TENNIS ELBOW

Sonographic findings and intratendinous injection treatment

by

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To use, but not abuse

To my family
Joakim, Johanna and Maja
# Contents

Abstract ....................................................................................................... 7  
Abbreviations .............................................................................................. 8  
Original papers ........................................................................................... 9  
Introduction .............................................................................................. 10  
  Classification and nomenclature ........................................................... 13  
Tennis elbow ............................................................................................. 14  
  History ................................................................................................... 14  
  Definition ............................................................................................... 14  
  Epidemiology ......................................................................................... 14  
  Anatomy ..................................................................................................15  
  Blood supply .......................................................................................... 16  
  Metabolism ............................................................................................ 16  
  Innervation .............................................................................................17  
  Pain mechanisms and vasoregulation ....................................................17  
  Biomechanics ....................................................................................... 18  
  Aetiology ................................................................................................20  
    Computer work ................................................................................... 21  
  Pathogenesis .......................................................................................... 21  
  Clinical history ..................................................................................... 23  
  Diagnostics ........................................................................................... 24  
    Clinical examination ........................................................................... 24  
    Differential diagnoses ....................................................................... 25  
    Ultrasound and Doppler examination ............................................... 26  
    Magnetic resonance imaging ........................................................... 27  
    Plain X-ray ..........................................................................................28  
Treatments ............................................................................................. 29  
  Natural course .................................................................................... 29  
  Rest ..................................................................................................... 29  
  Medication ............................................................................................ 29  
  Physiotherapy ..................................................................................... 30  
  Stretching ........................................................................................... 30  
  Muscle strengthening ......................................................................... 31  
  Manipulation techniques ................................................................... 32  
  Electrotherapeutic modalities ............................................................ 33  
  Acupuncture ....................................................................................... 33  
  Orthotic devices .................................................................................. 33  
  Injections ............................................................................................ 35  
  Surgery ................................................................................................ 36  
Outcome measurements ........................................................................38  
  Visual analogue scale (VAS) ............................................................... 38
Grip strength ......................................................................................38
Prevention ..............................................................................................39
Aims of the thesis ......................................................................................40
Subjects .....................................................................................................41
Inclusion and exclusion criteria ............................................................42
Methods ....................................................................................................43
Clinical examination .............................................................................43
Clinical tests and outcome measures ....................................................43
Ultrasound and Colour-Doppler ...........................................................44
Ultrasound-guided injection ...................................................................45
Biopsies ..................................................................................................47
Sampling ...............................................................................................47
Tissue preparation ..................................................................................47
Immunofluorescence (TRITC and FITC) technique ..................................47
Antibodies .............................................................................................48
Microscopic examination and evaluation ..............................................48
Control staining ....................................................................................49
Statistical methods ................................................................................49
Ethics .......................................................................................................50
Summary of papers ................................................................................51
Paper I ..................................................................................................51
Paper II .................................................................................................54
Paper III ................................................................................................56
Paper IV ................................................................................................57
Paper V ..................................................................................................58
Discussion .............................................................................................59
Conclusions ..........................................................................................65
Acknowledgements ...............................................................................66
Sammanfattning på svenska ....................................................................67
References .............................................................................................69
Abstract

Tennis elbow (TE) is a relatively common painful condition affecting the upper extremity. The aetiology is not known, but TE is most often seen in middle aged individuals using repetitive and forceful gripping at work or recreational activities, and is referred to overuse injuries. The pathogenesis is not known, but there are so-called degenerative changes in the wrist- and finger-extensor muscle origin (common extensor origin - CEO). The pain mechanisms involved have not been scientifically clarified.

The studies in the present thesis aimed to 1) evaluate the structure and blood flow using ultrasound (US) and colour Doppler (CD) examinations of the CEO in patients with TE, and in pain-free elbows, 2) evaluate the clinical effects of US- and CD-guided intratendinous injection treatment with the sclerosing substance polidocanol, 3) evaluate the long term (2 years) effects of injection treatment on the tendon structure and blood flow, and 4) investigate if there is a local production of sympathetic and parasympathetic signal substances in non-neural cells in the CEO.

Structural tendon changes and high blood flow was found in the CEO in patients with TE, but not in pain-free controls. Remaining structural changes and additional bone spur formation at the lateral epicondyle, but not high blood flow, were seen 2 years after successful injection treatment. In a randomised double-blind study, US- and CD-guided intratendinous injection treatment with sclerosing polidocanol or the local anaesthetic lidocaine combined with epinephrine, targeting the region with high blood flow, was found to reduce pain and increase grip strength in patients with TE. There were no differences in the outcome between the two treatment groups. A local production of catecholamines, but not acetylcholine, was found in fibroblasts in the CEO, in patients with TE.

This thesis presents results showing US and CD examinations to be useful methods to diagnose TE, and to evaluate structure and blood flow in the CEO after treatment. US- and CD-guided injection treatment targeting high blood flow in the region with structural changes can reduce pain symptoms in patients with TE. The localised high blood flow, and local production of catecholamines in the tendon cells in the CEO, might be involved in the pain mechanisms.
<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
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<tr>
<td>ACh</td>
<td>acetylcholine</td>
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<td>AChE</td>
<td>acetylcholine esterase</td>
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<td>BSA</td>
<td>bovine serum albumin</td>
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<td>C</td>
<td>Celcius</td>
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<td>CEO</td>
<td>common extensor origin</td>
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<td>CD</td>
<td>colour Doppler</td>
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<td>CGRP</td>
<td>calcitonin gene-related peptide</td>
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<td>ChAT</td>
<td>choline acetyltransferase</td>
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<td>ECRB</td>
<td>extensor carpi radialis brevis</td>
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<td>ECRL</td>
<td>extensor carpi radialis longus</td>
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<td>ECU</td>
<td>extensor carpi ulnaris</td>
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<td>ED</td>
<td>extensor digitorum</td>
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<td>EDM</td>
<td>extensor digiti minimi</td>
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<td>ESWT</td>
<td>extracorporeal shock wave therapy</td>
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<td>FGF-2</td>
<td>fibroblast growth factor 2</td>
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<td>FITC</td>
<td>fluorescein isothiocyanate</td>
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<td>MC</td>
<td>metacarpale</td>
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<td>MHz</td>
<td>mega Hertz</td>
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<td>MRI</td>
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<td>MWM</td>
<td>mobilisation with movement</td>
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<td>NSAID</td>
<td>non steroidal anti inflammatory drug</td>
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<td>PBS</td>
<td>phosphate-buffered saline</td>
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<td>PD</td>
<td>power Doppler</td>
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<td>PDGF</td>
<td>platelet-derived growth factor</td>
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<td>PGE$_2$</td>
<td>prostaglandin E$_2$</td>
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<td>RCT</td>
<td>randomised controlled trial</td>
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<td>SP</td>
<td>substance P</td>
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<td>SPSS</td>
<td>statistical package for the social sciences</td>
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<td>TE</td>
<td>tennis elbow</td>
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<td>TGF-β</td>
<td>transforming growth factor-β</td>
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<td>TH</td>
<td>tyrosine hydroxylase</td>
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<td>TRITC</td>
<td>tetramethylrhodamine isothiocyanate</td>
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<td>US</td>
<td>ultrasonography</td>
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<td>VAS</td>
<td>visual analogue scale</td>
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<td>VGEF</td>
<td>vascular endothelial growth factor</td>
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<td>X-ray</td>
<td>plain film radiography</td>
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Original papers

This thesis is based upon the following original papers, referred to in the text by their Roman numerals:


IV. Zeisig E, Ljung BO, Alfredson H, Danielson P. Immunohistochemical evidence of a local production of catecholamines in cells of the tendinous muscle origin tissue at the lateral and medial humeral epicondyles – of importance for development of tennis and golfer’s elbow? Manuscript.

Introduction

Pain from the lateral aspect of the elbow was first described in 1873, and has since then been given different names such as tennis elbow (TE), lateral epicondylitis, epicondylosis, epicondylalgia and lateral elbow pain. The most frequently used term is probably TE, implying a relationship with repetitive mechanical load while using a forceful grip, as in playing tennis (Shiri et al., 2006). However, the majority of patients with this condition are not tennis players. The prevalence of TE is 1-2 %, and the condition is mainly seen among middle aged people (Verhaar, 1994; Palmer et al., 2001; Walker-Bone et al., 2003, 2004; Shiri et al., 2006). TE causes pain and functional impairment, and many of the patients are unable to work during weeks, up to years, with a detrimental effect on productivity.

The aetiology and pathogenesis of TE is not known, but the condition is considered to be an overuse injury of degenerative nature (Jozsa and Kannus, 1997). A theory that repeated microscopic trauma affecting the structure in the common extensor origin (CEO) at the lateral epicondyle, leading to a tissue response with oedema and pain, is often proposed in the literature (Jozsa and Kannus, 1997). This tissue response has been interpreted as inflammation, and the condition has been called lateral epicondylitis. However, there is accumulating evidence that there are no signs of a prostaglandin mediated inflammation with involvement of inflammatory cells in the chronic stage (Nirschl, 1992; Regan et al., 1992; Potter et al., 1995; Alfredson et al., 2000). Therefore, the name epicondylitis does not seem correct.
Figure 1. The name tennis elbow is used for patients with pain from the common extensor origin, implying a relationship with repetitive mechanical load while using a forceful grip, like in playing tennis.

