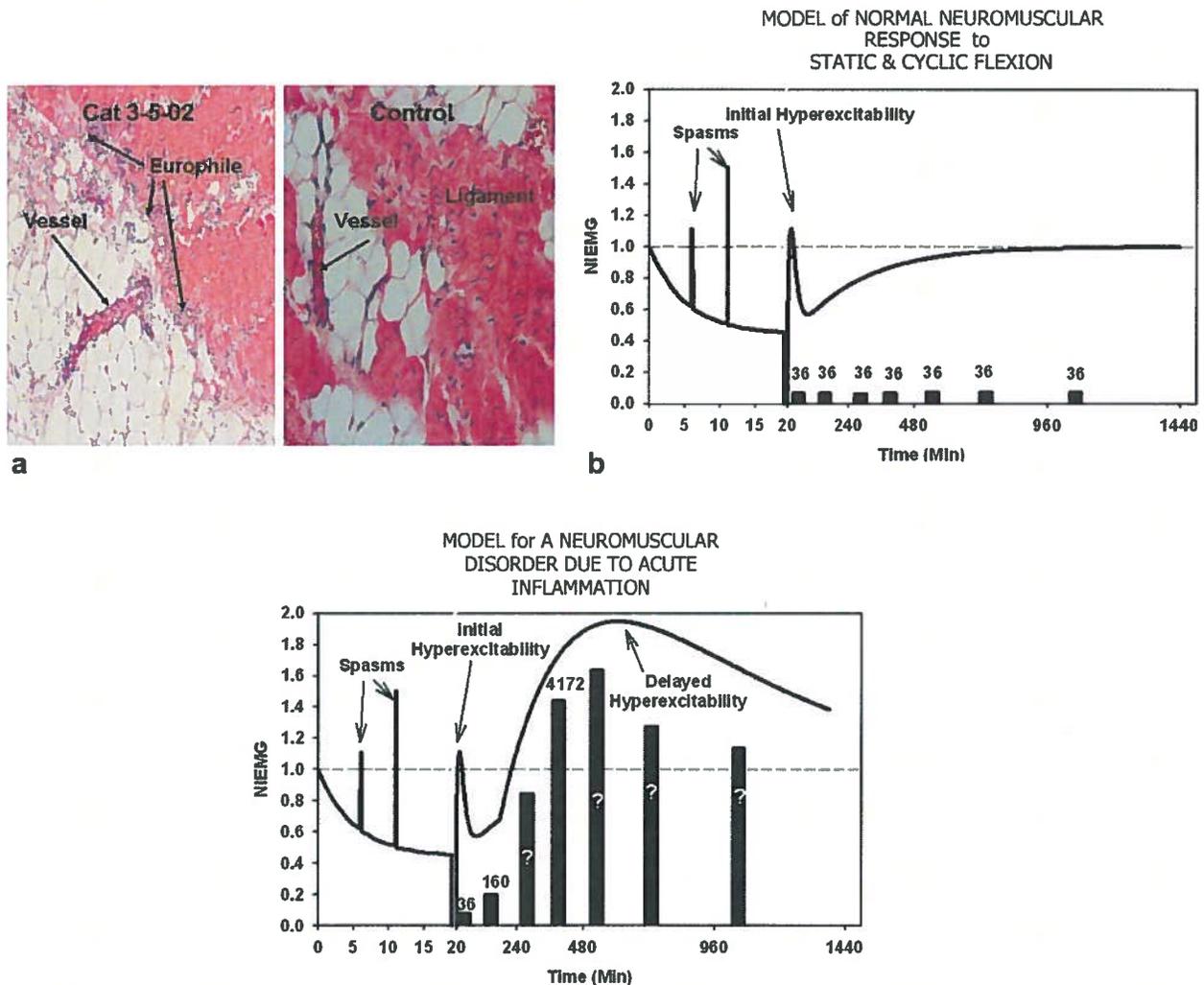


Fig. 13. (a) On the right is a slide showing the density of neutrophils in a ligament from the control group, not subjected to creep. Only spontaneous neutrophils appear. On the left is a slide showing the neutrophil density in a ligament subjected to overstimulation. The density is over 4000/mm² as opposed to 36/mm² in the control ligament. Note the higher magnification on the right slide. (b) A graphical presentation of the neuromuscular disorders model in a case where the risk factors load, load duration, load to rest ratio and repetitions were below the risk level. Note that during the recovery phase the NIEMG slowly recovers to its normal while the neutrophil density remains low and steady. (c) A graphical presentation of the neuromuscular disorder in a case where the risk factors exceeded the risk threshold triggering a delayed hyperexcitability associated with acute inflammation as expressed by the simultaneously rising neutrophil density in the ligaments. The question marks indicate time segments for which data is collected currently whereas the completed data is given by the number of neutrophils per mm².

An acute neuromuscular disorder associated with the creep of the ligament over time is therefore present and consists of reduced muscular activity as work goes on (and decreased spinal stability), development of spasms and the micro-fractures in the collagen fibers increase, significant increase in muscular activity 6–7 h after the work is completed and its association with acute inflammation. Such an acute neuromuscular disorder is the first step leading to chronic inflammation, and this phase should be avoided in any work or sports activity where a few days rest cannot be allowed. The long-term implications of inflammation and the associated neuromuscular disability are currently under intense investigations in our laboratory.

9. Model of neuromuscular disorder

Based on the large number of experiments on the spinal ligamento-muscular response to static and cyclic loading (or flexion-extension) we developed a model that can predict the neuromuscular response to a set of work and rest sequences. From the model, a determination could be made if a delayed hyperexcitability is present and in turn an acute inflammation. The model, therefore, can be useful in the assessment of risk factors (load magnitude, load duration, rest duration, load to rest duration ratio and loading repetitions) or their absence in a given work protocol. Safe work protocols could be designed also using the model.

