Methods in Diagnosing Chronic Anterior Compartment Syndrome

A Clinical Study in Patients with Exercise-Induced Leg Pain

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"Running is a big question mark that's there each and every day. It asks you, 'Are you going to be a wimp or are you going to be strong today?"

Peter Maher, Irish-Canadian Olympian marathoner and credited for a brief period with the world record time for 25km.

CONTENTS

ABSTRACT

Chronic anterior compartment syndrome (CACS) is a painful condition within one or more muscle compartment(s) in the lower leg. It impedes blood flow and muscular function due to elevated intramuscular pressure. The majority of patients who suffer from CACS are actively involved in sports. CACS can, however, also be present in persons with low activity levels. The diagnostic criteria are the subject of debate. At present, the measurement of intramuscular pressure (IMP) is the accepted method for establishing the diagnosis. The limitation is that it is invasive.This thesis evaluates the ability of near-infrared spectroscopy (NIRS), using three different devices, to diagnose CACS by monitoring changes in muscular oxygen saturation during rest and exercise. The aspect of experimentally induced hyperaemia was also analysed by NIRS. In addition, a new method, i.e. patient pain drawing (PPD), was assessed to support the diagnosis of CACS.

One hundred and seventy-six patients were included in Study I, 73 men and 103 women; median age 32 (range 14-76) years. One hundred and fifty-nine patients and 31 healthy subjects were included in Study III. The patient group consisted of 76 men and 83 women, median age 29 (range 14-67) years, and a control group of 14 men and 17 women, age 36 (range 20-60) years. Studies I and III utilised two different NIRS devices (Run-Man and InSpectra) to measure oxygen saturation in the tibialis anterior muscle during and after exercise that elicits patient's symptoms. The use of NIRS as a method for diagnosing CACS, by analysing the changes in muscular oxygen saturation during and after exercise, was evaluated. Twenty healthy subjects (10 women and 10 men), median age 43 (range 34-60) years, were recruited for Study II. Two NIRS devices (InSpectra and INVOS) were used to measure muscle oxygen saturation in healthy human skeletal muscle of the lower leg. The capability of the two NIRS devices to detect experimentally induced skeletal muscle ischaemia in the leg was compared. The influence on the measurement of the lower leg subcutaneous tissue thickness was further assessed. Study IV comprised 477 consecutive patients with exercise-induced leg pain, 258 men and 219 women; median age 31 (range 15-70) years. The study determined the sensitivity, specificity and predictive value of patient pain drawing (PPD) in identifying CACS patients. Intra-observer agreement was assessed.

In Studies I and III, the magnitude of intramuscular deoxygenation was shown to be a non-reliable method for diagnosing CACS. In Study I, the mean level of oxygenation (relative values) decreased to 33% (SD19) in patients with CACS and to 34% (SD19) in patients without CACS (p=0.107). In Study III, the deoxygenation at peak exercise was 1% in the CACS patients and 3% in the non-CACS patients (p=0.003). In Study II, both devices were able to detect experimentally induced skeletal muscle ischaemia in the leg. Moreover, the INVOS device was shown to be less affected by the skin and subcutaneous tissue thickness than the InSpectra device. Study IV showed that PPD can be used to support the diagnosis of CACS. The sensitivity of PPD to identify CACS ranged between 67-75%, specificity 54-65%, positive predictive value 47-51% and negative predictive value 78-80%. When assessing the agreement between the PPD and the gold standard, the correct diagnoses were established in 79% (Observer 1) and 82% (Observer 2) of the CACS patients (n=79).

Patients with CACS cannot be distinguished from patients with other causes of exercise-induced leg pain using NIRS during an exercise test and at rest after an exercise test. The NIRS device, INVOS, is able to detect experimentally induced skeletal muscle ischaemia in the human leg. Muscle oxygen saturation measurements using the INVOS are less affected by the skin and subcutaneous tissue thickness than those made by the InSpectra. NIRS may be useful in detecting leg muscle ischaemia in clinical situations with reduced blood circulation. PPD is useful to support the diagnosis of CACS.

Keywords: exercise induced leg pain, chronic compartment syndrome, muscle oxygen saturation

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SAMMANFATTNING PÅ SVENSKA

Kroniskt kompartment syndrom är ett tillstånd där ett ökat intramuskulärt tryck ger smärta vid ansträngning av muskulaturen i den aktuella muskellogen. Vanligtvis är det underbenets främre muskelloge som drabbas. Blodflödet och därmed den muskulära funktionen hindras pga. det förhöjda intramuskulära trycket och samtidigt upplever patienten smärta och ofta en känsla av att ”muskeln inte får plats”. Majoriteten av de drabbade är idrottsmän/kvinnor, men även personer med lägre aktivitets nivå kan drabbas. Diagnoskriterierna är omdebatterade, och dagens ”gyllene standard” är invasiv tryckmätning i den drabbade muskellogen efter ett arbetstest, som utlöser smärtan. Intramuskulär tryckmätning är en accepterad metod, men med begränsningen att den är invasiv, vilket innebär en viss smärta och obehag för patienten vid genomförandet av undersökningen. Intramuskulärt tryck, som överstiger 30 mmHg en minut efter ansträngning anses vara diagnostiskt för kroniskt kompartment syndrom.

Denna avhandling utvärderar förmågan av nära infraröd spektroskopi (NIRS) för att ställa diagnosen kroniskt kompartment syndrom. Tre olika NIRS-utrustningar har använts i dessa arbeten. Experimentellt inducerad ischemi analyserades också med NIRS. Utöver detta analyserades smärtritning, med avsikten att användas som tillägg vid diagnostisering av kompartment syndrom.

Avhandlingen omfattar 4 delarbeten. I delarbete I och III undersöktes patienter (delarbete I; 176 patienter, och i delarbete III; 159 patienter) med ansträngningsutlöst underbenssmärta. Patienterna genomgick klinisk undersökning, arbetstest och intramuskulär tryckmätning. Under och efter arbetstestet mättes förändring av syremättnad i muskelvävnaden med NIRS. Tidigare studier har visat att patienter med kroniskt kompartment syndrom har lägre syremättnad i muskulaturen under arbete jämfört med patienter med andra underbensbesvär av annan orsak, och även jämfört med friska individer. Därför har NIRS föreslagits som en användbar diagnostisk metod vid utredning av patienter med misstänkt kroniskt kompartment syndrom. Studie II var en experimentell studie som utfördes på 20 friska försökspersoner. Två olika NIRS-utrustningar jämfördes; InSpectra och INVOS. InSpectra utrustningen är väl beprövad i avseende att mäta syremättnad i muskulatur, medan INVOS framför allt används för att mäta syremättnad i hjärnan under hjärt-kirurgiska ingrepp. Under dessa ingrepp finns ibland ett behov av att mäta syremättnaden i muskulatur då man vid långa ingrepp löper en risk att utveckla akut kompartment syndrom i benen. I det fjärde arbetet utvärderades en i dessa sammanhang ny metod, smärtritning. Metoden är sedan länge känd och använd på patienter med ryggbesvär men ej utvärderad vid underbensbesvär.

Delarbete I och III visade ingen skillnad avseende nedgången i syremättnad i muskulaturen under arbetstestet mellan patienter med kroniskt kompartment syndrom och patienter med annan överbelastningsskada/annan orsak till smärtsyndrom i underbenen under arbetstestet. NIRS mätning under arbete kunde inte heller skilja friska försökspersoner från patienter med kroniskt kompartment syndrom. I vila efter arbetstest var dock återhämtningen förlängd hos patienter med kroniskt kompartment syndrom jämfört med övriga patienter i delarbete I, dock påvisades ingen sådan skillnad i delarbete III.

I delarbete II fann man att INVOS kan användas för att påvisa nedsatt syremättnad i muskulatur och att tjockleken på fettvävnad påverkar NIRS då endast en begränsad sträcka ned i vävnaden kan mätas. InSpectra visade sig vara mer känslig för ett tjockare fettlager jämfört med INVOS.

Delarbete IV visade att sensitiviteten avseende diagnostisering av kroniskt kompartment syndrom med smärtritning är endast 67-75% (två observatörer), men som en kompletterande undersökning kan smärtritning vara värdefull. Samsjukligheten (avseende underbensdiagnoser) hos patienter med kroniskt kompartmentsyndrom visade sig vare 53%.

Resultaten av studierna visar att NIRS är en olämplig metod för att ställa diagnosen kroniskt kompartment syndrom. Delarbete II visade att INVOS, som används för monitorering av syremättnad i hjärna också kan användas för monitorering av syremättnad i muskulatur. Delarbete IV visade att smärtritning hos patienter med ansträngningsutlöst underbenssmärta är ett bra och användbart komplement vid diagnostisering av kroniskt kompartment syndrom. Delarbete IV visar också att det finns en hög samsjuklighet bland patienter med underbenssmärta, där mer än varannan patient med kroniskt kompartment syndrom har ytterligare en diagnos så som t.ex. benhinneinflammation, muskelruptur eller nervinklämning.

LIST OF PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. Zhang Q, Rennerfelt K, Styf J

The magnitude of intramuscular deoxygenation during exercise is an unreliable method to diagnose the cause of leg pain.

Scand J Med Sci Sports. 2012;22(5):690-694.

II. Nygren A, Rennerfelt K, Zhang Q

Detection of changes in muscle oxygen saturation in human leg: a comparison of two near-infrared spectroscopy devices.

J Clin Monit Comput. 2014:28 (1):57-62.

III. Rennerfelt K, Zhang Q, Karlsson J, Styf J

Changes in muscle oxygen saturation have low sensitivity in diagnosing chronic anterior compartment syndrome of the leg.

Conditionally accepted, J Bone Joint Surg

IV. Rennerfelt K, Zhang Q, Karlsson J, Styf J

Patient Pain Drawing is a valuable instrument to assess the causes of exercise-induced leg pain.

Manuscript

ABBREVIATIONS

BMI	Body mass index
CACS	Chronic anterior compartment syndrome
non-CACS	Patients with other causes of exercise induced leg pain than CACS
EMG	Electromyography
CCS	Chronic compartment syndrome
non-CCS	Patients with other causes of leg pain than CCS
IMP	Intramuscular pressure
MAP	Mean arterial pressure
MRI	Magnetic resonance imaging
NIRS	Near-infrared spectroscopy
PP	Perfusion pressure
PPD	Patient pain drawing
VAS	Visual analogue scale
StO_2	Oxygen saturation

DEFINITIONS IN SHORT

From the curves showing StO_2 during measurements with NIRS the following expressions are used;

Baseline StO_2	Local muscle oxygen saturation (StO_2) before exercise
Peak exercise StO_2	The lowest level of StO_2 at highest effort
Ending exercise StO_2 (%)	The level of StO_2 at end of exercise
T_{50} (sec)	The time in seconds for StO_2 recovery by 50% of the exercise induced fall
T_{90} (sec)	The time in seconds for StO_2 recovery by 90% of the exercise induced fall
T_{100} (sec)	The time in seconds for StO_2 recovery by 100% of the exercise induced fall
Maximum recovery StO_2 (%)	The maximum level of StO_2 during recovery
R90 (sec)	Was defined as the time required for the level of oxygenation to rise from 10% to 90% of its baseline value after exercise
R100 (sec)	Was defined as the time required for oxygenation to reach its baseline value after cessation of exercise

introduction

Compartment syndrome is defined as a condition in which elevated intramuscular pressure compromises local blood flow and impairs function of the muscle tissue within a closed compartment (Matsen 3rd and Krugmire Jr 1978). Compartment syndromes are traditionally divided into an acute and a chronic form.

The acute form occurs after a traumatic injury that induces a rapid irreversible pressure increase within a specific muscle compartment. The acute compartment syndrome is a medical emergency and might require immediate surgical intervention. Chronic compartment syndrome is a recurrent, exercised-induced condition in which intramuscular pressure increases to extreme levels during exercise and it impedes local muscle blood flow and the neuromuscular function in the affected tissue. Chronic compartment syndrome usually occurs in athletes who participate in running or repetitive impact sports (Reneman 1975, Allen and Barnes 1986). The chronic compartment syndrome is a reversible form of abnormally increased intramuscular pressure during exercise. If the patient stops exercising, the symptoms will reverse.

In 1956, Mavor wrote a case report in which he described a professional football player who experienced exercise-induced leg pain. The football player was cured by fasciotomy (Mavor 1956). Patients with chronic compartment syndrome are free from symptoms during rest (Styf and Korner 1987, Styf 1989, Padhiar and King 1996, Ota et al. 1999, van den Brand et al. 2004). In patients with therapy-resistant leg pain, approximately 30% suffer from chronic compartment syndrome and it should be borne in mind that co-morbidity, such as medial tibial syndrome, peroneal tunnel syndrome and muscular rupture, is common in this group of patients (Styf 1988).

This thesis focuses on chronic anterior compartment syndrome (CACS) and how to establish the diagnosis. However, knowledge of the pathophysiology of acute compartment syndrome makes it easier to understand the development of elevated IMP in chronic compartment syndrome, the clinical presentation and the evaluation of the different diagnostic methods available.

ANATOMY

Knowledge of lower-leg anatomy provides an important base in the understanding of patients with exercise-induced leg pain.

The definition of compartment anatomy is not without its contradictions. Some researchers claim that there are five compartments in the lower leg, with the tibialis posterior muscle in a separate compartment (Davey et al. 1984). However, the most established definition is four compartments and this definition has been used in the present thesis (Figure 1).

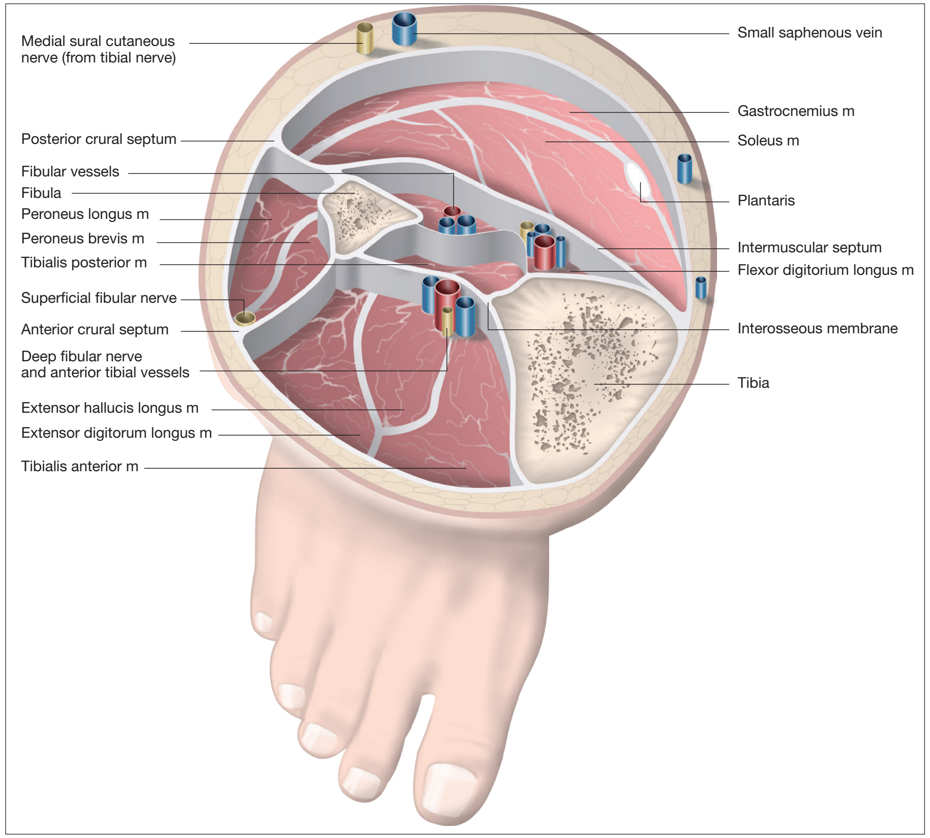


Figure 1. *Cross-section of the distal part of the lower leg illustrating the muscular compartments with vessels.*

Muscles

There are four compartments of the leg. The anterior compartment contains the following muscles; tibialis anterior, extensor digitorum longus, extensor hallucis longus and peroneus tertius. The lateral compartment contains the peroneus longus and brevis muscles.

The deep posterior compartment most commonly contains the tibialis posterior, flexor digitorum longus, flexor hallucis longus and popliteus muscles. Anatomical variations may, however, exist and the tibialis posterior muscle may be located in a separate compartment, as mentioned above. The superficial posterior compartment contains the gastrocnemius, soleus and plantaris muscles.

Arteries

The popliteal artery supplies the blood flow to the lower leg. After its exit from the popliteal fossa, an anterior branch (the anterior tibial artery) leaves medially towards the head of the fibula.

The anterior tibial artery (Figure 2) supplies the anterior compartment and the ankle region and it then continues as the dorsalis pedis artery to the dorsum of the foot.

Dorsally, after branching off the anterior tibial artery, the popliteal artery divides into the posterior tibial and peroneal arteries. The posterior tibial artery supplies the muscles of the deep posterior compartment and runs close to the tibial nerve posteriorly, down to the medial malleolus and further to the plantar region of the foot. In the plantar region, the posterior tibial artery branches into the medial and lateral plantar arteries. The peroneal artery supplies muscles of the lateral compartment and soleus muscle and gives rise to the calcaneal network.

