Pulse-Synchronous Intramuscular Pressure Oscillations

Clinical and experimental studies

Andreas Nilsson

Department of Orthopaedics

Institute of Clinical Sciences

Sahlgrenska Academy at University of Gothenburg

UNIVERSITY OF GOTHENBURG

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Cover illustration: Pulse-Synchronous Intramuscular Pressure Oscillations

To my loving daughter Linnéa

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Department of Orthopaedics, Institute of Clinical Sciences
Sahlgrenska Academy at University of Gothenburg
Göteborg, Sweden

ABSTRACT

Background

Intramuscular pressure (IMP) is measured in studies of tissue nutrition and in the diagnosis of compartment syndromes. Patients with compartment syndromes have an elevated IMP due to increased volume in a muscle compartment. In patients with exercise-induced leg pain, the measurement of IMP is commonly regarded as the gold standard in diagnosing chronic anterior compartment syndrome (CACS). However, recent studies have reported that IMP as a parameter in diagnosing CACS needs to be improved.

Oscillations of the IMP deriving from arterial pulsations have previously been detected in muscles with abnormally elevated IMP. The relationship between the amplitude of the IMP oscillations and the absolute IMP is, however, unknown.

Aims

The aims of the thesis were therefore to investigate the relationship between the IMP and the amplitude of the pulse-synchronous IMP oscillations and to evaluate the potential of using pulse-synchronous IMP oscillations in diagnosing compartment syndromes.

Methods

Pulse-synchronous IMP oscillations were studied at normal levels of IMP at rest, during experimental models of abnormally elevated IMP and at rest after exercise. The amplitude of the oscillations was measured in healthy subjects, patients with CACS and in patients with leg pain for reasons other than CACS.

Results
The amplitude of the IMP oscillations was higher for the CACS patients compared with the control subjects and patients with leg pain for reasons other than CACS.

During simulated compartment syndrome, the oscillations were observed in the entire IMP range seen in patients with chronic and acute compartment syndromes. The amplitude of the IMP oscillations varied with the absolute level of the IMP. The largest amplitudes were recorded when the level of the IMP was close to the level of the mean arterial pressure and the local perfusion pressure approached zero. The amplitude of the oscillations is a parameter with high sensitivity and specificity that may lend support when diagnosing CACS.

Among the CACS patients, women had an 11 mmHg lower IMP at rest after exercise compared with men ($p < 0.01$). The magnitude of the difference may be of clinical importance. The amplitude of the IMP oscillations did not differ significantly between men and women ($p > 0.5$).

The fluid injections used with traditional needle-injection techniques influences the measured IMP. Even small amounts of saline constitute a measurement problem, rendering an overestimated IMP reading. Fiber-optic pressure-measurement techniques may therefore improve IMP measurements.

Conclusion
The amplitude of the pulse-synchronous IMP oscillations reflects the IMP and the pathophysiological foundation in compartment syndromes. The patency of the catheter and the validity of the IMP measurement is assured when pulse-synchronous IMP oscillations are recorded. The amplitude has high sensitivity and specificity in identifying CACS patients. It may be an additional parameter in both research and diagnosing compartment syndromes.

SAMMANFATTNING PÅ SVENSKA

Bakgrund

Intramuskulärt tryck är en viktig parameter vid studier av vävnadsnutrition och vid fysiologiska studier av muskelaktivitet. Det intramuskulära trycket anses även vara ett objektivt komplement till anamnes och kliniska fynd vid diagnostik av kompartmentsyndrom.

Patienter med kroniskt kompartmentsyndrom har ett förhöjt muskeltryck efter muskelansträngning. En objektiv tryckparameter är därför nödvändig vid diagnostik av kompartmentsyndrom. Det har dock nyligen visats att intramuskulärt tryck som diagnostisk parameter behöver förbättras.

Pulssynkrona oscillationer hos det intramuskulära trycket har registrerats hos patienter med kompartmentsyndrom. Oscillationerna härrör från de arteriella pulsationerna och är ett tecken på minskad eftergivlighet i muskeln. Oscillationerna kan vara kopplade till det absoluta värdet på det intramuskulära trycket men detta har inte visats och den diagnostiska betydelsen är okänd.

Syfte

Huvudsyftet med avhandlingen var att utreda hur amplituden hos de pulssynkrona intramuskulära tryckoscillationerna är relaterad till det intramuskulära trycket och vilket diagnostiskt värde oscillationerna har.

Metod

I avhandlingens fyra delarbeten mättes de pulssynkrona oscillationerna hos friska forskningspersoner och hos patienter med misstänkt kroniskt kompartmentsyndrom i underben. Oscillationer hos deltagarna mättes i vila efter muskelarbete och under simulerat kompartmentsyndrom.

Resultat

Amplituden hos det intramuskulära trycket är högre hos patienter med kroniskt kompartmentsyndrom jämfört med friska forskningspersoner och patienter med andra orsaker till ansträngningsutlöst underbenssmärta. Amplituden varierar med det intramuskulära trycket. Den är som störst när det intramuskulära trycket är ungefär lika stort som medelartärtrycket och det lokala perfusionstrycket är nära noll. Amplituden av oscillationerna har hög sensitivitet och specificitet för att diagnosticera kroniskt kompartmentsyndrom.

Hos patienter med kroniskt kompartmentsyndrom hade kvinnorna 11 mmHg lägre intramuskulärt tryck än männen ($p < 0.01$). Trycket mättes i vila efter muskelarbete och är det tryck som vanligtvis används vid diagnostik. Däremot fanns ingen signifikant skillnad i amplitud mellan kvinnor och män ($p > 0.5$).

Vätskefyllda injektionssystem är tryckmätningssystem som kräver injektion av en liten mängd vätska för att fungera tillfredsställande. Resultaten visar att även små mänger injicerad vätska ökar det uppmätta trycket. Injektionssystem är därför benägna att mäta falskt förhöjda tryck vid tryckmätning. Fiber-optiska tryckmätningssystem kan därför vara värdefulla vid mätning av intramuskulära tryck.

Slutsats

De pulssynkrona oscillationerna är en spegling av det förhöjda muskeltrycket som ses hos patienter med kompartmentsyndrom. Amplituden hos oscillationerna har hög sensitivitet och specificitet för att diagnosticera kompartmentsyndrom. När oscillationer registreras av mätsystemet är det en garanti för att dynamiken hos mätsystemet är bibehållen och att ett korrekt intramuskulärt tryck registreras. Oscillationerna hos det intramuskulära trycket kan således vara en användbar parameter vid diagnostik av kompartmentsyndrom.

LIST OF PAPERS

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

I. Nilsson, A., Zhang, Q., & Styf, J. **Evaluation of a fiber-optic technique for recording intramuscular pressure in the human leg**, Journal of Clinical Monitoring and Computing, 2015:1-7.

II. Nilsson, A., Zhang, Q., & Styf, J. **The amplitude of pulse-synchronous oscillations varies with the level of intramuscular pressure in simulated compartment syndrome**. Journal of Experimental Orthopaedics, 2015;2(1):3.

III. Nilsson, A., Zhang, Q., & Styf, J. **Using the Amplitude of Pulse-Synchronous Intramuscular Pressure Oscillations When Diagnosing Chronic Anterior Compartment Syndrome**. Orthopaedic Journal of Sports Medicine, 2014;2(11):2325967114556443.

IV. Nilsson, A. & Styf, J. **The Amplitude of Intramuscular Pressure Oscillations in Compartment Syndrome** Manuscript. Submitted, 2015.

CONTENT

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ABBREVIATIONS

BMI   body mass index

CACS   chronic anterior compartment syndrome

CECS   chronic exertional compartment syndrome

EMG   electromyography

FOPT   fiber-optic pressure transducer

IMP   intramuscular pressure

LPP   local perfusion pressure

MAP   mean arterial pressure

PP   perfusion pressure

sEMG   surface electromyography

VAS   visual analog scale

DEFINITIONS IN SHORT

Compliance	Measure of elastic properties: delta volume/delta pressure
Elastance	Stiffness, the invers of compliance
EMG	Electromyography is a technique for recording electrical activity produced by skeletal muscles
Intramuscular pressure	Hydrostatic fluid pressure in the interstitial space
Pressure	Force applied perpendicular to the surface of an object per unit area over which that force is distributed (Pa)
Strain	Elongation versus initial length of specimen
Stress	Force per unit area within a structure/tissue in response to externally applied loads (N/m2)

1
Introduction

1 INTRODUCTION

1.1 Intramuscular pressure

Intramuscular pressure (IMP) is an important parameter to measure in studies of muscle tissue nutrition and viability since it participates in the regulation of transcapillary fluid shift (Aukland et al., 1981; Hargens et al., 1981; Parazynski et al., 1991). It is also a measure of muscle force generation from an individual muscle (Aratow et al., 1993; Styf, 2004). Elevated IMP is the effect of increased fluid volume load in the muscle, muscle contraction, external compression applied to the muscle or a combination of these. Abnormally elevated IMP is commonly used as an objective criterion in the clinical diagnosis of compartment syndromes (Hargens et al., 1989; Hargens et al., 1977; Matsen 3rd et al., 1976; Styf et al., 1987).

1.1.1 Interstitial space

The space between blood capillaries, lymph vessels and cells is called the interstitial space or tissue space. In this space, which is filled with interstitial fluid, nutrition is delivered to the cells, metabolic waste is removed and intercellular communication occurs. The interstitial space in a normally hydrated muscle is only about a few percent of the total volume, while it is the largest space, exceeding 90%, in the muscle tendon. The interstitial space constitutes approximately 15% of the total body weight. It serves as a fluid reservoir and elastic support. The solid structures in the space transfer tensile forces from the muscle cells to the muscle tendon. (Styf, 2004)

1.1.1.1 Pressures in the interstitial space

There are essentially two types of pressures acting in the interstitial space, pressure acting in solid components and fluid hydrostatic pressure. These pressures are fundamentally different, since the solid tissue pressure is a vector with a magnitude and direction, whereas the fluid hydrostatic pressure is a scalar and acts with the same magnitude in all directions. Furthermore, the pressure in a solid component should be described as

stress (force per unit area), since the distribution of force in a solid component is not uniform. The fluid in the interstitial space is in the form of free fluid and a gel phase (Guyton et al., 1971). As a result, the interstitial fluid does not have a uniform pressure distribution. The interstitial hydrostatic pressure in pockets of free fluid is commonly the pressure measured in studies of the IMP in a clinical situation. In this thesis, the IMP is therefore defined as the hydrostatic pressure in the interstitial space of a muscle.

The interstitial fluid hydrostatic pressure participates in the regulation of fluid shift across the capillary wall. The direction and magnitude of fluid shift depends on two hydrostatic and two osmotic pressures (Figure 1)(Starling, 1896). The two hydrostatic pressures are the intravascular pressure (P_c) in the capillary and the interstitial hydrostatic fluid pressure (P_t). The osmotic pressures are capillary blood osmotic pressure π_c and interstitial fluid osmotic pressure π_t.
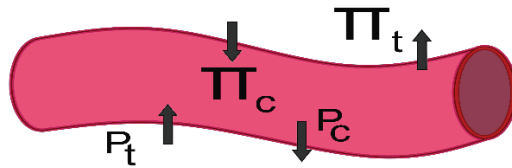
$$J_v = K_f\,(P_c - P_t) - \sigma\,(\pi_c - \pi_t)$$

J_v = Net trans-capillary fluid shift
K_f = Capillary filtration coefficient
P_c = Capillary blood hydrostatic pressure
P_t = Interstitial fluid hydrostatic pressure
σ = Capillary membrane reflection coefficient
π_c = Capillary blood osmotic pressure
π_t = Interstitial fluid osmotic pressure

Figure 1. The Starling equation describes the fluid shift across the capillary wall

Osmotic pressure describes the pressure, which needs to be applied to a solution to prevent the inward fluid flow across a semipermeable membrane.

The law of Laplace describes the relationship between the total tissue pressure P_{total}, intravascular pressure, P_i, and tension, T, in a vessel wall. It is defined as $P_i - P_{total} = T/R$ if thin walls are assumed and the vessel radius is R (Figure 2). The total tissue pressure is a combination of interstitial fluid hydrostatic pressure, semi-hydrostatic pressure from the gel and pressure from solid components acting on the vessel. For sake of simplicity, the total tissue pressure is sometimes assumed to equal the interstitial hydrostatic fluid pressure and Laplace's law can be expressed as $P_i - P_t = T/R$.

The SI unit for pressure is Pascal (Pa), but mmHg is often used in clinical work and in the medical literature.
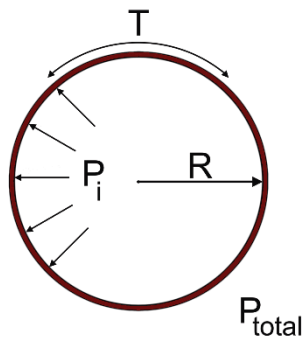
$$P_i - P_{total} = T/R$$

P_i = Intravascular pressure
P_{total} = Total tissue pressure
T = Wall tension
R = Radius

Figure 2. The law of Laplace if thin walls are assumed

1.1.2 Normal IMP

The IMP in a normally hydrated leg muscle of a healthy subject at rest is about 5-10 mmHg (Styf, 2004). These reported values were measured in supine subjects without interference from external compression. However, values between 0 and over 15 have been reported (Aweid et al., 2012; Roberts et al., 2012).