The choice of the model was based on the physiological and biomechanical properties of the tissue in question, e.g. the ligament. It is well established as a viscoelastic element with responses accurately estimated by exponential equations. During lumbar flexion-extension or knee flexion-extension, the overall response is not that of a single ligament but that of several ligaments, the cartilage, capsule and in the spine also the discs and facet capsules. These different collagen tissues are all viscoelastic, yet the proportion of viscosity and elasticity is different in each one. The disc, for example, contains gel, a fluid, in its internal space, and therefore is more viscous than the supraspinous ligament or the longitudinal ligaments. A good model, therefore, should include bi or tri exponential components to describe the viscoelasticity of each of the various collagen tissues in order to provide accurate output (Solomonow et al., 2000).

The original model (Solomonow et al., 2000), therefore, included bi-exponential description of the displacement of the lumbar spine due to static or cyclic flexion. One component was utilized to describe the exponential elongation/deformation due to fibrous collagen tissues such as ligaments, facet capsule, dorsolumbar fascia, etc. whereas the second component was used to describe the exponential deformation of the lumbar discs which contain significantly more viscosity. The two components are exponential, yet the time constants and coefficients are largely different. The constructed model was success-

fully used to describe experimental data with high accuracy.

Furthermore, since the reflexive EMG was elicited by the deformation of the viscoelastic tissues, it was assumed to follow its deformation pattern; e.g. exponential decrease. That was executed, also with high accuracy. However, one issue that deteriorated the accuracy of the EMG model was the spontaneous, unpredictable spasms that occurred during the loading periods and also during the following recovery. Since the spasms varied widely in their amplitude and appeared at any time during loading without any predictable pattern, it is impossible to model this phenomenon. The spasms being superimposed on the predictable decrease of reflexive EMG due to viscoelastic deformation introduced an unavoidable inaccuracy in the model, yet allowed the general pattern of the EMG to emerge fairly clearly.

Therefore, the model developed provides good estimates of the deformation of the viscoelastic tissues during the development of creep and its recovery with rest. Similarly, the reflexive muscular activity was estimated well during the loading and rest periods. The spasms, however, should be distinctly noted but lacked representation in the model.

In our model, we simplified the equation in order to obtain a general conceptual behavior of the ligamento – neuromuscular responses. Yet, the accuracy can simply be optimized if one wishes, just by adding additional components representing the tissues at hand.