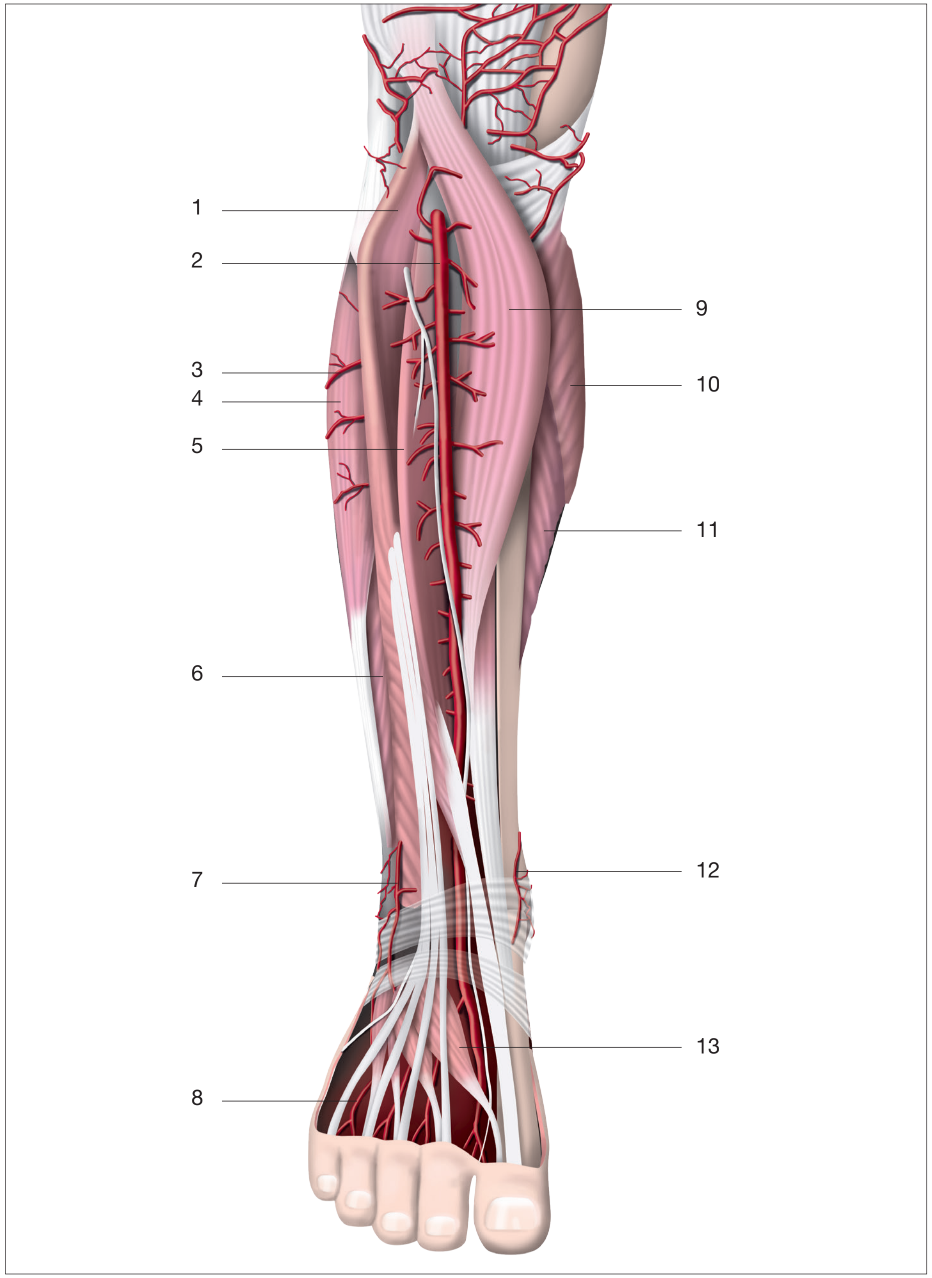


Figure 2. *Arteries and muscles in a frontal view of the leg. 1. Extensor digitorum longus muscle 2. Anterior tibial artery 3. Perforating branch of the peroneal artery 4. Peroneus longus muscle 5. Extensor hallucis longus muscle 6. Peroneus brevis muscle 7. Peroneus tertius muscle 8. Dorsal metatarsal arteries 9. Tibialis anterior muscle 10. Gastrocnemius muscle 11. Soleus muscle 12. Medial malleolar artery 13. Extensor digitorum brevis*

Nerves

Branches of the tibial nerve innervate the lower leg. The muscles of the anterior compartment are innervated by the deep peroneal nerve, the lateral compartment is innervated by the superficial peroneal nerve and the muscles within the two posterior compartments are innervated by the posterior tibial nerve. The superficial peroneal nerve runs in the anterior inter-muscular septum, between the anterior and lateral compartments, and enters through the crural fascia, after which it runs subcutaneously. It exits the fascia approximately 10 cm proximal to the lateral malleolus.

Veins

The anterior tibial vein partially drains the tissue of the foot; the foot is also drained into the superficial veins. The posterior tibial and fibular veins drain the medial and plantar veins. Posteriorly at the medial malleolus, the posterior tibial vein accompanies the posterior tibial artery. Posteriorly at knee level, the anterior tibial vein, posterior tibial vein and fibular veins unite and form the popliteal vein. The great saphenous vein drains the major part of the dorsum of the foot, entering the leg anterior to the medial malleolus and running subcutaneously in a proximal direction while merging with superficial veins along its path. Laterally, dorsal to the lateral malleolus, the small saphenous vein drains the lateral aspect of the foot, running subcutaneously on the posterior aspect of the calf.

MUSCULAR CIRCULATION

Haemodynamics in resting conditions

In resting conditions, skeletal muscle consumes only a small amount of oxygen. The blood flow is approximately 5-10 ml/min/100g. Compared with other organs, the blood flow in the skeletal muscle is much lower. For instance, brain tissue has a resting blood flow of 60-100 ml/min/100g (Korthuis 2011).

Haemodynamics during exercise

In trained individuals, the capacity to increase the blood flow during exercise is high. During high muscular activity, the blood flow can increase up to 80-100 ml/min/100g in order to supply the necessary oxygen. As the demand for oxygen increases, the vasodilation and the constricted vessels open to match the increased oxygen demands.

Hyperaemia (reactive and functional)

Following the occlusion of the arterial blood flow (either partly or completely), the blood flow at reperfusion re-establishes the haemodynamics. Reperfusion initially causes hyperaemia. This kind of hyperaemia is called reactive hyperaemia (Granger et al. 1976). The magnitude of the hyperaemia is proportional to the extent of reduced blood flow and the time of the reduction in blood flow. After maximum vasodilation is reached, the return to a normal blood flow is re-established.

Functional hyperaemia occurs after heavy muscle activity and can, at least partly, be explained by vasodilator metabolites that are released from the active muscle cells and contribute to the vasodilation (Björnberg et al. 1989, Korthuis 2011).

ACUTE COMPARTMENT SYNDROME

Pathophysiology

Acute compartment syndrome is a condition in which increased pressure within a closed space contributes to a reduction in oxygen perfusion and decreased blood flow. It can be due to arterial obstruction, after arterial clamping during surgery, affected venous flow or external pressure, for example. When the arterial blood flow (Figure 3) is affected by occlusion or prolonged external compression, the endothelial cells in the capillary membranes become damaged, which results in increased permeability. Ischaemia leads to an inflammatory reaction by triggering the immune system (Rodrigues and Granger 2010).

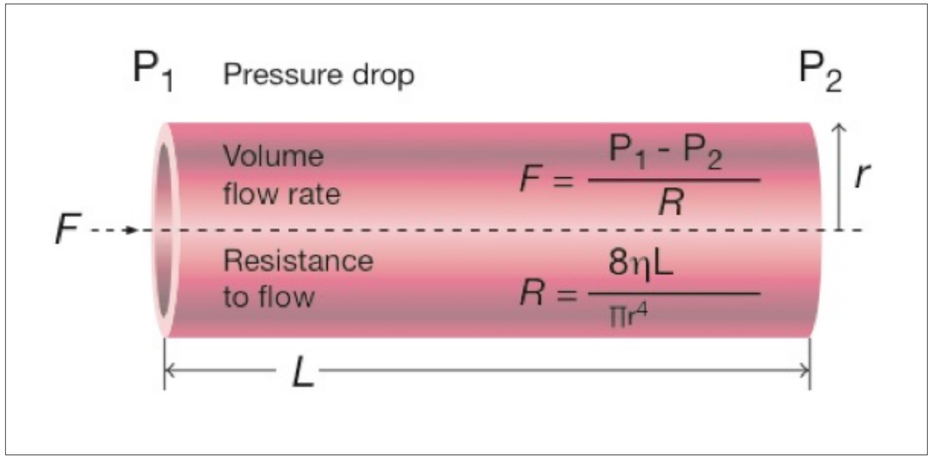


Figure 3. *The arterial flow rate is explained by the Poiseuille's Law. Volume flow rate is given by the pressure difference divided by the resistance. The impact on one aspect influences the other factors. F=Volume flow rate, P=pressure, R=Resistance to flow, η=viscosity, L=length, π=constant 3.14, r=radius.*

External pressure due to subcutaneous oedema or a tight dressing may contribute to an increase in intramuscular pressure (IMP), initially caused by compressed venous flow. In the case of trauma, damaged tissue requires a perfusion pressure exceeding 40 mmHg to meet the metabolic demands, whereas

healthy tissue requires less and needs perfusion pressure exceeding 30 mmHg (Heppenstall et al. 1988). The relationship between mean arterial pressure (MAP) and IMP is important to consider in the assessment in a situation with increased IMP and suspected acute compartment syndrome.

Mechanisms of trauma to the lower leg

Blunt trauma to the lower leg can contribute to soft-tissue bleeding, swelling and subsequent compartment syndrome (Matava et al. 1994). Fractures, especially closed tibial fractures, may contribute to acute compartment syndrome. External pressure during an extended period of unconsciousness, e.g. related to drug abuse, can induce crush syndrome. Of applied external pressure, 50-100% is transmitted into deep tissue (Brace and Guyton 1977). Moreover, massive tissue damage can occur in relation to burn injuries and this can subsequently lead to acute compartment syndrome.

Crush syndrome

Originally, crush syndrome was described after the earthquake in Messina, Sicily, in 1909 (Better 1997). Crush syndrome occurs after a high-energy trauma that results in major injuries to soft tissue and bone.

When rabdomyolysis occurs, toxic metabolites leak into the systematic circulation and eventually contribute to a life-threatening condition. Acute renal failure is caused by myoglobin precipitating the distal convoluted tubuli of the kidneys (Vanholder et al. 2000). At reperfusion, metabolites are washed out into the circulation. Leukocytes migrate to the damaged tissue only after reperfusion due to the need for oxygen. The production of free radicals begins when oxygen is available. Myoglobin, potassium, calcium and phosphorus leak into the vascular system and can contribute to renal failure, cardiac arrhythmias and even seizures. The hypoxic muscles produce lactic acid that is eliminated by the liver. Failure of this function due to hypovolemia will give rise to metabolic acidosis (Vanholder et al. 2000). Traumatic rabdomyolysis may also be caused by hyperthermia and electrical insults (Vanholder et al. 2000).

Symptoms and signs

The patient experiences severe pain and swelling of the affected body part. The most important patient-reported symptom is pain upon passive motion. If the lower leg is affected, passive motion of the ankle and increasing pain at rest are clinical signs. Paraesthesia and impaired circulation and, finally, pulselessness are late signs. Establishing the diagnosis of acute compartment syndrome based on clinical findings alone is not advisable (Elliott and Johnstone 2003).

Diagnosis

Monitoring IMP as a matter of routine is suggested in young patients or in those who are unconscious (Elliott and Johnstone 2003). The level of IMP

should also be considered in conjunction with the patient's circulatory status and the extent of tissue damage (Elliott and Johnstone 2003). The level of IMP is related to the MAP, as MAP minus IMP equals the perfusion pressure. It should be remembered that hypotension could lower the critical level of perfusion. The oxygen requirements of the tissue should also be considered, as damaged requires more oxygen. The IMP needs to be monitored continuously to observe the pressure changes.
Acute compartment syndrome in sedated patients and in patients with cerebral damage and impaired consciousness is difficult to diagnose, as communication between the patients and treating doctor is lacking. A delayed diagnosis can be devastating, as the sequelae are severe and young patients are often affected (McQueen 1996).

Treatment

The perfusion pressure must be considered when fasciotomy is decided on (Whitesides Jr et al. 1975). It has been demonstrated that fasciotomy within 12 hours after the onset of an acute compartment syndrome leaves 68% of all patients with no sequelae (Sheridan and Matsen 3rd 1976).

Fasciotomy is performed under tourniquet control, if possible. Using a 20-30 cm long, para-fibular incision, all four compartments can be reached through a single incision (Matsen et al. 1980). Two incisions, one lateral and one medial, can also be used. From the lateral incision, the anterior and lateral compartments can be reached and, from the medial incision, the superficial and deep posterior compartment can be reached (Mubarak and Owen 1977). During decompression of the lateral compartment, the superficial peroneal nerve should be decompressed as well, as it runs through the fascia tunnel (Styf and Morberg 1997). Care needs to be taken not to damage this nerve during fasciotomy.

CHRONIC ANTERIOR COMPARTMENT SYNDROME (CACS)

Chronic compartment syndrome is an exercise-induced reversible elevation of the intramuscular pressure within one or more affected compartments. The first reported case of chronic compartment syndrome was a self-experienced incident by Dr Edward Wilson in 1912, which took place during a race in which he was attempting to reach the South Pole before Roald Amundsen. In his diary, Dr Wilson wrote "My left leg is exceedingly painful .... and hobbled alongside the sledge on foot. The whole of the Tibialis anticus is swollen and tight …" (Freedman 1954).

Muscle volume changes that occur during exercise was described by Barcroft and Kato 1916 (Barcroft and Kato 1916). Some 40 years later, in 1956, Mavor reported on a young football player with exercise-induced leg pain that was relieved by fasciotomy (Mavor 1956). The connection between exercise-induced leg pain and increased intramuscular pressure was observed and demonstrated by intramuscular pressure measurements in a study by French and Price in 1962 (French and Price 1962).

Incidence

In relation to the entire body, chronic compartment syndrome occurs in the lower leg in 95% of all cases (Barnes 1996). The remaining 5% occur in the forearm, hand, thigh and occasionally the foot (Styf 2003). Among patients with exercise-induced leg pain, the incidence of chronic compartment syndrome is high. The patients reported in the literature are, however, from selected cohorts. In studies conducted on patients with chronic compartment syndrome, the patients are admitted to specialist clinics due to therapy-resistant, exercise-induced leg pain. Among these cohorts, the incidence is usually 20-30%, or even higher. Turnipseed et al. examined 400 patients and found 175 female patients and 74 male patients (62%) with chronic compartment syndrome (Turnipseed 2002). Styf and Körner found 22 patients of 80 (28%) (Styf and Korner 1987) and 11 of 46 patients (24%) in a later study (Styf and Korner 1986). With increasing physical activity in society, it appears likely that men and women will be represented more equally.

Physiology and pathophysiology

In exercising healthy muscle, the IMP increases as a physiological condition (Styf et al. 1989). The patients suffer from exercise-induced leg pain caused by elevated IMP due to the increased transudation of fluid during exercise (Reneman 1975, Hargens et al. 1978, Rorabeck and Clarke 1978). However, the factors leading to the pathological increase in IMP in patients with CACS are not fully known. In resting muscle, the blood flow rate is low and can in fact increase as much as 50 times during exercise in well-trained athletes (Sejersted and Hargens 1986) and the muscle volume may increase up to 20% during exercise (Barcroft and Kato 1916). At the onset of exercise, during the first 15 minutes, the fluid filtration increases from intravascular fluid to the interstitial space (Korthuis 2011). The forces are explained by Starling's equation (Figure 4). During the onset of exercise, the rate of fluid transported from the vascular space to the interstitial space exceeds the compensatory mechanism (Korthuis 2011). The muscle circulation is enhanced by arteriolar vasodilation to match the increased oxygen demands (Kjellmer 1965). The arteriolar surface is increased by recruiting closed capillaries (Kjellmer 1965). The increase in interstitial fluid is a consequence of the enhanced osmolality by the metabolites released from the exercising muscle into the interstitial space (Lundvall 1971). As the exercise progresses, the transcapillary filtration slows down and a balance is reached. In physiological conditions, these mechanisms are balanced and increased interstitial pressure during exercise enhances the lymphatic drainage (Kjellmer 1964). The muscular contractile forces with their rhythmic contractions function as a muscular pump for the lymphatic system.

The balance of net flow with IMP and blood pressure within normal range fails temporary in patients with CACS. There is a pathological elevation of the IMP during and after exercise and the compliance in the muscular compartment decreases in CACS patients in comparison to healthy individuals (Reneman 1975, Allen and Barnes 1986, Styf et al. 1987). The oxygen consumption during exercise in patients with CACS has been studied and a lower level of local muscular oxygen saturation compared with patients with other causes of leg pain during exercise has been observed (Mohler et al. 1997, van den Brand et al. 2005). Studies of muscular blood flow have shown a decreased level in patients with CACS compared with patients with other causes of leg pain (French and Price 1962, Styf et al. 1987, Abraham et al. 1998). During rhythmical muscular work, the muscular tissue contracts and relaxes. It is only during the relaxation phase that the musculature is perfused (Folkow et al. 1970). In patients with CACS, the IMP increases during exercise. As the IMP increases, the relaxation pressure also increases, which contributes to a decrease in muscle perfusion during exercise (Styf et al. 1987).

Histological findings

The histological structure of the fascia plays an uncertain role in chronic compartment syndrome. In a study by Turnipseed et al., an increase in the thickness of the fascia in patients with chronic compartment syndrome compared with healthy subjects was demonstrated (Turnipseed et al. 1995). In a study by Styf et al. in 1986, eight patients had a biopsy taken in conjunction with fasciotomy. These specimens were normal in terms of inflammatory changes and no other abnormalities in the fascia muscular tissue were seen (Styf and Korner 1986). In muscular biopsies, an increase in water content (Wallensten and Karlsson 1984) and water and lactate content (Qvarfordt et al. 1983) has been shown.

Capillary density has been shown to be reduced in muscular tissue, in biopsies from patients with CACS, compared with healthy individuals. One year after fasciotomy, the capillary density did not recover (Edmundsson et al. 2010).

Symptoms and signs

Patients with CACS typically experience pain in the anterior aspect of the leg during exercise. The average patient is 26-28 years of age and physically active (Detmer et al. 1985, Styf and Korner 1987, Turnipseed 2002). The patients' gender distribution varies in different studies between equal, predominantly women and predominantly men (Detmer et al. 1985, Turnipseed 2002, van den Brand et al. 2005, Van der Wal et al. 2014). The patients are commonly active in sport, usually running (Detmer et al. 1985, Slimmon et al. 2002, Waterman et al. 2013). Pain occurs within minutes after the initiation of activity and subsides at rest. Strenuous activity can result in pain persisting for hours. Moreover, symptoms, such as experiencing stabbing pain and eventually the inability to extend the ankle and sometimes numbness, can develop as well. The pain increases during activity and finally forces the athletes to cease the activity (Allen and Barnes 1986, Styf et al. 1987). Even if the main reported limitation relates to running, many patients also experience limitations while walking (Edmundsson et al. 2007). CACS is more compatible with activities such as cycling, swimming and gym training.