During muscle contraction, the IMP may increase to more than 250 mmHg (Styf et al., 1986). The muscle is therefore only supplied with blood flow between muscle contractions, which is during the relaxation phase of the muscular activity. At rest after exercise, the IMP usually returns to resting levels within about five minutes in a healthy leg. (Styf et al., 1987)

1.1.3 Abnormally elevated IMP

An abnormally elevated IMP reduces the local blood flow and perfusion pressure. Absolute IMP values of 30 to 50 mmHg have been reported to reduce the blood flow to such a degree that the nutrition and viability of the muscle tissue may be affected. Local perfusion pressure below 30-40 mmHg may induce ischemia (Heppenstall et al., 1988).

In patients with acute compartment syndrome, the IMP is irreversibly elevated to a level that impedes local blood flow and the viability of the tissues are compromised.

In chronic compartment syndrome, the IMP increases during exercise to levels that reduces muscle blood flow (Styf et al., 1987). This elicits pain and the patient must stop the exercise. Chronic compartment syndrome is reversible and the IMP returns to normal levels after a prolonged period of rest after discontinuing the exercise.

An abnormally elevated IMP may be seen in swollen legs. Swelling can be caused by edema, hemorrhage or a combination of these. In orthopaedic practice, swelling is seen in inflammatory diseases or following trauma. It is always a sign of disturbed microcirculation. Exercise-induced cramps are commonly seen in athletes. The cause of cramps is not fully understood and the role of the pressures in the interstitial space is unclear (Miller, 2015).

Muscular hypertension syndrome is an unusual cause of an abnormally elevated IMP that is seen in patients who have difficulty to relaxing their muscle (Styf et al., 1987). The condition is easily detected by simultaneous IMP and surface EMG recordings at rest after exercise.

The transition from the one-G environment on earth to microgravity in space induces a fluid shift within the human body (Berry et al., 1966). There is a shift of about 10% from the lower extremities to the upper body (Moore et al., 1987). This fluid shift may explain many of the symptoms and signs seen in astronauts during missions in microgravity. To study fluid shifts, all four Starling trans-capillary pressures were measured during an experimental model in humans in simulated microgravity (Parazynski et al., 1991). In the case of microgravity, the interstitial hydrostatic fluid pressure increased in the upper body.

Metabolic diseases like diabetes may increase the risk of abnormally increased IMP in the leg (Edmundsson et al., 2008; Edmundsson et al., 2011).

1.1.4 Muscle compliance

Compliance, C, is a measure of elastic properties and is defined as $C = \Delta V/\Delta P$, that is volume change per unit of pressure change. The inverse of compliance is elastance (stiffness). The volume of muscle tissue increases during exercise and patients with compartment syndrome have an elevated IMP due to increased volume in the affected muscle (Eliassen et al., 1974; Styf et al., 1987; Wallensten, 1983). The increased volume load reduces the compliance of the compartment. Muscle compliance may also be affected by a change in properties in the surrounding fascial and cutaneous tissues. In a muscle compartment with reduced compliance, a small increase in fluid volume load in the muscle causes a large increase in IMP.

1.2 Techniques for measuring IMP

The pioneering publications of tissue pressure measurements were produced by Landerer in 1884 and Starling in 1896 (Starling, 1896). They measured tissue pressure following injections of several ml of saline into the tissue. Techniques for measuring IMP can be divided into fluid-filled systems and transducer-tipped systems (Hargens et al., 1995).

1.2.1 Fluid-filled systems

Fluid-filled systems use a catheter linked to an extracorporeal transducer. Since the transducer is extracorporeal, the level of the measurement catheter tip must not change in relation to the transducer during measurements. This is to avoid a biased reading due to a change in the height of the fluid column. A fluid-filled system should be kept free from air bubbles and the solution should be kept at the same temperature as the ambient temperature to avoid micro-bubbles. Techniques that require injection of fluid during measurement to keep the catheter patent create local edema near the catheter tip and measure a pressure which is above the equilibrium hydrostatic fluid pressure (Hargens et al., 1977). Fluid-filled systems need to be calibrated with respect to the level of the catheter tip in relation to the extracorporeal transducer and to the atmospheric pressure.

For fluid-filled systems, the design of the catheter tip is crucial. The fluid by the catheter tip needs to have a large enough contact area with the surrounding fluid in the tissue and the tip needs to be designed to avoid clothing to maintain patency (Hargens et al., 1995; Styf, 1989). This can be accomplished by increasing the area at the tip of the needle and different approaches, such as Wick catheter (Mubarak et al., 1976; Scholander et al., 1968), Slit catheter (Rorabeck et al., 1981) and the Myopress catheter (Styf et al., 1986; Styf et al., 1989), have been used. Needles with a side port or side holes avoid the erroneously high IMP readings associated with simple needles (Boody et al., 2005; Hammerberg et al., 2012; Moed et al., 1993; Styf, 1989). Some of the fluid-filled systems, such as the Wick, have low dynamic properties and they are therefore only used for measurements of the IMP at rest (Hargens et al., 1995; Styf et al., 1986).

1.2.1.1 Needle-injection technique

Needle-injection systems have been evaluated (Styf, 1989) and used throughout the history of IMP measurements from the early beginnings, during a period of development (French et al., 1962; Reneman, 1975; Whitesides et al., 1975) to today's commonly used hand-held Stryker intracompartmental device (Awbrey et al., 1988). They require injections of fluid to establish and maintain catheter patency. One survey reported that 77% of the responding specialists use needle injection systems for IMP measurements (Hislop et al., 2011). However, needle-injection techniques are only suitable for measurements at rest (Styf, 1995).

Stryker intracompartmental needle-injection system

The Stryker intracompartmental device is a needle-injection system (Awbrey et al., 1988). It has been used in evaluations of IMP systems and it is commonly used in clinical settings to measure abnormally elevated IMP in order to diagnose compartment syndromes (Boody et al., 2005; Uliasz et al., 2003; Uppal et al., 1991).

1.2.1.2 Pump-infusion technique

The pump-infusion technique is a constant infusion technique. It gives the same amount of infused volume regardless of the IMP (Matsen et al., 1980). It may therefore increase the risk of erroneously high IMP readings during muscle contraction and other states of elevated IMP (Styf et al., 1986).

1.2.1.3 Micro-capillary infusion technique

The micro-capillary infusion technique is used with a flexible polytetrafluoroethylene (PTFE) catheter (Myopress) with multiple side-holes at its tip (Styf et al., 1986; Styf et al., 1989). The micro-capillary is connected to a transducer line via a three-way stop-cock. The infusion speed can be altered. The infused volume depends on the difference between the tissue pressure and the pressure gradient over the micro-capillary. This technique has good dynamic properties and is suitable for measurements of IMP both at rest and during exercise (Styf et al., 1986; Styf et al., 1989).

1.2.2 Transducer-tipped systems

In contrast to fluid-filled measurement systems with extracorporeal transducers, transducer-tipped systems have the transducer placed at the tip of the catheter, thereby eliminating the influence of hydrostatic artefact caused by the height difference between the limb and the transducer. As a result, these systems are less susceptible to calibration errors and they are suitable for measurements during exercise (Crenshaw et al., 1992; Styf, 1995). Transducer-tipped catheters used for IMP measurements include the solid-state transducer intra-compartment catheter (STIC) (McDermott et al., 1982), the transducer-tipped fiber-optic catheter (Camino) (Crenshaw et al., 1990) and the transducer-tipped catheter system (Willy et al., 1999). The STIC system is a transducer-tipped system that is used with infusion.

1.2.2.1 Fiber-optic systems

The first fiber-optic pressure transducer (FOPT) for medical applications (intravascular) was proposed in 1970 by Lindström (Lindstrom, 1970). Today, fiber-optic systems are frequently used in biomedical and biomechanical applications (Roriz et al., 2013). FOPTs are lightweight, flexible, biocompatible, inherently immune to electro-magnetic interference, MRI compatible and do not conduct electricity (Mishra et al., 2011; Poeggel et al., 2015; Taffoni et al., 2013). Many of them are small in size and minimally invasive. The fiber-optic systems for medical application have inherent properties that make them suitable for IMP measurements, e.g. small size, low compliance and good dynamics (Poeggel et al., 2015).

Three basically different technologies are mainly used in FOTPs in the biomedical field; intensity-based, fiber Bragg gratings and Fabry-Pérot (Poeggel et al., 2015; Taffoni et al., 2013).

Intensity-based sensors usually emit light in one or more fibers on-to a deflecting diaphragm. The deflected light is transmitted back in one or more fibers and measured. The measured light is a function of the external pressure applied to the diaphragm.

Fiber Bragg grating sensors are based on the concept that a short segment of the optical fiber has a grating that reflects particular wavelengths of light. The grating is affected by the applied strain. The pressure applied on the sensor induces strain and this modulates the measured light. In short, a Fiber Bragg sensor works as a strain gauge modulating light.

Fabry-Pérot pressure sensors utilize the interference pattern of a single wavelength, multiple-band or broadband light created by a Fabry-Pérot cavity diaphragm placed at the sensor tip (Figure 3). Applying pressure to the tip changes the geometry of the cavity and thus modulates the light that is reflected. In an overview paper on fiber-optic sensors, it was concluded that the Fabry-Pérot technology offered the best combination of properties for medical applications, i.e. pressure range, sensitivity and size (Pinet, 2011).
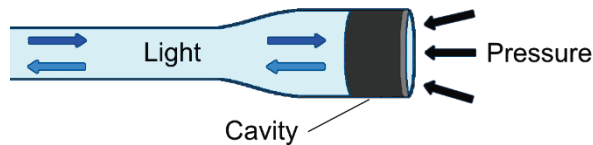
Figure 3. Schematics of a forward sensing Fabry-Pérot fiber-optic transducer

A Fabry-Pérot fiber-optic sensor system was selected for Studies I and II in this thesis.

Regardless of the system used for measuring the IMP, the measured value may be influenced by several non-system-specific factors, such as the placement depth of the catheter in the muscle, physiological reactance due to the invasiveness of the catheter, external pressure applied to the leg and influences from solid structures on the measurement catheter (Nakhostine et al., 1993; Styf, 2004).

1.2.3 Anatomy of the leg

The leg is traditionally divided into four compartments: anterior, lateral, deep posterior, and superficial posterior (Figure 4). There is a controversy about whether the tibialis posterior muscle can be regarded as being confined in a separate fifth compartment (Davey et al., 1984; Hislop et al., 2003; Kwiatkowski et al., 1997; Ruland et al., 1992).

The anterior compartment of the leg is surrounded by unyielding osteo-fascial structures. The tibialis anterior artery supplies the tibialis anterior, the extensor hallucis longus and the extensor digitorum longus muscles. It is an end artery. Venous return leaves the compartment through the foramen in the membrana interossea, the same structure through which the artery enters the compartment. The deep peroneal nerve passes through the compartment. The lateral compartment contains the peroneal muscles and the peroneal nerve. It is supplied by several arteries. The deep posterior compartment contains the flexor muscles of the ankle joint, the tibialis posterior, flexor digitorum longus, flexor hallucis longus, popliteus, the tibial nerve and the posterior tibial artery and vein. The superficial posterior compartment holds the soleus, gastrocnemius and plantaris muscles together with the sural nerve.
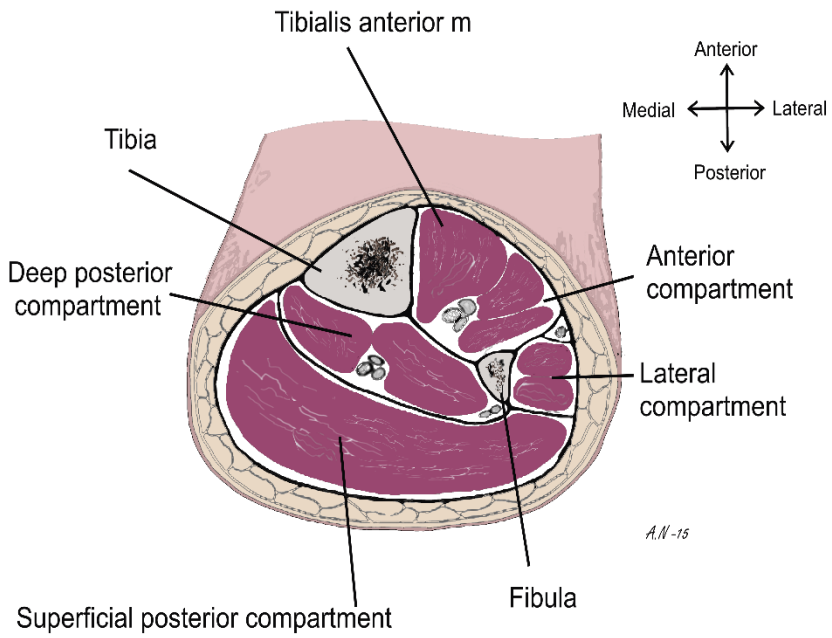
Tibialis anterior m

