Acta Orthop. Belg., 2014, **80**, 331-335

ORIGINAL STUDY

Carpal Tunnel Syndrome etiology update : where do we stand ?

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Keywords : animal model ; etiology ; carpal tunnel syndrome ; CTS ; subsynovial connective tissue.

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy (*27*), leading to a substantial cost to society.

The most common finding in CTS is an increased carpal tunnel pressure (*3,11,12,42*). It used to be unclear whether this was due to a reduction of the size of the carpal tunnel or an increase of its content, but several authors have stated that the increase in volume is caused by a noninflammatory synovial fibrosis of the connective tissue within the carpal tunnel (*20,25,26,43*).

The etiology of CTS is considered idiopathic in most cases (*4,5,23,39,41,44*). Currently, conservative treatment consists of splinting or corticosteroid injections, and surgical release of the carpal tunnel is the treatment of choice when conservative treatment fails (*15,16,33,50*).

Because the etiology is unknown, the current treatments are still focused on decompressing the median nerve, rather than trying to prevent the progression of disease. Further research is necessary to fully understand the etiology, to develop new treatment strategies and to try to prevent the development of carpal tunnel syndrome.

In order to accomplish this goal, it is necessary to study both affected and normal human carpal tunnel biology, and to develop a valid animal model in which to test potential promising treatments and to compare them to the current gold standard.

ANATOMY AND ETIOLOGY

The carpal tunnel consists of the flexor tendons and the median nerve. These structures are surrounded by the subsynovial connective tissue (SSCT), which consists of multiple layers of fibrous tissue that are interconnected by collagenous fibers (*2,6,36*) (Fig. 1). Guimberteau reported that blood and lymphatic vessels, which irrigate the tendons, are also present in the SSCT (*14*). The SSCT is surrounded by a radial and ulnar bursa (*1, 5,7,10,17,18,36*).

A noninflammatory synovial fibrosis of the connective tissue is the most common finding in carpal tunnel syndrome (*20,25,26,43*), but the reason why this fibrosis develops remains unclear.

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No benefits or funds were received in support of this study. The authors report no conflict of interests.

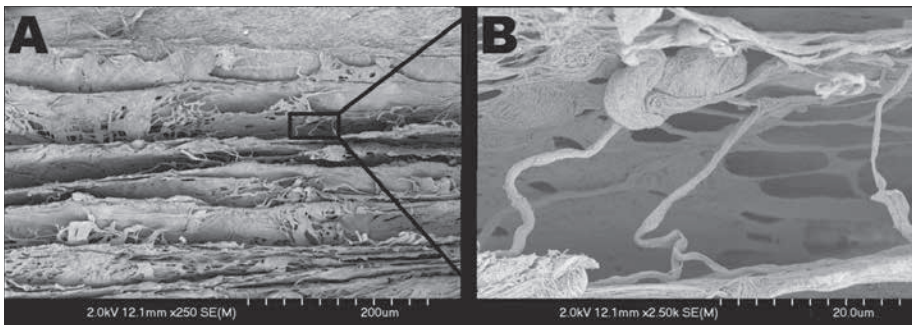

Fig. 1. — **A.** Scanning electron microscope images of the SSCT, with different SSCT layers connected by loose collagenous fibers (SEM, ×250) ; **B**. Focus on the interconnecting collagenous fibers (SEM, ×2.50K).

Ettema *et al* reported that collagen type III is more present in the SSCT of patients with CTS than in individuals unaffected by CTS. Ettema et al also reported the presence of increased levels of transforming growth factor-beta receptor type 1 (TGF-β RI) in the fibroblasts in the SSCT of patients. These two findings are consistent with an injury response, and suggest that CTS patients may have sustained some kind of injury to the SSCT (*5*). Oh *et al* came to the same conclusion when looking at the collagen morphology in CTS patients compared to unaffected individuals. He found that in CTS patients the collagen fibril diameter was increased, but the collagen density was decreased, with deformation of the collagen fibrils (*29*).

Osamura *et al* found that the shear modulus of the SSCT in CTS patients was higher and that the SSCT in CTS patients fails at lower displacements and higher loads than does the SSCT in unaffected individuals (*31*). This finding suggests that the SSCT of CTS patients is more prone to further injury, and this could lead to a vicious circle. Oh *et al* also found vascular changes in the SSCT of CTS patients in combination with decreased amounts of elastin in blood vessel walls and around blood vessels. They believed this could be explained by chronic hypoxia of the SSCT, and that these vascular changes could also lead to a further increased susceptibility to damage (*28*).

Gelberman was one of the first to study the pressure within the CT, and found an increased interstitial pressure in CTS patients (*13*). Later, it was also found that injuries to the SSCT can lead to alterations in the absorptive function and in the permeability in CTS patients (*32*). Eventually this could contribute to the build-up of pressure within the carpal tunnel (*32,40*). Van Doesburg *et al* used ultrasound to evaluate the SSCT, and found that the SSCT is thicker in CTS patients compared to unaffected individuals (*47*).