To understand the background of the present thesis, it is of importance to have some insight in the current knowledge of pain mechanisms and treatments of other overuse tendon injuries. Ultrasound (US) and colour Doppler (CD) examinations of painful Achilles and patellar tendons (tendinosis) have demonstrated high blood flow, also called “neovessels”, inside and outside the region with tendon changes (Weinberg et al., 1998; Öhberg et al., 2001; Alfredson et al., 2003; Cook et al., 2005a; Gisslen and Alfredson, 2005). Immunohistochemical studies of tendon tissue from Achilles and patellar tendinosis have shown sensory and sympathetic nerves in close relation to these “neovessels” outside the deep side of the tendon (Andersson et al., 2007; Danielson et al., 2008). Presence of sensory nerves, with immunoreactivity for the neurotransmitters Substance P (SP) and calcitonin gene-related peptide (CGRP), glutamate and sympathetic innervation has been demonstrated in close relation to vessels in extensor carpi radialis brevis (ERCB) from patients with TE (Ljung et al., 1999a, b; Alfredson et al., 2000; Uchio et al., 2002). These findings in Achilles and patellar tendons, high blood flow and nerves, have led to a new treatment regime with US- and CD-guided injections of the sclerosing substance polidocanol, targeting the region with vessels and nerves outside the tendon. Such injections have reduced the pain, and allowed a majority of the patients to return to their previous level of activity (Öhberg and Alfredson, 2002, 2003; Alfredson and Öberg, 2005a, b; Hoksrud et al., 2006).
These findings indicate that the region with high blood flow and nerves might be the source of pain?

Figure 2. Achilles tendinosis. CD shows high blood flow in region with structural changes (longitudinal view).

Figure 3. Painful patellar tendon (jumper’s knee). CD shows high blood flow in the region with structural changes (longitudinal view).

Furthermore, recent studies of other tendinopathies (Achilles and patellar tendon) have shown a local catecholamine production inside non-neural cells, and that these cells express adrenergic receptors. These findings might possibly play a role in the regulation of blood flow, pain and local changes in the tissue (Danielson et al., 2007a, b, 2008; Bjur et al., 2008a). Another classical neurotransmitter that has been studied is acetylcholine (ACh). ACh has been found to be produced by non-neural cells in tendons of patients suffering from Achilles and patellar tendinopathies (Danielson et al., 2006; Bjur et al., 2008b). It is not known if such a local catecholamine and/or acetylcholine production is present in TE.
Classification and nomenclature

As mentioned in the introduction, several names are used to describe this condition, such as; tennis elbow, lateral epicondylitis, lateral epicondylalgia, lateral elbow tendinopathy, lateral elbow pain, lateral elbow tendinosis, ECRB (extensor carpi radialis brevis)-tendinosis, extensor tendinosis, epicondylosis. Obviously the term epicondylitis is misleading since there are no signs of a traditional prostaglandin mediated inflammation. The term lateral epicondylalgia is sometimes used, but it is too general; it will also include a haematoma after a local strike. Recently, it was suggested to use the name tendinopathy for chronic (more than three months of duration) tendon pain, and when objective evaluations with US, MRI or biopsies show structural changes (intratendinous degeneration) in the painful region; the term tendinosis should be used (Stasinopoulos and Johnson, 2006).

In this thesis the nomenclature tennis elbow (TE) is used for patients with pain from the common extensor origin (CEO), because this term is since many years well known among the general population, and well describes the problem with painful gripping.

Figure 4. The wrist extensors counteract the flexion moment when using a powerful grip.
Tennis elbow

History

The first description of symptoms indicating a painful condition in the CEO was given in 1873 by Runge, who called the condition writer’s cramp. The term TE was introduced in 1882 by Morris, but Momberg (1910) was likely the first person to describe the condition in detail. Occupation related epicondylar pain was described as early as 1896 by Bernhardt (Goldie, 1964; Nirschl, 1992; Runeson and Haker, 2002).

Definition

TE is primary a clinical diagnosis based on a typical history, and clinical examination showing tenderness over the CEO close to the lateral epicondyle, and pain provoked in this region by resisted wrist extension. The history often includes repetitive and forceful gripping, and pain or weakness during gripping activities (Brukner and Khan, 1993).

Epidemiology

The prevalence of TE is described to be 1-2 % in a general population between 30 and 64 years of age. The highest incidence is between 40 and 60 years of age and, there are no differences between men and women (Verhaar, 1994; Palmer et al., 2001; Walker-Bone et al., 2003, 2004; Shiri et al., 2006). In occupational populations the prevalence is between 2-23% (Allander, 1974; McCormack et al., 1990; Leclerc et al., 2001). Differences in the prevalence in different studies may be related to different definitions; self reported symptoms or clinical examination (Kryger et al., 2007). Tennis players appear to be affected even at younger age, 16-36 years (Maffulli et al., 1990), and there are reports of a prevalence of up to 35-42 % among tennis players (Carroll, 1981; Silva, 2008).

Most of the patients suffering from TE are treated by general practitioners; the incidence has been shown to be 4-7/1000 per year in general practice (Assendelft et al., 1996). Although, only
55% of all persons with TE are treated by physicians (Verhaar, 1994).

**Anatomy**

The pathology found in TE is addressed to the extensor carpi radialis brevis (ECRB) muscle origin (Nirschl and Pettrone, 1979). The ECRB muscle is one of the muscles that originate from the lateral epicondyle, the lower third of the lateral epicondylar ridge of the humerus. The lateral epicondyle is also the origin for extensor carpi radialis longus (ECRL)-, extensor digitorum (ED)-, extensor digiti minimi (EDM)- and extensor carpi ulnaris (ECU)-muscles. These muscles uniform into the common extensor origin (CEO), and it is difficult to distinguish one from the other, both macro- and microscopically. This is especially difficult for the ECRB- and ED-origin (Greenbaum et al., 1999), which should be kept in mind during clinical tests and treatment. ECRL- and ECRB-muscles inserts on metacarpale (MC) II and III, respectively. The ECU-muscle inserts to the base of MC, and the ED-muscle onto the dorsal aponeurosis of fingers II-V.

![Diagram](image)

Figure 5. The anatomy of the common extensor origin.
Some authors claim that the superficial head of the supinator muscle arises from the lateral epicondyle, but the role of the supinator muscle in TE is unclear. A small study on cadavers found the largest increase in tension at the CEO coming from ECRB and ED, but there was also a moderate tensional increase caused by the superficial head of the supinator. ECRL and ECU contributed little to tensile forces (Erak et al., 2004).

**Blood supply**

The arterial blood supply for the ECRB mainly comes from the radial recurrent artery. The posterior branch of the radial collateral artery, and the interosseus recurrent artery, also contributes. The vascularisation is seen as a network of small vessels on the surface of the tendon. The deep part of the origin is almost avascular, and some regions are described as “hypovascular zones” (Schneeberger and Masquelet, 2002; Bales et al., 2007).

**Metabolism**

Tendons in general have all three main pathways for energy metabolism; the aerobic Krebs cycle, anaerobic glycolysis and pentose phosphate shunt. With increasing age, the activity of the
Krebs cycle and the pentose phosphate shunt decreases, while the anaerobic glycolysis remains. The synthetic activity of matrix, collagen, elastin, proteoglycans and glycoproteins, is diminished with age, and is influenced of factors such as physical activity, hormones and surrounding physical conditions. Even in the same tendons the enzyme activity varies at different anatomical sites (Jozsa and Kannus, 1997).

The low metabolic rate with anaerobic energy production is essential, since the tendon carries loads and remains in tension for long periods of time, to minimise risk of ischemia and necrosis. On the other hand, this low metabolic rate will also influence the possibilities to recover after activity and injury (Jozsa and Kannus, 1997).

**Innervation**

The muscles composing the CEO are innervated by the radialis nerve (C₆-C₇). The sensory innervation is sparsely described in the literature, and there is no complete picture. The roles of the sympathetic and parasympathetic nerves are unclear. A local dysfunction of the sympathetic nervous system has been shown in the dermal micro-vascular bed overlying the enthesis in TE (Smith et al., 1994).

**Pain mechanisms and vasoregulation**

The pain mechanisms associated with TE have not been fully understood. Pain is experienced from the tendon part of the CEO at the lateral epicondyle, and is provoked directly by pressure on the region by palpation during clinical examination, and indirectly by forces applied from contraction of muscles originating from the CEO.

There are no signs of a traditional prostaglandin mediated inflammation; no elevated concentrations of prostaglandin E₂ (PGE₂) was found in microdialysate, and absence of inflammatory cells in biopsies have repeatedly been shown (Nirschl, 1992; Regan et al., 1992; Potter et al., 1995; Alfredson et al., 2000). However, there might be involvement of a so-called neurogenic inflammation, causing vasodilatation and plasma extravasation (Wiesenfeld-Hallin and Xu, 1993; Uchio et al., 2002). Glutamate, a potent neurotransmitter in the central
nervous system, was detected by microdialysis in high concentrations in the ECRB in patients with TE (Alfredson et al., 2000). The importance of that finding has yet not been clarified. The substances calcitonin gene-related peptide (CGRP) and Substance P (SP), together with receptors for SP, have also been shown in the CEO (Ljung et al., 1999a, b; Uchio et al., 2002; Ljung et al., 2004). These substances are involved in transmitting nociceptive information to the spinal cord, but they also have efferent effects that might lead to neurogenic inflammation (Wiesenfeld-Hallin and Xu, 1993).

The mechanisms for regulation of blood flow in the CEO are not known, but presence of a sympathetic innervation, has been shown along the vascular tree (Ljung et al., 1999a, b). Catecholamines, a group of neurotransmitters including epinephrine, norepinephrine and dopamine, might be involved in modulating pain sensations besides modulating vasoregulation (Baron et al., 1999). Sympathetic innervation is distinguished by using antibodies to tyrosine hydroxylase (TH), the rate limiting enzyme in the catecholamine pathway.

Acetylcholine (ACh), a classical parasympathetic neurotransmitter, has never been identified in tendinous muscle origins of the upper extremity. Besides vasoregulation, ACh might have a role in modulating peripheral nociception, and possibly also in inducing pain (Vogelsang et al., 1995). The presence of acetylcholine is shown by detection of the synthesising enzyme choline acetyltransferase (ChAT).