Anterior

Medial ⟷ Lateral

Posterior

Tibia

Deep posterior compartment

Anterior compartment

Lateral compartment

A.N -15

Superficial posterior compartment

Fibula

Figure 4. Schematic cross section of the right leg

1.3 Compartment syndromes

Compartment syndrome was defined by Matsen as "a condition in which the circulation and function of tissues within a closed space are compromised by increased pressure within that space" (Matsen III, 1975). Compartment syndromes may be acute or chronic and are manifested by abnormally elevated IMP. The acute syndrome is often caused by trauma. It is non-reversible and requires immediate treatment. If left untreated, permanent tissue damage will occur. Chronic compartment syndrome is the reversible form of compartment syndromes. It is almost exclusively exercise-induced and the typical symptoms are exercise-induced pain, swelling, and impaired muscle function which abates after discontinuing the exercise. (Reneman, 1975; Styf, 2004)

1.3.1 Chronic anterior compartment syndrome (CACS)

Chronic compartment syndrome is one of the lower limb overuse injuries seen in athletes (Burrus et al., 2014). It is typically found in runners, but it is also found in athletes performing other sports such as soccer, field hockey and basketball (Davis et al., 2013; Detmer et al., 1985). However it is not only limited to athletes (Edmundsson, 2010; Edmundsson et al., 2007). Bilateral occurrence in over 60% has been reported in larger studies (Davis et al., 2013; Detmer et al., 1985; Raikin et al., 2005; Turnipseed, 2002). The anterior compartment of the leg is reported as being the most affected (Aweid et al., 2012; Reneman, 1975; Roberts et al., 2012). Compartment syndrome may occur in all compartmental muscles. It has been reported in the thigh (Raether et al., 1982), erector spinae musculature (Styf et al., 1987), hand (Phillips et al., 1986; Styf et al., 1987), forearm (Kutz et al., 1985; Pedowitz et al., 1988; Söderberg, 1996) and foot (Lokiec et al., 1991; Middleton et al., 1995). In 1975, Reneman reported on the first large study comprising 61 patients with chronic compartment syndrome in the anterior and lateral compartments (Reneman, 1975). The first patient was described by Mavor in 1956 (Mavor, 1956). This patient was a 24-year-old soccer player with an exercise-induced reversible bilateral compartment syndrome. This first case can serve as an example of the typical patient, athlete, in the mid-20s with bilateral occurrence of the syndrome.

The incidence of compartment syndrome in men and women is not known. Early studies generally comprised men, mainly due to patient selection from military personnel and competitive sports. Today, more women are participating in sports. Recent publications contain more women with compartment syndrome. Fairly large studies have recently reported 60% and 68% women respectively among patients with chronic compartment syndrome (Davis et al., 2013; Packer et al., 2013).

Despite the fact that the syndrome has been recognized since the mid-1950s, there are no clear guidelines for diagnosing the syndrome.

CACS is often referred to as the more general chronic exertional compartment syndrome (CECS). Other terms used to describe the syndrome include, anterior tibial pain, recurrent compartment syndrome, idiopathic compartment syndrome, chronic anterior compartmental syndrome, non-traumatic compartment syndrome of the lower extremities, transient paralysis of limbs and anterior tibial syndrome (Styf, 2004).

1.3.1.1 Pathophysiology

The pathophysiology of CACS is an abnormally increased IMP during and following exercise. The elevated IMP impairs the local muscle blood flow and impedes the function of the tissues within the affected compartment. The abnormally elevated IMP is usually induced by volume load induced by exercise. The volume may increase by up to 20% during exercise (Eliassen et al., 1974; Gershuni et al., 1982). The abnormally elevated pressure does not induce irreversible ischemic changes in patients with CACS.

1.3.1.2 Diagnosis

A history of CACS includes anterior leg pain (often throbbing) that forces the patient to discontinue the exercise. The symptoms abate after cessation of the exercise. Clinical findings after an exercise test that elicits the patient's symptoms include, muscle swelling, impaired muscle function and sometimes sensory dysfunction. (Styf, 2004)

The measurement of IMP is often regarded as the gold standard for diagnosing CACS, since history and clinical signs alone are insufficient to

establish the diagnosis (Fronek et al., 1987; Pedowitz et al., 1990; Rorabeck et al., 1983; Rorabeck et al., 1988; Rorabeck et al., 1988; Styf, 1988; Styf, 1989).

In spite of the fact that IMP measurement is regarded by many as the gold standard, it is not known how frequently the diagnosis is confirmed by IMP measurement. One study from the United Kingdom reported that 83% of the responding orthopaedic surgeons used IMP measurement in diagnosing the syndrome (Tzortziou et al., 2006).

1.3.1.3 IMP parameters in diagnosing CACS

French and Price were the first to report on abnormally elevated IMP before surgery and a normalized IMP after surgery in a patient with suspected CACS (French et al., 1962). Since then, different IMP criteria have been suggested for diagnosing CACS; at rest, during exercise and IMP at rest after exercise.

IMP criteria at rest

The IMP in the anterior compartment of the leg in healthy subjects is often reported to be less than 10 mmHg (Crenshaw et al., 1992; Gershuni et al., 1984; Hargens et al., 1981; Styf et al., 1986; Wiger et al., 1998). Resting pressure exceeding 10 and 15 mmHg has frequently been used as an indication of chronic compartment syndrome (Barnes, 1997; Turnipseed, 2002). However, resting pressures in healthy subjects may sometimes exceed 15 mmHg (Aweid et al., 2012; Roberts et al., 2012). The IMP at rest before exercise may therefore be an unreliable parameter for confirming CACS.

IMP criteria during exercise

Since exercise elicits the abnormally elevated IMP and leg pain in patients with CACS, the IMP has been measured during exercise and different criteria have been suggested. However measuring the IMP during exercise is a challenging task that requires IMP measurement systems with good dynamic properties. Furthermore, the IMP depends on the type of exercise. Eccentric exercise causes significantly higher IMP in the anterior compartment than concentric exercise (Friden et al., 1986). The situation is complex since the measured pressure can be divided into muscle contraction pressure, mean muscle pressure and muscle relaxation pressure.

Muscle contraction pressure

Muscle contraction pressure is an estimate of the force generated during exercise. It depends on the exercise and is therefore not directly related to the symptoms of compartment syndrome. (Styf et al., 1987)

Muscle relaxation pressure

Muscle relaxation pressure is the IMP in the relaxation phase of an exercising muscle. It is related to the swelling (volume load) of the muscle and it is more accurate than the mean muscle pressure (Styf et al., 1986). It was also an exception from the validity issue with IMP measurements reported by Roberts et al. (Roberts et al., 2012).

Mean muscle pressure

Mean muscle pressure is the mean of the contraction pressure and the relaxation pressure. If IMP is measured with a measurement system with poor dynamic properties, the measured IMP will be almost the same as the mean muscle pressure. The mean muscle pressure has been used in the diagnosis of CACS with different limits to indicate compartment syndrome (Aweid et al., 2012). A few of the suggested thresholds include, IMP > 50 mmHg (Puranen et al., 1981), IMP > 75 mmHg (Awbrey et al., 1988) and IMP > 85 mmHg (McDermott et al., 1982). More recently an IMP exceeding 105 mmHg with a specific protocol was suggested (Roscoe et al., 2014).

The mean muscle pressure depends on the exercise performed. Mean muscle pressure measured during running is often reported to induce a greater mean muscle pressure compared with the mean muscle pressure measured during ankle dorsiflexion (Roberts et al., 2012). There is a simple explanation for this; the mean muscle pressure during exercise is influenced by the contraction pressure and is therefore a function of both the load and frequency of the exercise. The mean muscle pressure also depends on the duration of the muscle contraction time in relation to the muscle relaxation time. The mean muscle pressure has consequently been found to be unreliable as a diagnostic criterion for CACS (Styf et al., 1987).

IMP criteria at rest after exercise

During exercise, the IMP increases to many times the resting pressure, even in connection with moderate exercise. In healthy subjects, the IMP returns to levels close to the resting pressure within a short period of time after cessation of the exercise. In patients with CACS the IMP remains abnormally elevated for an extended time period. This fact has been used to set criteria for the diagnosis of CACS. Different criteria have been described in a review (Aweid et al., 2012). A few worth mentioning are IMP > 30 mmHg one minute after exercise (Pedowitz et al., 1990; Styf et al., 1987), IMP > 20 mmHg five minutes after exercise (Pedowitz et al., 1990), > 15 mmHg six minutes after exercise, > 15 mmHg 15 minutes after exercise (Rorabeck et al., 1988) and a "normalization" within six minutes (Styf et al., 1987) and different combinations of the times and levels.

Area under a pressure curve

Even the area under a 4-point pressure curve (before, immediately after, and one and five minutes after an exercise test) has been suggested as a way of combining several pressure levels at different times. This was, however, suggested for the deep posterior compartment. (Winkes et al., 2012)

Despite the fact that IMP measurement is regarded as the objective gold standard in diagnosing CACS, no consensus has been reached on the IMP criteria that should be used (Aweid et al., 2012; Barnes, 1997; Franklyn-

Miller et al., 2012; Roberts et al., 2012). The criteria defined by Pedowitz et al. of resting pressure of ≥15 mmHg and/or a one minute after-exercise pressure of ≥ 30 mmHg and/or a 5 minute after-exercise pressure of ≥20 mmHg have been described as the most universally used criteria (Aweid et al., 2012; Franklyn-Miller et al., 2012; Pedowitz et al., 1990). Survey studies have shown that 35-51% of the responding physicians uses the criteria set by Pedowitz et al. (Hislop et al., 2011; Tzortziou et al., 2006). The study by Pedowitz et al. has, however, been criticized as the compartment syndrome patients and the controls were preselected by their differences in intramuscular pressure (Franklyn-Miller et al., 2012).

Recent papers have reviewed the IMP criteria and reported conflicting evidence regarding the validity of the IMP levels, as well as an overlap in IMP between patients and healthy subjects when dichotomized by the different IMP criteria (Roberts et al., 2012; Tiidus, 2014). It has also been reported that the evidence for the commonly used IMP criteria is weak and that there is an overlap in the reported mean IMP levels between patients and control subjects, except for the IMP values measured at rest one minute post-exercise. (Aweid et al., 2012). Furthermore, the IMP criteria have shown high sensitivity and low specificity (Pasic et al., 2015).

No criterion that relates the IMP to the patient's blood pressure has been suggested in the diagnosis. However, in the diagnosis of acute compartment syndrome, calculated values based on local perfusion pressures have been suggested and are often used in the clinical diagnosis (Heppenstall et al., 1988; McQueen, 1996; McQueen et al., 2014)

To summarize, there is currently no consensus on the criteria that should be used and there appears to be scope for improvement of IMP as an objective parameter in diagnosing CACS.

1.3.2 Acute compartment syndrome

Acute compartment syndrome may arise from increase in the volume of the compartment contents, external compression of the compartment, reduced size of the compartment or any combination of these. An increase in volume may arise from traumatic injuries and inflammatory reactions. Long-term external compression, which is sometimes seen in patients with drug overdose or in earthquake victims, may initiate an ischemic reperfusion injury due to endothelial dysfunction after the circulation is restored. A reduction in the size of the compartment envelope may be seen in circumferential severe burn injuries. The impaired muscle blood flow induces ischemic pain, impaired nerve function and induces sensory and motor dysfunction. If the condition is left untreated, it may result in ischemic contracture (Volksmann's contracture) and functional impairment of the affected tissues. (Elliott et al., 2003; McQueen et al., 2014; Styf, 2004)

1.3.2.1 Pathophysiology

The pathophysiology of acute compartment syndrome is abnormally increased IMP that impedes local muscle blood flow in the affected compartment. It induces muscle ischemia, which impairs the function of the tissue within the compartment. (Heppenstall et al., 1988; Matsen III et al., 1979)

1.3.2.2 Diagnosis

Acute compartment syndrome is diagnosed by clinical means. Patients complain of ischemic pain and impaired neuro-muscular function. The circumference of the affected limb increases and the pain may become resistant to medical treatment. Clinical investigation reveals muscle weakness and sensory dysfunction of the tissues in the affected compartment. (Ali et al., 2014; Matsen III et al., 1979; McQueen, 1996; Styf, 2004). Clinical findings have reported sensitivities of between 13 and 64% and specificities of between 63 and 98% (McQueen et al., 2014).