Model: The model considered is based on our previous work where continuous 20-minute static load was followed by a 7-hour recover period (Solomonow et al., 2000, 2003d; LaBry et al., 2004; Courville et al., 2005; Claude et al., 2003).

The Normalized Integrated EMG (NIEMG) during the cyclic loading period was described by Eq. (1) as follows:

$$\text{NIEMG}(t) = Ae^{-t/T_1} + \text{NIEMG}_{ss} \quad (1)$$

where NIEMG_{ss} is the steady state amplitude, A the amplitude of the exponential component, T_1 the time constant of the exponential component, and t is the time.

Correspondingly, the NIEMG during the long-term recovery was modeled by the following equation as:

$$\text{NIEMG}(t) = tBe^{-t/T_2} + E(1 - e^{-t/T_3}) + C(t - T_d)e^{-(t-T_d)/T_4} + \text{NIEMG}_{ss} \quad (2)$$

where B , C , and E are the amplitudes of the three terms; tBe^{-t/T_2} represents the initial hyperexcitability, which decays within one hour while reaching its peak in the first 10 min; $C(t - T_d)e^{-(t-T_d)/T_4}$ represents the delayed hyperexcitability; this term is initiated during the rest period, mostly after the second hour of rest, with no effect in the first 2 h; $E(1 - e^{-t/T_3})$ represents the steady state recovery; this term is a slowly rising exponential throughout the rest period; T_d the time delay associated with the initiation of the delayed hyperexcitability; and NIEMG_{ss} is the steady state amplitude as defined in Eq. (1).

In order to convert Eqs. (1) and (2) to describe a series of work periods spaced by rest periods; two new components are defined:

- T_W is the time period over which load was applied to the spine.
- T_R is the period of rest between any two work periods (T_W).
- n is the number of work periods.

Eq. (1) describing the NIEMG behavior during each of the work periods is rewritten as Eq. (3):

$$\text{NIEMG}(t) = A_n e^{-\frac{[t - n(T_W + T_R)]}{T_{n1}}} \left| \begin{array}{l} (n + 1)T_W + T_R \\ n(T_W + T_R) \end{array} \right| + \text{NIEMG}_{ss} \quad (3)$$

It was assumed that A and NIEMG_{ss} are not constant throughout the work/rest periods and are changing from one work period to the next.

Furthermore, it was assumed that T_1 might not be the same for all the work periods.

Since this study uses only 10 min of rest, the first transient component of Eq. (2) will be dominant and the steady state component contribution as well as the delayed hyperexcitability term could be neglected for this particular case. During the rest periods, therefore, the modified Eq. (4) is as follow:

$$\text{NIEMG}(t) = (t - [(n - 1)T_W + nT_R]) \times B_n e^{-\frac{t - [(n + 1)T_W + T_R]}{T_{n2}}} \left| \begin{array}{l} (n + 1)(T_W + T_R) \\ (n + 1)(T_W + nT_R) \end{array} \right| + \text{NIEMG}_{ss} \quad (4)$$

It was also assumed that the amplitudes of NIEMG_{ss} and B will vary from one rest period to the next and that T_2 may vary as well. The graphical representation of the model after being subject to non-inflammatory and inflammatory workloads is shown in Fig. 13b and c, respectively.

Similarly, the equation describing the development of displacement, a reflection of creep of the viscoelastic tissue, during a series of work periods spaced by rest periods is given by the following equation:

$$\text{DISP}(t) = \left[D_{0n} + D_{Ln} \left(1 - e^{-\frac{[t - n(T_W + T_R)]}{T_{n5}}} \right) \right] \left| \begin{array}{l} (n + 1)T_W + nT_R \\ n(T_W + T_R) \end{array} \right| \quad (5)$$

where $\text{DISP}(t)$ is the displacement as a function of time, D_{0n} the elastic component of amplitude, D_{Ln} the viscoelastic component of amplitude, and T_{n5} is the time constant governing the development of creep during flexion.

The recovery of the displacement during the rest periods is described by the following equation:

$$\text{DISP}(t) = \left[D_{0n} + R_n + (D_{Ln} - R_n) e^{-\frac{t - [(n + 1)T_W + nT_R]}{T_{n6}}} \right] \times \left| \begin{array}{l} (n + 1)(T_W + T_R) \\ (n + 1)T_W + nT_R \end{array} \right| \quad (6)$$

Such that R is the residual creep at the end of each rest period and T_{n6} is the time constant governing the recovery of creep in each rest period.