**Biomechanics**

ECRL and ECRB work to counteract the flexion moment generated at the wrist by the digital and wrist flexors. Increased muscle activities of the wrist extensors maintain the wrist in a position of slight extension, allowing the digital flexors to function near their ideal length-tension relationship, and thus generate maximal grip strength (Snijders et al., 1987). As the name imply, the muscles originating from the CEO extend the fingers and the wrist, but seldom with high forces. The high forces are achieved when the grip is used, and there is a need to stabilise the wrist (Lieber and Friden, 1998; Shiri et al., 2006).

The maximum muscle strain on ECRB is obtained during elbow extension, forearm pronation, and wrist flexion-ulnar deviation (Briggs and Elliott, 1985; Takasaki et al., 2007). This is important to keep in mind when the working position is
evaluated ergonomically, and during stretching exercises. During the so called “working position”, the ECRB passes straight from the epicondyle to the forearm. Working position is defined as elbow flexion and semi-pronated wrist.

The ECRB-muscle and the other wrist and finger extensor muscles have special biomechanical properties due to the fact that they act over more than one joint. The CEO is proximal to the axis of rotation for flexion and extension at the elbow, and is subjected to shearing stress in all movements of the forearm. The head of the radius is rotating under the ECRB-tendon during pronation of the forearm; this will contribute to the forces applied to this region (Briggs and Elliott, 1985). The undersurface of the CEO is also vulnerable to abrasion against the lateral edge of the capitulum humeri during elbow motion (Bunata et al., 2007).

Figure 7. Increased muscle activity in the ECRB stabilises the wrist during gripping activities.
**Aetiology**

The aetiology to TE is unknown, but there are multiple theories. In a general population TE is seldom seen before the age of 30. Consequently, age is most likely an important aetiological factor (Roto and Kivi, 1984). With aging, over 30 years of age, the amount of proteoglycans, glycoproteins, elastic components and water content decline. The collagen turnover declines and the quality decreases. The reparative ability is thought to decline due to decreased blood flow and tenoblastic activity. With increasing age the metabolic pathways for energy changes from aerobic to more anaerobic. All these changes, in quantity and quality, might lead to a tissue more vulnerable to stress (Jozsa and Kannus, 1997). In middle aged cadavers, without a known history of clinical symptoms, microscopic damage has been shown, why some authors claim TE to be a degenerative disease (Milz et al., 2004).

There is a general agreement that the ECRB origin plays a central role in the development of the painful condition (Coonrad and Hooper, 1973; Regan et al., 1992; Friden and Lieber, 1994; Potter et al., 1995; Lieber et al., 1997; Ljung et al. 1999c). The wrist extensors play a central role in stabilising the wrist during gripping. Repetitive and forceful movements during gripping are associated with TE, and TE is believed to be one of the most common mechanical overuse tendon injuries (Shiri et al., 2006). Poor blood supply in combination with repetitive or constant high tension of the wrist extensors, are thought to reduce the ability to regenerate the tissue (Jozsa and Kannus, 1997). TE is seldom seen after an acute trauma, but instead has a gradual onset and occurs often spontaneous in individuals used to work related repeated monotonous movements engaging the forearm (Kivi, 1983).

Cold exposure has been described to negatively influence work-induced TE. These observations might be explained by cold induced arteriole vasoconstriction in a region with already poor blood supply, resulting in tissue hypoxia and cell damage (Kurppa et al., 1991; Jozsa and Kannus, 1997).

It is believed that there is an increased risk to get TE when the grip is used in non-neutral postures (Haahr and Andersen, 2003). In tennis, faulty backhand technique often causes TE, and players with a double handed backhand strike seldom suffer from this condition (Roetert et al., 1995).
Computer work

From epidemiological studies the increase in computer and mouse use has been associated with an increased prevalence of pain disorders like TE in the upper extremity (Leclerc et al., 2001; Sillanpaa et al., 2003; Gerr et al., 2006). However, epidemiological studies have their restrictions since they are often based on questionnaires, with low answer rates and self reported symptoms (Van Eerd et al., 2003; Gerr et al., 2006). There is no possibility to differ TE from other causes of lateral elbow pain in a questionnaire. There are also studies indicating a high prevalence of posterior interosseus neuropathy among computer workers (Jepsen, 2004). However, these epidemiological studies only give a hint of the prevalence. When it comes to the use of mouse and elbow pain, there is no convincing association between duration of use and pain. There is a stronger relationship with poor ergonomics at work, having poor placement of keyboard and the mouse, and TE. Among individuals having computer work, age has also been considered to be a risk factor for TE (Sillanpaa et al., 2003; Lassen et al., 2004).

Pathogenesis

The pathogenesis to TE is unknown, but there are multiple theories. The general opinion is that TE is an overuse injury (Jozsa and Kannus, 1997; Shiri et al., 2006). The pathogenesis of an overuse injury is thought to be a result from cumulative microtrauma that weakens the structural and vascular elements of the tendon. Microtrauma to a mechanical structure occurs even if the loads are within the material’s strength limits, and is due to fatigue after repetitive loads. The repetitive strain also fatigues the tenocytes, and the ability to repair is overwhelmed. If the muscle is weak or fatigued, the energy absorbing capacity of the whole muscle-tendon unit is reduced, and tendon stress will increase. With adequate time after stress, the tendon can recover (Jozsa and Kannus, 1997; Kraushaar and Nirschl, 1999).

Most patients in published papers have TE in the chronic stage, i.e. duration of pain symptoms more than 3 months. In the chronic stage, a so called neurogenic inflammation, with vasodilatation and plasma extravasation, but without presence of inflammatory cells (leucocytes or lymphocytes), might be present.
(Nirschl, 1992; Regan et al., 1992; Wiesenfeld-Hallin and Xu, 1993; Potter et al., 1995; Jozsa and Kannus, 1997).

Nirschl (1992) have described the microscopic appearance as a degenerative process, characterised by the presence of dense populations of fibroblasts, vascular hyperplasia (angiofibroblastic hyperplasia) and disorganised collagen without signs of inflammation, and called the condition angiofibroblastic tendinosis. These findings are in line with findings from others; microscopic findings of disruption of normal tendon fibres, invasion of fibroblasts and vascular granulation-like tissue (Goldie, 1964; Coonrad and Hooper, 1973; Nirschl and Pettrone, 1979; Regan et al., 1992; Moore, 2002; Milz et al., 2004). The macroscopically appearance of the ECRB-tendon is dull, grey, friable and oedematous (Nirschl, 1992).
**Clinical history**

Pain is the main symptom and is experienced from the lateral side of the elbow, having a maximum just distal to the lateral epicondyle. In some cases the pain radiates into the proximal forearm extensors. The onset of pain may be acute or gradual. In cases with a more acute onset, there is often a recent change in mechanical load, technique or equipment (Brukner and Khan, 1993). The severity of pain ranges from minor in a specific situation, to more severe pain with disturbed sleep. The pain symptoms are closely related to activity level, otherwise other causes of lateral elbow pain should be considered (Brukner and Khan, 1993). The pain is aggravated by gripping activities, from more forceful gripping during industrial work, to gripping during trivial daily activities such as gripping the milk bottle in the fridge and the tooth brush. The pain during gripping activities is aggravated depending on the position of the elbow. The most painful position is with straight elbow, and the second most painful position is with the elbow in maximal flexion. There is also often stiffness after having the elbow in the same position for a longer period of time; especially after sleeping or carrying load.

![Figure 8. Using the grip during daily activities can provoke pain in tennis elbow.](image)
**Diagnostics**

**Clinical examination**

Criteria for the diagnosis TE are; pain on palpation of the lateral epicondyle and the CEO, and pain in the CEO during resisted extension of the wrist or third finger.

Other tests to provoke pain in the CEO are the Mill’s test (the wrist pronated and radially deviated during extension), or chair lifting test (Gardner, 1970). Another method suggested to confirm the diagnosis is by testing the maximum grip strength (De Smet et al., 1998; Sluiter et al., 2003).

Active and passive movements of the elbow and wrist are seldom limited (Jozsa and Kannus, 1997).

Figure 9. Palpation of the common extensor origin.
Figure 10. Resisted extension of the wrist.

**Differential diagnoses**

Referred pain from the cervical spine is occasionally the source of lateral elbow pain, and might be combined with hyperaesthesia and weakness of the hand. A history of neck and shoulder symptoms should lead to an extended clinical examination (Berglund et al., 2008). The three main nerves of the upper extremity should be tested, especially the radial nerve. Signs of increased neural tension, with or without posterior interosseus nerve entrapment, must be examined. Entrapment of the posterior interosseus nerve, “radial tunnel syndrome”, goes with pain on palpation of the site for entrapment (most often in the Frohse’s arcade), and pain induced by resisted extension of the middle finger and resisted supination (Lawrence et al., 1995). Differentiation between TE and radial tunnel syndrome is primarily based on the character and location of the pain, and the site for maximal tenderness (Field and Savoie, 1998). It is relatively common that these two conditions, TE and radial tunnel syndrome, exist in conjunction.

A pain-inducing synovial fold from the capsule of the elbow joint, just above the superior edge of the annular ligament, has been described (Kim et al., 2006; Ruch et al., 2006). This has been regarded as a “pseudo-meniscus” between capitulum and the edge of fovea radialis. Histological analysis has shown fibrous tissue, not fibromyxoid structure as in proper meniscus
(Duparc et al., 2002). This tissue might be subjected to impingement causing lateral elbow pain.

Synovitis and arthritis of the radiohumeral joint can be suspected if there is restricted and painful range of motion. If palpation of the radial head during forearm pro- and supination is painful, arthritis should be suspected, and further investigations should follow. During US examination excess of joint fluid, and osteofytes of the radiohumeral joint, can be detected.