IMP measurements in diagnosis of acute compartment syndrome
Using IMP measurement and a delta pressure (diastolic blood pressure - IMP) threshold of less than 30 mmHg for more than two hours has a

sensitivity of 94% and a specificity of 98% (McQueen et al., 2014; McQueen et al., 2013; Whitesides Jr et al., 1975). Several review studies have however reported that there are recommendations for using both an absolute level of IMP or IMP in relation to blood pressure (delta pressure) (Ali et al., 2014; Hayakawa et al., 2009; McQueen et al., 2014; Ozkayin et al., 2005; Taylor et al., 2012; Tzioupis et al., 2009)

### 1.3.3 Surgical treatment of compartment syndromes

The surgical treatment of compartment syndromes is based on the normalization of the abnormally increased IMP. In acute compartment syndrome, this is accomplished by fasciotomy and leaving the wound open. Post-operative edema reduction in the compartment will enable secondary wound closure, usually after a few days. Patients with chronic compartment syndrome are treated by subcutaneous fasciotomy or sometimes partial fasciecotomy through limited skin incisions. The surgery may be performed with or without arthroscopic assistance. The wound is primarily closed (Irion et al., 2014; Kitajima et al., 2001; Knight et al., 2013; Mubarak et al., 1977; Pasic et al., 2015; Rorabeck et al., 1988; Styf, 2004; Styf et al., 1986; Wallensten, 1983; Wittstein et al., 2010). Guidelines for rehabilitation following fascial release in chronic compartment syndrome patients have been suggested as means of improving the long-term outcomes (Schubert, 2011).

1.4 Experimental models to induce abnormally elevated IMP

A number of models to elevate the IMP to simulate compartment syndromes and to reduce local perfusion pressure in humans have been developed over the years. Common models are venous obstruction, venous obstruction combined with a plaster cast restricting the expansion of the leg and external compression. Animal models have also been used, but they are outside of the scope of this thesis. Nevertheless, they have been summarized by Wiger (Wiger, 1999).

1.4.1 Venous obstruction

French and Price were the first to study IMP in a CACS patient when venous return was restricted by a thigh cuff (tourniquet) inflated to 80 mmHg (French et al., 1962). Venous obstruction has been suggested as a model for simulated chronic compartment syndrome (Figure 5) (Birtles et al., 2003).
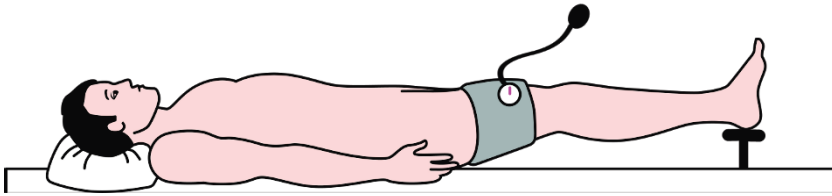
Figure 5. Venous obstruction as a model for simulated chronic compartment syndrome

1.4.2 Venous obstruction and volume-restricting plaster cast

To induce the levels of abnormally elevated IMP seen in compartment syndrome, a thigh tourniquet in combination with a volume-restricting plaster cast applied to the leg has been developed (Styf et al., 1998) and used to simulate compartment syndrome (Figure 6) (Styf et al., 1998; Wiger et al., 1998; Wiger et al., 2000; Zhang et al., 2004; Zhang et al., 2001). An inflated thigh tourniquet reduces venous return from the leg and muscle swelling occurs in the leg muscles.
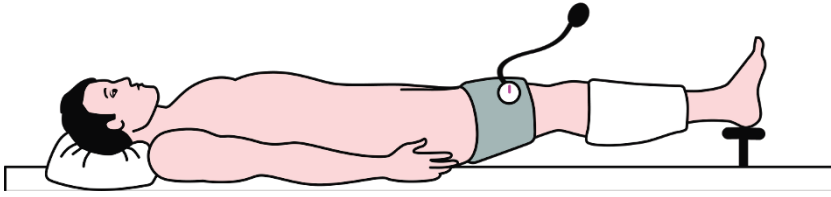
Figure 6. Model of abnormally elevated IMP induced by venous obstruction and a plaster cast

1.4.3 External compression

Abnormally elevated IMP has been induced by external compression of the leg by air splints, thigh tourniquet placed on the leg (Figure 7), locally applied pressure to one or more compartments, or by placing the leg in a small pressure chamber (Ashton, 1966; Crenshaw et al., 1990; Hargens et al., 1993; Lee et al., 2013; Matsen et al., 1977; Styf, 1990; Wiger et al., 2000).
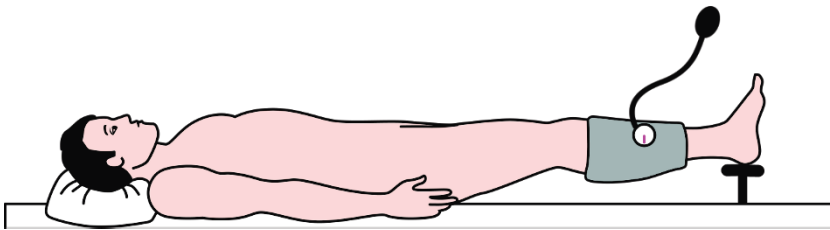
Figure 7. Abnormally elevated IMP in the leg induced by a tourniquet

1.4.4 Limb elevation and venous obstruction of a casted leg

Using this method, it is possible to combine elevated IMP with reduced local mean arterial pressure. To simulate abnormally elevated IMP and local hypotension, the local perfusion pressure was reduced by limb elevation and venous obstruction of a casted leg (Styf et al., 1998; Wiger et al., 1998). This method was used to elicit sensory dysfunction and motor weakness in healthy subjects (Styf et al., 1998; Wiger et al., 1998).

1.5 Intramuscular pressure oscillations

Pulse-synchronous oscillations in the IMP may be recorded in patients with abnormally elevated IMP (Styf, 1995). The oscillations in the IMP are a manifestation of pulsations deriving from the arterial pulsations. The IMP oscillations are therefore synchronous with the local arterial pulsations. The amplitude of the IMP oscillations has been reported to decrease significantly from 5 mmHg before surgery to 1.0 mmHg after fasciotomy in patients with CACS (Styf et al., 1986). At rest after an exercise test the mean amplitude of the IMP oscillations was approximately 6 mmHg in 36 legs of patients with CACS and less than 1 mmHg in 116 legs of patients with other causes of leg pain (Styf et al., 1987). However, no pulse-synchronous IMP oscillations were found at normal IMP levels in healthy subjects indicating that the amplitude of the IMP oscillations is related to the reduced compliance, abnormally elevated IMP and the pathophysiology in compartment syndrome patients (Styf et al., 1998).

However, these pioneering papers reporting on oscillations did not investigate the relationship between the amplitude of the oscillations and the absolute IMP or whether the oscillations are of diagnostic value.

In this thesis on pulse-synchronous IMP oscillations, the starting point is abnormally elevated IMP seen in CACS.

2

Aims

2 AIMS

The overall aim of this thesis was to investigate the amplitude of IMP oscillations in relation to the IMP in normally hydrated muscle, in abnormally elevated IMP and to evaluate the potential of using pulse-synchronous IMP oscillations in diagnosing compartment syndromes.

2.1 Detailed aims of each study

Study I

The aim was to evaluate and compare a forward-sensing fiber-optic pressure recording technique with a commonly used needle-injection technique before, during and after the application of an experimental model of abnormally elevated IMP (simulated compartment syndrome). The effect of the fluid injections, associated with fluid-filled injection systems, on IMP was also studied.

Study II

The aim was to investigate whether the amplitude of pulse-synchronous IMP oscillations is correlated to the absolute level of IMP during an experimental model of abnormally elevated IMP (simulated compartment syndrome).

Study III

The aims of this study were (1) to investigate the correlation between IMP and the amplitude of the pulse-synchronous IMP oscillations in patients with or without CACS and in healthy control subjects and (2) to determine the sensitivity and specificity of the amplitude of the IMP oscillations in diagnosing CACS.

Study IV

The aim was to study the relationship between the IMP and the amplitude of the IMP oscillations in the whole IMP range seen in patients with compartment syndromes.

3
Methods

3 METHODS

3.1 Ethical considerations

The studies were approved by the regional Research Ethics Committee (reference number 776-08). All subjects gave their informed consent prior to participating in the study. The patients in Studies III and IV were part of a clinical routine investigation for patients with exercise-induced leg pain and suspected CACS.

3.2 Subjects

3.2.1 Studies I & II

Seven subjects (four females and three males) with no history of leg pain requiring medical attention with a mean age of 28 (SD = 5) years, median of 26 years and range 23-38 years and a mean body mass index (BMI) of 23 (SD = 2) and range 20-26 kg/m², volunteered to participate in the studies. The studies were performed on twelve legs in these subjects.

3.2.2 Study III

The study comprised 89 consecutive patients (49 women, 40 men) with a mean age of 31 (SD = 13) years, range 15-69 years, with exercise-induced pain in the anterior part of the leg. They were all referred to the Department of Orthopaedics at Sahlgrenska University Hospital (Gothenburg, Sweden) between January 2012 and October 2013 for suspected CACS.

Nineteen healthy control subjects (ten women, nine men) with no history of leg pain requiring medical attention were also included in the study. Their mean age was 27 (SD = 6) years and range 20-42 years.

3.2.3 Study IV

The study comprised 12 patients with CACS and eight healthy controls with no history of leg pain requiring medical attention. The patients were four women and eight men with a mean age of 31 (SD = 10) years, median of

29 years and a BMI of 25 (SD = 3) kg/m². The control group comprised four women and four men with a mean age of 29 (SD = 7) years, median of 26 years and range 21-39 years and mean BMI of 23 (SD = 3) kg/m².

3.3 Intramuscular pressure measurements

During all IMP measurements, the supine subject had his/her foot placed on a heel support to prevent external compression on the calf. As the position of the knee and ankle affects the IMP, the foot was kept in a neutral relaxed position (Figure 8) (Gershuni et al., 1984; Tsintzas et al., 2004; Weiner et al., 1994). The height of the support was adjusted to keep the anterior tibialis muscle at heart level, defined as 5 cm below the manubrium sterni. All IMP measurements were performed in the tibialis anterior muscle.

The foot was kept in a neutral relaxed position

The foot was placed on a heel support to prevent external compression on the calf
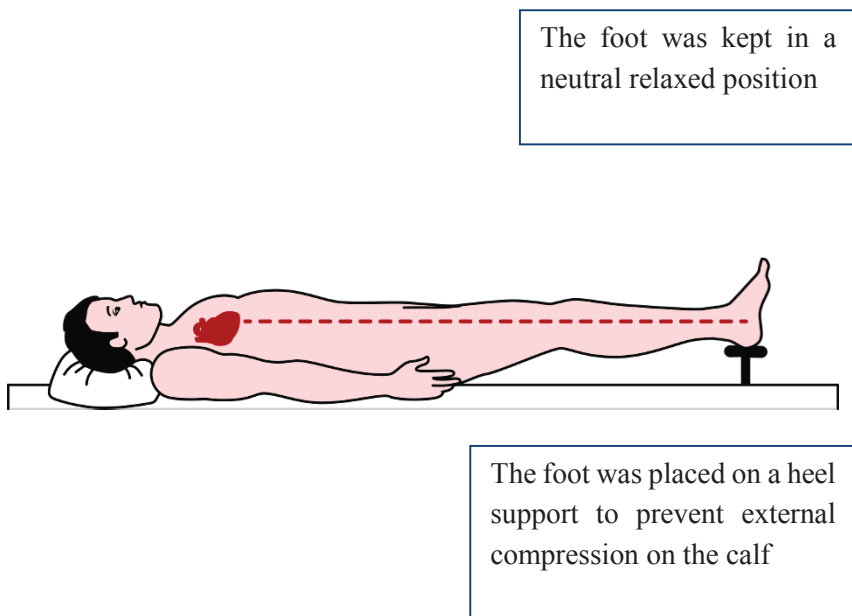
Figure 8. All IMP measurements were performed at rest with the subject in a supine position

Before measurements, the dynamic properties of the IMP recording-systems, location of the catheter tip and catheter patency were checked by applying light pressure to the anterior tibialis muscle via the investigator's fingertip over the tip of the catheter. Calibration of the pressure recording-systems was performed before and checked after each measurement.