Again, D_0 , D_L , and R were assumed to be a variable from one work/rest session to the next. T_{n5} and T_{n6} were also assumed to vary from one session to the next.

The long-term recovery after the work/rest session was modeled by Eq. (2).

Once the mean \pm SD of the experimental data were calculated, attempts were made to generate the best fit models described above using the Marquardt–Levenberg non-linear regression algorithm; in some cases, the algorithm failed to converge satisfactorily; in these cases, initial and/or final values were arrived at by sequential recursive iteration, optimizing for regression coefficient.

10. Verification in human subjects

The research conducted on CTD development was carried out on the feline. Two distinct projects were conducted using human subjects in order to confirm that such neuromuscular disorders can be elicited in humans from the same or similar mechanical inputs (e.g. high loads, high number of repetitions, short rest, etc.). One project examined the responses of the lumbar paraspinal muscles to periods of static and cyclic flexion (Solomonow et al., 2003a; Olson et al., in press). The second project assessed the response of the ACL of human subjects to static and cyclic loads (Chu et al., 2003; Sbriccoli et al., 2005).

Spasms in the muscles and significant changes in muscular synchronization was observed after static and cyclic activity of the spine and the knee (see Figs. 14 and 15) confirming the development of an acute disorder. For safety purposes, the work or load was limited to mild exertion or short duration, yet it is evident that adverse functional changes are elicited.

The results in both projects reveal that similar response to those obtained in the feline are observed from normal, healthy subjects subjected to mild static or cyclic (repetitive) activity. Furthermore, similar behavior could be obtained from the ligaments of the lumbar spine and the ACL of the knee.

Recently, additional confirmation that static and cyclic lumbar flexion in humans elicits a neuromuscular disorder similar to those depicted in the feline model were reported by Granata et al. (2005), Rogers and Granata (2006), Dickey et al. (2003), Kang et al. (2002), McGill and Brown (1992), and Shultz et al. (2004).