Instability of the lateral collateral ligament is occasionally mentioned as a source of pain, but its clinical relevance is limited. The lateral collateral ligament is located beside the CEO, and sometimes there is no clear distinction between them (Milz et al., 2004).

In osteochondritis dissecans there might be loose bone fragments in the joint space.

Compartment of the anconeus muscle has been described as a differential diagnoses. The origin of the anconeus muscle is at the lateral epicodyle, and it inserts on the posterior surface of the ulna. The pain symptoms have ischemic character during forced extension activities in the elbow (Abrahamsson et al., 1987).

**Ultrasound and Doppler examination**

Ultrasound (US) examination has been shown to be an easy accessible, cost-effective, and risk-free method to examine tendons (Maffulli et al., 1987; Åstrom et al., 1996; Movin et al., 1997; Paavola et al., 1998). Considering the CEO, the anatomical landmarks, such as the bony lateral epicodyle and the elbow joint with the head of radius, make it easy to be orientated in this region. It is not possible to distinguish the different tendons in the CEO from each other, nor the lateral collateral ligament. The method is very much dependent on the experience of the operator. The structure is evaluated (hypoechoic regions and diffuse heterogeneity), and calcifications and bone spurs can be seen (Connell et al., 2001; Levin et al., 2005).

Doppler sonography is an established technique to study blood flow non-invasively (Omoto et al., 1984). The colour Doppler (CD) technique visualises both the velocity and the direction of the blood flow. An even more sensitive method to study blood flow is power Doppler (PD), but the direction of the flow is not visualised (McDicken et al., 1992). There is no reliable method to calculate the blood flow. Different methods are being used, but
are limited by the high operator dependency (Cook et al., 2005b; Connell et al., 2006; de Vos et al., 2007; Pfirrmann et al., 2008). The operator can affect the flow by varying the pressure on the probe, where high pressure decreases the blood flow (Khoury and Cardinal, 2008). Also, the patient’s arm position, muscle tension, and activity level before the examination are of importance. Consequently, when trying to overcome the limitations with US and CD examinations, the best alternative is to use the same and experienced radiologist in all examinations.

**Magnetic resonance imaging**

Magnetic resonance imaging (MRI) is an excellent method to detect oedema and/or fatty degeneration in tendons. In patients with TE this is seen as increased signal intensity in the CEO (Pasternack et al., 2001; Savnik et al., 2004). In a systematic review the sensitivity for signal increase in tendons was 0.90. The specificity was calculated to 0.86 when healthy subjects served as controls, and 0.65 when the contralateral symptom-free elbows served as controls (Pasternack et al., 2001). MRI is non-dynamic, and blood flow cannot be evaluated. The image correlates well with surgical and histological findings (Potter et al., 1995). Using MRI to evaluate the treatment response has shown disappointing results. The increased signal intensity was shown to persist despite clinical improvement, and an injection of corticosteroids into the CEO may alter the signals for up to one month (Pasternack et al., 2001; Savnik et al., 2004).

Figure 11. MRI showing tennis elbow. Note the increased signal intensity in the common extensor origin (arrow).
Plain X-ray

Plain X-ray is only used to exclude differential diagnoses such as osteocondritis dissicans, degenerative joint changes or bone tumours. Occasionally there might be findings like calcifications, local osteoporosis, or sclerosis at the edge of the epicondyle. However, in most cases the plain X-ray examination is normal (Jozsa and Kannus, 1997; Meknas et al., 2008).
**Treatments**

There are systematic reviews from the Cochrane Library for treatments of TE using shock wave therapy (ESWT), acupuncture, orthotic devices, deep transverse friction massage, surgery and non-steroidal anti-inflammatory drugs (NSAIDs) (Brosseau et al., 2002; Buchbinder et al., 2002; Green et al., 2002a, b; Struijs et al., 2002; Buchbinder et al., 2005). Most reviews conclude little scientific evidence for the treatment due to small sample sizes and differences in study designs; patient selection, follow-up periods and different outcome measure. There is little evidence for or against good effects of any treatment.

**Natural course**

The natural course for TE is not known, but the common opinion is that the condition is self-limiting, and has a good prognosis. The average duration of a typical pain episode is eight to twelve months, but some cases are recalcitrant. Recurrences seem unusual (Cyriax, 1936). RCTs have shown the same clinical results 12 months after instituted treatment, regardless of type of therapy or placebo (Hay et al., 1999; Luginbuhl et al., 2008). However, despite the seemingly self-limiting character, many individuals seek medical attention for TE.

**Rest**

Rest is useful for pain relief since the symptoms are activity related (Paoloni and Murrell, 2004). There is no evidence that rest will contribute to an earlier recovery. It is difficult to achieve total rest without using a splint, or palsy after injection of botulinum toxin, since the grip is used during daily activities.

**Medication**

Medication with pain-killers is often tried. In one study, medication with the NSAID naproxen was compared with the effect of a non-guided single betamethasone injection. Placebo was used for both groups, placebo tablets and injection with
saline, respectively. There were no apparent differences in pain or grip strength between the two groups after two weeks (Saartok and Eriksson, 1986). Since there are no signs of a prostaglandin mediated inflammation in the CEO, the use of NSAIDs, locally or systemically administrated, should logically have no effects on the underlying process (Green et al., 2001). However, a more recently published RCT has shown pain relieving effects of topically administered diclofenac epolamine (NSAID) (Spacca et al., 2005).

Ionophoresis is used to introduce topically applied physiologically active ions through the skin. This technique is more attractive since it is non-invasive, pain-free and non-traumatic. However, in a double-blind controlled study, comparing corticosteroid and placebo ionophoresis, no difference in effects on the pain were shown in the outcome measures (Runeson and Haker, 2002).

Topical administration of nitric oxide has been shown to have pain relieving effects in patients with TE (Paoloni et al., 2003). The mechanisms behind the good effects have not been scientifically clarified.

**Physiotherapy**

The treatments of choice among physiotherapists in Sweden are: ergonomic counselling, stretching, acupuncture, muscle strengthening exercises (predominately eccentric) and orthotic devices (Peterson et al., 2005). More than eighty years ago Cyriax introduced a method of deep friction massage and mobilisation that is still commonly used (Cyriax, 1936; Stasinopoulos and Johnson, 2004). Deep transverse friction massage of the affected region when the tissue is under tension (wrist flexed) is also used (Brosseau et al., 2002).

**Stretching**

Stretching exercises is often included in the standard physiotherapy treatment for TE. Maximal muscle strain on the ECRB is obtained with the elbow in extension, forearm in pronation, and wrist in flexion-ulnar deviation (Takasaki et al., 2007). In one study there were no statistical differences in the outcomes between stretching alone (one group), and two groups
with strengthening exercises (eccentric and concentric, respectively) (Martinez-Silvestrini et al., 2005).

Figure 12. Stretching exercise for tennis elbow. Maximal muscle strain on the extensor carpi radialis brevis is obtained with elbow extension, forearm in pronation and wrist in flexion-ulnar deviation.

**Muscle strengthening**

Eccentric exercise is often tried since it has shown good treatment results on other chronic painful tendons (Stanish et al., 1986; Mafi et al., 2001; Purdam et al., 2004; Jonsson and Alfredson, 2005). A problem to repeat the good results from the Achilles and patellar tendon might be that the ECRB passes several joints. The most effective position for eccentric training is so far not known. In most programs, the hand is pronated and hangs over an edge, but the position of the elbow differs from full
extension to 90°-flexion. Some protocols include stretching exercise as well (Manias and Stasinopoulos, 2006). Svernlöv and Adolfsson (2001) designed a special eccentric training programme and found indications that eccentric training was superior to conventional stretching. Also it was shown that the good results from eccentric training were regardless of symptom duration.

Figure 14. Eccentric training in tennis elbow. The weight, and the affected wrist, is lifted up to the start position by the other hand.

**Manipulation techniques**

In general, the mechanism by which manipulation may work is poorly understood. In TE, it is mainly the elbow that is manipulated (mobilisation-with-movement MWM) (Vicenzino et al. 2001; Paungmali et al., 2003), but there is also some manipulation of the wrist (Struijs et al., 2003). In a systematic review, Bisset el al. (2005) found some evidence indicating positive effects of elbow manipulative therapy techniques.
Electrotherapeutic modalities

Shock wave therapy (ESWT) involves application of single pulsed acoustic waves targeting the painful region. The anti-nociceptive effect of ESWT is unknown. Some authors have hypothesised an over-stimulation of nerve fibres (hyper stimulation analgesia), and long-term effects by inducing a healing process. One problem with ESWT is to find the optimal frequency and dosage. The method can be combined with radiological or US imaging, to ensure that the ESWT is directed towards the target region. The method might induce pain, why local anaesthetic injections are sometimes used prior to treatment. Since the 1990s, benefits from ESWT treatment have been reported, but systematic reviews have shown conflicting results (Buchbinder et al., 2005; Rompe and Maffulli, 2007). Some authors claim no benefits of ESWT compared to placebo (Speed et al., 2002; Bisset et al., 2005).

Ultrasound as treatment has not been shown to be more effective than placebo (Labelle et al. 1992; Bisset et al., 2005).

Laser therapy has been used to treat musculoskeletal disorders for nearly three decades. In systematic reviews of clinical trials, there are conflicting results whether laser therapy has any effects compared to placebo on pain symptoms from TE (Bisset et al., 2005; Bjordal et al., 2008).

TENS is a percutaneous electrical stimulation of excitable tissue, which is thought to activate pain relieving systems. No evidence for effects on TE has been shown (Peterson et al., 2005).

Acupuncture

Treatment with acupuncture has been tried to diminish the pain in patients with TE. A systematic review has shown that there is no evidence to either support or refute the use of acupuncture (Green et al., 2002a).