Insertion technique for the catheters

The type of pressure catheters varied between the studies but the insertion technique was essentially the same. The supine patient was asked to keep his/her ankle joint dorsiflexed. A introducer was inserted through the skin and fascia of the anterior tibial muscle in a distal direction at an angle of 30 degrees. The subject was then asked to relax his/her leg and keep the foot in a neutral position. The catheter was thereafter advanced about 40 mm (insertion point to needle tip) as parallel as possible to the tibialis anterior muscle fibers in a distal direction. The angle of insertion was kept as parallel to the muscle fibers as possible to reduce discomfort, pain and physiological reactance. (Styf, 1995)

3.3.1 Studies I & II

Fiber-optic systems have properties suitable for IMP measurements including small size, low compliance and good dynamics (Poeggel et al., 2015). A Fabry-Pérot FOPT (Samba Sensor, Samba AB, Gothenburg, Sweden) was used for IMP measurements. It has previously been evaluated and used for purposes other than measuring IMP in humans. The properties of the system have been described (Sondergaard et al., 2002). It has been evaluated for cardiovascular measurements and IMP measurement in mice (Ozerdem, 2009; Woldbaek et al., 2003). The Samba system with a high-pressure transducer has been used for measurements in the intervertebral discs of animals and humans (Hebelka et al., 2010; Hebelka et al., 2013; Hebelka et al., 2013; Roriz et al., 2014). The FOPT has shown good linearity in a water-column test (Ozerdem, 2009), an accuracy of 0.37 mmHg, a resolution of 0.08 mmHg (Cottler et al., 2009) and a flat frequency response between 0 and 200 Hz (Woldbaek et al., 2003).

The forward-sensing transducer was placed at the end of the optic fiber. It had a diameter of 0.42 mm and an estimated volume of 0.072 mm^3. The

transducer was connected to a control unit (Samba Sensors AB, Gothenburg, Sweden). The system was set to measure pressure in mmHg. It was calibrated at room temperature before catheter insertion but after sterilization. During measurements, the sensor was placed in a Venflon tubing. This protected the tip from the influence of solid components.

Needle-injection technique

As a reference system, a needle-injection technique (Stryker Intra-Compartmental Pressure Monitor) was used in Studies I& II. It was used with a side-ported needle 1.3x60 mm interconnected with a 20 cm long piece of tubing. The syringe and the interconnecting tubing were prefilled with room-tempered saline. The system was kept free from air bubbles. The needle-injection technique was calibrated (zeroed) as described in the instructions provided with the monitor before insertion into the anterior compartment. During measurements, the monitor was kept at the same level as during calibration to avoid offset bias from the fluid column. No external connections are available on the monitor for external data-acquisition systems. As a result, the IMP values were read on the digital display of the monitor during measurements.

3.3.2 Study III

Before the needle was introduced, it was connected to a transducer line filled with saline. The transducer line was connected to a pressure recording-system (Hemo 4; Siemens) and a monitor (Siemens SC 9000; Siemens). It was kept free from bubbles. A micro-capillary infusion technique was used during insertion (the estimated infused volume was less than 8 μL) to create a fluid pathway and establish needle patency. The micro-capillary infusion was stopped once the needle was located in the muscle. It was kept closed during the measurements to avoid biased IMP readings due to infused volume load at the tip of the needle. The IMP was displayed in real time on the monitor. The oscillations of the IMP were registered from the monitor readings.

3.3.3 Study IV

The pressure recording-system used in Study III was used with a Myopress catheter (Styf, 1989) in Study IV. The microcapillary infusion was set at 1.5 ml/h (Styf et al., 1986; Styf et al., 1989). The infusion assured a fluid pathway and established catheter patency. The total infused volume was estimated at less than 125 µl during the measurements. The IMP system was connected to a standard PC equipped with hardware from National Instruments (National Instruments, Austin, TX) and custom-designed LabView software. The IMP was sampled at 200 Hz (Poeggel et al., 2015).

3.4 Exercise test

Each participant in Studies III and IV performed an exercise test to induce muscle swelling and elevated IMP in the tibialis anterior muscle. In Study III, the exercise test was individually designed to elicit each patient's symptoms. The test often, but not always, included running on a treadmill until the symptoms were provoked. This was always followed by repeated maximum concentric dorsiflexion of the ankle joints (toe-lifts) at a rate of about 1 Hz in standing position to further provoke the symptoms. The control subjects in Study III and the participants in Study IV performed only toe-lifts. The exercise continued until the participant was unable to continue because of pain and/or leg muscle fatigue.

3.5 Criteria for CACS (Studies III & IV)

Inclusion criteria for CACS:

1. *History of exercise-induced leg pain.*
2. *Clinical findings consistent with CACS during examination before and after an exercise test that elicited the patient's typical symptoms.*
3. *IMP > 30 mmHg, at rest one minute after exercise.*
4. *IMP > 20 mmHg, at rest five minutes after exercise.*

3.6 Models of elevated IMP

To simulate the abnormally elevated IMP levels seen in patients with compartment syndromes, two models were used, venous obstruction in combination with a plaster cast and external compression.

3.7 Venous obstruction and plaster cast (Studies II & III)

Abnormally elevated IMP was induced by obstructing venous return using a thigh tourniquet and a volume-restricting plaster cast applied to the leg. The circumferential plaster cast was applied from slightly below the knee joint to the distal part of the test leg (Figure 9). The proximal part of the plaster cast was molded to make sufficient room for two IMP measurement catheters. A pneumatic tourniquet was placed around the thigh and inflated to 65 mmHg to obstruct venous return from the leg.
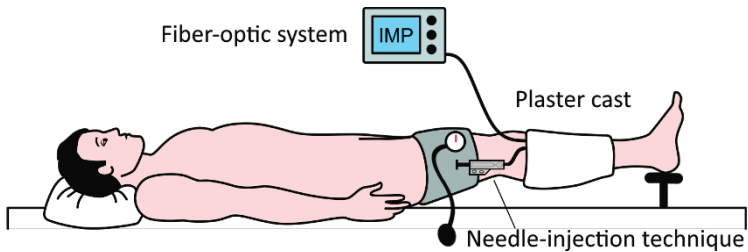
Figure 9. Measurement setup in Studies I & II

3.8 External compression (Study IV)

External compression was used in Study IV since this model may induce IMP values exceeding the systolic blood pressure, which is not possible with other models. This model was used to elevate the IMP to levels comparable with the high levels of IMP that can be observed in some patients with chronic or acute compartment syndrome.

At rest after exercise, a 23 cm wide tourniquet was placed on the subject's leg (Figure 10). The tourniquet was then inflated stepwise, in 40 mmHg increments, from 0-160 mmHg in 10-second intervals, and then deflated stepwise in the same way back to 0 mmHg.
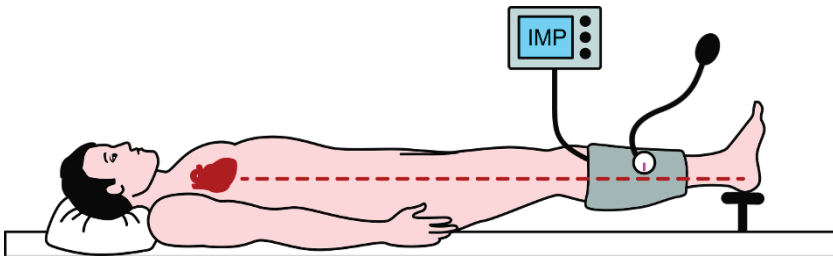
Figure 10. Measurement setup in Study IV

3.9 Electromyography, EMG (Study III)

The IMP may be elevated initially at rest post-exercise due to the patient's inability to relax the leg muscles due to leg pain (Styf et al., 1987; Zhang et al., 2011). For this reason, surface EMG was recorded with pre-gelled disposable electrodes (Blue Sensor, Medicotest/Ambu, Denmark). The electrodes were placed 3 cm distal to the tip of the pressure needle. The signal was pre-amplified (gain, 100) close to the electrodes, filtered with a second-order Butterworth filter with a 10 Hz to 2 kHz passband, amplified with variable gain and sampled at 4 kHz with a custom-built data-acquisition system. All the cables were kept short. The root mean square of the EMG recording from the anterior tibialis muscle was used to ensure muscle relaxation (no EMG activity) at rest after exercise, thereby preventing a biased IMP.

The surface EMG signal often requires filtering. A high-pass filter to reduce motion artefacts or signal noise and a low-pass filter to remove high frequencies before sampling are normally used. Typical recommendation is second order Butterworth-filter corresponding to 12 dB/octave slope for general use. The recommendation varies between 5 and 20 Hz for the high pass corner frequency and approximately 500 Hz for the low pass corner frequency. (De Luca et al., 2010; Merletti et al., 1999)

3.10   Ultrasonography (Studies I & II)

The distance between the overlying muscle fascia and the tip of the pressure measurement catheter and the angle between the catheter and the fascia were measured by ultrasonography (Acuson CV-70, Siemens Medical Solutions USA Inc., USA).

3.11 Blood pressures and pulse rate (Studies I, II, III & IV)

Systolic and diastolic blood pressure and pulse rate (bpm) were measured with a noninvasive blood pressure manometer (NAIS; Matsushita Electronic Works) placed on the left forearm.

3.11.1 Mean arterial pressure

Mean arterial pressure (MAP) was defined as:

MAP = diastolic pressure + 1/3 (systolic pressure - diastolic pressure)

3.11.2 Perfusion pressure

Local compartment perfusion pressure (PP) was calculated as:

$PP = MAP - IMP$

3.12 Pain, VAS (Studies III & IV)

Leg pain intensity was rated with a 10 cm visual analog scale (VAS) extending from 0 (no pain) to 10 (worst imaginable pain) (Scott et al., 1976).

3.13   Data collection and analysis

The Samba control unit (Studies I & II) and the micro-capillary system (Studies II & IV) were connected to a computer (PC) equipped with a DAQ-card from National Instruments (National Instruments, Austin, TX) and custom-developed LabView-based software. To minimize internal temperature drift, all the systems were turned on at least 30 minutes before the start of IMP measurements.

According to the Nyquist's theorem (Nyquist, 1928) a signal should be sampled at a sampling frequency at least twice as high as the highest frequency present in the signal, to avoid aliasing. For this reason, low-pass filters with a cut-off frequency set at half the sampling rate should be used. For surface EMG signals, the frequencies of interest are below 500 Hz (De Luca et al., 2010; Merletti et al., 1999). The lowest suitable sample rate is therefore 1000 Hz, To study other medical signals like invasive blood pressure a suitable sampling rate is 5-10 times the highest fundamental frequency, resulting in a recommended sampling rate of about 200 Hz (Poeggel et al., 2015).

The amplitude of the IMP oscillations was defined as the peak-to-peak value (Figure 11).
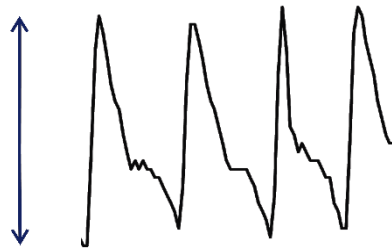
Figure 11. Peak-to-peak amplitude of the IMP oscillations

3.13.1   Studies I & II

The IMP was recorded for five minutes for baseline data, ten minutes during the model of abnormally elevated IMP, followed by five minutes of recovery after the model was removed (Figure 9, Figure 12).
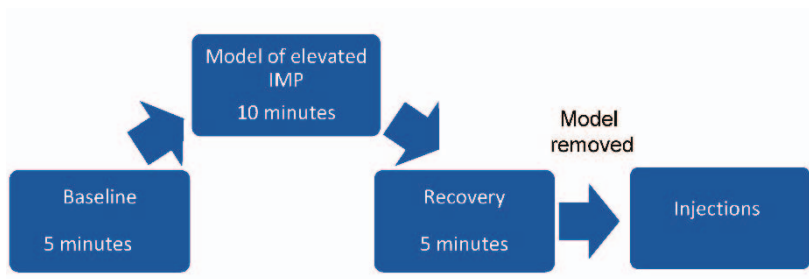
Figure 12. Experimental protocol for studies I & II

After five minutes of restitution, the IMP was measured during an injection of 0.1 ml of saline simultaneously into both pressure catheters. The IMP was collected every ten seconds for one minute. This procedure was repeated three consecutive times. The IMP measured by the FOPT was collected at 20 Hz during the first part and 100 Hz during the second part.

Mean IMP values were calculated for five minutes during baseline (normal IMP), the last five minutes during simulated compartment syndrome and five minutes during recovery for Study I. For Study II, the peak-to-peak amplitude of the IMP oscillations was analyzed for IMP values between 20 and 40 mmHg.

3.13.2 Study III

The IMP was continuously monitored and recorded within 15 to 30 seconds after the exercise test with the patient in a supine position (Figure 13). The amplitude was displayed on the monitor of the measurement equipment as the peak-to-peak value of the oscillations. The continuous IMP data and the RMS of the sEMG signals were displayed on monitors.
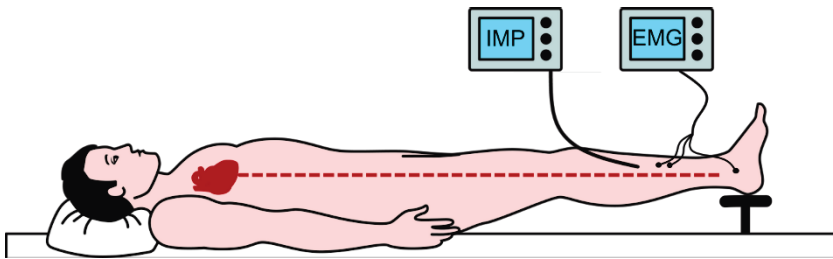
Figure 13. Measurement setup in Study III

3.13.3 Study IV

The IMP was recorded and the absolute IMP and the corresponding peak-to-peak amplitude of the IMP oscillations were analyzed for the following tourniquet pressure values 0, 40, 80, 120, 160, 120, 80, 40 and 0 mmHg (Figure 10).