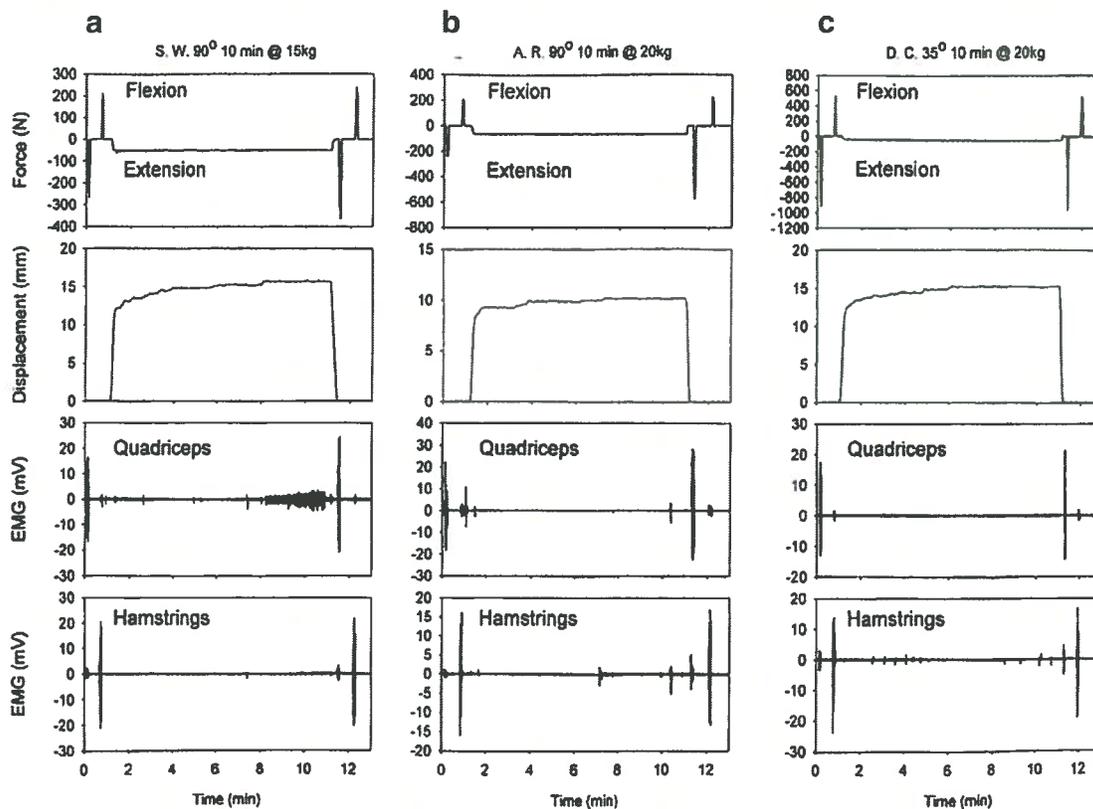


Fig. 14. (a–c) Three typical recordings from three different subjects at 90° and 35° knee angle showing the extension and flexion MVC forces before and after the 10 min loading session (top trace), the anterior displacement of the tibia during the 10 min loading period (second trace from top), quadriceps EMG (third trace) and hamstring EMG (bottom trace). Note the strong continuous burst of spasms in the quadriceps EMG trace of (a) from the 8th minute to the 11th minute. Similarly, in (b), two bursts of spasms are seen, one at about the 7th minute and the second just after the 10th minute, with a corresponding spasm in the quadriceps. IN (c) short bursts of spasms are seen in the hamstrings EMG throughout the 10 min loading period. Note the large increase in quadriceps force at MVC (negative peak) after the 10-minute period of loading the ACL.

11. Translational research – clinical applications

As most research, the ultimate benefit of many years of wondering in the different highways and alleyways of basic and applied medical investigations is some modicum of practical improvement of medical care offered to the patient population, and the associated improvement of the patients lifestyle. Preventive measures are also significant and beneficial.

The lesson we learned so far tells us that in order to maintain knee stability, weighted posteriorly directed force has to be applied to the tibia in the appropriate range of motion. Such a force comes from the ACL in the intact human in the range of motion of 60° flexion to near full extension. Furthermore, such force is not coming exclusively from the ACL, but also from the hamstrings via the ACL-hamstrings reflex. In the ACL deficient patient, the ACL tension is absent and so is the contribution of the hamstrings. In order to allow as close a function to normal as possible, any external device, e.g. orthosis, needs to supply such forces.

In 1983, we surveyed the available knee braces to ACL deficient patients as well as the literature evaluating them.

It was clear that most braces consisted of thigh/calf uprights and a knee joint with some connecting members or straps. A posteriorly directed force in the appropriate range of motion was not provided by the braces and the literature evaluating the braces confirmed that they had little impact, if any, on knee stability as required.

We developed a new knee brace (US Patent No. 4,781,180) which incorporated mechanical programmable bilateral levers connected to an anterior retaining strap placed over the proximal tibia as shown in Fig. 16a. The mechanical programming was provided by the knee joint such that at near 60° flexion the levers were activated and developed a constant or gradually increasing posteriorly directed force to the proximal tibia throughout full extension. This “Smart Brace”, therefore, provided the knee with a similar function of the absent ACL.

In its commercial phase, the “Smart Brace” was available from the Bledsoe Brace System (Grand Prairie, Texas) and was consequently evaluated by Acierno et al. (1995). It was found, as shown in Fig. 16b, that ACL deficient patients could generate isokinetic maximal voluntary extension effort throughout the full range of motion with significantly increased quadriceps activation and without