Patients with CACS have a higher reported physical activity level than that reported in the general population (Styf and Korner 1987). The CACS can be at least partly explained by strenuous exercise that affects the soft tissues as a result of micro-trauma and inflammatory reaction. The reason why the anterior compartment is most often exposed could be due to the anatomical restrictions caused by the deep osteofascial membranes, tibia and fibula and the tight superficial muscular fascia.

Diagnosis

The diagnostic methods and criteria are still the subject of debate (Barnes 1997, Aweid et al. 2012). For many years, the gold standard for diagnostics has been the measurement of intramuscular pressure (IMP) (French and Price 1962, Reneman 1975, Hargens et al. 1977, Styf et al. 1987). At present, this is still the most accepted method, but it has the limitation of being invasive. Non-invasive methods have therefore been requested and several methods have been evaluated. Blood flow during and after exercise has been investigated to study the pathophysiology, where the increase of blood flow during exercise in healthy individuals is not seen in patients with CACS (French and Price 1962, Styf et al. 1987). Amendola et al. did not find indications of ischaemia (Amendola et al. 1990). Magnetic resonance imaging (MRI) after exercise has shown oedema in the affected muscle (Verleisdonk et al. 2001). Ultrasound after exercise has shown increased fluid in the interstitial space but no increase in muscular volume (Birtles et al. 2002, Birtles et al. 2003). However, none of these has been shown to be convincing in clinical practice.

The characteristics of patients with chronic compartment syndrome

- Normal clinical findings at examination
- In some patients, fascial defects; usually more pronounced with muscular herniations after exercise
- Exercise-induced leg pain with tender and hard muscles
- In some cases, impaired muscular function and numbness after activity
- Exercise-induced leg pain over the anterior compartment with reversed symptoms at rest
- Swelling and tenderness over the anterior compartment immediately after exercise
- IMP ≥ 30 mmHg, one minute after exercise
- IMP ≥ 20 mmHg, five minutes after exercise

TREATMENT OF CACS

Non-surgical treatment

The non-surgical treatment of CACS has produced unsatisfactory results (Detmer et al. 1985, Styf et al. 1987, Van der Wal et al. 2014). In a study by Styf, the symptoms in CACS patients were persistent, despite various conservative treatments, such as diuretics, anti-inflammatory drugs, physiotherapy and stretching. Shoe modification has also been tried, as well as different training programmes. No benefits are reported after the conservative treatments (Styf 1988).

Surgical treatment

In 1956, Mavor presented a case report in which a professional football player, 24 years of age, suffered from what was clinically diagnosed as CACS. The patient was successfully operated on with fasciotomy of the anterior compartment. Fasciotomy of the compartments of the leg can be performed safely and satisfactorily according to reports from Detmer and Sharpe, who presented a report of fasciotomy in 100 patients and 233 compartments (Detmer et al. 1985).

Release of the anterior and lateral compartments

Using a vertical incision on the ventral part of the leg, both the anterior and the lateral compartments can be reached using the technique developed by Mubarak. However, it is important to make sure that the fascial split in the distal direction is long enough not to cause a muscular herniation in the distal “V” (Mubarak and Owen 1977, Detmer et al. 1985). Sensory nerves exit from the lateral portion of the anterior compartment and care should be taken (Detmer et al. 1985). The fascia is split using scissors one centimetre lateral to the anterior margin of the tibia, beginning on the mid-portion of the tibia and continuing in the distal and proximal direction. The intramuscular septum must be identified and the fascia of the lateral compartment should be split, in the proximal direction as well as distally, where care needs to be taken with the superficial peroneal nerve.

Surgical outcome

The surgical outcome has been reported as good or excellent in several studies (Wallenstein 1983, Styf and Korner 1986, Fronek et al. 1987, Rorabeck et al. 1988, Schepsis et al. 1993, van den Brand et al. 2004). In a study by Edmundsson et al., the results in 57 patients were excellent in six, good in 35, fair in 15 and poor in one (Edmundsson et al. 2007). A recent study comprising 611 patients who had varying types of compartment syndrome (anterior, lateral, posterior) in the lower leg indicated that 28% were not able to return to full activity after fasciotomy (Waterman et al. 2013). There were, however, limitations to this study, with a lack of information relating to IMP values and surgical methods.

Detmer et al. reported that as many as 90% improved partially or fully (mean follow-up 4.5 months) in their study of 100 patients (Detmer et al. 1985) and a similar result was reported by Styf and Körner in 19 patients (mean follow-up 25 months) (Styf and Korner 1986). Slimmon et al. performed a long-term follow-up (mean follow-up 51 months) to evaluate the results of fasciotomy, combined with partial fasciectomy. Of 50 patients who underwent surgery, 60% reported a good or excellent outcome, but 58% returned to activity at a lower level than before the injury. Surgery without a satisfactory outcome might be due to the insufficient length of the fascial split (Puranen and Alavaikko 1981, Bell 1986).

Co-morbidity in patients with exercise-induced leg pain is not extensively reported in the literature. Co-existing diagnoses, such as medial tibial syndrome periostitis, peroneal tunnel syndrome, popliteal entrapment syndrome or muscular rupture, were reported in 42% of the patients with CACS in a study by Styf (Styf 1988). The pain from elevated IMP during exercise might mask other sources of pain that can be revealed after fasciotomy.

DIFFERENTIAL DIAGNOSES IN EXERCISE-INDUCED LEG PAIN

Patients with CACS might have additional diagnoses. A discussion of differential diagnoses in patients with exercise-induced leg pain is important. In a study by Styf, as many as 42% of all patients with CACS suffered from co-morbidities, such as periostitis, peroneal tunnel syndrome and medial tibial syndrome (Styf 1988). The additional diagnoses might be expressed during rest and blur the clinical picture of CACS. The affected patients are limited in physical activities, as the symptoms are not spontaneously relieved. The following diagnoses are commonly found to co-exist with CACS.

- Medial tibial syndrome
- Periostitis
- Muscle rupture

Medial tibial syndrome and periostitis

Medial tibial syndrome gives rise to symptoms in the form of exercise-induced pain over the distal third of the posteromedial aspect of the tibia. Devas reported this syndrome in the literature in 1958 (Devas 1958). The pain often subsides at rest, but some patients have consistent pain for hours or even days after strenuous exercise. Physical examination reveals local tenderness in the distal third of the medial border of the tibia.

Medial tibial syndrome may co-exist in patients with CACS and has been observed (Styf 1988). Previously, medial tibial syndrome was divided into three types, according to Detmer, Types I, II and III (Detmer 1986). Type I was related to radiological bony changes, sometimes with micro-fractures, at the osteofascial border at the origin of the soleus muscle (Holder and Michael 1984). The radiological changes correlate with histological changes with the proliferation of osteoblasts. However, in the periosteum, no evidence of inflammatory changes has been demonstrated (Johnell et al. 1982). Type II was defined as periostalgia and traction periostitis. Type III was defined as a chronic compartment syndrome in the deep dorsal compartment. In a study by Barbour et al., biopsies were taken from the patients during fasciotomy. The study comprised 19 patients with deep posterior compartment syndrome and 11 controls. Fibroblastic activity, chronic inflammatory cells and increased vascularity were seen in the biopsy material from the patients with deep dorsal compartment syndrome (Barbour et al. 2004).

In a study by Moen et al., 52 athletes with medial tibial syndrome were examined with MRI. Periosteal and bone marrow oedema were found in more than 40% of the patients (Moen et al. 2014). However, no significant differences were found between symptomatic and non-symptomatic legs from the MRI examinations.

Medial tibial syndrome might be explained by rapidly increasing activity. Histologically, no inflammatory changes have been shown in the periosteum, but, in the crural fascia, 13 of 33 biopsies revealed inflammatory changes in a study by Johnell et al. (Johnell et al. 1982). The patients with medial tibial syndrome experience pain, which intensifies during activity.

Periostitis does not respond well to treatment with anti-inflammatory medication, or physiotherapy. Reduced activity will contribute to less pain. The clinical outcome after surgical treatment, i.e. fasciotomy, is not as successful as in patients with CACS.

Muscle rupture

The patients experience pain, which is usually located in the medial muscle belly of the gastrocnemius, close to the muscle-tendon junction. This condition is common in recreational runners, but it is most typical in fast eccentric-action sports, such as tennis or floorball. The muscle fibres are strained due to overstretching and the mechanism is load by flexion of the ankle joint with the knee extended. Clinical examination reveals pain at the muscle-tendon junction. Ultrasonography may reveal scar tissue close to the muscle-tendon junction. The primary symptom is usually acute pain while running. The patient often describes the pain in a similar manner as in Achilles tendon rupture (Styf 2003). Treatment with physiotherapy to regain full muscle strength is successful. The healing time is usually three to six weeks.

Tibial stress fractures comprise almost 50% of all stress fractures in athletes. Running is the most common activity leading to stress fracture of the tibia (Matheson et al. 1987). Usually stress fractures are seen in the push-off/landing leg according to a study in 29 patients by Ekenman et al. (Ekenman et al. 1996). In a study comprising 295 military recruits, 31% were found to have stress fractures and more than 50% of these fractures were located in the tibia. Of the total numbers of stress fractures, 35% were asymptomatic (Milgrom et al. 1985). During running, the external impact force must be absorbed by bone and soft tissue. Bone mainly absorbs the energy, while the soft tissue does so to a lesser extent (Burr and Milgrom 2001). The remodelling of bone occurs when the forces are in harmony according to Wolf's Law (Chamay and Tschantz 1972). Bone remodelling occurs due to microtrauma in order to maintain its strength. During heavy training, as the muscles become fatigued, the bone must absorb more of the load from the external forces. The load absorption function will be impaired and this can lead to stress fractures (Burr and Milgrom 2001). Stress fractures are more common in women due to a higher rate of muscle fatigue, resulting in increased tension of the tibia (Burr and Milgrom 2001).

In arterial entrapment, the symptoms are divided into anatomical and functional (Turnipseed 2002). Functional popliteal entrapment is regarded as an overuse injury in a similar manner to CACS. Venous insufficiency is uncommon in patients with exercise-induced leg pain.

INTRAMUSCULAR PRESSURE

Definition

Intramuscular pressure (IMP) is measured as the hydrostatic pressure in the muscular interstitial space. In resting muscle, this pressure is normally below 10 mmHg. IMP can be defined by the Starling equation. Starling defined tissue pressure in 1896 (Starling 1896). A change in IMP is due to a shift in fluids or external impact. The net filtration rate is described by the Starling equation (Figure 4).

Four different pressures act over the capillary membrane

- Pc = vascular hydrostatic pressure
- Pt = interstitial hydrostatic pressure
- πc = vascular oncotic pressure
- πt = interstitial oncotic pressure

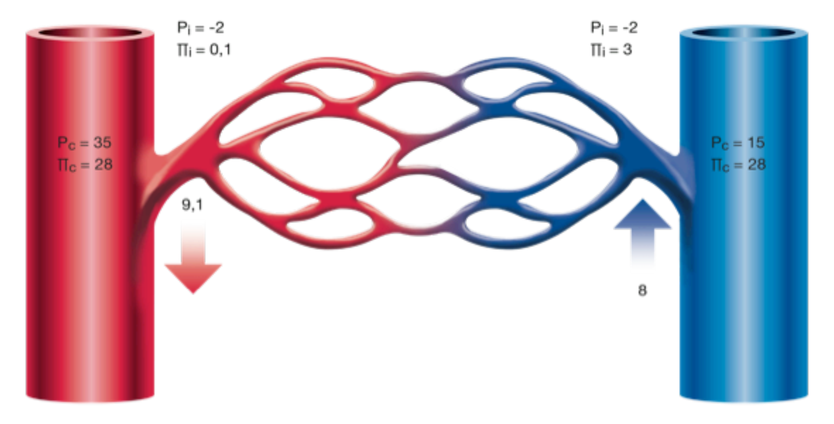


Figure 4. *Starling's Law explains the net fluid across the capillary membrane as the equation* $Jc=Kf((Pc-Pt)-\beta(\pi c- \pi i))$*. Pressure in mmHg.*

The forces according to Starling's Law

JV = transcapillary fluid transport (ml/min/100g tissue)
Kf = capillary filtration coefficient (ml/min/100g tissue)
Pc = capillary fluid hydrostatic pressure (mmHg)
Pt = tissue fluid hydrostatic pressure (mmHg)
β = capillary membrane reflection coefficient (0-1, no dimension)
πC = capillary fluid oncotic pressure
πt = tissue fluid oncotic pressure

INTERSTITIAL SPACE (IMP)

The interstitial space is approximately 10% of the skeletal muscle weight (Aukland and Reed 1993). It contains three quarters of the body fluid content (Aukland and Reed 1993). The interstitial space consists of a heterogeneous mixture of fluid and gel. The two phases of fluid and gel were described by Guiton et al. back in 1971 (Guyton et al. 1971). The framework or matrix is composed of collagen fibres. The interstitial space is located in the space between the capillary network and the lymphatic system. The change in interstitial-space volume is explained by the Starling equation and fluid shift is seen as changes in the tissue pressure (Figure 5). Lymphatic drainage exports the fluid back to the vascular system (Aukland and Reed 1993).

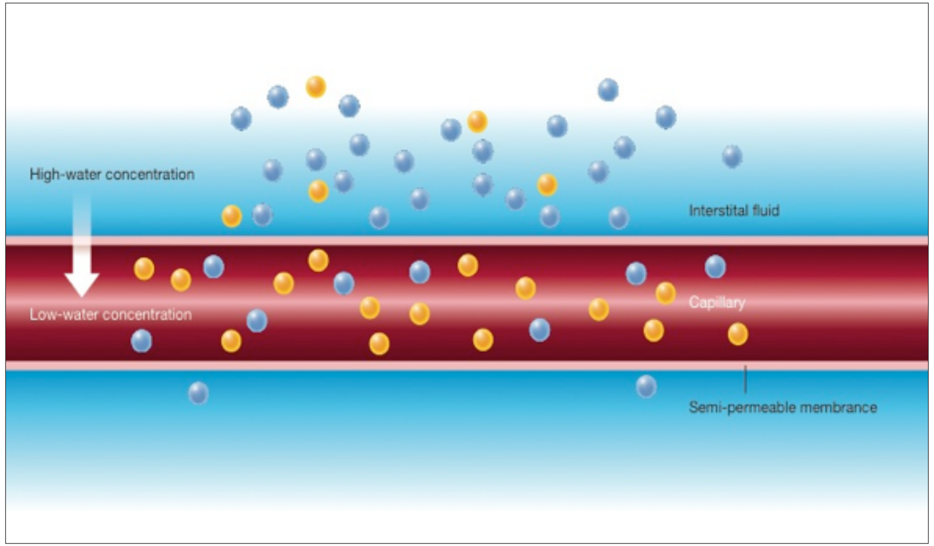


Figure 5. *The interstitial space consists of a heterogeneous mixture of fluid and gel. Pressures from the interstitial space and from intravascular forces determine the shift in the fluids.*

HISTORICAL PERSPECTIVES OF IMP

In 1962, French and Price performed an analysis of how to diagnose CACS (French and Price 1962). The study comprised two patients with exercise-induced leg pain and 18 healthy subjects. The study was performed with tissue pressure measurements of the anterior compartment and clearance of radioactive sodium to monitor the blood flow. The tests were followed by an exercise test. An exercise test with external pressure produced by an inflated tourniquet, was also performed, to observe changes in pain and intramuscular pressure during intramuscular pressure elevation. These tests are still up to date in modified forms when it comes to observing intramuscular pressure and changes in blood flow (Styf et al. 1987, Breit et al. 1997, Mohler et al. 1997, Abraham et al. 1998). Elevated tissue pressures in the lower leg were found in patients with clinical signs of chronic anterior compartment syndrome (CACS), while elevation in blood flow post-exercise was absent in the patients with CACS compared with the healthy individuals with elevated IMP (French and Price 1962). Normal arterial pulsations were observed in the affected compartment, as well as clinically observed oscillations of the affected compartment explained by systolic pulsations.

IMP CHANGES

The anatomical structure of the anterior compartment with rigid walls most probably makes it especially vulnerable to elevations of IMP. In a study by Allen and Barnes, there was a more pronounced elevation of IMP in the anterior compartment compared with the deep posterior compartment after the infusion of a small amount of fluid in amputated legs (Allen and Barnes 1986).

IMP BEFORE, DURING AND AFTER EXERCISE TEST

There is no universally accepted IMP level to establish the diagnosis of CACS (Aweid et al. 2012, Roberts and Franklyn-Miller 2012). According to the literature, different criteria have been used. The intramuscular pressure in normal resting muscle tissue is 5-11 mmHg (Fronek et al. 1987, Nkele et al. 1988, Rorabeck et al. 1988). Intramuscular pressure during activity has been studied in detail (Styf et al. 1989, Barnes 1997) and pressure above 50 mmHg has been identified as diagnostic for CACS (Puranen and Alavaikko 1981, McDermott et al. 1982, Allen and Barnes 1986). Today, the criteria formulated by Pedowitz et al. (Pedowitz et al. 1990) are commonly used, but, in actual fact, the criteria differ in different studies (Tzortziou et al. 2006, Edmundsson et al. 2010). Moreover, there is no general standard in terms of the levels of IMP and the most optimal time point at which the pressure measurement should be performed. In a recent study by Aweid et al., overlapping values were found in the groups of patients with chronic compartment syndrome (mainly CACS, but all compartments of the lower leg were included) and healthy individuals (Aweid et al. 2012).

IMP criteria by different authors

IMP criteria during activity
Puranen and Alavaikko 1981 (>50mmHg)
Allen and Barnes 1986 (>50mmHg)
McDermott et al. 1982 (>85mmHg)

IMP criteria during rest before exercise
Turnipseed 2002 (>15mmHg)

IMP criteria during rest after exercise
Styf and Korner 1987 (>30mmHg)
Pedowitz, Hargens et al. 1990 (>30mmHg)
Fronek et al. 1987 (>10 mm Hg at rest and/or >25 mm Hg 5 min after exercise)

However, overlapping values have not been found in reported mean IMP levels between patients and control subjects when IMP was measured one minute post-exercise.