Finally, some authors have stated that repetitive hand or wrist motion can contribute to the development of idiopathic CTS, and should be considered as a risk factor (*38,51*). These papers were based on epidemiologic studies, and so far no histological or biomechanical tests have been permformed on the SSCT within the CT to confirm this theory.

ANIMAL MODEL

The development of a valid animal model of CTS is crucial to test new treatment strategies, and to compare them to the current gold standard. Once such a model is validated, it could also contribute to learning more about the etiology of CTS in humans.

Before thinking about developing an animal model for CTS, though, a species must be selected. Ettema *et al* were the first to investigate which species had an anatomy and morphology of the CT and SSCT similar to the human. They concluded that both the baboon and the rabbit would be suited

for use as animal models, and that the rabbit would likely be the most practical (*7*).

In 1972, Gilliat's group was the first to setup an animal model for peripheral nerve compression. They placed a pneumatic tourniquet around the hind-limb of baboons, and studied the resulting anatomical changes (*9*).

Mackinnon *et al* were the first to develop a median nerve compression model. They banded a silicone tube around the median nerve in cynomologous monkeys, and observed that there was no difference between simple decompression or decompression combined with operative neurolysis after chronic compression of the nerve (*21,22*).

Another model was published by Diao *et al*. They placed an inflatable catheter in the carpal tunnel of New Zealand white rabbits and found a direct relationship between pressure in the carpal tunnel and median nerve dysfunction (*4*).

Several authors studied the effect of acute pressure elevation by injecting saline into the carpal tunnel. This model was applied in both rabbits and monkeys and has been used to study the neuropathology, diagnosis and treatment of CTS (*19,34,37*).

Lluch attempted to create a rabbit animal model for CTS by tightening the flexor retinaculum and thereby decreasing the volume of the CT. He found histological changes similar to those observed in the synovium of CTS patients (*20*).

These CTS models mainly focused on the compression neuropathy, but only few have been setup to create SSCT fibrosis. Rosen *et al* were the first to setup a model for carpal tunnel syndrome without the use of a foreign body to increase the pressure in the carpal tunnel. They injected 'Hydrox-polyethoxy dodecan' into the rabbit carpal tunnel. After 6 months they found extensive granulation tissue in the CT, with electrophysiologic changes similar to those in CTS (*35*). However, they did not perform a direct postoperative EMG, thus it is not clear whether the neurological changes were due to a direct neurotoxic effect of the injected substance.

Finally, a 10% dextrose solution was used to setup another chemically-induced animal model for CTS. At 12 weeks after injection into the CT, SSCT fibrosis and changes in motor latency were found consistent with those in patients with CTS (*30,52,53*).

As mentioned before, some authors have suggested that repetitive tendon motion might contribute to the development of CTS in humans (*38,51*). So far, no mechanically-induced animal model has been validated to create sustained SSCT fibrosis.

RECENT DEVELOPMENTS

Recently, some papers have been published investigating the mechanical properties of the SSCT. First, the mechanical response of the SSCT in a rabbit model was investigated, and it appeared that motion within the physiological tendon excursion can be sufficient to cause damage to the SSCT (*24*). Then, a similar setup was used to study the mechanical properties of the SSCT in human cadavers. One research article looked at the effect of tendon excursion on the SSCT. A progressive, stepwise damage occurred in the SSCT as the tendon excursion increased. Similar to the rabbit study, the damage seemed to initiate within the physiological range of tendon excursion (*49*). Another paper studied the effect of different tendon velocities on the SSCT. They found a lower SSCT damage threshold with higher velocities, starting at 60% of the physiological excursion (*8*). At low velocity, the damage initiated at 90% of the physiological excursion (*49*).

Finally, a rabbit model for CTS has been developed to understand a potential traumatic etiology of CTS. In this model, a one-time stretching injury to the SSCT caused sustained fibrosis to the SSCT, which is also characteristic of human CTS. Severe median nerve neuropathy was not found in this model, due to the increased rabbit carpal tunnel compliance compared to humans. This model may be useful to further understand the role of stretch injury to the SSCT on the pathogenesis of human CTS and to study new treatments.

FUTURE DIRECTIONS

The first step would be to detect the people at risk. As shown in the recent human cadaver studies, people performing repetitive finger motion or those using relatively large finger excursions may be at higher risk for developing CTS, and there is some epidemiologic evidence to support this

possibility (*38,51*). Another way might be to detect people at risk by some sort of genetic or epigenetic analysis. Ideally such population could be screened for SSCT thickening by some noninvasive means. Ultrasound is particularly attractive because it can assess changes in the SSCT associated with various hand and wrist movements (*45-48*), it is portable and therefore capable of imaging subjects in the workplace, and because the cost is far less than other imaging modalities, such as MRI.

Once detected, preventive strategies should be sought to prevent further damage to the SSCT. To do this, motion analysis or further mechanical testing of the SSCT might provide more information about the exact orientation of the connecting fibers between the different collagen layers of the SSCT.

Finally, the animal model for carpal tunnel should be further refined and validated so that new surgical or drug treatments could be tested.

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