4

Statistics

4 STATISTICS

Unless otherwise stated, pressure values are presented as the mean and standard deviation (SD) or standard error (SE).

4.1.1 Study I

Wilcoxon signed rank test was used for comparisons and significance was set at $p < 0.05$.

4.1.2 Study II

Correlations are given with Pearson's r. For comparisons, Wilcoxon signed-rank test was used and statistical significance was set at $p < 0.05$.

4.1.3 Study III

Differences between groups were determined with the Mann-Whitney U test. The level of significance was defined as $p < 0.05$. Correlations are given with Pearson's r.

To test the association between CACS and pulse-synchronous IMP oscillations, sensitivity and specificity, were calculated for the values collected one minute after exercise. A diagnosis of CACS was considered as the reference standard. Pulse-synchronous IMP oscillations with a peak-to-peak amplitude of > 2 mmHg were chosen as the cut-off value to indicate CACS.

4.1.4 Study IV

Comparisons between groups were made using the Mann-Whitney U test, with significance set at $p < 0.05$.

5

Results

5 RESULTS

5.1 Study I

The FOPT was able to record pulse-synchronous oscillations of the IMP during simulated compartment syndrome (Figure 14).
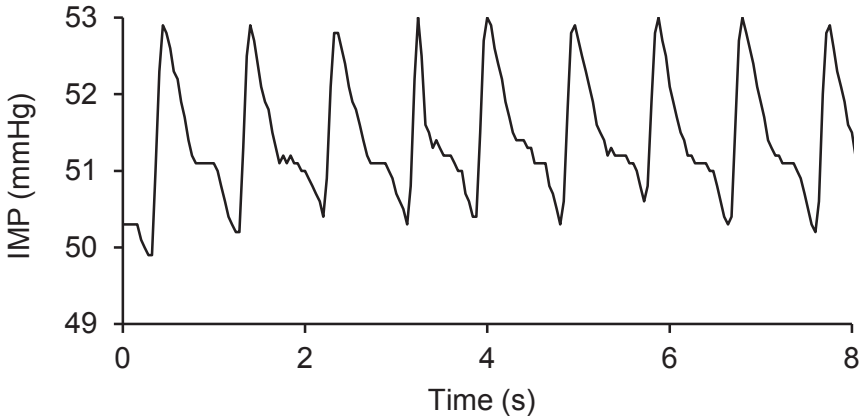
Figure 14. Example of pulse-synchronous oscillations of the IMP recorded with a fiber-optic technique during simulated compartment syndrome

The IMP measured with the FOPT was significantly lower at baseline ($p < 0.001$) and during recovery post elevated IMP ($p < 0.001$) compared with the needle-injection technique. It did not differ significantly during abnormally elevated IMP ($p > 0.05$) (Table 1).

IMP (SD), mmHg			
	Baseline	Elevated pressure	Post elevated pressure
FOPT	5.1 (2.6)	48.5 (6.9)	4.5 (1.6)
Needle injection	7.1 (2.5)	47.6 (6.6)	7.3 (3.3)

Table 1. The mean IMP values were calculated for five minutes during baseline, the last five minutes during simulated compartment syndrome and five minutes during recovery after abnormally elevated pressure

The transient in the IMP caused by saline injections was recorded with the FOPT (Figure 15).
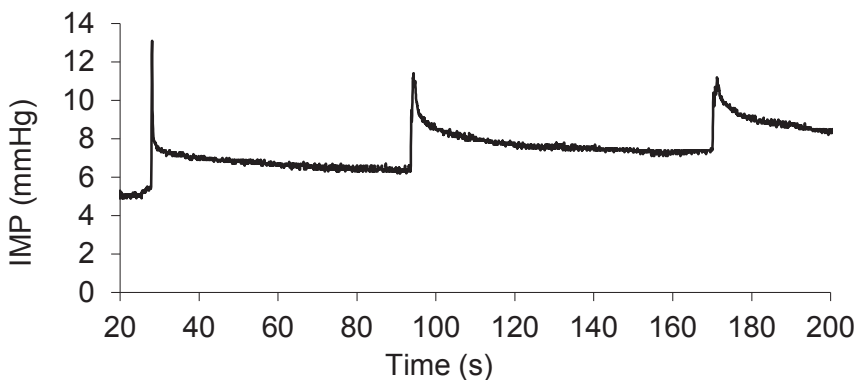
Figure 15. Example of transients in the IMP caused by flushing a catheter with 3 x 0.1 ml saline in a relaxed muscle at rest

A significant increase in IMP was recorded by both systems, following each injection of 0.1 ml of saline (p < 0.01). The IMP was still elevated 60 seconds after injection (Figure 16).
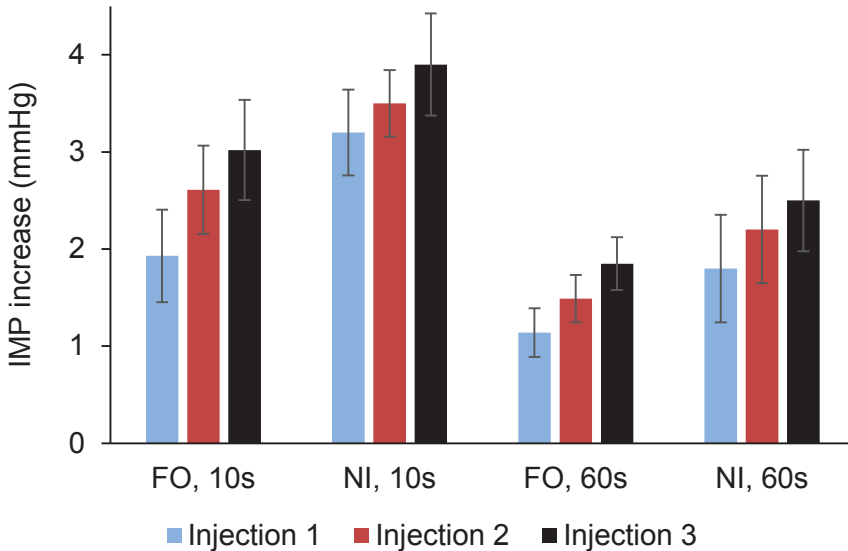
Figure 16. The increase in intramuscular pressure ± SE (mmHg) from baseline measured with a fiber-optic system (FO) and a needle injection system (NI) 10 and 60 seconds following three consecutive injections of 0.1 ml saline

The distance between the skin and the catheter tip was 10.8 (SD = 2.6) mm for the FOPT and 10.9 (SD = 2.0) mm for the needle-injection technique (p = 0.62). The distance between the muscle fascia and catheter tip was 6.6 (SD = 1.7) mm for the FOPT and 7.2 (SD = 1.1) mm for the needle-injection technique (p = 0.48). The mean pennation angle was 9.4 (SD = 2.4) degrees for the FOPT and 13 (SD = 2.5) degrees for the needle-injection technique.

The subjects were pain free before the experiment. The median VAS was 0 (range 0-8) for both catheters at catheter insertion. It was 0 (range 0-2) during the experiment.

5.2 Study II

Before the plaster cast was applied (baseline), no oscillations that were synchronous with the arterial pulse could be detected. When the plaster cast was applied, the IMP increased to 15 mmHg. After the thigh tourniquet was inflated to 65 mmHg, venous return was restricted and the IMP increased to over 40 mmHg within two minutes.

After ten minutes with the model of abnormally elevated IMP, the amplitude of the IMP oscillations was 3.9 (SD = 1.4) mmHg, while the IMP was 48.6 (SD = 7.1) mmHg. During recovery, the IMP returned to baseline and the amplitude was no longer detectable.

The peak-to-peak amplitude of the IMP oscillations was analyzed for an IMP range of 20 to 40 mmHg (Table 2). In this range, the amplitude of the oscillations showed a positive correlation ($r = 0.59$, $p < 0.01$) to the level of the IMP. Correlation between IMP and the amplitude of the IMP oscillations for each subject during is shown in Figure 17.

IMP	Amplitude	
mmHg	mmHg	SD
20	1.4	0.4
25	1.6	0.4
30	1.9	0.6
35	2.2	0.7
40	2.7	0.9

Table 2. The peak-to-peak amplitude of the oscillations increased with the absolute value of the IMP, when the model of simulated compartment syndrome was applied
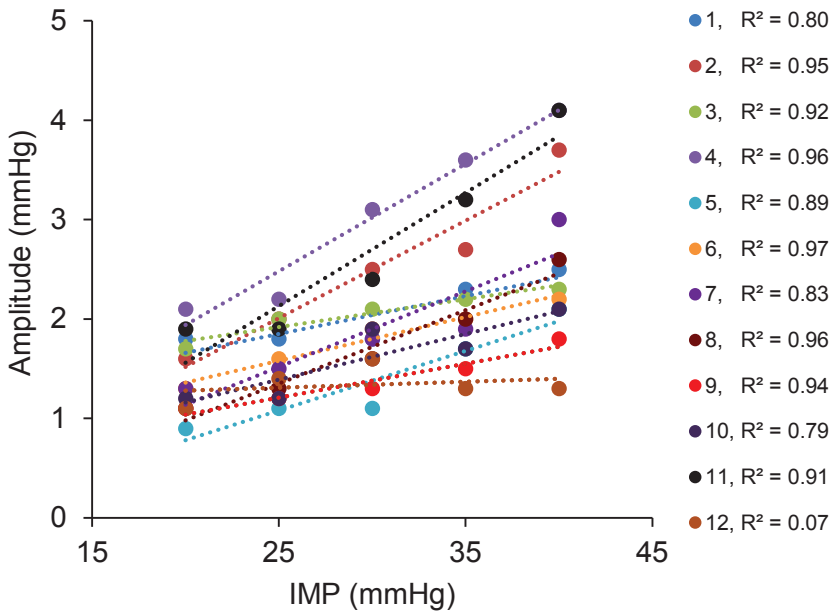
Figure 17. Correlation between IMP and the amplitude of the IMP oscillations for each subject during a model of abnormally elevated IMP. No correlation was found for subject 12

The local perfusion pressure decreased from 75 to 33 mmHg when the model of abnormally elevated IMP was applied (p < 0.01), while the mean arterial pressure and pulse rate were essentially unchanged throughout the experiment (p > 0.05) (Table 3).

	MAP		PP		Pulse	
	(mmHg)	SD	(mmHg)	SD	(bpm)	SD
Baseline	80	5	75	5	62	7
Elevated IMP	82	5	33	10	61	9
Recovery	82	7	78	8	59	7

Table 3. Mean arterial pressure (MAP), local perfusion pressure (PP) calculated from the IMP measured with the fiber-optic system and pulse rate measured at baseline, at abnormally elevated IMP and after the model of elevated pressure

5.3 Study III

After clinical evaluation and IMP measurements, 53 patients (60%) were diagnosed with CACS and 36 patients had other causes of leg pain. The CACS patients had a mean age of 29 years, median of 25 years, range 15-58 years. Their BMI was mean 27 kg/m², range 20-40 kg/m².

The non-CACS patients had a mean age of 34, median of 31 years, range 16-69 years and BMI was 25 kg/m², range 18-35 kg/m².

Among the control subjects, the mean age was 28 years, median of 26 years, range 20-42 years. Their BMI was 24 kg/m², range 20-34 kg/m².