Orthotic devices

The most commonly used orthotic devices in the treatment of TE are orthoses that stabilise the wrist, or the epicondylitic counterforce band. However, in a systematic review, no effects of
these orthotic devices were shown (Struijs et al., 2002). If a counterforce brace is used, it is of importance to apply the brace correctly. The brace should be sited approximately 10 cm below the elbow joint, not over the most painful region (Takasaki et al., 2008).

Figure 15. Orthotic device stabilising the wrist for patients with tennis elbow.

Figure 16. Epicondylitic counterforce band for patients with tennis elbow.
**Injections**

Different substances for injection treatment have been tried to affect the pain in TE. The majority of the injection treatments are non-guided, and aiming for the most tender spot, while some are US- and Doppler-guided. Corticosteroid injections have been used for decades with varying success (Assendelft et al., 1996; Smidt et al., 2002a). The reason to the generous attitude towards injections with corticosteroids is that the risk for rupture at the tendon insertion has been thought to be low. The target for injection is the most tender point, and US- and Doppler-guided approach is seldom used. There seems to be a positive effect in the early management (less than 6 weeks) of TE, but not over time (Verhaar et al., 1996; Hay et al.; 1999; Smidt et al., 2002a, b; Bisset et al., 2006; Tonks et al., 2007).

Another method is non-guided (blind) injections of platelet rich plasma (PRP) together with a local anaesthetic (Mishra and Pavelko, 2006). Platelets are rich in growth factors (PDGF, VGEF, TGF-β, FGF-2), possibly enhancing healing by favouring production of collagen (Molloy et al., 2003). Another similar attempt to enhance the healing response is US-guided injections of autologous blood together with a local anaesthetic (Connell et al., 2006). Both these two types of injections have shown promising clinical results, but no conclusions about their role in the treatment of TE can yet be drawn.

Non US- and Doppler-guided prolotherapy was first introduced in the 1950s, and has been used mostly as an injection treatment for painful tendons and ligament attachments (Rabago et al. 2005; Scarpone et al. 2008). Dextrose and sodium morrhuate are two common prolotherapy injectants. There are animal studies indicating strengthening of ligament and tendon insertions after prolotherapy. Treatment for TE includes 3-6 treatment sessions, at monthly intervals. A recent RCT reported decreased elbow pain and improved strength after a treatment session with 10.7% dextrose and 14.7% sodium morrhuate in combination, compared to a control group given injections with 0.9% saline (Scarpone et al., 2008).

Non-guided injections of glycosaminoglycan polysulfate have indicated good results in one study on patients with TE. One injection per week, for five weeks, was given (Åkermark et al., 1995). The pharmacological effects of glycosaminoglycan polysulfate are suggested to be inhibition of thrombin, fibrin
formation, and catabolic enzymes, active in connective tissue degeneration.

In all injection treatments targeting the CEO there might be some simultaneous “needling” or “peppering effect”. In one study the tender region was peppered non-guided with 40-50 subcutaneous redirecting and reinserting injections. The patients were randomised to get either plain lidocaine injections, or lidocaine combined with the corticosteroid triamcinolone. The results after 2 months were “excellent” in both groups (Altay et al., 2002).

Injections with botulinum toxin in the ECRB and ED muscles have been tried during the last decade, without convincing good results (Hayton et al. 2005; Wong et al., 2005; Placzek et al., 2007). The injection paralyses the muscle and no tensile forces act on the CEO. However, there is also loss of function for up to three months (Hayton et al., 2005; Wong et al., 2005).

**Surgery**

Different surgical procedures have been tried in the treatment of TE; open, arthroscopic and percutaneous approaches. Most published papers show good clinical results (Szabo et al., 2006). The classical Homan procedure was introduced in 1933, and the most used methods today are the classic or modified Homan technique, dividing the CEO close to the bone and allowing the tissue to retract approximately 1 cm distally. Obviously, this will denervate the region, but theoretically also initiate a healing response (Goldie, 1964; Nirschl and Pettrone, 1979; Verhaar et al., 1993; Svernlöv and Adolsson, 2006). Sometimes the Homan procedure is combined with decortication of the lateral epicondyle in an attempt to improve the local blood supply. Another technique is the Garden procedure, i.e. lengthening of the distal ECRB tendon (Garden, 1961). The theory behind this technique is that the sarcomere lengthening will affect the pain through a decreased passive muscle tension. Since there is an increase in active muscle force, the lengthening does not necessarily result in muscle weakness (Friden and Lieber, 1994; Buchbinder et al., 2002). Fractional lengthening has also been described in the proximal ECRB tendon (Wang and Erak, 2007).

A recent study showed a quicker pain relief and improved grip strength in patients treated with radiofrequency microtenotomy of the CEO, compared with open extensor tendon release (Meknas et al., 2008). Radiofrequency has been shown to
promote angiogenesis, thereby starting an early healing response. In another recent study of TE, good clinical results were reported after US-guided percutaneous needle tenotomy under local anaesthesia (McShane et al., 2008).

Different techniques are described using an arthroscopic approach. The methods include intra-articular release of the ECRB, tendon debridement and decortication (Kuklo et al., 1999; Baker and Baker, 2008). One obvious risk is to accidentally debride the lateral collateral ligament, resulting in posterolateral rotatory instability. However, the ligament remains intact if the debridement does not extend posterioly to the axis of the radial head (Smith et al., 2003). Also extra-articular arthroscopic release has been described. This technique has advantages since there is a direct visualisation of the diseased structures, and only requires a small capsulotomy (Brooks-Hill and Regan, 2008).

An advantage with intra-articular arthroscopy is the possibility to detect and treat a degenerative capsular fold or hypertrophic synovial plica possibly causing impingement on the radial head, especially in the fully extended elbow (Mullett et al., 2005; Kim et al., 2006; Ruch et al., 2006).

In systematic reviews, there are no randomised controlled studies evaluating surgical treatment. Therefore the conclusion is that the choice of surgical procedure is up to the surgeons based on their experiences (Buchbinder et al., 2002; Lo and Safran, 2007). There are different opinions about the role of surgery for treatment of TE. However, interestingly, the general opinion today, considering treatment of other tendinopathies, is that surgical treatment give unreliable results (Tallon et al., 2001).
Outcome measurements

Pain and pain-associated symptoms are the dominant reasons to seek medical attention for TE. All treatment methods aim to reduce pain. The relation between global impression of change and reduction of pain intensity has a high correlation. A 30-50% reduction in pain intensity is considered to represent a clinically important improvement (Farrar et al., 2000, 2001; Rowbotham, 2001).

Visual analogue scale (VAS)

VAS is presented as a 100-mm long line which starts with “no pain” and ends with “worst imaginable pain”. The patient is asked to mark the pain intensity during a certain activity, or at rest. The obvious limitation of VAS is that it has to be administered on paper or electronically. The scale is not necessarily linear, and low pain intensity gives a statistical problem when showing improvement (Rowbotham, 2001).

In a critical review of commonly used pain rating scales, the conclusion was that the VAS is valid, reliable and sensitive, and a most robust scale statistically (Williamson and Hoggart, 2005). The test-retest reliability is very high (intraclass correlation coefficient 0.97) for acute pain (Bijur et al., 2001).

Grip strength

The history from patients with TE includes pain during gripping activities. Therefore, grip strength is useful as an outcome measure, and gives a quantitative measure of the treatment results (Thurtle et al., 1984). Grip strength can also be used to diagnose TE, it is related to resisted wrist extension on clinical examination (Pienimaki et al., 2002; Dorf et al., 2007). Grip strength is tested in full elbow extension, having the shoulder and radioulnar joints in neutral rotation. Some authors prefer to have the patient in a supine position during testing to minimise the effect of the dynamometer weight. In the “pain-free grip strength” test, the patients are supposed to slowly squeeze a dynamometer until they begin to feel discomfort. The pain-free grip strength is measured three times, and the mean value is
calculated and used for analysis. In the “maximum grip strength” test, the patient is asked to squeeze the dynamometer as hard as they can three times, with short rest in between. The maximum value is used for analysis. The tests have a good interobserver reproducibility, with an intraclass correlation coefficient of 0.97-0.98 (Smidt et al., 2002c).

Figure 17. Grip strength testing in tennis elbow using a hand dynamometer.

**Prevention**

There are no prevention studies on TE.
Aims of the thesis

- To use ultrasound (US) and colour Doppler (CD) examinations to evaluate the tendon structure and blood flow in the common extensor origin in patients with tennis elbow (Paper I)

- To investigate whether treatment with US- and CD-guided intratendinous injections of the sclerosing substance polidocanol, targeting the region with high blood flow in the common extensor origin, would reduce pain in patients with tennis elbow (Paper II-III)

- To use US and CD examinations to evaluate the structure and blood flow in the common extensor origin 2 years after injection treatment for tennis elbow (Paper V)

- To investigate whether there is a local production of sympathetic and parasympathetic signal substances in non-neural cells in the common extensor origin in patients with painful tennis elbow (Paper IV)
Subjects

When the studies included in this thesis started, most patients from the Västerbotten region having TE were referred from the general practitioners to the Hand Surgery Unit, at Umeå University Hospital. Consequently, 8 of the patients in Paper I, 2 in Paper II, and 22 in Paper III, were recruited from the waiting list at the Hand Surgery Unit at Umeå University Hospital. The other 18 patients were primarily referred to the Sports Medicine Unit at the Umeå University Hospital. In total, in all clinical studies (Paper I-III and V) there are 50 included patients (60 elbows), 27 females and 23 males, with a mean age of 46 years (range 27 to 66 years). The majority of the patients had had a long duration of symptoms (mean 22 months, range 3-102). Previous treatments included; NSAIDs (n=38), cortisone injection (n=33), eccentric training (n=30), stretching (n=27), orthotic device (n=27), acupuncture (n=19), ultrasound (n=12), injection with botulinum toxin (n=5), massage (n=3) and surgery (tendon lengthening) (n=2).