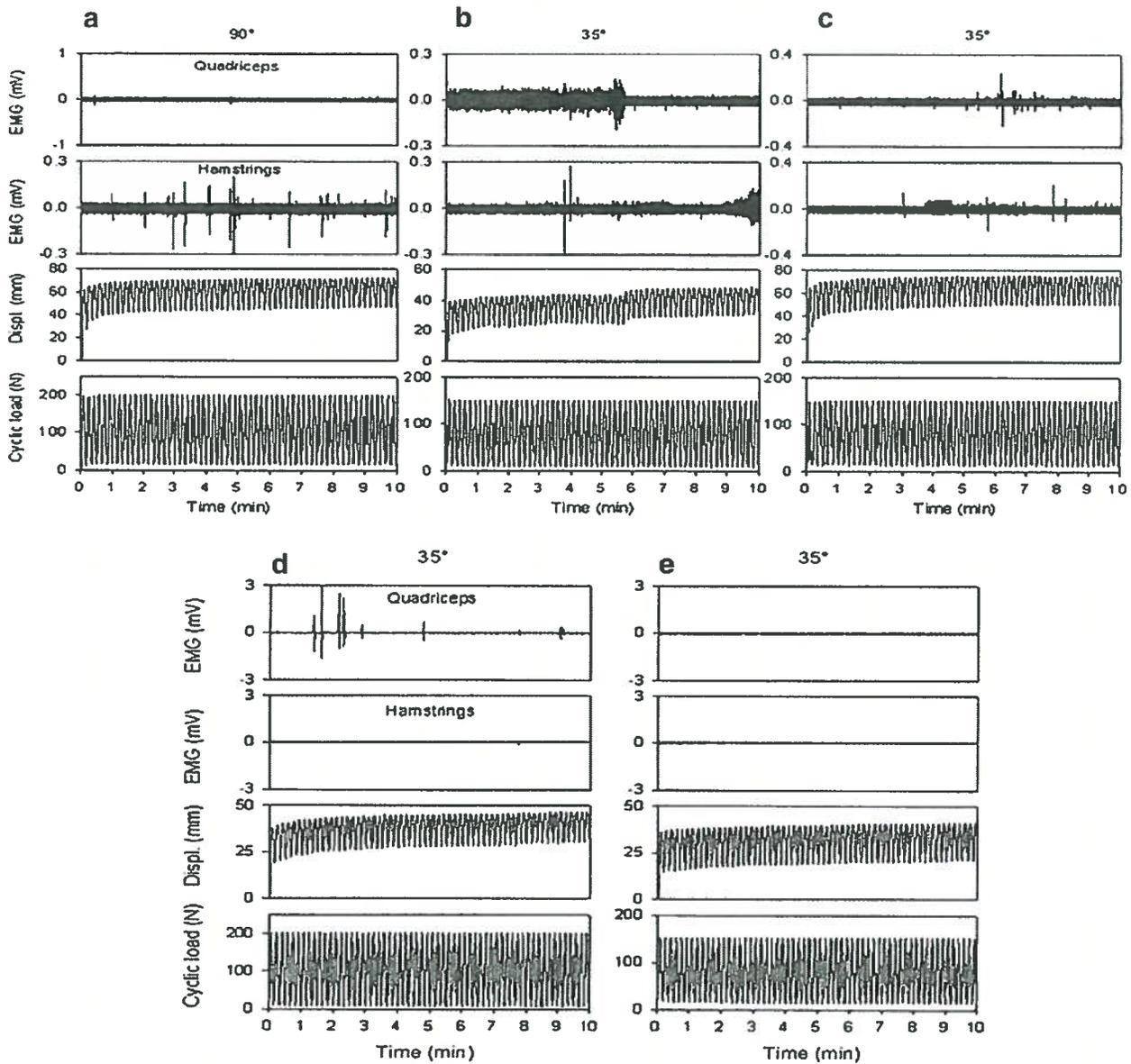


Fig. 15. (a–e) Five typical recordings from five different subjects exposed to cyclic loading of the ACL for 10 min at 90° and 35°. IN the top 2 traces, the EMG recordings from quadriceps and hamstrings during the 10-minute cycle are shown. The two bottom traces represent the anterior tibial displacement and the cyclic load, respectively. Note the presence of EMG spasms in both the quadriceps and hamstrings (a–d). An example with no reflex EMG activity is also reported (e). Displ, displacement.

episodes of knee subluxation. A noticeable decrease in hamstrings co-activation was also noted, as it was not required. The “Smart Brace” found wide acceptance in clinics around the world and performed well, especially in the post-injury period and in daily life of patients with chronic episodes of knee subluxation secondary to ACL rupture.