The amplitude of the IMP oscillations was significantly higher in CACS patients than in the control subjects (p < 0.0001), but no difference was

found between non-CACS patients and control subjects (p > 0.61) at rest after exercise (Figure 18).
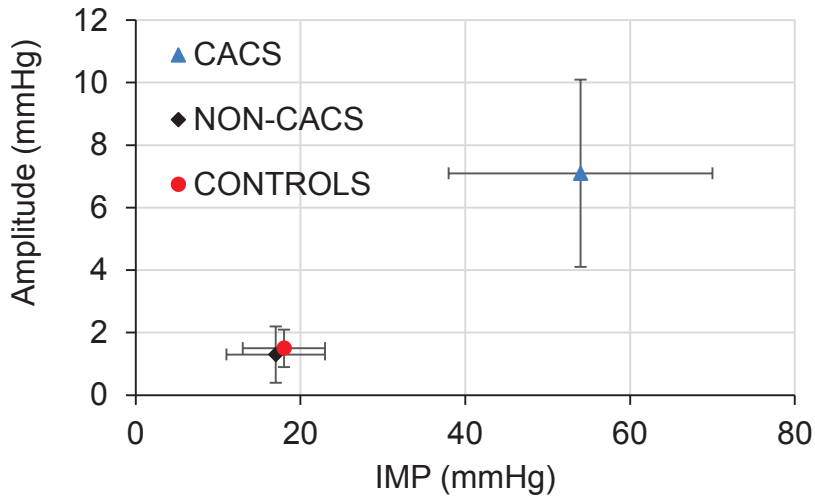
Figure 18. The mean IMP and amplitude of the IMP oscillations with SD at rest one minute after exercise for 53 CACS patients, 36 non-CACS patients and 19 healthy control subjects

The correlation (r **=** 0.6) between the IMP and the amplitude of the IMP oscillations recorded at one minute is shown in Figure 19. Linear regression yielded;

Amplitude (mmHg) = 1.2+ 0.11 x IMP (mmHg)
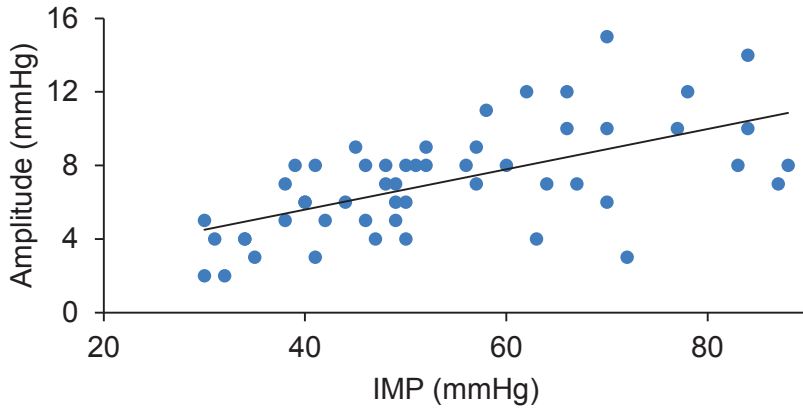
Figure 19. The correlation (r = 0.6) between the peak-to-peak amplitude of the IMP oscillations and the level of IMP one minute after an exercise test that elicited the symptoms in patients with CACS

Post-exercise IMP oscillations at rest one minute after exercise with an amplitude exceeding 2 mmHg were highly associated with CACS, with a sensitivity of 96% and a specificity of 94%.

The CACS group comprised 43% women and 57% men. The non-CACS group comprised 73% women and 27% men. As a result, women were more likely to have other causes of leg pain than men were.

Among patients diagnosed with CACS the IMP was 48 (SD = 14) mmHg for women and 59 (SD = 16) mmHg for men ($p < 0.01$). The amplitude of the IMP oscillations was 6.8 (SD = 2.7) mmHg for women and 7.4 (SD = 3.1) mmHg for men and did not differ significantly between genders ($p > 0.5$).

The mean arterial pressure did not differ significantly between CACS patients and control subjects ($p > 0.2$) or between CACS patients and non-CACS patients ($p > 0.7$).

The local perfusion pressure correlated (r **=** 0.66) with the amplitude of the
IMP oscillations (Figure 20). Linear correlation yielded;

Amplitude (mmHg) = 10.7 - 0.10 x local perfusion pressure (mmHg)
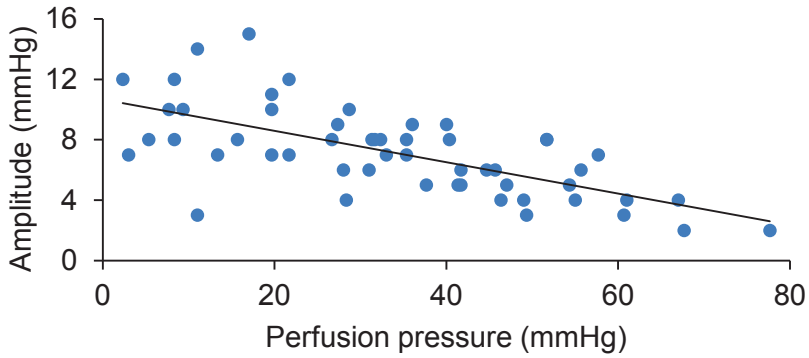
*Figure 20. The correlation (r = 0.66) between peek-to-peek amplitude of IMP
oscillations and local perfusion pressure in patients with CACS at rest one
minute after exercise*

There was no correlation between the pulse pressure and the amplitude of the IMP oscillations (Figure 21).
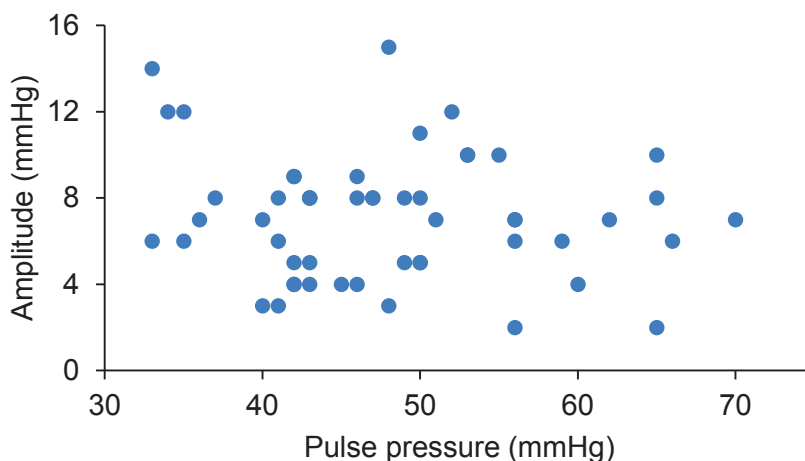
Figure 21. A low correlation (r = 0.13) was found between the amplitude of the IMP oscillations and pulse pressure in patients with CACS

The correlation was low between IMP and age (r = 0.12), as well as between age and the amplitude of the IMP oscillations (r = 0.06).

The EMG signal at rest after exercise was silent in all participants, signifying that the measured IMP was not influenced by leg muscle activity.

5.4 Study IV

The amplitude of the IMP oscillations increased with IMP and reached a maximum when the IMP was roughly equal to the participants' MAP and local perfusion pressure approached zero (Figure 22). It decreased when the IMP approached the systolic blood pressure.
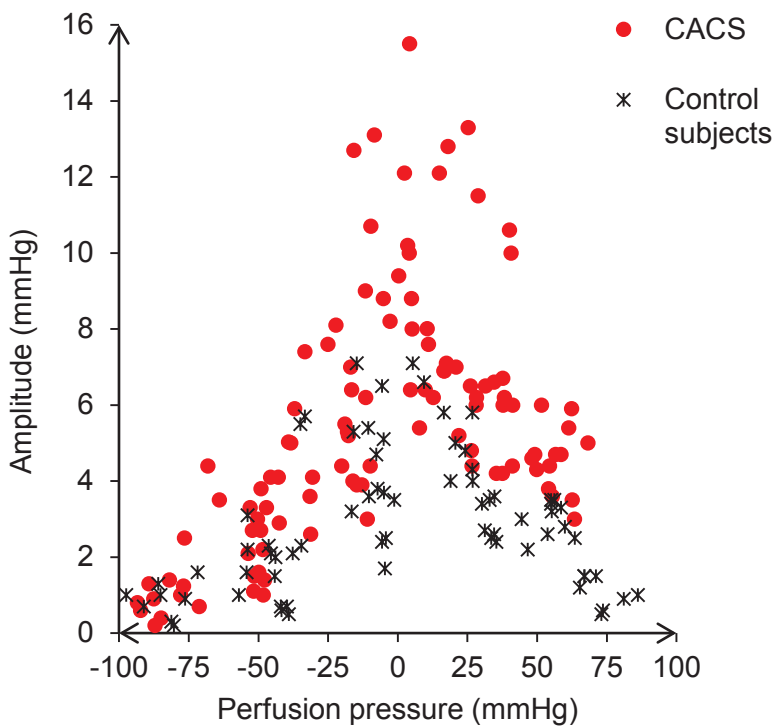
Figure 22. Local perfusion pressure and the amplitude of IMP oscillations in patients with CACS and healthy controls during external compression of the leg.

The amplitude for the CACS patients are shown in Figure 23.
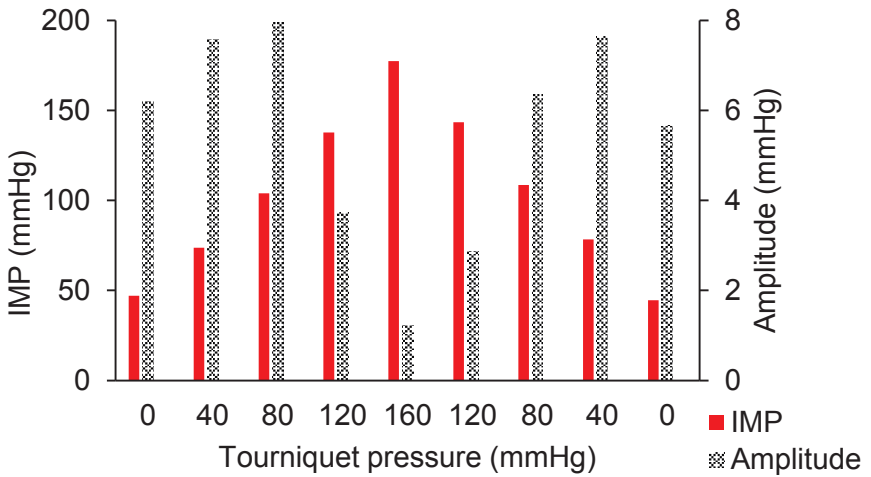
Figure 23. The mean IMP and amplitude of the IMP oscillations in with CACS during external compression of the leg

The amplitude was higher for CACS patients compared with control subjects (p < 0.001) (Figure 22 & Figure 24).

To study the amplitude of the IMP oscillations in relation to the patients' diastolic and systolic blood pressures and MAP, six IMP subcategories were created (Figure 24).
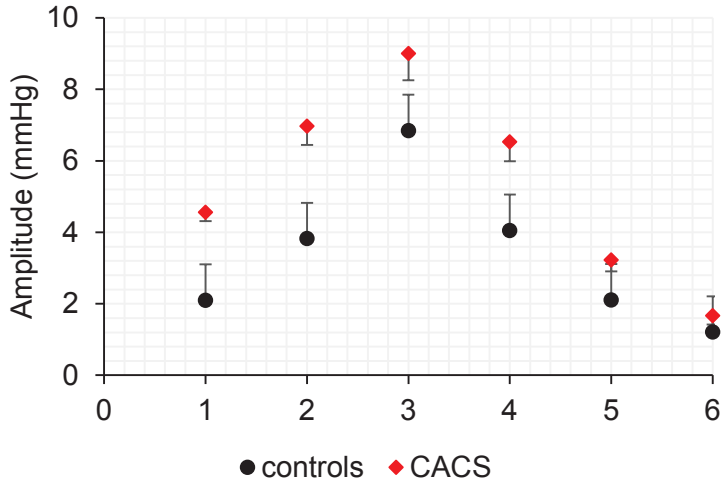
1. IMP < diastolic-30 mmHg	2. diastolic-30 mmHg< IMP < diastolic
3. diastolic < IMP < MAP	4. MAP < IMP < systolic
5. systolic < IMP < systolic+20 mmHg	6. systolic+20 mmHg < IMP

Figure 24. The amplitude (SE) of the IMP oscillations in relation to the patients' diastolic and systolic blood pressures and MAP, divided into six IMP subcategories

Blood pressures and pulse rate for the CACS patients and healthy control subjects are shown in Table 4 and Table 5.

	CACS patients							
	Systole		Diastole		MAP		Pulse rate	
	mmHg	SD	mmHg	SD	mmHg	SD	mmHg	SD
Before exercise	120	6	73	3	88	4	76	12
After exercise	132	15	78	6	96	9	84	11
During compression	129	14	79	5	95	8	79	10
After compression	126	11	75	5	92	7	78	12

Table 4. Blood pressures and pulse rate for the CACS patients

	Control subjects							
	Systole		Diastole		MAP		Pulse rate	
	mmHg	SD	mmHg	SD	mmHg	SD	mmHg	SD
Before exercise	115	8	69	4	85	5	73	13
After exercise	121	8	70	6	87	7	71	9
During compression	116	6	68	6	84	5	66	8
After compression	114	9	67	5	83	6	69	9

Table 5. Blood pressures and pulse rate for the healthy control subjects

No significant difference in pulse pressure was found between CACS patients and healthy subjects (Table 6).

	CACS		Controls	
	Mean	SD	Mean	SD
Pre exercise	47	2.4	46	7.7
Cuff = 0 mmHg	54	10	50	3.4
Cuff = 160 mmHg	50	10	48	6.0
Cuff = 0 mmHg	51	6.4	47	8.2

Table 6. Pulse pressures (mmHg) during the experiment

Pain intensity on the VAS was 3.0 when the healthy subjects were no longer able to continue the exercise test due to pain and/or muscle fatigue. It was 0.9 during the external compression of the leg.

No complication from the procedure was reported and the IMP normalized in all participants.