In Paper IV, a majority of the biopsies were collected from patients having surgical treatment years 1999-2000, when open surgery in the ECRB muscle origin was suggested to be the best option for treatment for patients resistant to conservative treatments. Eight specimens from 7 patients with TE (one female had bilateral TE), 3 females and 4 males, with a mean age of 43 years (range 35 to 52 years) were studied. For control purpose, tissue samples from healthy asymptomatic individuals, 1 female and 5 males, with a mean age of 31 years (range 24 to 40 years), were investigated. As a reference, the tendinous flexor muscle origin from the medial epicondyle in patients with golfer’s elbow, 2 females and 2 males with a mean age of 46 years (range 37 to 64 years), was also studied. Golfer’s elbow is a painful condition affecting the flexor origin at the medial epicondyle. The condition is referred to overuse injuries, like TE.

The control group in Paper I was recruited from a university department, and consisted of 5 females and 6 males, with a mean age of 45 years (range 30 to 61 years).
Table 1. Patients included in Paper I-V, respectively. Some patients are included in more than one study. *One patient had one elbow included in Paper III and Paper IV, while the other elbow was included only in Paper IV.

**Inclusion and exclusion criteria**

**Inclusion criteria:**
- pain on palpation of the CEO on the lateral epicondyle
- pain elicited from the CEO during resisted extension of the wrist
- symptoms for more than 3 months
- no interventions for the condition during the last three months.

**Exclusion criteria:**
- arthritis
- synovitis of the proximal radio-ulnar joint
- entrapment of the radial nerve
- generalised pain-syndrome
- radiculopathy from the cervical spine
- other diseases (medial epicondylalgia, impaired sensibility, paralysis etc.) that would affect the outcome measure
- previous trauma or surgery in the region of the lateral epicondyle and CEO.
Methods

Clinical examination

All patients and controls were examined with palpation of the extensor origin on the lateral epicondyle, and resisted extension of the wrist. The diagnosis TE was considered present if these two examinations were painful. Further examination of the patients included palpation of the extensor muscles, Frohse’s arcade, the radial head and range of motion in the elbow joint, to try to exclude differential diagnoses.

Clinical tests and outcome measures

Visual analogue scale (VAS) for pain was used as the primary outcome measure. The elbow pain asked for was the most painful situation during gripping activities in daily life; including work situations, the week before the examination (Paper I, II, III and V), using a 100-mm long VAS, the patient recorded the amount of elbow pain when using the grip, where “no pain” is recorded as “0” and “severe pain” as “100”.

Satisfaction with the results of the treatment was recorded as satisfied (Yes) or not satisfied (No) (Paper II, III and V). Also, the percentage of satisfaction with the result was recorded on a 100-mm VAS, where “no satisfaction” was recorded “0” and “fully satisfied” as “100”. (Paper II).

Maximum voluntary grip strength was evaluated by using a hydraulic hand dynamometer (FEI Irvington, NY, USA). During the dynamometer-test, the arm was held in the horizontal plane, with the elbow straight, and the wrist in neutral position. Maximum grip strength was measured three times, and the highest value was used for statistical analysis (Paper I, II, III and V). In Paper I, pain-free grip strength was measured. The position was the same, but in this test the patients were supposed to grip until they felt a sensation of pain. The test was performed three times, and the mean value was used as outcome measure. Some patients managed to perform the test adequately, while others had large variations between the achieved attempts. This resulted in that this method was excluded as an outcome measure in the following papers.
**Ultrasound and Colour-Doppler**

All tendons were examined with high resolution grey scale-ultrasound (US) and colour Doppler (CD), Acuson Sequoia 512 (with 8-13 MHz frequency).

During the ultrasound examination the patient is seated with arm the resting on a bench (Figure 18). The elbow is in 70-80º of flexion, with the wrist pronated. The posture must be comfortable to avoid tension in the wrist and finger extensors. When the lateral epicondyle is identified, a generous amount of contact gel is placed on the skin over the CEO. The tendon is examined in transversal and longitudinal view to identify structural changes (hypoechoic regions and diffuse heterogeneity), and calcifications and bone spurs.

After the grey-scale US examination, there was CD examination of the CEO. It is important to have plenty of contact gel to minimise the pressure applied with the probe. To high pressure of the probe might cease the blood flow. The vessels are too small to be identified, and it is only the blood flow (movement of blood corpuscles) that is seen. There are no reliable methods to quantify the blood flow identified with CD. Therefore, we decided to characterise the flow as; present flow, or not present flow.

All US and CD examinations were performed by the same experienced radiologist.

![Image](image.png)

**Figure 18. Ultrasound and colour Doppler examination of the common extensor origin at the elbow.**
Ultrasound-guided injection

We used polidocanol (10mg/ml) or lidocaine hydrochloride (10mg/ml) with epinephrine (5µg/ml), as injectants. The sclerosing substance polidocanol is an aliphatic, non-ionised nitrogen free substance. Polidocanol has been widely used as a sclerosing agent in the treatment of varicose veins in the legs and oesophagus, haemorrhoids, and teleangectasis in the skin (Guex, 1993; Conrad et al., 1995). The action of polidocanol is a sclerosing effect by acting directly on the intimae layer in the vascular wall, or indirectly by compressive effects on vessels through tissue expansion. There is also a local anaesthetic effect. Lidocaine hydrochloride has a local anaesthetic effect, and was combined with epinephrine to provide a vasoconstrictive effect.

During injection, the patients are seated in the same position as during the US and CD examination. Before treatment, the skin is washed with a solution of chlorhexidine and alcohol. The injection is performed with a 0.7x50mm needle connected to a 2 ml syringe. The injection is performed dynamically, with the aid of real time grey-scale US- and CD-technique, to inject in the target region with high blood flow in the CEO. When the tip of the needle is positioned in the region with high blood flow, a small volume (0.5) ml is injected.

The doctor handles the probe and places the needle in position, while an assistant is injecting. Altogether, including washing and the US- and CD-guided injection, the procedure takes about 10-15 minutes. A bandage with minor pressure applied on the injected region, is used the first day.

After injection, the patients are informed to use their arm, but not to participate in heavy elbow loading activity the first 2 weeks. Thereafter, there are no restrictions for activities. The patients are also informed that there might be increased pain in the extensor origin during the first 2 weeks after injection.

In Paper III (RCT), we used two different substances for the injection treatment, polidocanol (10mg/ml) and lidocaine hydrochloride (10mg/ml) in combination with epinephrine (5µg/ml) (control group). It was important to use substances with the same instant effect to ensure that the treatment was blinded both to the operator and the patient. The equipment was the same for all treatments, and there were no visible differences in colour or density between the two different substances.

The patients were given one injection (Paper II and III), and if remaining pain and high blood flow in the extensor origin at the
3 months follow-up, an additional injection was given (Paper III).

There were no complications related to the treatment. Four patients in Paper II complained of stiffness and severe pain in the extensor origin after injection treatment. In Paper III; there were no complaints of stiffness, but two patients complained of increased pain during the week following the injection treatment.

Figure 19. The ultrasound- and colour Doppler-guided injection treatment procedure.
**Biopsies**

**Sampling**

The 12 biopsies from 11 patients with TE or golfer’s elbow were collected from the ECRB at the lateral epicondyle and the tendinous flexor muscle origin at the medial epicondyle, respectively. The operations were performed under regional intravenous anaesthesia (prilocaine, 5 mg/ml) (n=9), general anaesthesia (n=2), or local anaesthesia (lidocaine 10 mg/ml with epinephrine 5 µg/ml) (n=1). Using a tourniquet applied to the upper arm, the biopsy specimens were taken through a 6-cm-long skin incision. The tissue specimens, measuring approximately 5x8 mm, were taken by sharp detachment as close to the bone insertion as possible. The 6 biopsies from controls were taken, under local anaesthesia, from the superficial part of the CEO through a 2-cm-long skin incision.

**Tissue preparation**

Specimens from all three groups were treated by immersion overnight at 4°C in a solution of 4% formaldehyde in 0.1 M phosphate buffer, pH 7.0. The specimens were thereafter thoroughly washed in Tyrode’s solution, containing 10% sucrose, at 4°C overnight, mounted on thin cardboard in OCT embedding medium (Miles Laboratories, Naperville, IL), frozen in propane chilled with liquid nitrogen, and thereafter stored at –80°C until sectioning. Series of 7 µm thick sections of specimens from all groups were cut using a cryostat. The sections were mounted on slides pre-coated with chrome-alum gelatin. They were dried and then processed for immunohistochemistry or stained with hematoxylin-eosin for delineating tissue morphology.

**Immunofluorescence (TRITC and FITC) technique**

The sections were first pre-treated with acid potassium permanganate for 2 min, a procedure that was used to enhance specific immunofluorescence reactions (Hansson and Forsgren, 1995), and thereafter followed by rinsing three times for 5 min
each in phosphate-buffered saline (PBS). After incubation for 20 min in a 1% solution of detergent Triton X-100 (Kebo Lab, Stockholm) in 0.01 M PBS, pH 7.4, the sections were rinsed three times for 5 min each in PBS, and were thereafter incubated for 15 min at room temperature in either 5% normal swine serum (code: X0901; Dako, Denmark) in PBS supplemented with 0.1% bovine serum albumin (BSA) (staining for tyrosine hydroxylase, TH), or, in the case of staining for choline acetyltransferase, ChAT, 5% normal donkey serum (code: 017-000-121; Jackson ImmunoReserach, PA) in PBS. Then the sections were incubated with the primary antibody, diluted in PBS with BSA (TH) or in PBS without supplementary BSA (ChAT), in a humid environment. Incubation was performed for 60 min at 37°C. After another three 5 min washes in PBS, and incubation in normal serum as described above, the sections were incubated with secondary antibody for 30 min at 37°C. In the case of the sections stained for TH, the secondary antibody corresponded to tetramethylrhodamine isothiocyanate (TRITC)-conjugated swine antirabbit IgG (code: R0156; Dako, Denmark), diluted 1:40, whereas the sections stained for ChAT were incubated with secondary antibody corresponding to fluorescein isothiocyanate (FITC)-conjugated AffiniPure donkey antigoat IgG (code: 705-095-147; Jackson ImmunoReserach, PA), diluted 1:100. The sections were finally mounted in Vectashield microscopy mounting medium after a last 3 x 5 min wash in PBS.