The criteria for CACS formulated by Pedovitz et al. are widely used, but they have been discussed and criticised due to the fact that they are based on a small number of patients (n=45) (Roberts and Franklyn-Miller 2012).

One or more of the following were considered to be present to fulfil the criteria for chronic compartment syndrome; 1) resting pressure of ≥ 15 mm Hg, 2) a one-minute post-exercise pressure of ≥ 30 mm Hg, or 3) a five-minute post-exercise pressure of ≥ 20 mm Hg. The patients underwent clinical examination followed by an exercise test. The clinical findings were normal, but several patients had muscular herniation of the lower leg.

IMP CRITERIA FOR CACS

The criteria formulated by Pedowitz et al. (Pedowitz et al. 1990) are well documented. The diagnostic criteria for CACS used in this thesis are a modification of the criteria formulated by Pedowitz et al. Clinical signs of CACS, exercise-induced leg pain and a minimum of 30mmHg one minute post-exercise were used to establish the diagnosis of CACS in the present thesis. No examination of IMP during rest before exercise was however performed. During he IMP measuring adequate investigation technique and correct use of the equipment must be controlled.

TECHNIQUES FOR MEASURING IMP

The emphasis is on an IMP-measurement post-exercise test. IMP measurement can be performed using needle or catheter techniques with infusion or non-infusion (Figure 6). Several monitoring techniques, such as a needle manometer (Brace et al. 1975), wick catheter (Mubarak et al. 1976) and the microcapillary infusion system (Styf and Korner 1986), have been described.

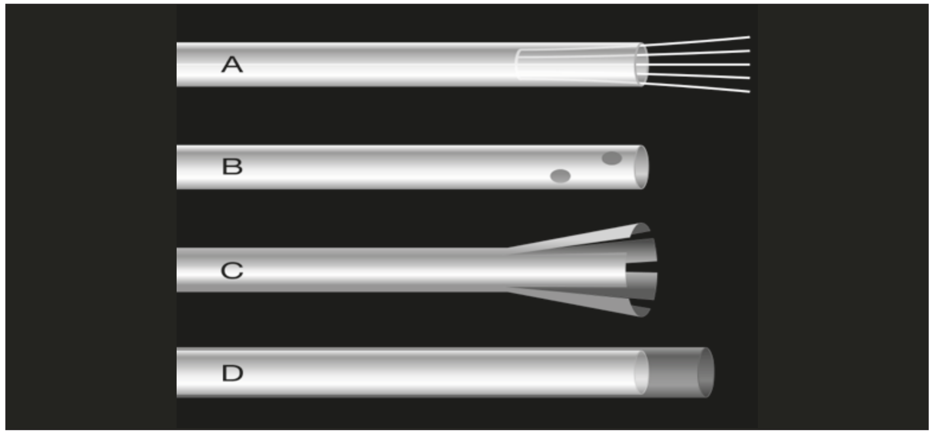


Figure 6. *Occlusion of the catheter tip is a problem that can be caused by blood clotting or tissue inside the tip of the needle. To prevent this, several methods have been developed with different constructions at the tip of the needle. A. Wick catheter B. Catheter with multiple side-holes C. Slit catheter D. Catheter with a cover for a SLIT catheter or catheter for optical use.*

Different needles

In a study by Boody and Wongworawat, three different IMP devices and three different needles were compared with a reference model (Boody and Wongworawat 2005). The study revealed clinically significant differences between different devices and needles. It is important to be aware of the differences when making the measurements in day-by-day clinical work. One important result is that straight needles without side-holes should not be used, due to the risk of false high measurements. Different devices are available and a detailed knowledge of the exact technique and the potential pitfalls of each method is necessary (Figure 6).

Infusion techniques

IMP can be measured using a continuous or non-continuous microcapillary infusion system. The volume of saline solution used in the non-continuous microcapillary fluid system is significantly lower compared with that in the continuous infusion system (Styf 2003). To monitor an exercise test, a rapid response is necessary and the microcapillary fluid-filled system has been shown to be suitable (Styf and Korner 1986).

Non-infusion techniques

There is a risk of blood or tissue clotting if no infusion is used. A wick catheter has been shown to possess low dynamic properties (Styf and Korner 1986) and a slit catheter requires fluid to be intermittently flushed to prevent clotting (Allen and Barnes 1986). Both techniques need fluid to function.

Optical techniques

Optical transducers have been shown to have properties that are well suited to IMP (Crenshaw et al. 1990). These devices are suitable for measurements during exercise and during rest.

PERFORMING IMP MEASUREMENTS

The position of the needle and possible clotting by blood or tissues at the tip of the needle are sources of uncertain or even false results. The position of the needle is of the greatest importance. The pressure has been shown to differ according to the depth of the needle or catheter in the muscular tissue (Sejersted et al. 1984). The position of the ankle helps to increase or reduce the IMP (Gershuni et al. 1984). The time point of measurement is also of major importance. As an increase in IMP during exercise is a physiological process (Puranen and Alavaikko 1981, Styf et al. 1989), the pressure measurement performed one minute after exercise enables the physiological process in patients with other causes or exercise-induced leg pain to decline in pressure. The IMP in patients with CACS does not normalise for five minutes (Pedowitz et al. 1990). The person making the IMP measurement must be aware of the possible pitfalls during the IMP measurement procedure to avoid false results.

Measurement position

To insert the needle correctly, anatomical landmarks must be identified to penetrate the correct muscle compartment. The needle should be inserted parallel to the muscle fibres to reduce the tissue trauma during insertion (Zhang et al. 2011). Occlusion of the needle sometimes occurs and this can be avoided by penetrating the skin with a separate needle which is withdrawn before placing the needle used for the IMP (Styf 2003). Local anaesthesia can be applied, but it is not necessary. To control the position of the needle, external compression can be performed by the investigator running his/her fingertips over the needle tip. The curve of the IMP will show a direct rise in amplitude if external compression is applied directly over the needle tip (Styf 2003).

Control of functioning needle/catheter

- Increased intramuscular pressure during active muscular contraction
- Needle positional control by ultrasound
- The needle should be at heart level during measurement of the IMP in order to avoid an incorrect increase or decrease in IMP.
- External pressure over the needle is followed by a quick rise in amplitude on the IMP curve.

Anatomical landmarks of the muscular compartments

Active extension and flexion of the ankle joint usually enables the muscle bellies to be well defined. A good knowledge of anatomical landmarks is essential for correct intramuscular pressure measurements.

Reproducibility

Different devices have been used and reproducibility is one important concern (Boody and Wongworawat 2005). Variations in measurements can be due to different devices or incorrect measurement techniques but also to biological variations in compartment pressure.

Factors affecting pressure measurements and the level of IMP

- The pressure transducer should be kept at the same level as the patient's heart.
- Occlusion by tissue or blood clotting
- Timing of measurement in relation to the exercise test
- Muscular tension at rest after exercise
- External compression
- Level of effort made by the patient during the exercise test
- Ability to reproduce pain by an accurate exercise test
- Correct muscular compartment
- Correctly placed needle in the tissue in relation to muscle fibers and vessels

Risks during IMP measurement

The risk of injury, such as bleeding and infection, is small, but the procedure may create some discomfort and pain for the patient (Mohler et al. 1997, van den Brand et al. 2005).

NEAR-INFRARED SPECTROSCOPY (NIRS)

NIRS is a non-invasive method. Since the end of the 1980s, NIRS has been used to study local muscle oxygenation at rest and during exercise (Ferrari et al. 2011). The blood changes in colour depending on the level of oxygenation. This is due to the optical properties of haemoglobin, which are used by NIRS at wavelengths between 700 and 900 nm (Figure 7).

Oxygenated blood is bright red and deoxygenated blood is deep red, dark or almost blue, depending on the optical spectra. When it comes to monitoring the systemic oxygenation, pulse oximetry is an established method. However, local muscle oxygenation can also be monitored. Haemoglobin changes its optical properties when binding to oxygen (Figure 8). The chromophore, the part of the haemoglobin molecule that binds oxygen, absorbs and reflects light (Scheeren et al. 2012). Oxygenated haemoglobin binds wavelengths at 830 nm and deoxygenated haemoglobin binds them at 780 nm. Myoglobin and haemoglobin are not possible to differentiate, as they are covered in the same optical spectra (Mohler et al. 1997). The difference between admitted and received light is defined as the change in muscle oxygen saturation.

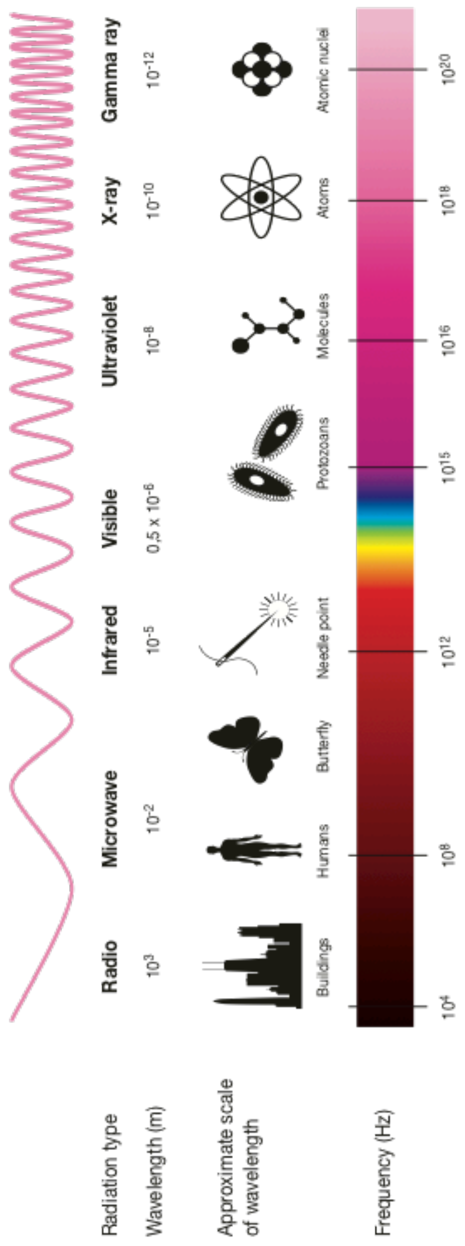


Figure 7. *Spectrum of wavelengths found in daily life and medical practice.*

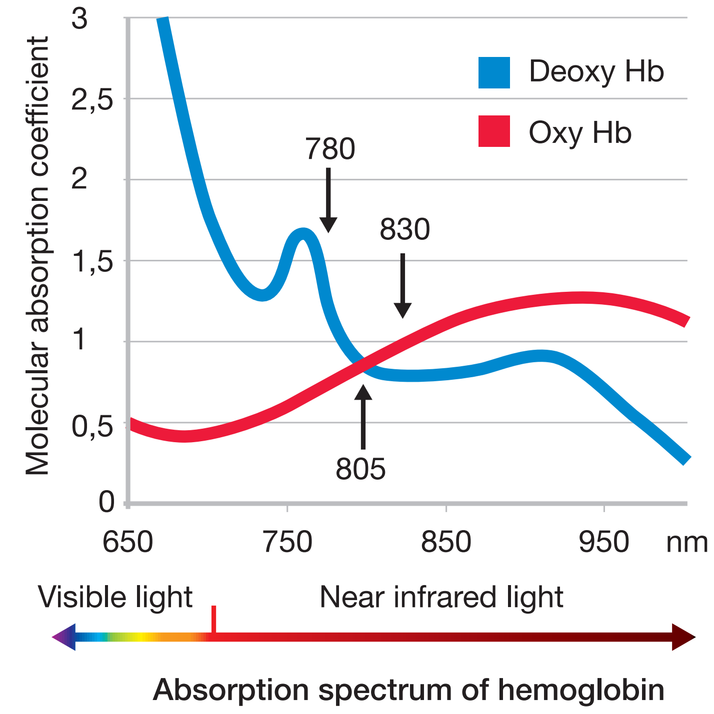


Figure 8. *Graph showing the optical properties of oxygenated and deoxygenated haemoglobin. Myoglobin is covered within the wavelengths and cannot be separated by NIRS.*

There are a number of different NIRS devices, such as RunMan, InSpectra, INVOS, NIMO and NIRO. In the present thesis, three of them were used and they are described below. The NIRS probe is placed on the skin and has an adhesive surface. It is placed on the surface of the muscle of interest. The adhesive stickers are used to limit the motion of the probe and to restrict light from the surroundings interfering with the light emitted by the light source on the probe (Scheeren et al. 2012). In addition to the light source, the probe contains a receiver. The light is emitted through the tissue from the light source. Of the emitted light, approximately 95% is absorbed by the receiver. The distance/depth of the emitted light into the tissue is 95% of the distance between the light source and the receiver. The distance of the emitted light is, for example, 23 mm when using InSpectra (Figure 9) (model 325, Hutchinson Technology, Hutchinson, Minnesota). The recorded values are continuously collected by the receiver and printed every 3.5 seconds (InSpectra model 325).

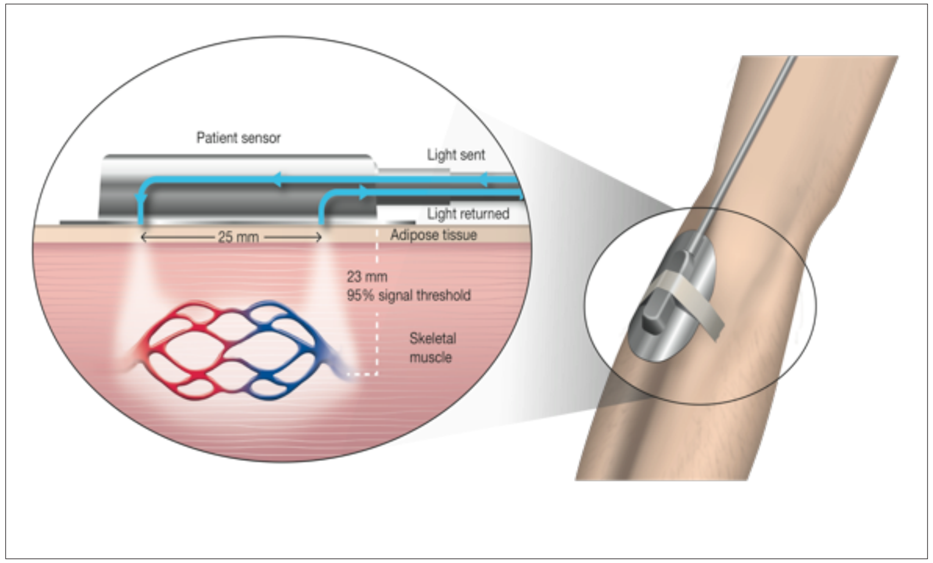


Figure 9. *Illustration showing a probe from the NIRS device, InSpectra. The light is emitted from a light source, transmitted into the tissue and 95% is re-absorbed by the receiver, while 5% is scattered through the tissue. An algorithm calculates the differences between emitted light and absorbed light by the receiver as an absolute value of* StO_2.

During the last decade, NIRS has been further developed. The equipment used in Study I was Run-Man (Run-Man CWS-2000, NIM, Philadelphia, Pennsylvania, USA). Run-Man equipment shows the changes in muscle oxygen saturation as a relative value and a dual wavelength was used (Chance et al. 1992, Breit et al. 1997, Zhang et al. 2012). As the technique has progressed, the NIRS device currently used is InSpectra model 325 (Figure 9) (Hutchinson Technology, Hutchinson, Minnesota), which presents absolute values of the local muscle oxygen saturation.

The INVOS 4100 employs infrared light with two wavelength signals between 730 and 810 nm. It measures the ratio of oxygenated and total haemoglobin, displayed as a percentage of the regional oxygen saturation. The INVOS device is used clinically to monitor the oxygen saturation in the brain (Scheeren et al. 2012). The depth of measurement is between 15 mm and 20 mm from the surface (Figure 10).

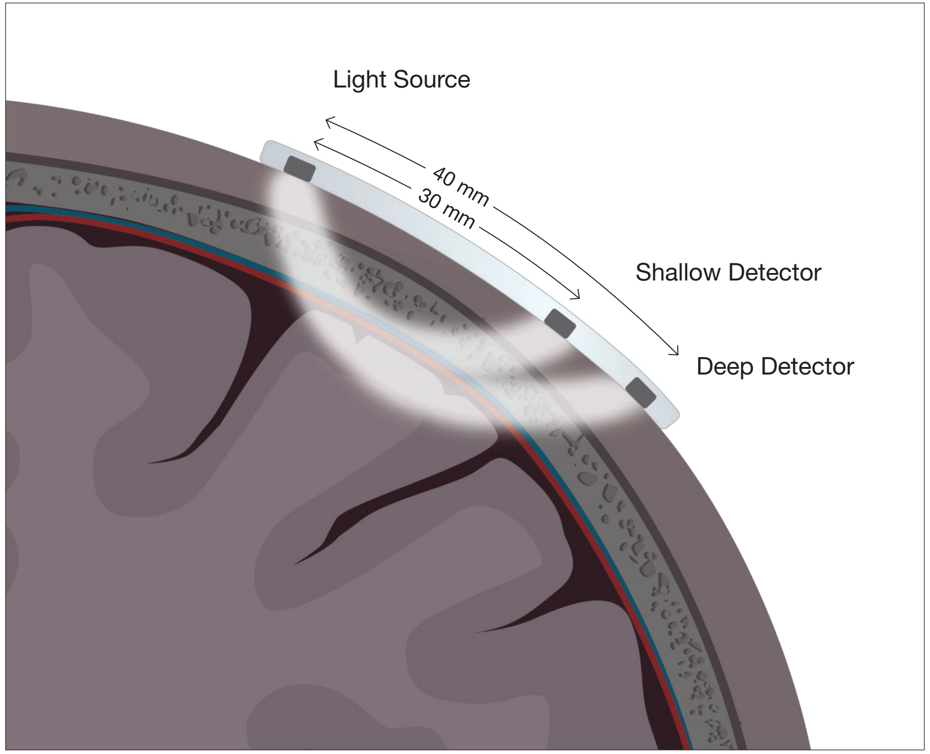


Figure 10. *Illustration showing a probe from the NIRS device, INVOS. A slightly different spectrum is used and the measurement takes place between the two light paths, making the INVOS device less sensitive to the outermost tissue layer.*

The use of NIRS in detecting CACS has been assessed in several studies (Breit et al. 1997, Mohler et al. 1997, van den Brand et al. 2004, van den Brand et al. 2005) and it has been found that patients with CACS consume more oxygen during exercise compared with non-CACS patients and healthy individuals (Breit et al. 1997, Mohler et al. 1997, van den Brand et al. 2005). Moreover, the delayed recovery of StO_2 after exercise has been reported (Mohler et al. 1997).