One of the limitations of knee braces made of metal, plastic or composite materials is that their weight is applied to an inverted cone, the thigh. During activity, gravity tends to cause gradual migration of the brace to the lower leg and reduction in its effectiveness. One approach to prevent this problem is the tightening of the attachment straps

to the limb. This, however, applied excessive pressure to the skin and occluded circulation resulting in discomfort and pain within a short duration of use.

A second generation of the “Smart Brace”, an electronic version, was consequently developed and applied (US Patent No. 5,628,722). The new version consisted of a light weight elastic sleeve worn over the knee. A miniature electronic sensor monitored knee angle and triggered a muscle stimulator to deliver weighted activation of the hamstrings via surface electrodes incorporated in the elastic sleeve. The posteriorly directed force to the proximal tibia was delivered this time by the hamstrings which were activated in the desired range of motion. The results to date

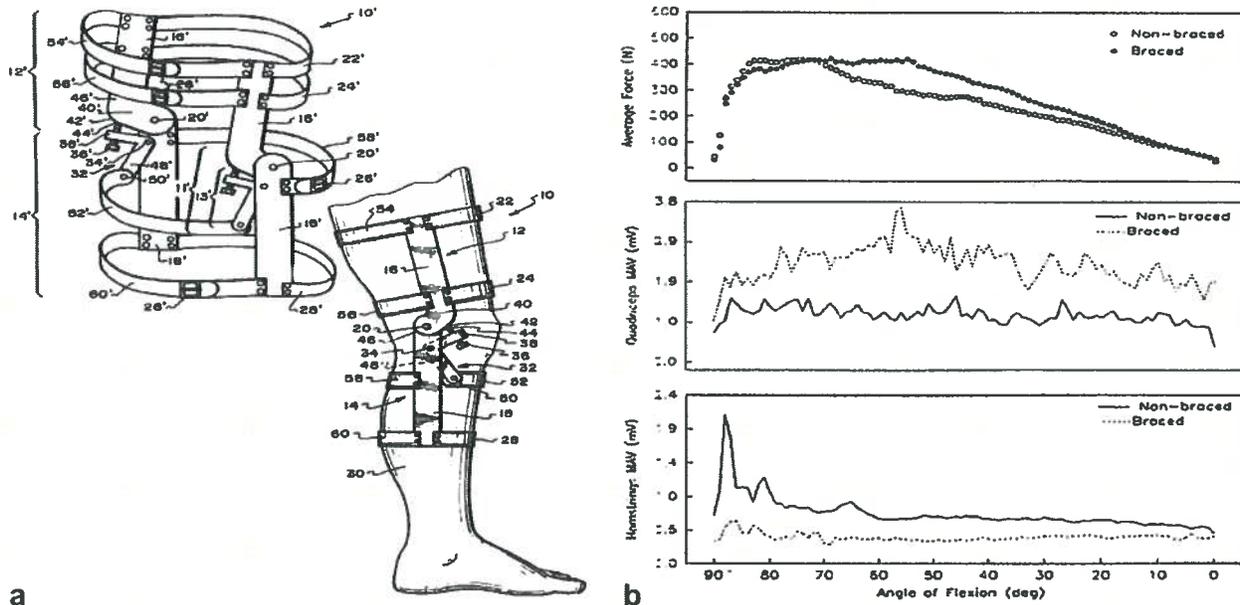


Fig. 16. (a) A schematic of a "Smart Brace" which generates a function similar to that of the ACL in the proper range of motion. (b) Average results from four trials for a symptomatic subject showing average force (top trace), quadriceps MAV, and hamstrings MAV (third trace) also as a function of joint angle. Note the increase in quadriceps MAV and the decreases in hamstring MAV when the brace is worn, demonstrating a return to normal muscle function due to the use of the brace.

demonstrate that the triggered coactivation of the hamstrings could be adjusted as necessary for the condition and convenience of the patient while preventing knee subluxation. An additional finding demonstrated that within a few days of use, a muscle re-learning occurs, with the spontaneous hamstrings coactivation is elevated to prevent subluxation even if the "Smart Brace" is deactivated (Fig. 17).