**Antibodies**

The ChAT antibody (Chemicon) was raised against human placental ChAT. The antibody is reported by the supplier to be reactive with ChAT in a number of species. The antigen for the TH antibody is a SDS-denatured, purified recombinant rat and bovine TH. It is by the supplier reported to cross-react with all mammalian forms of TH tested to date.

**Microscopic examination and evaluation**

The evaluations were performed blinded, the investigators did not know which patients or controls the section belonged to when evaluating the tissue morphology and immunoreactions. Sections were examined under a Zeiss Axioskop 2 plus
microscope equipped with epifluorescence optics and an Olympus DP70 digital camera.

**Control staining**

For control purposes regarding the specificity of the TH antiserum, comparative stainings were performed on sections of rat adrenal medulla. Regarding the evaluation of ChAT-stainings, sections of fixed human colonic tissue were analysed in parallel. Also fixed patellar tendon tissue (tendinopathy patients), stained for both ChAT and TH, was examined simultaneously as a control for intracellular reactions in tenocytes.

**Statistical methods**

The SPSS package (version 14.0, SPSS Inc, Chicago, Ill, USA) was used for all statistical calculations. Non-parametric tests were used since the numbers of participants were relatively low. Differences between groups concerning continuous data were calculated with the Mann-Whitney U-test. When data was categorical, the Fisher’s exact test was used. Differences over time, within the groups, were calculated with Wilcoxon Signed Ranks Test. A p-value of <0.05 was considered statistically significant.

Power analysis was done before the RCT (Paper III), based on data from the pilot study (Paper II).
Ethics

All investigations were approved by the Ethical Committee of the Medical Faculty, Umeå University, Sweden and concerning the biopsies (Paper IV); an approval was also obtained from the local Committee on the Use of Human Subjects at Huddinge Hospital, Stockholm, Sweden. All participants were informed orally and written before consent.
Summary of papers

Paper I

Extensor origin vascularity related to pain in patients with tennis elbow

The aim of the study was to evaluate the grey-scale ultrasonography (US) and colour Doppler (CD) findings in the common extensor origin (CEO), in patients with tennis elbow (TE). In this investigation, US and CD was used to examine the CEO in 17 patients with the diagnosis TE in altogether 22 elbows, and in 11 controls with 22 pain-free elbows. During US examination, in all patients, but in no controls, there were structural changes (hypoechoic regions and diffuse heterogeneity). During CD examination, in 21/22 elbows with chronic pain from the CEO, but only in 2/22 pain-free elbows, high blood flow was demonstrated in the CEO. Theses findings indicate that the region with structural changes and high blood flow might be related to pain symptoms.
Figure 20 a-b. Longitudinal view of the common extensor origin in a pain-free individual. (a) Ultrasound showing a normal structure in the common extensor origin (b) Colour Doppler – no high blood flow could be demonstrated.
Figure 21 a-b. Patient clinically diagnosed to have tennis elbow. The common extensor origin shown in a longitudinal view. (a) Ultrasound showing irregular structure in the common extensor origin. (b) Colour Doppler showing high blood flow in the region.
**Paper II**

**Sclerosing polidocanol injections in chronic painful tennis elbow – promising results in a pilot study**

The aim of the study was to investigate whether treatment with US- and CD-guided injections of the sclerosing substance polidocanol, targeting the region with high blood flow in the CEO, would reduce the pain symptoms in patients with TE. In this pilot study, 11 patients (7 females and 4 males, mean age 46 years) with the diagnosis of TE in altogether 13 elbows were included. All patients had a long duration of pain symptoms (mean 23 months), and US and CD examination showed structural changes (hypoechoic regions and diffuse heterogeneity), and high blood flow corresponding to the painful region in the CEO. All patients were treated with one US- and CD-guided injection of the sclerosing substance polidocanol, targeting the region with high blood flow. At follow-up after 8 months, there were good clinical results in 11/13 elbows. Pain during gripping activities (recorded on a VAS-scale) was significantly reduced (VAS from 75 to 34; \( p<0.003 \)), and maximum grip strength measured with a hand dynamometer, was significantly increased (from 29 to 40 kg; \( p<0.025 \)). The results in this study indicate that one treatment with US- and CD-guided sclerosing polidocanol injection, targeting the region with high blood flow, has a potential to reduce pain and increase grip strength in patients with TE.
Figure 22a-b. Patient clinically diagnosed to have tennis elbow. The common extensor origin shown in a longitudinal view. (a) Findings on ultrasound and colour Doppler examination before injection treatment. High blood flow is shown. (b) Findings on ultrasound and colour Doppler examination after injection treatment. No remaining high blood flow is seen. Note the tip of the needle (arrow).
Paper III

Pain relief after intratendinuous injections in patients with tennis elbow: results of a randomised study

The aim of this study was to evaluate the effects of US- and CD-guided injections of the sclerosing polidocanol and the local anaesthetic lidocaine with epinephrine, targeting the region with high blood flow, in patients with TE. The hypothesis was that sclerosing polidocanol, but not lidocaine with epinephrine, would affect pain and grip strength. In this RCT study, 32 patients (36 elbows), with a mean age of 46 years (range 27 to 66 years), and a long duration of elbow pain diagnosed as TE, were included. Two patients were excluded due to other interventions during the study period. The patients were randomly selected to treatment with sclerosing polidocanol or lidocaine with epinephrine. All patients were followed up with clinical examination and tests 3 and 12 months after treatment.

At the 3 month follow-up, there were no differences in the results between the group that was treated with sclerosing polidocanol injections and the group treated with the local anaesthetic lidocaine with epinephrine. The patients in both groups were equally satisfied with the results of treatment, 9/18 and 10/16, respectively, and there were no significant differences in pain (VAS) during daily activity and grip strength. After 3 months, all patients with remaining symptoms were offered an US- and CD-guided polidocanol injection (cross-over for the lidocaine with epinephrine-group). In all patients, at follow-up after 12 months, pain had decreased significantly and grip strength had increased significantly, and 27/34 patients were satisfied with the effect of treatment. The conclusions were that US- and CD-guided intratendinious injections gave pain relief in patients with TE, and polidocanol and lidocaine with epinephrine gave similar results.
Table 2. Outcome in Group I and Group II. Pain during tendon loading activity was recorded on a 100 mm long visual analogue scale (VAS). Maximum grip strength (kg) was measured with a hand dynamometer.

**Paper IV**

**Immunohistochemical evidence of a local production of catecholamines in cells of the tendinous muscle origin tissue at the lateral and medial humeral epicondyles – of importance for development of tennis and golfer’s elbow?**

The aim of this study was to find out whether catecholamines and/or acetylcholine (ACh) is produced by the cells (fibroblasts) in the common extensor origin in patients with TE. Using immunohistochemistry, there was presence of tyrosine hydroxylase (TH) in the fibroblasts of tissue samples from 4/7 TE patients, but in 0/6 of the controls. No reactions were seen for the ACh synthesising enzyme choline acetyltransferase (ChAT). As a reference, the tendinous muscle origin tissue at the medial humeral epicondyle in patients with golfer’s elbow was also studied. The results were the same as for TE. Altogether the results show evidence of a local, non-neural production of catecholamines, but not ACh, in the fibroblasts of the CEO in patients with TE, and in the flexor origin in patients with golfer’s elbow.
Paper V

A 2-year sonographic follow-up after intratendinous injection therapy in patients with tennis elbow

The aim of the study was to use US and CD examination to study the structure and blood flow in the CEO 2 years after intratendinous injection treatment for TE. In this follow-up study, all 30 patients (34 elbows), who were included in the RCT (Paper III), were asked to participate in a 2 year follow-up. Of these 30 patients (34 elbows), 25 patients (28 elbows) were included; two patients did not show up and were considered as drop outs (3 elbows), and three patients (3 elbows) were excluded due to other interventions (surgery, one by tendon lengthening and two by decompression). In the sonographic follow-up 2 years after injection treatment with polidocanol and/or lidocaine and epinephrine into the CEO, structural changes were seen in 20/28 elbows, and high blood flow in 4/28 elbows. At baseline, all patients had structural changes and high blood flow in the CEO. A majority of the satisfied patients with a good clinical result after treatment had no visible blood flow (17/20), but there were remaining structural changes in 13/20. Bone spurs were seen in 20/28 elbows, compared to 7/28 two years earlier. The conclusions from this study were that Doppler findings, but not structure, might be related to the clinical results after intratendinous injection treatment of TE.
Discussion