Monitoring local muscle oxygen saturation during exercise tests

The aim of the exercise test must be to elicit the patient’s symptoms. As the exercise starts, the muscular oxygenation decreases due to oxygen consumption. The exercise continues until the patient experiences fatigue, impaired muscle function and leg pain. At the end of the exercise, the recovery phase begins and the muscle oxygenation increases. The reoxygenation exceeds the baseline, due to exercise hyperaemia. The test can also be standardised (van den Brand et al. 2005).

When NIRS is used for diagnostic purposes in the examination of patients with suspected CACS, an exercise test must be performed, as it is the changes in oxygenation that are the parameter of interest. A probe is attached to the skin (Figure 7) and the muscular oxygenation is expressed in per cent on the monitor. The baseline value before the start of exercise functions as the baseline reference for the changes in muscle oxygen saturation during exercise. The model of NIRS that was previously in practical use was the RunMan device. It presented the local muscular oxygenation saturation as a relative value. The NIRS device used today is the InSpectra device, which presents an absolute value for the muscular oxygen saturation.

PATIENT PAIN DRAWING (PPD)

The use of patient pain drawing (PPD) has not been validated when it comes to determining exercise-induced leg pain. PPD was originally used by Palmer in 1949. The initial idea was to divide pain into organic and non-organic pain (Palmer 1949). It is widely used in the diagnostic evaluation of back pain (Ransford et al. 1976, Undén et al. 1988, Sturesson et al. 1997, Reigo et al. 1998, Hägg et al. 2003). The idea of using PPD in patients with exercise-induced leg pain was to distinguish anterior pain from posterior pain, to overview the co-morbidity and to find an additional instrument for diagnosing patients with overuse injuries to the lower leg. As the patients are symptom free at rest, a screening test for general orthopaedic practice would be useful. The forms containing body manikins are used in such a way that the patients fill them out approximately two weeks before admission to the clinic (Figure 11). The patients answer a questionnaire and, on the human manikin, they mark the pain they experience. No difference is made in terms of different characteristics of the pain.

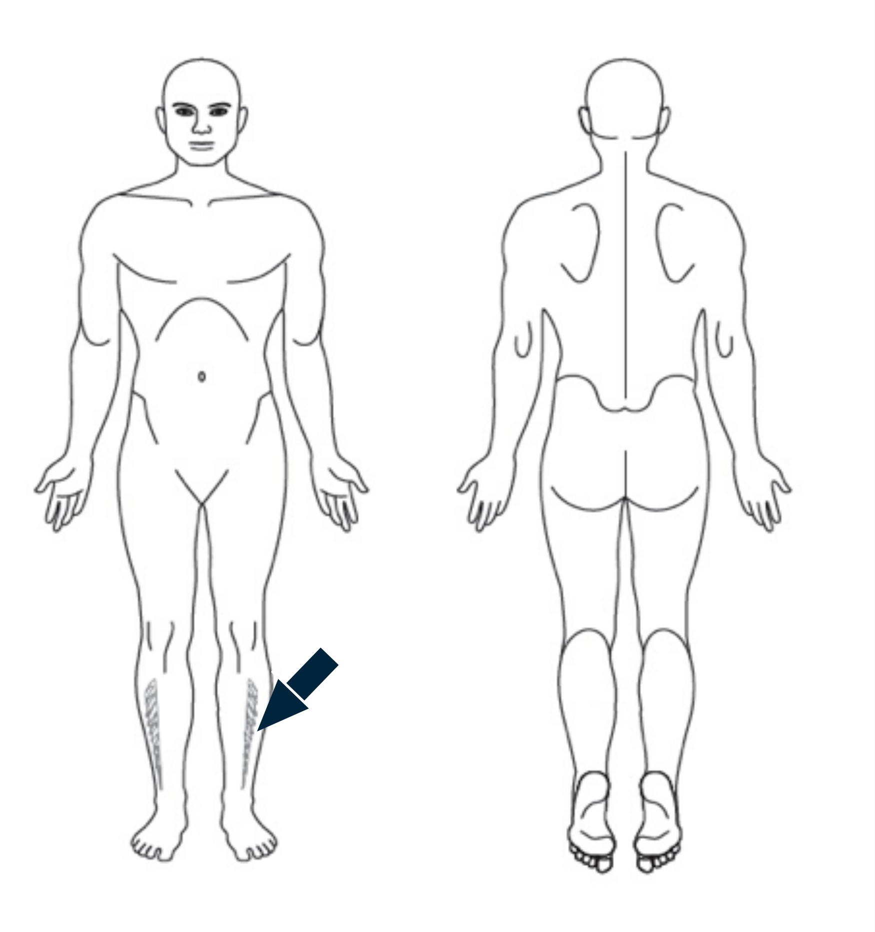


Figure 11. *The figure illustrates the body manikins that are sent out to the patients prior to the visit. The pain is indicated by the patient on the pain drawing.*

aims

The overall aim of this thesis was to investigate/evaluate near-infrared spectroscopy (NIRS) and patient pain drawing (PPD) in diagnosing chronic anterior compartment syndrome (CACS) in patients with exercise-induced leg-pain.

More specifically, the aims were to

- Investigate whether the magnitude of intramuscular oxygenation during exercise and the reoxygenation time at rest after exercise, following an exercise test, using NIRS, are reliable measurements for diagnosing CACS (Studies I and III),

- Compare two NIRS devices (INVOS and InSpectra) in healthy individuals with experimentally induced ischaemia in leg skeletal muscle (Study II),

- Investigate the effect of subcutaneous tissue thickness on measurements made with NIRS devices (Study II) and

- Validate the usefulness of PPD in identifying CACS in patients with exercise-induced leg pain (Study IV).

why is this thesis needed?

Intramuscular pressure (IMP) is regarded as the gold standard method for establishing the diagnosis of chronic anterior compartment syndrome (CACS). However, other methods for diagnosing CACS are the subject of debate, as are the exact cut-off levels for regarding an IMP as pathological (Barnes 1997, Aweid et al. 2012, Roberts and Franklyn-Miller 2012). Variations in IMP can be caused by the examination techniques and the placement of the needle or catheter (Gershuni et al. 1984, Nakhostine et al. 1993, Waterman et al. 2013). This contributes to the uncertainty of relying on IMP measurements. New methods have been suggested and assessed, but none of these has as yet been found to be superior to IMP measurement. The lack of symptoms at rest also suggests that the exercise test is of major importance in establishing the diagnosis of CACS. Further research in this field was therefore needed when this thesis was initiated, to improve the diagnostic procedure and to validate the diagnostic methods in current use. One of the new diagnostic methods is near-infrared spectroscopy (NIRS), which, in previous studies, has been suggested to be useful (Mohler et al. 1997, van den Brand et al. 2004). However, there was a need for larger studies to evaluate NIRS in more detail. Moreover, pain drawings produced by patients with exercise-induced leg pain could contribute to the differentiation of patients with CACS from patients with other causes of leg pain. Pain drawings have mostly been used in patients with lumbar pain (Hägg et al. 2003). The clinical usefulness of PPD in diagnosing the causes of exercise-induced leg pain and its sensitivity and specificity as a diagnostic instrument need to be studied.

methods

The Research Ethics Committee at the University of Gothenburg approved all the studies in this thesis (ID no 617-08).

PATIENTS

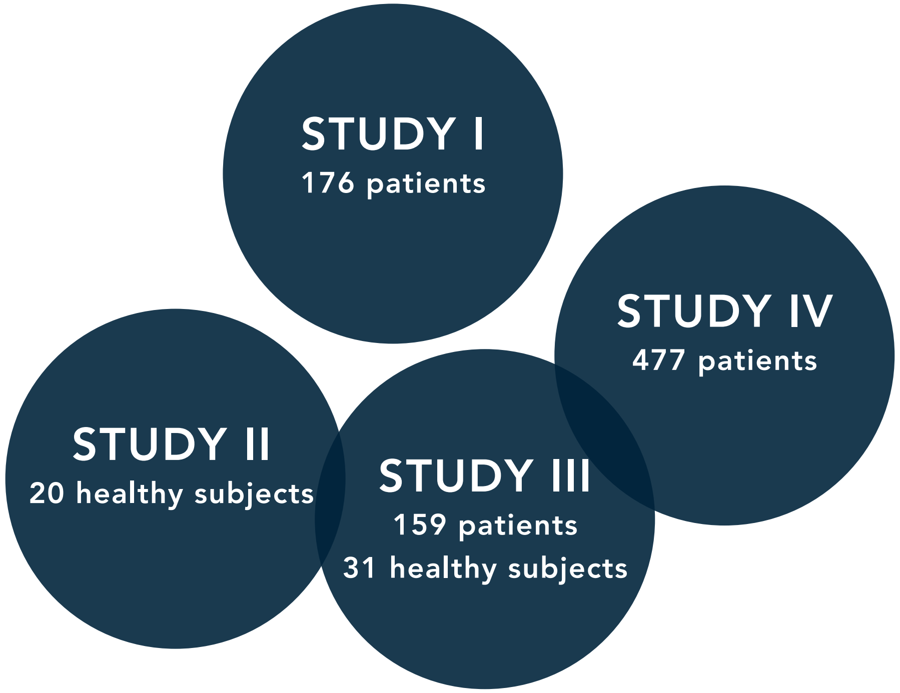


Figure 12. *During the time period 2000-2013, 653 patients and 31 healthy subjects were included in the studies in this thesis. The healthy subjects from study II were also included in study III, and patients from study III were also included in study IV.*

Study I

One hundred and seventy-six patients were included in the study during the time period 2000-2005, 73 men and 103 women; mean age was 34 (SD=15) years. The duration of pain was 71 (range 3-360) months. The patients were referred due to exercise-induced leg pain, with clinical signs of chronic anterior compartment syndrome (CACS) and all patients referred during this period were included provided the ability to perform an exercise test. The study was non-randomized.

Study III

One hundred and fifty-nine patients were included in the study during the time period 2009-2012, 76 men and 83 women, with a median age of 29 years (range14-67) years. All patients were referred due to exercise-induced leg pain and clinical signs of chronic anterior compartment syndrome (CACS). All patients referred during this period were included provided the ability to perform an exercise test.

Study IV

The study comprised 477 consecutive patients, 258 men and 219 women, with a median age of 31 (range 15-70) years, all with exercise-induced leg pain. The patients were referred to the orthopaedic department during 2009-2013.

HEALTHY SUBJECTS

Study II

Twenty healthy subjects (10 women and 10 men) were recruited for this study. Median age was 43 (range 34-60) years. BMI mean 24 (SD 3). The patients had no history of vascular disease that necessitated medical intervention.

Study III

Thirty-one healthy subjects, 14 men and 17 women, with a median age of 36 (range 20-60) years were included. Twenty of them were also included in study II.

INTRAMUSCULAR PRESSURE (STUDIES I, III AND IV)

The measurements were performed in the most symptomatic leg in all patients. Intramuscular pressure (IMP) was measured 60 seconds after the exercise test in all patients in the supine position using a micro-capillary infusion system (Hemo 4, Siemens, Erlangen, Germany) and monitor (Siemens SC 9000, Siemens, Gothenburg), (Zhang et al. 2011). The skin was penetrated by a 1.2 mm diameter needle, with four side-holes at its tip. The needle was inserted at a 30° angle to the long axis of the leg in the distal direction, into the belly of the tibialis anterior muscle (Zhang et al. 2011) parallel with the muscle fibres. To maintain the bulging of fluid at the tip of the needle at the beginning of the measurement, an infusion of 0.9% saline solution was given through the system and continuing to the tip of the needle, with an infusion rate of 0.2 ml/h. There was no continuous infusion throughout the rest of the test time. The tip of the catheter and the transducer were placed at heart level to minimize the hydrostatic artefacts and the position of the tip of the catheter was controlled using ultrasonography. The patient lay supine in a relaxed position with the legs straight (Gershuni et al. 1984).

NEAR-INFRARED SPECTROSCOPY (STUDIES I, II AND III)

StO_2 was monitored by InSpectra (an (near-infrared spectroscopy) NIRS device, tissue spectrometer model 325, Hutchinson Technology, Hutchinson, Minnesota). InSpectra employs infrared light with wave-length signals between 650 and 900 nm. The distance between the light source and the detector is 25 mm and approximately 95% of the detected optical signal is from a depth between zero and 23 mm. The registration is continuous with data given every 3.5 seconds throughout the measurements. The time for initiation of the exercise was indicated, as well as the finish of the exercise and the end of the recovery time. Before every patient or healthy subjects calibration was performed by placing the probe in the calibration-box.

InSpectra records the local oxygen saturation of the tibialis anterior muscle before, during and after the exercise test. The NIRS probe was placed centrally over the tibialis anterior muscle in the most symptomatic leg and the measurements were randomised between right and left leg. The measurement started with the patient/healthy subject resting in a supine position, followed by exercising in standing position, and thereafter a recovery period with the patient resting supine. The measurable range of StO_2 is between 1 and 99%.

INVOS 4100 employs infrared light with two wavelength signals between 730 and 810 nm, it measures the ratio of oxygenated and total haemoglobin, displayed as a percentage of the regional oxygen saturation. INVOS measures continuously every 4 seconds. INVOS uses one light source emitting light and two detectors. The two detectors are located 30 and 40 mm from the light source. The penetration depth of INVOS device is generally accepted to be half the distance between the light source and the sensor, 15 and 20 mm respectively. The sensor was placed directly on the skin, centrally over the tibialis anterior muscle randomly on either right or left leg and the local muscular oxygen saturation was analysed every 4 seconds.

The measurable range of StO_2 is between 15 and 95%.
Reoxygenation at rest after exercise was calculated as the time period required for the level of muscular StO_2 to rise from the level of StO_2 at the end of exercise to 50% (T_{50}), 90% (T_{90}) and 100% (T_{100}) of the baseline value.

BLOOD PRESSURE (STUDIES I, II AND III)

Blood pressure was measured before and after the exercise test in all study objects using a pressure manometer (NAIS, Matsushita, Electronic Works, Japan). Local perfusion pressure was calculated as the difference between the mean arterial blood pressure and IMP.

ULTRASONOGRAPHY IMAGING (STUDIES II AND III)

The skin and subcutaneous tissue above the crural fascia and the distance between the skin and the tip of the IMP needle were measured using ultrasonography imaging, with a linear probe (L10-5, Acuson CV70, Siemens Medical Solutions Inc, USA). This was performed with the subject in the supine position and with relaxed muscles.

SURFACE ELECTROMYOGRAPHY, EMG (STUDY III)

By using EMG the muscular activity can be controlled. During IMP measurement, the muscles must be relaxed in order not to influence the results of the IMP. Two bipolar surface electrodes were used (pre-gelled, Blue Sensor, Medicotest A/S, Denmark). They were placed 15 cm below the knee joint and a reference electrode was placed on the lateral malleolus. The EMG signal was recorded before, during and after the exercise test. The signals from the EMG were amplified in two steps – first by a custom-made pre-amplifier (gain 100 pass second-order Butterworth filter; fo = 10Hz) and then by the main amplifier (variable gain 1-196, low pass second-order Butterworth filter; fo = 2 kHz) before recording with a data acquisition system (Pentium III PC, 12-bits DAQ board and Lab View software, National Instruments Corporation, Austin, TX)(Zhang et al. 2011).

VISUAL ANALOGUE SCALE (STUDIES I, II AND III)

The intensity of leg pain was evaluated with a 10 cm visual analogue scale (VAS) ranging from 0 cm (no pain) to 10 cm (worst imaginable pain).

STATISTICAL METHODS

Study I

The recorded intramuscular oxygenation data for each patient were analyzed as follows:
Definitions of recovery time for intramuscular oxygenation after exercise are shown on a typical curve obtained from near-infrared spectroscopy measurement before, during, and after an exercise test in one patient (Figure 16). R90 is defined as the time required for the level of oxygenation to rise from 10% to 90% of its baseline value after exercise. R100 is defined as the time required for oxygenation to return to its baseline value after end of exercise.

1. Level of intramuscular oxygenation during exercise; the lowest value of oxygenation recorded during exercise with a thigh tourniquet was defined as the physiological minimum, 0%. For analysis of the data, the levels of oxygenation that were recorded for each patient were normalized to a scale that ranged from 0% (the physiological minimum) to 100%.

2. Baseline value of muscular oxygen saturation was defined as the average level of intramuscular oxygenation recorded during the 30-s rest period before exercise (100%). R90 was defined as the time required for the level of oxygenation to rise from 10% to 90% of its baseline value after exercise. R100 was defined as the time required for oxygenation to reach its baseline value after cessation of exercise.

The time of intramuscular reoxygenation after exercise is presented as mean and standard deviation (SD). Difference between the patients with and without CACS was evaluated with analysis of variance. The Mann–Whitney U-test was used for comparison between groups (CACS and non-CACS). The level of significance was defined as $p<0.05$.

Study II

The measured values of muscle oxygen saturation (StO_2) are presented as mean, median, standard deviation (SD) and range. Baseline StO_2 values detected by two NIRS devices were compared with values obtained during ischemia and post-ischemia recovery. VAS data are presented as median and range. Wilcoxon signed rank test was used to compare matched pairs. The significance of intergroup differences was determined using the Mann–Whitney U-test. The level of significance was defined as $p<0.05$. Correlations between baseline StO_2 and change in StO_2 level (difference between baseline StO_2 and lowest StO_2) and the skin and subcutaneous tissue thickness were determined using Pearson's correlation test. Based on their skin and subcutaneous tissue thickness, below or above the median thickness level, the subjects were divided into two groups. Bland–Altman analysis was used to assess agreement between two devices at baseline and during exercise-induced change for all subjects, and the groups divided by skin and subcutaneous thickness.

Study III

The results are given as the median (range). The level of significance was defined as $p<0.05$. The intergroup difference was determined using the Mann-Whitney U-Test. The correlation between the time for re-oxygenation expressed as T_{90} and PP was determined using Pearson's correlation test. Sensitivity and specificity were calculated in the analysis of changes in StO_2 for diagnosing CACS.