Similar conditions exist in workers engaged in repetitive (cyclic) or static activities of the lumbar spine. The ligaments and other viscoelastic structures of the lumbar spine

become stretched or lax after a period of activity and the afferents within the tissues generate a significantly decreased or corrupted stimulus for activation of the ligamento-muscular reflex. The muscular activity which maintains lumbar stability decreases or becomes absent leaving the spine exposed to injury. A lumbar "Smart Brace" was

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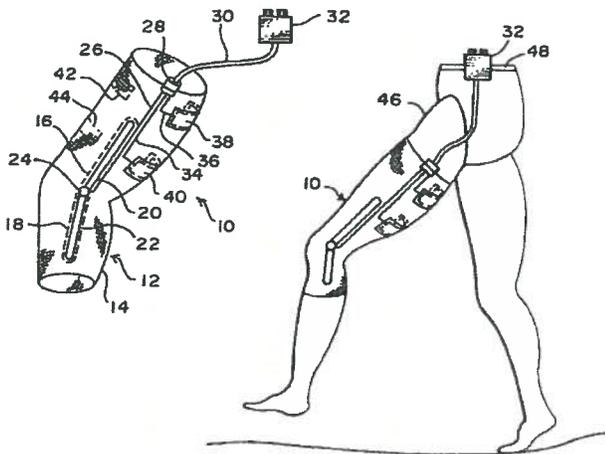


Fig. 17. A schematic diagram of the electronic version of the "Smart ACL Brace" where a sensor about the knee joint triggers surface stimulation of the hamstrings to prevent excessive anterior translation of the tibia and subluxation.

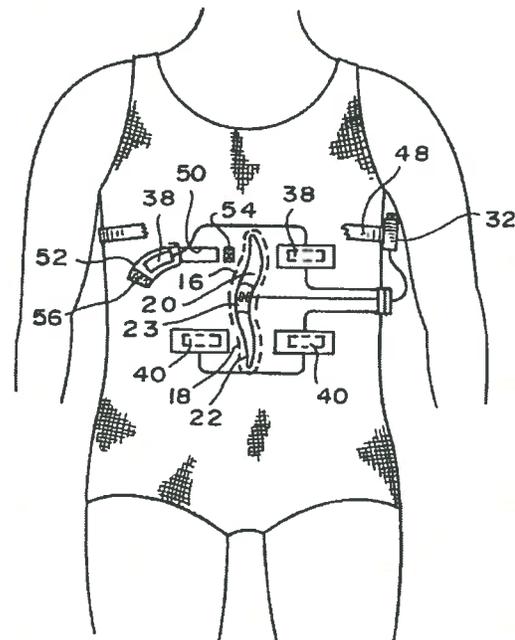


Fig. 18. A schematic of a lumbar electronic "Smart Brace" restoring muscular forces lost due to creep/laxity of the ligaments.

developed (US Patent No. 5,643,329) (see Fig. 18) and is in the stage of evaluation. The brace consists of an elastic garment commonly worn for dance or sport with miniature sensors over the lumbar spine. A muscle stimulator is activated by the sensors and the stimulus delivered via surface electrodes over the bilateral paraspinal muscles. The muscles contract in a weighted mode in the appropriate range of motion as we identified in the studies exploring the flexion-relaxation phenomena (Solomonow et al., 2003a; Olson et al., 2004, in press).

12. Conclusions

Ligaments are not passive tissue. From the sensory standpoint and from their sensory-motor function, ligaments are highly dynamic and non-stationary, yet predictable important organs. The inherent structure of ligaments and their response to static and cyclic loads, as found in work and sports activities, allow us to predict non-stationary behavior as expressed by creep, hysteresis, tension-relaxation, etc. These responses in turn, diminish activity of sensory perception and reflexive coordination of muscular activity such as excitation and inhibition and consequently reflect adversely on joint stability and movement.

The same stimuli or inputs can adversely affect the ligament when applied for long duration, large loads or repetitively without sufficient rest to result in an acute inflammation and its associated acute neuromuscular disorder. The acute disorder is the first stage, if not allowed to resolve with sufficient rest, of a chronic disorder which is devastating and non-reversible, inflicting misery and losses to society.

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