In this thesis, the general findings in patients with Tennis elbow (TE) were the combination of structural changes (hypoechoic regions and diffuse heterogeneity) and high blood flow in the common extensor origin (CEO) (Paper I-III and V). This is in line with the findings in studies evaluating other tendinopathies, like in Achilles and patellar tendinopathy (Öhberg et al., 2001; Gisslen and Alfredson, 2005; Lind et al., 2006). In the studies in this thesis, there was high blood flow in all patients having the clinical diagnosis TE. This is not in accordance with a recently published paper where the authors found high blood flow in 81 per cent of the patients clinically diagnosed to have TE (du Toit et al., 2008). This difference might possibly be related to that the ultrasound (US) and colour Doppler (CD) examinations in our studies were performed directly after painful clinical examination and provocative tests. In the study by du Toit et al. (2008), there was a time delay between the clinical examination and the US- and CD-examination. Hypothetically, if the CEO not is provoked by painful examination or tendon loading activity, i.e. pain free, the blood flow would possibly be less high and more difficult to detect by CD examination. US and CD examination were found to be useful methods not only to investigate the CEO in patients with the clinical diagnosis TE, but also to guide injection treatment of TE (Paper II-III). However, there are some limitations using US and CD examinations. One limitation is that this technique is highly operator dependent, the assessments are subjective. For US examinations, the intraobserver reliability is high, but the interreader reliability is lower (Levin et al., 2005). Therefore, in this thesis all US and CD examinations were performed by the same experienced radiologist, having 25 years experience using ultrasound. We used CD examinations to evaluate the blood flow. There is a difference between CD and power Doppler (PD). The CD technique visualises both the velocity and the direction of the blood flow (Omoto et al. 1984), while PD is a somewhat more sensitive method to study the blood flow, but does not visualise the directions of the flow (McDicken et al., 1992). Both methods are very sensitive to show blood flow in small vessels. Positioning and pressure on the probe will affect the findings. Using to high pressure on the probe will decrease the blood flow (Khoury and Cardinal, 2008).
The Doppler examination is also depending on the patient, if there is high tension in the wrist extensors, due to muscle contraction or by palmar flexion of the wrist, the blood flow is affected (decreased). Consequently, it is important to use a standardised examination technique. Another limitation is that there is no reliable method to quantify the blood flow when using Doppler examinations. Different methods to try to quantify blood flow shown with CD or PD have been used in other studies (Cook et al., 2005b; Connell et al., 2006; de Vos et al., 2007; Pfirrmann et al., 2008), but due to the limitations, we decided to characterise the blood flow as present, or not present.

In the 2 year follow-up study of patients treated with intratendinous injections of polidocanol and/or lidocaine with epinephrine (Paper V), a majority of the satisfied patients had remaining structural changes, but no remaining high blood flow, in the CEO. Considering the structure, this is in contrast to Croisier et al. (2007), who found a normalised structure shortly after treatment with eccentric training, but in line with a study by Connell et al. (2006), who showed remaining structural changes 6 months after US-guided intratendinous autologous blood injections. Interestingly, from another tendon (mid-portion Achilles), an improved tendon structure was shown at a 2-year follow-up after treatment with sclerosing polidocanol injections outside the ventral tendon (Lind et al., 2006). From these studies, it seems that intratendinous treatments are associated with remaining structural changes, while extratendinous treatments are associated with improved tendon structure. Considering the relative absence of pain in the satisfied patients this indicates that the high blood flow, not the structural changes, in some way is associated with the pain mechanisms in TE. Thus, the region with high blood flow seen on CD examination is probably where the pain is elicited in tennis elbow. Similar findings, no remaining high blood flow in pain-free tendons, but remaining high blood flow in painful tendons, have been shown also in follow-ups of patients successfully treated for mid-portion Achilles tendinopathy (Öhberg and Alfredson, 2004; Lind et al., 2006).

Paper II and III showed good clinical results with US- and CD-guided injections targeting the region with high blood flow in the CEO. Interestingly, not only the active substance polidocanol (Paper II and III), but also the substance that was believed to be non-active (lidocaine with epinephrine) (Paper III), was shown to give good clinical results. This raises the question whether it is the substance itself that is of importance, or whether it is the
positioning of the injection (US- and CD-guided targeting of the region with high blood flow)? Other authors have used US-guided targeting of the region with structural changes, with autologous blood as injectant, having similar good clinical results (Connell et al., 2006). Interestingly, already in 1954 Freeland and Gribble, from a small study material, comparing non-guided injections of corticosteroids and a local anaesthetic (no epinephrine), concluded that it is most likely not the substances, but instead the positioning of the substance that is of importance. On the other hand, Day et al. (1978) found non-guided corticosteroid injections superior to a local anaesthetic (no epinephrine). Though in this study the majority of the patients had had symptom duration of less than 3 months, while all the patients in Paper II and III had had symptoms for longer than 3 months.

Other substances used for local injection treatment, non US- and CD-guided targeting of the most tender point, are corticosteroids, platelet rich plasma (PRP) and prolotherapy (Smidt et al., 2002a, b; Mishra and Pavelko, 2006; Scarpone et al. 2008). Corticosteroids are probably the most commonly injected substance, though the clinical results are varying, and mainly short-term results (less then 6 weeks) have been presented (Bisset et al., 2006).

The study design in the RCT (Paper III) included a cross-over for the control group after 3 months, receiving polidocanol instead of lidocaine with epinephrine. This was done because the local anaesthetic was not expected to have more than a temporary effect. With the final study results in mind, similar results in the groups, this cross-over design can be questioned.

We chose the VAS, as the main outcome measure, for evaluating pain in the CEO during daily activities. VAS is known to be a reliable instrument to score differences in pain over time (Bijur et al., 2001; Williamson and Hoggart, 2005). Still, it has its restrictions, since the scoring needs to be related to the same level of activity each time. Less pain often leads to an increased activity level that sometimes induces more pain. This might be the reason to why female patients often have a higher VAS; they have less grip strength and reach their maximum grip strength more often during daily activity? However, in our studies this did not affect the statistical analysis since we have calculated by paired samples. Grip strength was also used as an outcome measure. Grip strength is considered to be the best objective outcome measure to evaluate the effects of treatment for tennis elbow (De Smet et al., 1998). Grip strength was measured with
extended elbow, because it seems logical to perform the test in the position that is most painful (Dorf et al., 2007). When the elbow is straight, there is an impingement of the CEO between the lateral epicondyle and the radial head, causing pain (Mullett et al., 2005).

Figure 23a-b. Patient clinically diagnosed to have tennis elbow. The common extensor origin shown in a longitudinal view. Elbow flexed 70-80°. (a) Ultrasound shows structural changes in the common extensor origin. Note the distance between lateral epicondyle (LE) and the radial head (RH) (b) Colour Doppler shows high blood flow in the region with structural changes.
Figure 24a-b. The same patient as in figure 23. Elbow straight. (a) Note the narrow space (impingement of the common extensor origin) between the lateral epicondyle (LE) and radial head (RH). (b) Colour Doppler shows no high blood flow in the region with structural changes.

In Paper IV, it was shown that there is a local production of catecholamines, but not acetylcholine, in non-neural tendon cells, in biopsies from patients with TE. These biopsies were taken from the region with high blood flow in the structurally changed CEO. The findings of a local production of catecholamines in tendon cells correspond to resent findings in painful Achilles and patellar tendon tissue (Danielson et al., 2007a, b; Bjur et al., 2008a). However, in contrast to the findings in these painful tendons, it was not possible to show a local production of acetylcholine in the CEO. Already in previous studies by Ljung et al. (1999a, b), sympathetic and sensory nerves were found in association with blood vessels in the ECRB origin. Altogether, the results indicate evidence that the source of pain in TE is the region with high blood flow, and the CD examinations can therefore possibly be used as a “visual marker”. The pain mechanism has still to be clarified, and the
role of the sympathetic and sensory nerves needs to be understood. Catecholamines have been suggested to modulate pain (Baron et al., 1999) and the production of catecholamines, but not acetylcholine, in TE, indicates a possible interference with blood vessel regulation and pain sensation. An interesting observation was that in patients with TE there seems to be a formation of bone spurs over time, so called “lateral epicondyle enthesophytes” (Paper V). It is tempting to believe that this is a consequence of bone remodelling due to increased stress from overload. At later stages of TE, when the patients still experience some pain, but not in the extent that they have positive clinical signs and need further treatment, the bone spur in itself may be the source of pain, rather the forces applied to the CEO?

Figure 25. Patient clinically diagnosed to have unilateral TE. Longitudinal ultrasound-view of the common extensor origin on both sides two year after treatment, note the bone spur (arrow) on the affected side (left).
Conclusions

- Using ultrasound (US) and colour Doppler (CD) examination, structural changes and high blood flow were seen in the common extensor origin (CEO) in the majority of patients with tennis elbow.

- One US- and CD-guided injection treatment with the sclerosing substance polidocanol decreased the pain and increased the grip strength in patients with tennis elbow.

- There was no difference in the clinical results between injection treatment with sclerosing polidocanol and the local anaesthetic lidocaine with epinephrine.

- Two years after successful treatment, the structural changes, but not the high blood flow, in the common extensor origin, remained. There was a formation of bone spurs on the lateral epicondyle over time.

- A local production of sympathetic catecholamines was found in the tendon cells in the common extensor origin.
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Tennisarmbåge – fynd vid ultraljudsundersökning och intratendinös injektionsbehandling


Studierna i denna avhandling syftade till 1) att med ultraljud (US) och färdgoppler (CD) utvärdera strukturen och blodflödet i CEO hos patienter med tennisarmbåge, samt hos kontroller, 2) att utvärdera den kliniska effekten av US-och CD-vägledd injektionsbehandling med det skleroserande ämnet polidokanol, 3) att med US och CD utvärdera strukturen och blodflödet i CEO 2 år efter injektionsbehandling och 4) att undersöka om det föreligger en lokal produktion av sympatiska och/eller parasymptatiska signalsubstanser i CEO.


I detta avhandlingsarbete visar resultaten att ultraljud- och färdgopplerundersökning kan bidra vid diagnostiken av tennisarmbåge, och att utvärdera behandlingsresultat. Ultraljud- och färdgopplervägledd injektionsbehandling riktad mot område med högt blodflöde i det strukturellt förändrade
extensorursprunget kan minska smärtsyntomen och öka greppstyrkan vid tennisarmbåge. Det ökade blodflödet och den lokala produktionen av katekolaminer i celler i det gemensamma extensorursprunget kan möjligen ha betydelse för smärtmekanismen.
References


Eva Zeisig

Tennis elbow