Study IV

The Student's t-test was used to determine the significance of intergroup differences. The level of significance was defined as $p<0.05$. Sensitivity and specificity of PPD were calculated in relation to the correct diagnosis based on the complete clinical examination. The level of agreement between the observers was analysed using the Cohen's kappa test. The kappa test is a measure of agreement for categorised variables.

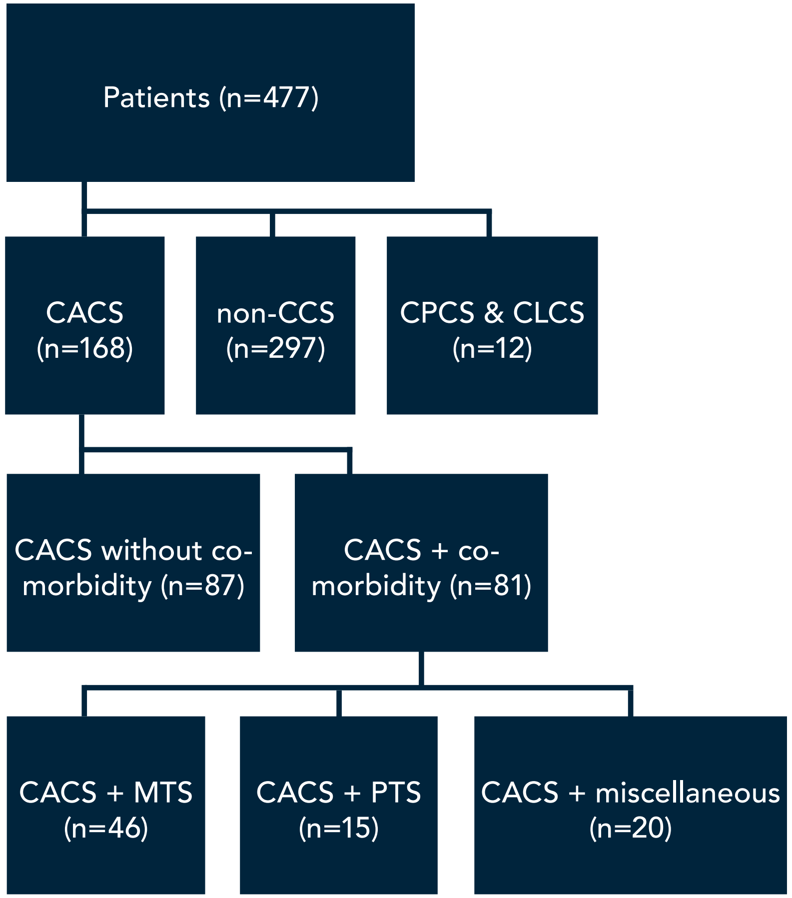


Figure 13. *The 477 patients were allocated into the following groups: CACS, chronic anterior compartment syndrome; non-CCS, patients with other causes of exercise-induced leg pain; CLCS, chronic lateral compartment syndrome; CPCS, chronic posterior compartment syndrome; MTS, medial tibial syndrome; PTS, peroneus tunnel syndrome.*

summary of papers

STUDY I

Why was this study performed?

The study was performed to evaluate the use of near-infrared spectroscopy (NIRS) to diagnose chronic anterior compartment syndrome (CACS). During the study time period, the NIRS device RunMan was used (Breit et al. 1997, Mohler et al. 1997). Previous studies have indicated differences between CACS and other causes of leg pain during exercise when NIRS is used. A greater degree of tissue deoxygenation during exercise has previously been observed in patients with CACS, as well as a delay in muscular oxygen saturation compared with patients who have other causes of leg pain. The study by Breit et al. was performed on healthy individuals and the compartment syndrome was induced by external pressure (Breit et al. 1997). As ischemia has been discussed as an important factor in the development of CACS, it is of great interest to monitor muscular oxygen saturation since other diagnostic methods have focused on different parameters.

Hypothesis

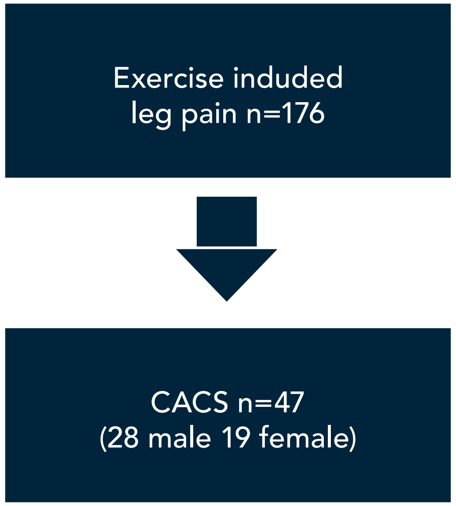
Exercise-induced leg pain in patients with CACS is related to muscle ischemia, and NIRS is useful to detect patients with CACS and compromised tissue perfusion.

Methods

One hundred seventy-six consecutive patients (73 men, 103 women) with a mean age of 34 (range 14–76) years were studied between 2000 and 2005. They all had clinical signs of CACS. The diagnosis of CACS was confirmed by a thorough history and clinical examination before and again after an exercise test that elicited the symptoms.

Exercise test monitored by NIRS;
A NIRS probe was placed centrally over the tibialis anterior muscle of the most symptomatic leg. The patients performed two intensive indoor exercise tests to elicit symptoms – maximal concentric dorsiflexion of both feet (60 cycles/min) in the standing position until they were unable to continue because of muscle fatigue, leg pain, impaired

muscle function, or a combination of these factors; and an exercise test with induced ischemia to record the lowest value of oxygenation by NIRS. The lowest value was defined as the physiological minimum, 0% StO_2. The ischemic test was performed by maximum dorsi- and plantar flexion of the ankle joint in supine position with ischemia induced by a thigh tourniquet inflated to a pressure of 100 mm Hg above the systolic blood pressure. Muscular oxygen saturation was continuously monitored and reported every 3 seconds.



Results

Of 176 patients, 47 (28 men and 19 women, mean age 31 years (SD=12)) were diagnosed with CACS. Other causes of leg pain were found in 129 patients; 45 men and 84 women, mean age 35 years (SD=15). The other diagnoses were periostalgia over the anterior margin of the tibia, medial tibial syndrome, peroneal tunnel syndrome, or facial defects without CACS.

The duration of exercise was 60±24 seconds in patients with CACS and 66±36 seconds in patients without CACS (p=0.107). The level of oxygenation decreased during exercise compared with its baseline value (100%) both in patients with CACS and in patients who did not have CACS. The level of deoxygenation between the two groups showed no significant differences. The time of reoxygenation, i.e. the rise time R90, was 42±22 s in patients in CACS patients and 33±16 s in patients diagnosed with other causes of leg pain (p=0.030). The sensitivity was 60% and specificity 45% if R90 ≥30 s. A significant difference was found in recovery phase, where CACS patients needed prolonged time to recover. Recovery time R100 was 61± 34 s in patients with CACS and 46 ± 20 s in patients without CACS. Patients with CACS had a significantly longer recovery time than patients without CACS (p<0.05). Patient pain drawings (PPD) were performed by 19 patients with CACS. Out of these 10 patients (53%) marked one single pain location and 9 (47%) marked multiple pain locations.

Conclusion

We conclude that the magnitude of intramuscular deoxygenation during exercise is an unreliable measure to diagnose CACS. However, the time for reoxygenation returning to baseline level following an exercise test is a valuable adjunct to establish the diagnosis of CACS.

STUDY II

Why was this study performed?

The study was performed to compare two NIRS devices; INVOS and InSpectra. INVOS is in clinical use in thoracic surgery for monitoring StO_2 of the brain during surgery. There is often a need to monitor muscule oxygen saturation in extremity during thoracic surgery, due to suspicious ischemia after extended time of reduced blood circulation. InSpectra has been used for many years monitoring changes of muscular oxygen saturation in extremities in specialist orthopaedic clinic. INVOS measures the muscular oxygen saturation at the distance between 10mm and 15mm from the surface and InSpectra measures the muscular oxygen saturation 0-23mm from the surface. Due to this difference in area of monitored tissue, the influence of subcutaneous tissue distance could also be observed.

Hypothesis

The hypothesis was that the cerebral/somatic oxygenation device, (INVOS) can detect changes in StO_2 in human leg during exercise test and by experimentally induced ischemia. And, that NIRS device is affected by the skin and subcutaneous thickness.

Methods

Tissue oxygen saturation in the tibialis anterior muscle was measured simultaneously by using InSpectra tissue spectrometer model 325 (Hutchinson Technology, Hutchinson, Minn) in one leg and INVOS 4100 (Somanetics, Troy, MI) in the contralateral leg. The two devices were randomly allocated to their application side for each subject.

The subjects were placed in supine position on a medical examination table in a laboratory at a temperature of approx. 21°C. Skin and subcutaneous thickness, and blood pressure were determined. StO_2 in the tibialis anterior muscle of both legs was then measured simultaneously using the two NIRS devices. All subjects underwent an exercise test and were, after a recovery time, randomized to perform either arterial occlusion with an exercise test or arterial occlusion alone test.

Exercise test (n=20): The subject rested supine for 2 minutes and baseline StO_2 was measured. The subject was then asked to perform maximal concentric dorsiflexion of both feet (60 cycles/min) in standing position until muscle exhaustion and/or the leg pain, followed by 8 min recovery in supine position.

Arterial occlusion with an exercise test (n=10): The subject rested supine and 14 cm wide pneumatic thigh tourniquets were placed on both thighs, INVOS on one leg and InSpectra on the other. The measurements started with a 2 min baseline period. Ischemia was then induced by inflation of the thigh tourniquets to 100 mmHg above the subject’s systolic blood pressure. The subject performed maximal concentric dorsiflexions of both feet (60 cycles/min) until muscle exhaustion and/or leg pain. The tourniquets were then released and measurements were continued during 8 min of recovery.

Arterial occlusion alone test (n=10): The subject rested supine and 14 cm wide pneumatic thigh tourniquets were placed on both thighs, INVOS on one leg and InSpectra on the other. The measurement was started with a 2 min rest period, the thigh tourniquets were then inflated to 100 mmHg above the subject's systolic blood pressure for up to 5 min depending on tolerance, followed by deflation and 8 min of recovery (Table I).

Results

Skin and subcutaneous tissue thickness was 3.9 ± 0.9 mm (median 3.9 mm) and there were no significant difference between men (3.5 ± 0.7 mm) and women (4.3 ± 0.9 mm), (p = 0.052). The skin and subcutaneous thickness was not correlated to BMI (p=0.72).

Baseline StO_2 was 87 ± 8 % (median 89, range 71–98 %), (InSpectra) and 76 ± 6 % (median 76, range 58–84 %) (INVOS). The difference between the two devices was significant (p <0.001).

Table I *Muscular oxygen saturation expressed (%) during exercise- and occlusion test.*

	INVOS	InSpectra	p-value
StO_2 during Peak exercise	17 (15-42)	1 (1-26)	0.001
Arterial occlusion + exercise-test	15 (15-36)	1 (1)	
Arterial occlusion test	15 (15-40)	1 (2-26)	

A significant negative correlation was found (r = -0.78, p <0.01) between skin and subcutaneous tissue thickness and baseline StO_2 for InSpectra. In women the correlation was more pronounced (p < 0.01) compared with men (p = 0.02). A significant negative correlation (r = -0.65, p = 0.002) was found between skin and subcutaneous tissue thickness and change in StO_2 for InSpectra.

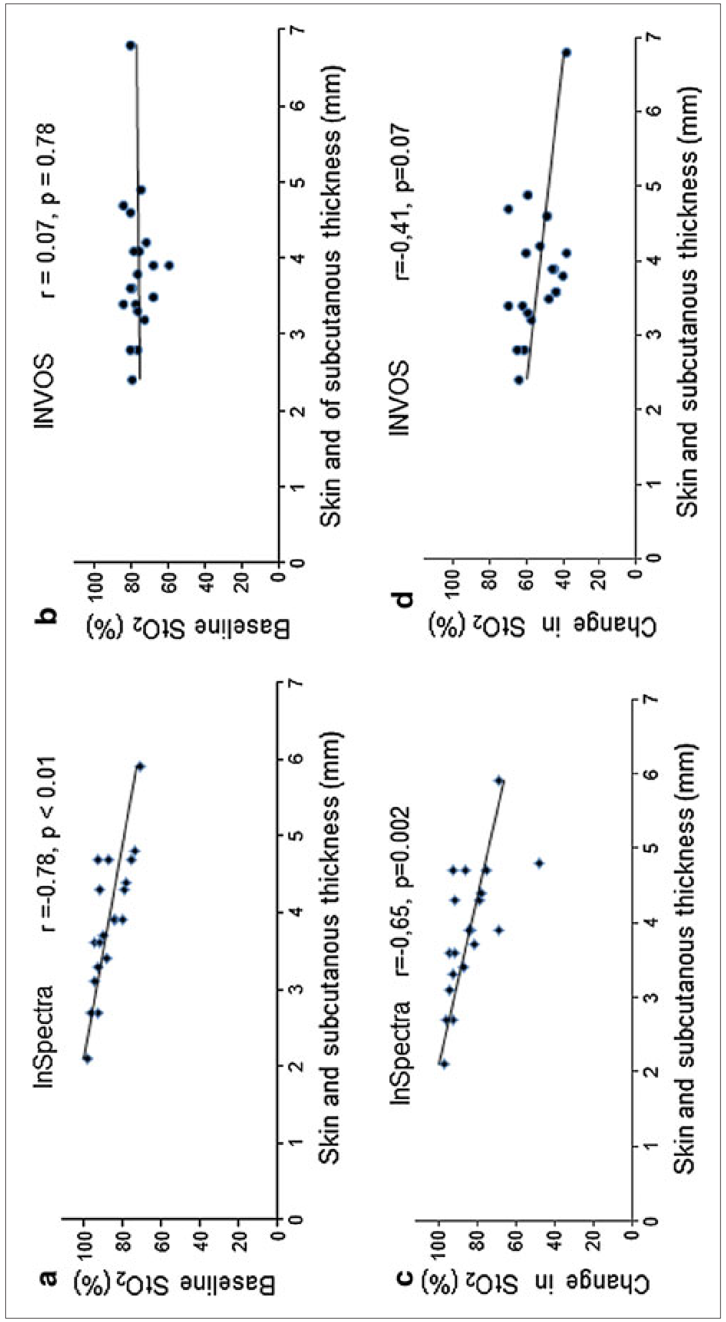


Figure 14. *Both baseline muscle oxygen saturation (StO_2) and change in measured by InSpectra (a and c) were negatively correlated with skin and subcutaneous tissue thickness (a, c). No significant correlation was discovered between skin and subcutaneous thickness and baseline StO_2 or change in StO_2 measured by INVOS (b, d).*

Conclusion

The NIRS-device INVOS is able to detect experimentally induced skeletal muscle ischemia in the human leg. Muscle oxygen saturation measurement by INVOS is less affected by skin and subcutaneous thickness than InSpectra. The use of NIRS may be helpful to detect leg muscle ischemia during clinical situations with decreased blood circulation.

STUDY III

Why was this study performed?

The purpose of the present study was to evaluate the NIRS-device InSpectra in diagnostic purpose of CACS. Previous study has shown differences between deoxygenation during exercise in patients with CACS and patients with other causes of exercise induced leg pain(Mohler et al. 1997, van den Brand et al. 2004).

Hypothesis

Muscle oxygen saturation decreases more during exercise and the time period for reoxygenation after exercise is longer in CACS patients compared with non-CACS patients.

Methods

The study comprised 159 consecutive patients with median age of 29 years (14-67) years all with exercise-induced leg pain (Figure 15). Thirty-one healthy subjects were also included in the study. All the participants performed an exercise test that elicited leg pain and muscle fatigue. StO_2 in the tibialis anterior muscle was measured continuously before, during and after the test using NIRS. One minute post-exercise, intramuscular pressure (IMP) was recorded in the same muscle. The cohort was divided into CACS patients and non-CACS patients according to diagnostic criteria, which were based on 1) exercise-induced leg pain over the anterior compartment with reversed symptoms at rest, 2) swelling and tenderness over the anterior compartment immediately after exercise, 3) impaired muscle function during activity, 4) IMP of ≥ 30 mmHg one minute after exercise 5) IMP of ≥ 20 mmHg five minutes after exercise.

Reoxygenation at rest after exercise was calculated as the time period required for the level of muscular StO_2 to rise by 50% (T_{50}), 90% (T_{90}) and 100% (T_{100}) of the baseline value (Table II).

Results

There were no differences between CACS and non-CACS patients in StO_2 –changes neither at peak-exercise nor in recovery after exercise (Table III and Table IV).

Cut-off values for sensitivity and specificity were determined. The sensitivity was 34% and the specificity was 43% when the level of StO_2 at peak exercise was ≤8%, indicating CACS. Median time in seconds at T_{90} in patients with CACS was 28 seconds. The sensitivity of the StO_2 was 38% and the specificity was 50% to diagnose CACS among patients with exercise-induced leg pain when the cut-off value was T_{90} ≥30 seconds. The positive predictive value was 48% and the negative predictive value was 40%.

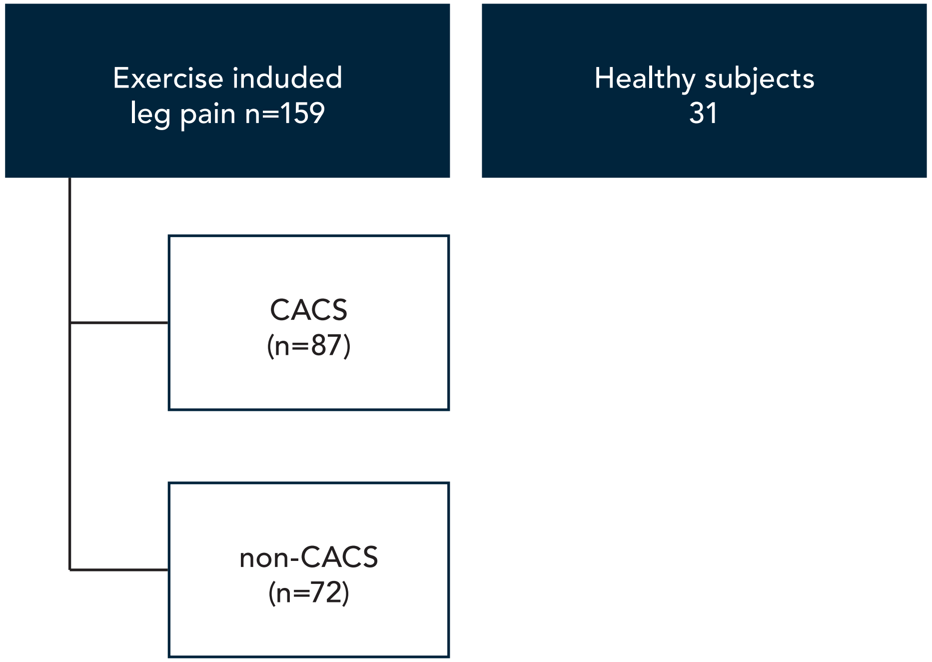


Figure 15. *Patients in study III (n=159), which were divides into chronic anterior compartment syndrome (n=87) and non-chronic anterior compartment syndrome (n=72). Thirty-one healthy subjects were included.*

Table II *Definition of observation points*

Points of observation	Definition
Baseline of StO_2	The level of StO_2 before exercise
During Exercise	
Peak exercise StO_2 (%)	The lowest level of StO_2 at maximum effort
End of exercise StO_2 (%)	The level of StO_2 at the end of exercise
At rest after exercise	
T_{50} (sec)	The time period required for the level of StO_2 from the end of the exercise to reach 50% of its baseline
T_{90} (sec)	The time period required for the level of StO_2 from the end of the exercise to reach 90% of its baseline
T_{100} (sec)	The time period required for the level of StO_2 from the end of the exercise to reach 100% of its baseline
Maximum recovery StO_2 (%)	The maximum level of StO_2 during recovery

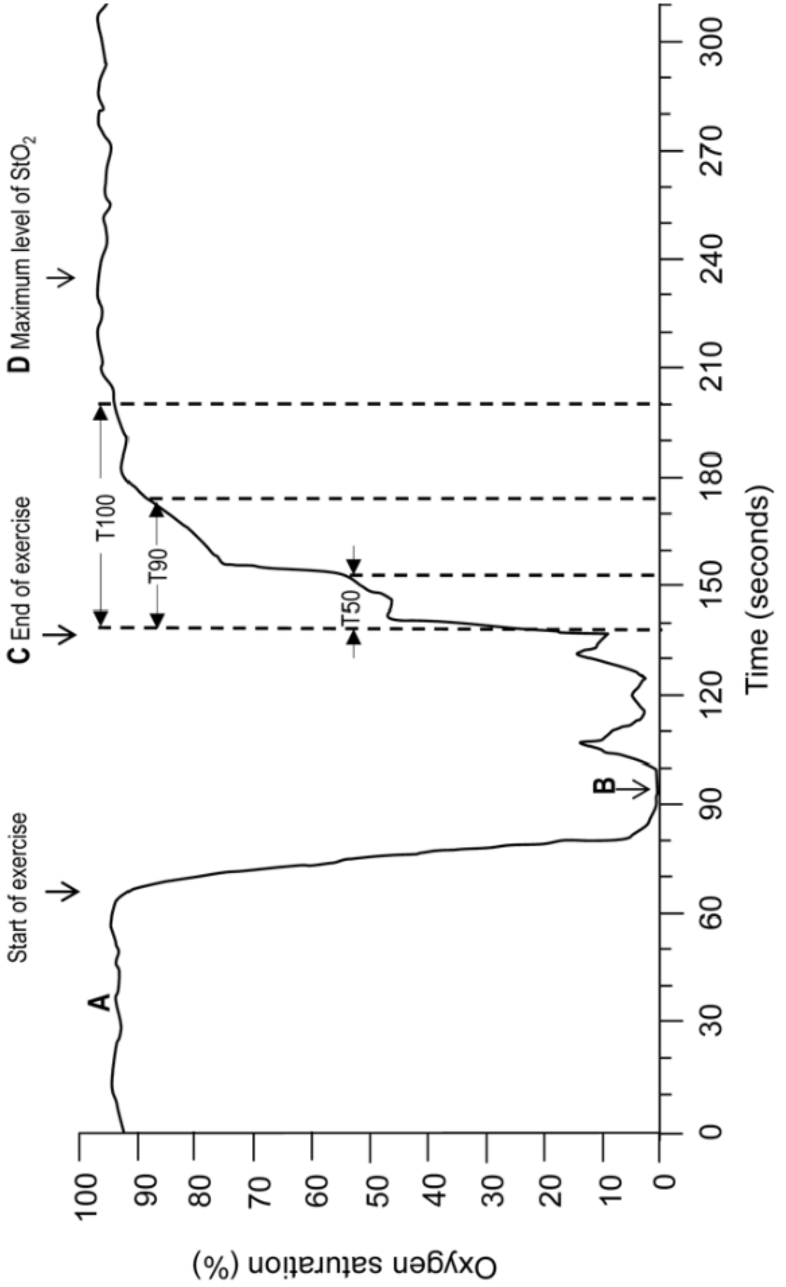


Figure 16. *Muscle oxygen saturation (StO_2) before, during and at rest after exercise. A: Baseline, prior to the exercise test. B: The lowest level of StO_2 during exercise. C: End of exercise followed by reoxygenation phase. T_{50}, T_{90} and T_{100} describe the time in seconds required for the level of StO_2 from the end of exercise to reach 50, 90 and 100% of its baseline. D: The maximum level of StO_2 at rest after exercise.*

Table III *Outcome results at various points*[a]

Parameter	A.CACS Patients (n=87) median (range)	B. Non-CACS Patients (n=72) median (range)	C. Healthy Subjects (n=31) median (range)	P Value A vs B	P Value A vs C
Baseline of StO_2	92 (45-98)	84 (40-98)	88 (59-98)	0.005	NS
During Exercise					
Peak exercise StO_2 (%)	1 (1-36)	3 (1-54)	1 (1-44)	0.003	NS
End of exercise StO_2 (%)	1 (1-68)	17 (1-69)	1 (1-54)	0.001	NS
At rest after exercise					
T_{50} (sec)	7 (1-43)	10 (1-49)	9 (1-34)	0.001	NS
T_{90} (sec)	28 (7-77)	32 (4-138)	24 (5-58)	0.013	NS
T_{100} (sec)	42 (7-200)	48 (4-180)	31 (11-86)	NS	0.001
Maximum recovery StO_2 (%)	95 (57-98)	93 (38-98)	97 (76-98)	0.001	0.016

[a]*Values are expressed as median (range); CACS, chronic anterior compartment syndrome; StO_2, muscle ocygen saturation.*

Table IV *Outcome results at various parameters*[a]

Parameter	A.CACS Patients (n=87) median (range)	B. Non-CACS Patients (n=72) median (range)	C. Healthy Subjects (n=31) median (range)	P Value A vs B	P Value A vs C
Post-exercise IMP (mmHg)					
All patients	45 (30-111)	16 (5-28)		0.001	NA
Female patients	38 (30-72)	16 (5-28)			
Male patients	47 (30-111)	17 (6-25)			
MAP (mmHg)					
Before exercise	88 (73-106)	83 (72-128)	86 (74-104)	0.005	NS
At rest after exercise	92 (92-129)	89 (68-129)	86 (76-103)	0.014	0.010
Post-exercise PP (mmHg)	47 (-11-73)	71 (50-117)		0.001	NA
Exercise time (sec)	52 (12-315)	59 (27-174)	106 (30-307)	NS	0.001
VAS (cm)					
Before exercise	0 (0-8)	0 (0-6.3)	0 (0)		
Maximum during exercise	**6.7 (0-10)**	6.7 (0-10)	5.0 (0-9)	**NS**	**0.034**
The thickness of skin and subcutaneous					
All participants	4.4 (2.2-10.4)	5.2 (1.8-13.7)	4.3 (2.1-8.9)	NS	NS
Female participants	6.4 (2.8-9.3)	6.0 (2.2-13.7)	4.6 (3.3-8.9)		
Male participants	3.7 (2.2-10.4)	3.6 (1.8-9-6)	3.7 (2.1-5.0)		
Distance between fascia and the tip of the IMP needle (mm)					
All patients	5.8 (2.4-13.6)	6.0 (0.8-13.6)		NS	

[a]*Values are expressed as the mean ± standard deviation, apart from VAS values, which are expressed as medians (range); CACS, chronic anterior compartment syndrome; IMP, intramuscular pressure; MAP, mean arterial blood pressure; PP, perfusion pressure; VAS, visual analogue scale.*

Conclusion

Assessments of changes in muscle oxygen saturation (StO_2) during and after an exercise test (Figure 16) that elicits leg pain are unable to distinguish between patients with CACS and patients with other causes of exercise-induced leg pain. The time of recovery after depletion of muscular oxygenation during exercise does not differ significant between patients with CACS and patients with other causes of exercise-induced leg pain.

STUDY IV

Why was this study performed?

The concept of patient pain drawing (PPD) was introduced by Palmer in 1949. The basic idea was to differentiate between functional and organic pain by using a pain chart made by the patient, as a diagnostic instrument (Palmer 1949). PPD has especially been used in the diagnostic evaluation of patients with low back pain (Hägg et al. 2003) and it has shown high inter-observer reliability and intra-observer agreement (Undén et al. 1988). However, the clinical utility of PPD in diagnosing the causes of exercise-induced leg pain and its sensitivity and specificity as a diagnostic tool, have not been reported before.

The purpose of this study was to validate patient pain drawing (PPD) as an instrument in establishing the diagnosis of chronic anterior compartment syndrome (CACS) in patients with exercise-induced leg pain. PPD has not been evaluated in this manner previously.

Hypothesis

The hypothesis was that PPD is a valuable diagnostic instrument to identify CACS.

Methods

The study comprised 477 consecutive patients, 258 men and 219 women, with a median age of 31 (range 15-70) years, all with exercise-induced leg pain and clinical signs of CACS. The patients were divided into different groups according to diagnoses (Figure 17).

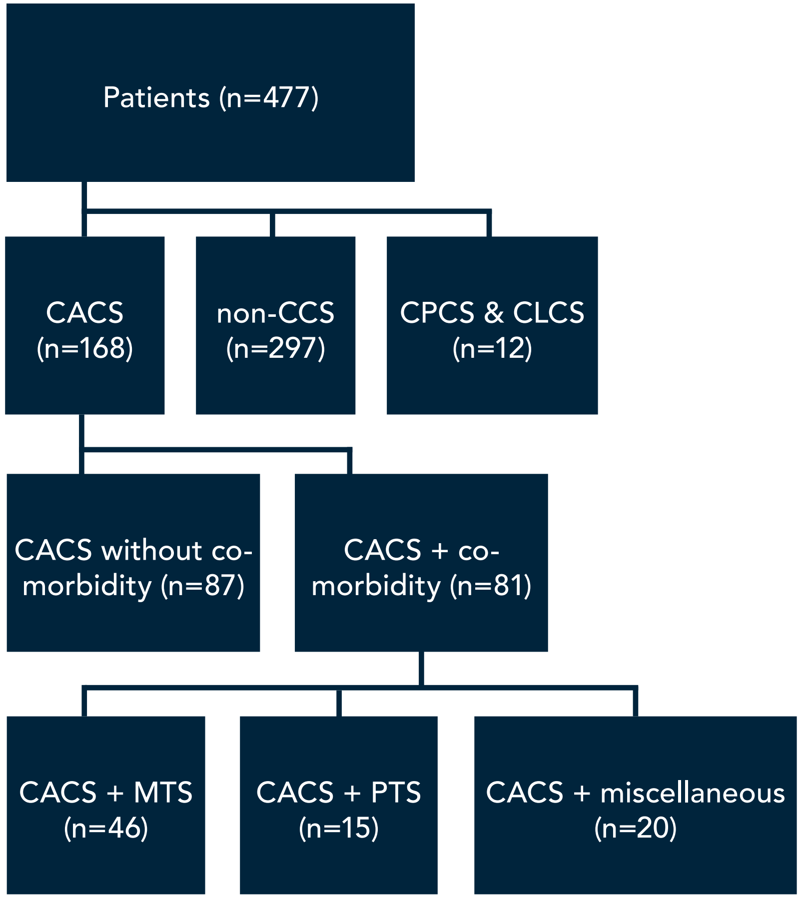


Figure 17. *The 477 patients were allocated into the following groups: CACS, chronic anterior compartment syndrome; non-CCS, patients with other causes of exercise-induced leg pain; CLCS, chronic lateral compartment syndrome; CPCS, chronic posterior compartment syndrome; MTS, medial tibial syndrome; PTS, peroneus tunnel syndrome.*

Two independent orthopaedic surgeons (Observer 1 and 2) diagnosed the causes of leg pain based only on the PPD forms. To avoid recall bias the procedure was done at least one year after the patient's clinical appointment. For validation a secondary test-retest was performed one year further after the primary assessment and 100 drawings were re-assessed. Related to the drawings, the observer could select one or more diagnoses from a list of six diagnoses and one group of miscellaneous; i.e. chronic anterior compartment syndrome, chronic lateral compartment syndrome, chronic posterior compartment syndrome, medial tibial syndrome, peroneal tunnel syndrome, muscle rupture and group of miscellaneous.

Patient Pain Drawing (PPD)

All patients completed a questionnaire received by mail two weeks prior to their visit at the clinic. The questionnaire included a human body manikin with anterior, posterior and lateral views (Figure 18). The patients indicated the afflicted areas of pain on the PPD (Figure 19). The drawings were discussed as a part of the patient's history during the meeting between the patient and doctor.

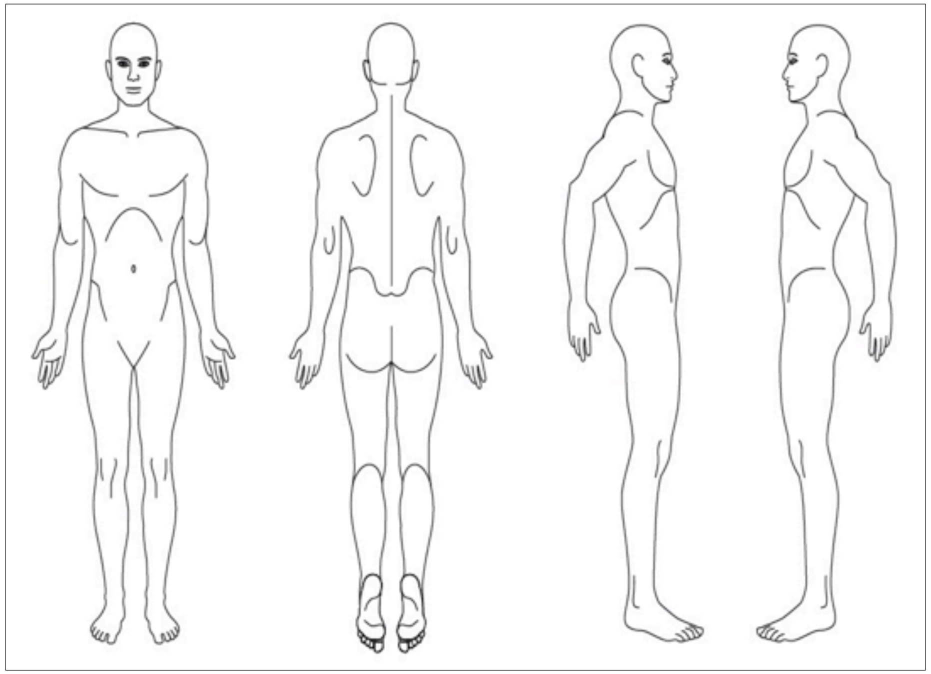


Figure 18. *Antero-posterior and lateral views of a human body manikin.*

Before the assessments by the observers were done, a pre-test comprising 10 drawings was performed to discuss the way of interpretation of the drawings. The same observers re-evaluated 100 PPD forms one year after the primary assessments to estimate the test-retest reliability.

Results

IMP was 48 (SD 16) mmHg in 168 CACS-patients and it was 17 (SD 6) mmHg in the 256 non-CACS-patients ($p<0.01$).

Sensitivity and specificity

The sensitivity, specificity, positive and negative predictive values based on PPD in diagnosing CACS among the 477 patients are shown in Table V.

Table V

Parameter	Observer 1	Observer 2
Sensitivity (%)	75	67
Specificity (%)	54	65
Positive Predictive value (%)	47	51
Negative predictive value (%)	80	78

Sensitivity and specificity of patient pain drawing (PPD) to correctly identify chronic anterior compartment syndrome (CACS) in 477 patients with exercise-induced leg pain.

Intra-observer agreement

When assessing the agreement between the PPD and the gold standard, the correct diagnoses were assessed in 79% (Observer 1) and 82% (Observer 2) of the CACS patients (n=79). The agreement was 80% (Observer 1) and 75% (Observer 2) in the CACS patients with co-morbidity (n=89) (Table 2).

Inter-observer reliability

Kappa values for the two observers and percentage of agreement between the two observers are shown in Table VI.

Intra-observer agreement (test-retest)

One hundred forms were re-evaluated in a test-retest. The intra-observer agreement was 84% for both observers and the test-retest reliability coefficient was 0.7.

Co-morbidity

In the present study, 53% of the CACS patients were diagnosed with co-morbidity. The distribution of the CACS patients with co-morbidity (n=89) was medial tibial syndrome in 55%, miscellaneous in 24% and peroneal tunnel syndrome in 21%.

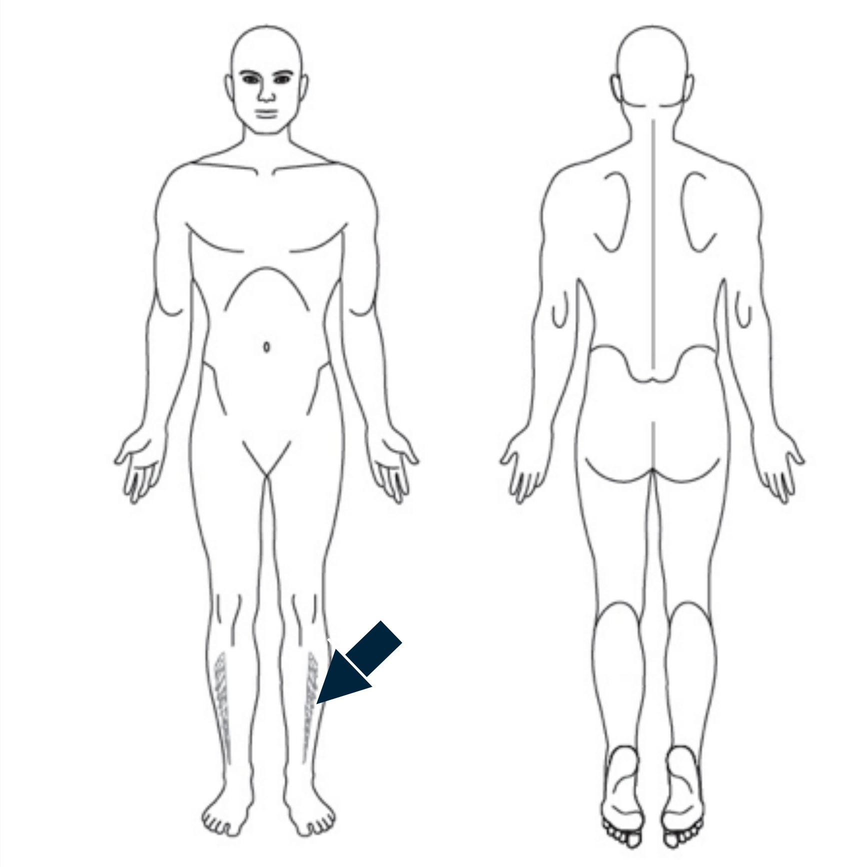


Figure 19. *A typical illustration of a human body-manikin with drawing completed by a patient with CACS.*

Table VI *Inter-observer agreement and kappa values*

Parameter	Agreement (%)	kappa
All patients (n=477)	80	0.55
CACS (n=168)	77	0.48
CACS without co-morbidity (n=79)	85	0.56
CACS with co-morbidity (n=89)	79	0.34

CACS, Chronic anterior compartment syndrome.

Conclusion

PPD is a valuable instrument to diagnose the causes of exercise induced leg pain. It is helpful in identifying CACS both with and without co-morbidity.

conclusions

The main conclusions in this thesis

- Near-infrared spectroscopy (NIRS) is not a reliable instrument for diagnosing chronic anterior compartment syndrome (CACS) due to the inability to differentiate CACS patients from patients with other causes of exercise-induced leg pain (Studies I and III).

- The two NIRS devices, InSpectra and INVOS, are able to measure muscular oxygen saturation in experimentally induced acute ischaemia in the leg (Study II).

- The INVOS is a more reliable device than the InSpectra for measuring muscle oxygen saturation in patients who have relatively thick subcutaneous tissue (Study II).

- Patient pain drawing (PPD) facilitates the overall evaluation of CACS patients – not only in establishing the diagnosis but also in identifying co-morbidity and planning the compartment(s) in which intramuscular pressure measurements should be performed (Study IV).

discussion

Elevated intramuscular pressure has been known as a possible cause of exercise-induced leg pain in recreational runners and athletes since the 1960-70s. It is usually the anterior muscular compartment in the lower leg that is involved in the syndrome known as chronic anterior compartment syndrome (CACS). Exercise elicits the pain and the patients are free from symptoms at rest. To diagnose CACS, the measurement of intramuscular pressure by inserting a needle has long been the method regarded as the gold standard (Reneman 1975, Wallensten and Eriksson 1984, Styf et al. 1987). However, it would be desirable if a reliable, non-invasive diagnostic method for this patient group was available.

The main focus of this thesis was to investigate the potential for using near-infrared spectroscopy (NIRS) as an alternative method to IMP measurement to diagnose CACS. NIRS measures the local muscular oxygen saturation. Three different devices based on NIRS methodology were investigated in three of the four studies included in this thesis. In addition, the opportunity to acquire information from patient pain drawings (PPD) in order to establish the CACS diagnosis was investigated. The findings in CACS patients were compared with those in patients with other established diagnoses, causing lower leg pain. Moreover, in Studies II and III, healthy individuals were included in the comparison of the two modern NIRS devices.

NIRS as a diagnostic method for CACS

The first generation of NIRS, called RunMan, was used in Study I. The measurement of muscle oxygenation is given as a relative value by the RunMan. The further development of the methodology resulted in the InSpectra device, which delivers an absolute value for the local muscle oxygen saturation. Another NIRS device called INVOS was developed to monitor the local oxygen saturation of the brain during cardiothoracic surgery, where it is currently used in daily practice (Scheeren et al. 2012). Due to the need sometimes to monitor skeletal muscle in the leg when suspicions of hypoxia might arise, Study II was designed.

The use of NIRS to diagnose CACS was suggested, based on the finding that patients with CACS differ in muscular oxygen saturation during exercise compared with patients who have other causes of leg pain, as well as when compared with healthy individuals (Breit et al. 1997, Mohler et al. 1997, van den Brand et al. 2005). The affected muscles in patients with CACS have been observed to deoxygenate to a lower level and to reoxygenate after exercise during a prolonged period, compared with the muscles in patients with other causes of leg pain (Breit et al. 1997, Mohler et al. 1997, van den Brand et al. 2004, van den Brand et al. 2005, Zhang et al. 2012).

Findings using the first generation of NIRS device (RunMan) in CACS patients

Study I consists of a relatively large cohort, comprising 47 CACS patients and 129 patients with other causes of leg pain. In the two sub-cohorts, i.e. patients with and without CACS, the muscles in the lower leg were found to deoxygenate to the same extent during exercise and no significant differences between these two groups could be observed. These results are, however, not in line with the results presented by Mohler et al. (Mohler et al. 1997). The divergent results were surprising and no explanation was found when comparing the design of these two studies. The exercise test used in Study I appears to be comparable to the exercise test performed by Mohler et al. and the tests were performed in a similar manner. So the differences in the results in Study I and in the study performed by Mohler et al. are difficult to explain.

When comparing with the study by Mohler et al., it has to be remembered that all their study objects were continuously monitored with IMP. This is a strength of that study, confirming the diagnosis by using the gold standard method. However, the study by Mohler et al. had limitations, as it only comprised 10 patients with CACS and eight patients with other causes of leg pain. The 10 healthy volunteers in their study can be regarded as a strength.

Findings using the second generation of NIRS device in CACS patients

In order to further investigate the opportunity to use NIRS as a diagnostic instrument in patients with CACS, Study III was designed, using a more modern NIRS device than that used in Study I; i.e. the InSpectra device. Moreover, a larger patient cohort was included in this study; a total of 159 patients with lower leg pain, plus 31 healthy individuals. As far as we know, this is the largest patient cohort with CACS (n=87) investigated using the NIRS technique in the literature.

In Study III, findings similar to those in Study I were observed with regard to the deoxygenation phase. It was observed that the magnitude of deoxygenation during exercise did not differ in clinical terms between patients with CACS and patients with other causes of leg pain. The magnitude of deoxygenation during exercise reflects a variation in work intensity and might be influenced by leg pain among the patients.

The current results also differ from the results presented by Mohler et al. in terms of the increased magnitude of deoxygenation in patients with CACS compared with patients with other causes of leg pain (Mohler et al. 1997). Moreover, in the study by van den Brand et al., patients with CACS (n=42) were reported to have more pronounced deoxygenation compared with patients with other causes of leg pain (van den Brand et al. 2005). However, both these studies included a limited number of patients with other causes of leg pain. There were eight control patients in the study by Mohler et al. and only three in the study by van den Brand et al.

Moreover, no differences during deoxygenation were recorded between CACS patients and healthy individuals in Study III. This finding also differed from the findings of Mohler et al., where healthy individuals (n=10) were included as well. The reasons for the different findings in the present study and other previous studies are not completely clear, but they may be related to the relatively large inter-individual variation, which can easily cause large differences when the sample size is small, and to the performance of the exercise test.

In Study I, and in the study by Mohler et al., the recovery time for muscular oxygenation (time for the oxygenation to return to the baseline value, T_{100}) was found to be prolonged in patients with CACS when compared with patients with other causes of leg pain. In the study by van den Brand et al., there were no indications of a prolonged reoxygenation phase (van den Brand et al. 2004). The impact of the reoxygenation period is therefore not really clear considering the results in Study I.

However, as the results from Study III showed no differences in the recovery phase between patients with CACS and patients with other causes of leg pain, the impact of the recovery period could be regarded as not being especially useful. However, when CACS patients, as well as patients with lower leg pain caused by other conditions, were compared with healthy individuals in Study III, a prolonged recovery time was observed for both patient groups compared with the controls. As both patient groups showed similar changes, the recovery phase does not appear to be a valuable instrument in distinguishing patients with CACS from patients with other causes of lower leg pain. Furthermore, the poor sensitivity (38%) and specificity (50%) when analysing the level of muscle oxygen saturation at T_{90} indicate several limitations in diagnosing CACS.

Assessing agreement between INVOS and In Spectra in healthy individuals

In Study II, the two NIRS devices, InSpectra and INVOS, both representing the second generation of NIRS devices, were compared. The INVOS is used in daily practice during cardiac surgery to monitor StO_2 of the brain. Both devices show absolute oxygen saturation values. The study investigated the changes in StO_2 in a muscular compartment in the lower extremity of 20 healthy individuals during experimentally induced muscle ischaemia, using both methods. The most important finding was that the INVOS, which was developed to monitor the oxygenation of brain tissue, can also be used to detect skeletal muscle ischaemia.

There are some differences between the two methods and they may play a role in some conditions. The InSpectra measures the spectrum of light between 650-900 nm. The wide range of changes in haemoglobin saturation that can be detected by the InSpectra is therefore between 1-99%. The INVOS, on the other hand, detects the spectrum of light between 730-810 nm and this corresponds to changes in oxygenation between 15-95% saturation. In clinical terms, this means that the InSpectra is able to detect changes within a wider range of light compared with the INVOS. If the INVOS is used clinically during suspected severe hypoxia in skeletal muscle, values below 15% of oxygen saturation must be considered as somewhere between 1-15% of saturation.

One known advantage of the INVOS is that it does not monitor the most superficial tissue layers. It measures the oxygen saturation of the muscle at a tissue depth of approximately 15-20 mm (Figure 10). This means that the most superficial layer is not within the range of the light. It was also clearly demonstrated in Study II that the INVOS was less sensitive to a thick layer of subcutaneous tissue than the InSpectra, when the two methods were compared in individuals with thick subcutaneous tissue (Figure 14).

Evaluation of pain drawings as a diagnostic instrument in patients with CACS

Establishing the diagnosis of CACS is a complex process, as it cannot be performed by observing only one parameter or by using a single test available today. As a result, one of the aims of the present thesis was to investigate whether pain drawings (PPD) produced by patients with exercise-induced leg pain were able to help to differentiate the patients with CACS from a group of patients with other diagnoses of lower leg pain. In Study IV, PPDs from patients, all diagnosed with CACS using clinical findings and IMP measurements (n=168), were compared with those produced by a group of patients with lower leg pain with other causes (n=309). In this study, the sensitivity of two independent observers in diagnosing CACS in a cohort of 477 patients with exercise-induced leg pain was 67-75%. The specificity was 54-65%, the positive predictive value 47-51% and the negative predictive value 78-80%. The results might appear to be fair, but, as an additional diagnostic instrument, PPD should be considered to be valuable.

When it comes to pain drawings, the method has previously been used to discriminate between organic and non-organic pain (Palmer 1949). Pain drawings have mostly been used in patients with lumbar pain (Hägg et al. 2003). The patient simply indicates the affected area on a body manikin. The clinical usefulness of PPD in diagnosing the causes of exercise-induced leg pain, together with its sensitivity and specificity as a diagnostic instrument, has not been reported before.

Even if the predictive value of selecting the CACS patients from a non-specific group of patients with lower leg pain was relatively low, PPD might be valuable as an additional instrument in the diagnostic evaluation of CACS. Using PPD to select patients at primary care level for referral to a specialist is, however, not advisable, based on these results.

Limitations and strengths of the studies

Study I

The CACS diagnosis in Study I was determined clinically. Only in cases of uncertainty were IMP measurements performed, which is a limitation of this study. A further limitation in this study was that no healthy volunteers were included. On the other hand, Study I consisted of a large cohort of 47 CACS patients and 129 patients with other causes of leg pain.

Study III

A limitation of Study III is that the 31 healthy controls did not undergo IMP measurement. A major strength of Study III was the large number of patients included, 87 patients with CACS, 72 patients with other diagnoses resulting in lower leg pain. All the patients in this study were examined with IMP measurements and the position of the measurement needle was controlled using ultrasound. The diagnosis of CACS was based on IMP measurements, together with the patient history and clinical examination.

Study II

One of the limitations of Study II was that the comparison of the two methods was performed in healthy individuals, in which an ischaemic condition of the muscle was induced by exercise and arterial occlusion with and without exercise to the leg. However, the limitation of the NIRS method is that, in patients with relatively thick subcutaneous tissue, it will cause the same inaccuracy in a cohort of patients during thoracic surgery as in healthy individuals. The strength of this study was that it was carried out in a controlled manner in a healthy group of patients.

Study IV
One of the limitations is that the evaluated instrument was not created to discriminate between different organic pain diagnoses. A strength was that a large number of patients with lower leg pain were evaluated (477 patients).

The value of the exercise test in diagnosing CACS using different methods measuring changes in muscle parameters

No solitary test measuring muscular changes, such as intramuscular pressure or oxygen saturation, can indicate changes specific to CACS and the clue to the diagnosis might be the exercise test. As the patients are free of symptoms during rest, it is important that the test really does elicit the symptoms.

The pain that is elicited by exercise is usually severe, but only for a very short time. Pain in patients with CACS can be partly explained by traction of the periosteum, as the IMP is elevated and the pacinian corpuscles of the fascia are stimulated (Balduini et al. 1993). In all patients, the physiological increase in metabolites, such as potassium and hydrogen ions and lactate, develops as oxygen decreases and pain will thereby increase. Patients who suffer from additional diagnoses, i.e. co-morbidity, such as medial tibial syndrome, peroneal tunnel syndrome or muscle rupture, might experience different components of pain that may be difficult to distinguish from CACS.

However, based on the results in the present thesis, the exercise test appears to be dependent on the intensity of the performance at exercise. It can be speculated that an athlete, who is used to exercising in painful conditions, can focus on the exercise test as a challenge and thereby reach low levels of muscular oxygen saturation despite pain, whereas other patients might give up much earlier during the test. This could explain the findings in some previous studies, where a lower level of muscular oxygenation during exercise in patients with CACS compared with other patients has been observed.

A confounding factor when it comes to the exercise test is the co-morbidity of lower leg pain. Co-morbidity was observed in Study IV in more than every second patient and might influence the performance ability during the exercise test. These patients can be misdiagnosed, as the pain during the test may limit the performance and force the patient to stop before the IMP has increased. Increased knowledge of additional diagnoses can be acquired from PPD and this is an advantage when adjusting the exercise test. Most probably, the exercise test should be individualised.

Present knowledge of aetiology and diagnosis of CACS

The aetiology of CACS is still unknown. Ischaemia has been a major issue in the discussion of chronic compartment syndrome and reduced blood flow has been observed in patients with CACS (Qvarfordt et al. 1983, Styf et al. 1987). Opposite findings, such as no indication of ischaemia, have also been reported (Amendola et al. 1990). An additional and important finding in Study III was that, post-exercise, 86% of the patients with CACS had a perfusion pressure equal to or above 30 mmHg. In previous studies, local perfusion pressure exceeding 30 mmHg has been indicated to be satisfactory for healthy tissue (Heppenstall et al. 1988). It might therefore be correct to conclude that, in patients with CACS, who have elevated IMP after exercise for only a very short time if at all, the perfusion pressure is below the tissue demands. Moreover, the knowledge that a large proportion of patients fulfilling the criteria of CACS also suffer from other lower leg conditions (lower leg co-morbidity) might blur the clinical picture.

In conclusion, based on current knowledge, the diagnosis of CACS should be made in a multifaceted procedure, including a detailed patient history, patient pain drawing and an exercise test adjusted to elicit the symptoms, followed by IMP measurement. Non-invasive tests, such as NIRS, have not been shown to be able to replace the invasive IMP measurement.

future perspectives

Even if our understanding of chronic anterior compartment syndrome (CACS) has improved dramatically since the first reports on this condition in the 1960s, there are still knowledge gaps to be filled. Why does this happen? Are some patients more prone to develop this condition than others? Do genetics or specific exercise patterns predispose people to developing CACS? For diagnostic evaluation and treatment, these questions may not have the highest priority, but an increased knowledge of aetiology and pathophysiology may be valuable when it comes to possible prevention.

To diagnose CACS, the development of non-invasive techniques measuring intramuscular pressure, preferably by continuous monitoring during muscle activation in real life and not just in a laboratory setting, would be of benefit. This type of monitoring would then also be able to detect increased intramuscular pressure. As the treatment of CACS is a relatively simple surgical procedure, but still a surgical intervention with a possible risk of post-operative morbidity, diagnostic instruments of this kind would be highly desirable.

Considering the diagnostic aspect, larger studies, especially with men and women evaluated in different cohorts, would be desirable. It is probable that the diagnostic criteria would be different in these two groups.

Studies with long-term follow-up after conservative (non-surgical) treatment, especially in young girls, would be valuable, since the surgical outcome often reveals co-morbidity.

Finally, the exercise test might need to be standardised for study purposes. Or, on the other hand, confirmation that the exercise test should be individualised is required.

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paper I

Zhang Q, Rennerfelt K, Styf J

The magnitude of intramuscular deoxygenation during exercise is an unreliable method to diagnose the cause of leg pain

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paper II

Nygren A, Rennerfelt K, Zhang Q

Detection of changes in muscle oxygen saturation in human leg: a comparison of two near-infrared spectroscopy devices

J Clin Monit Comput. 2014:28 (1):57-62

paper III

Rennerfelt K, Zhang Q, Karlsson J, Styf J

Changes in muscle oxygen saturation have low sensitivity in diagnosing chronic anterior compartment syndrome of the leg

Conditionally accepted, J Bone Joint Surg

paper IV

Rennerfelt K, Zhang Q, Karlsson J, Styf J

Patient Pain Drawing is a valuable instrument to assess the causes of exercise-induced leg pain

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