5.5 Main findings

5.5.1 Study I

Study I showed that the forward-sensing fiber-optic technique can be used to measure the IMP at rest in a normally hydrated muscle (normal IMP) and in a condition of abnormally elevated IMP (simulated compartment syndrome). The dynamic properties of the system make it suitable for recording the amplitude of pulse-synchronous IMP oscillations. The IMP increased significantly following each injection of 0.1 ml of saline and remained elevated during the observation period.

5.5.2 Study II

A positive correlation between the amplitude of the IMP oscillations and the absolute IMP level was found in Study II. This indicates that the amplitude can be used to verify the diagnosis of compartment syndromes.

5.5.3 Study III

The amplitude of the pulse-synchronous IMP oscillations at rest after exercise was significantly higher in patients with CACS compared with non-CACS patients and control subjects. Oscillations with an amplitude of more than 2 mmHg one minute after exercise have a sensitivity of 96% and a specificity of 94% to identify CACS. Among the CACS patients, women had 11 mmHg lower IMP at rest after exercise compared with men. The amplitude of the IMP oscillations did not differ significantly between men and women.

5.5.4 Study IV

The oscillations were observed in the entire IMP range that is seen in patients with acute and chronic compartment syndromes. The amplitude of the IMP oscillations varies with the absolute level of the IMP. The largest amplitudes were recorded when the level of the IMP was close to the level of the MAP and local perfusion pressure approached zero. The amplitude of the IMP oscillations was higher for the CACS patients compared with the control subjects.

6
Discussion

6 DISCUSSION

Pulse-synchronous IMP oscillations were studied at normal IMP at rest, during models of abnormally elevated IMP and at rest after exercise. The amplitude of the oscillations was measured in healthy subjects, patients with CACS and in patients with leg pain for reason other than CACS.

No pulse-synchronous oscillations in healthy subjects at rest

No pulse-synchronous oscillations in the IMP were detectable at rest in healthy subjects that were not exposed to volume load, exercise or external compression (Studies I, II & IV). At this baseline level, the IMP was about 5 mmHg. These results are in line with previous reports on IMP oscillations (Styf et al., 1986; Styf et al., 1998; Styf et al., 1987). Small disturbances and signal noise are always present when measuring IMP. This noise may, for example, derive from small motion artefacts. Motion artefacts from breathing are commonly seen. Breathing artefacts and other noise are, however, not synchronous with the pulse rate and do not have the typical curve form of the pulse-synchronous IMP oscillations.

The amplitude in healthy subjects during abnormally elevated IMP (Studies I & II)

During abnormally elevated IMP with compartment syndrome by venous obstruction and a volume-restricting plaster cast, the IMP increased to almost 50 mmHg. The amplitude of the pulse-synchronous oscillations was then approximately 4 mmHg. The amplitude showed a positive correlation with IMP (r = 0.59). Figure 17 shows the correlation for each of the subjects. The correlations range from r = 0.89 to r = 0.98, with the exception of one outlier with r = 0.26. Since the correlation coefficient, Pearson's r, is sensitive to outliers, the overall correlation was lowered by this outlier. However, no obvious reason for exclusion was found. Previously, a mean amplitude of IMP oscillations of 3.6 mmHg has been recorded with this model of abnormally elevated IMP (Styf et al., 1998). However, no correlation with the IMP has been reported previously.

The dynamic properties of the FOPT allowed for recordings of a detailed curve form of the IMP oscillations. To our knowledge, a high fidelity recording of the curve form of the IMP oscillations like that in Figure 14 has not previously been published.

The amplitude at rest after exercise (Studies III & IV)

The amplitudes of IMP oscillations were detectable at rest one minute after exercise in healthy subjects, patients with other causes of leg pain and in patients with CACS. Healthy subjects and patients with leg pain (not CACS) had a mean amplitude of approximately 1.5 mmHg, while the mean amplitude was over 7 mmHg in patients with CACS. The mean IMP was about 17 mmHg for the healthy subjects and the non-CACS patients, while it was 53 mmHg in patients with CACS. These results are in line with reported amplitudes of 5.8 (SD = 2.7) mmHg in 36 CACS legs, less than 1 mmHg in 31 non-CACS legs and not detectable in 85 non-CACS legs at rest post-exercise (Styf et al., 1987).

The amplitude during external compression (Study IV)

IMP oscillations with an amplitude of 2.9 mmHg have been reported during compartment syndrome simulated by external compression (Styf et al., 1998). However, it can be assumed that the IMP was less than the MAP. The results in Study IV demonstrate that IMP oscillations are present even when the IMP exceeds the MAP, indicating that the amplitude of IMP oscillations was also present when the calculated perfusion pressure was less than zero. This is in line with a previous study that reported that the amplitude of fascial oscillations first increased with an increase in the IMP and then decreased when the IMP exceeded the level of the MAP (Garabekyan et al., 2009).

One explanation of the preservation of oscillations in the IMP when the local perfusion pressure is close to zero is offered by the tidal wave theory (Dahn et al., 1967). This suggests that the artery is not open long enough to allow for flow into the arteries of the compartment. The energy in the blood flow is too low to complete the opening process of the arteries. The partly completed opening process may, however, induce oscillations. The fact that

the oscillations were still present for IMP levels exceeding MAP supports this theory.

The study also showed that the amplitude of the oscillations decreased when the IMP approached the systolic blood pressure. This result indicates that, when the arterial flow is severely restricted by high IMP, less of the energy from arterial pulses is transmitted to the surrounding tissue.

Compliance

The pathophysiological basis for the increase in the IMP at rest after exercise that causes changes in muscle tissue compliance is increased volume of the muscle tissue. This is caused by increased fluid content in the interstitial space, muscle cells and an increase in blood volume in the compartment due to increased metabolic demand and venous tamponade or a combination of all of these. As the compliance of the muscle decreases, due to both normal and/or abnormal swelling, each arterial pulse that reaches into the compartment is expected to increase the corresponding amplitude of the IMP oscillation. As a sign of reduced compliance, patients with CACS are expected to have a higher amplitude of their IMP oscillations after exercise compared with healthy control subjects and patients with exercise-induced leg pain for other reasons. The higher amplitudes may explain the throbbing leg pain experienced by some CACS patients in Study III. The oscillations in the IMP may have induced nociceptive pain in addition to possible ischemic pain.

Experimentally elevated IMP may also be achieved by large amounts of saline injected into the compartment. An injection of 5 x 10 ml of saline solution into the tibialis anterior muscle of one participant induced abnormally elevated IMP and pulse-synchronous oscillations were detected. (Willy et al., 1999). However, the amplitude was not quantified.

Propagation of the IMP oscillations

The characteristic shape of the intra-arterial pulsations was clearly reflected in the shape of the recorded IMP oscillations in Figure 14. The arterial pulsations also propagate to the muscle fascia and induce fascial oscillations (Garabekyan et al., 2009; Lee et al., 2013; Lynch et al., 2009;

Wiemann et al., 2006). The waveform of the fascial oscillations has been explored with non-invasive ultrasound (Lynch et al., 2009). One report showed that Fast Fourier Transform (FFT) frequency analysis of the fascial displacement waveform revealed a linear correlation between the ratio of the amplitude of the fundamental frequency and the amplitude of the second harmonic frequency and invasively measured IMP (Wiemann et al., 2006). On the other hand, in an experimental animal model, the FFT analysis revealed no significant interaction between the fundamental harmonic to second harmonic and the IMP (Garabekyan et al., 2009). Since oscillations were detected in the whole range of IMP values seen in patients with compartment syndromes in the studies in this thesis, it is possible that the oscillations originating from arterial pulsations might be useful for indirect measurements of the IMP using non-invasive techniques.

Characteristics of the fascia

The IMP may be elevated due to reduced compliance in the compartment (Eliassen et al., 1974; Styf et al., 1987). It has been suggested that the thickness and elasticity of the fascia plays a role in the reduction in compartment compliance and the increase in IMP in patients with abnormally elevated IMP (Detmer et al., 1985; Hurschler et al., 1994; Turnipseed et al., 1989; Turnipseed et al., 1995). On the other hand, the stiffness and thickness did not differ between chronic compartment syndrome patients and healthy subjects in a recent study (Dahl, 2011). The reduction in IMP in patients with CACS following surgical treatment by fasciotomy indicates an increase in compliance in the compartment (Styf et al., 1986; Wallensten, 1983). An increase in compliance may also be the explanation of the reported reduction in the amplitude of the IMP oscillations from 4.9 mmHg before surgery to 1.0 mmHg following surgery in patients with CACS (Styf et al., 1986). If the higher amplitudes of the IMP oscillations seen in CACS patients compared with healthy subjects seen in Study IV reflects a reduction in muscle compliance, this can be ascribed to an increase in muscle fluid volume and not to a conceivable difference in fascial properties. This may be assumed, since the external pressure applied by the tourniquet was high. It is therefore proposed that the difference in amplitude between CACS patients and healthy controls is due to difference in the fluid volume load induced by the exercise test.

6.1 Factors influencing the measured IMP

The measured IMP is affected by the properties of the measurement system. However, it is also affected by the way the tissue that is going to be measured is treated. In patients with CACS, the elevated IMP is a result of the volume load in the muscle induced by exercise. Each patient has an individual capacity to elevate his/her IMP by exercise. Most of the factors that influence the measured IMP are expected to influence the measured amplitude of the IMP oscillations.

Catheter patency

Artificially high readings may be recorded at rest after exercise if the catheter is partially or totally occluded (Styf et al., 1989). However, the controversial suggestion that the abnormally elevated IMP that slowly declines at rest after exercise is a result of an occluded catheter rather than a finding of pathological relevance (Barnes, 1997) has not been supported by others. A declining IMP at rest was found in Study III, while the patency of the catheter was assured by the recorded pulse-synchronous IMP oscillations.

Physiological reactance

Physiological reactance includes the undesirable effects of the measurement instrument on the physiological event that is being measured. Fluid injection or infusion affect the measured IMP. The transients recorded with the FOPT are due to local fluid volume load in the muscle. Transients recorded with fluid-filled systems with extra-corporeal transducers are also affected by the fluid resistance in the tubing and in the needle, if the pressure is measured during injection. The IMP was significantly higher following the 0.1 ml injections of saline in Study I. It remained elevated during the one-minute observation period. The injections were only 0.1 ml compared with the maximum of 0.3 ml recommended in the instructions for the needle-injection technique. Consequently, the IMP measurements after injections of 0.3 ml in compartment syndrome patients are likely to be even more biased. The magnitude of the bias is of clinical importance. Our results indicate that an injection of 0.1 ml is sufficient to maintain catheter patency with the needle-injection system.

The needle-injection technique in Study I, produced higher readings compared with the FOPT at normal IMP levels, 40% higher at baseline and 60% during recovery. This is in line with previous results that reported that needle-injection techniques measured erroneously high values at low IMP levels (Boody et al., 2005; Styf et al., 1989). The FOPT does not require injections to measure IMP. The purpose of the injections in combination with the FOPT was to record the influence of injections on the IMP with a measurement system with good dynamic properties.

The introduction of a catheter in the muscle causes reactance. In an effort to reduce trauma, needles of a size smaller than the commonly used 18 G have been explored (Mars et al., 1997; Staudt et al., 2008). Being able to use a FOPT with a small diameter but without the protective tubing would be a large step towards keeping physiological reactance to a minimum. However, without the Venflon, the sensor tip may be affected by pressure from solid structures. Biased readings may also be obtained if the catheter is placed close to the tendon (Nakhostine et al., 1993; Styf, 1995). This can be avoided by confirming the catheter placement with ultrasonography.

Factors that may affect the IMP in patients with CACS
A multifactorial etiology may not be the only factor to influence the level of IMP. Several other factors have been described; they include the intensity and type of exercise, type of sports, level of competition and even anthropometrics (Davis et al., 2013). The IMP at rest after exercise is also affected by each patient's ability to exercise his/her leg muscles.

Gender
Despite the fact that IMP values for chronic compartment syndrome patients have been reported for more than 40 years, IMP values have not been analyzed separately for men and women. Study III was the first report on a significant difference in the IMP at rest after exercise between men and women. The IMP was 11 mmHg lower in women compared with men. No difference in MAP between genders was found. This indicates that the local perfusion pressure differs between genders in patients with CACS. As previously mentioned, the IMP criteria used in the diagnosis of CACS have been questioned. Possible differences between genders may be one factor

behind the issue of absolute IMP criteria to indicate surgery. A preliminary report on 100 patients with CACS (Nilsson et al., 2015) also demonstrated an IMP difference between genders. IMP values should therefore be reported separately for men and women in studies of the pathophysiology and diagnosis of compartment syndromes. The amplitude of the IMP oscillations did, however, not differ significantly ($p > 0.5$) between men and women in Study III.

The exercise test

The IMP measured at rest after exercise is partly dependent on the intensity and duration of the exercise. The exercise test in Studies III & IV continued until the participant was unable to continue due to muscle fatigue or pain. Each participant decided when he or she was no longer able to continue. Several factors influence this self-selected endpoint. The effort-factor/motivation is highly individual, even if the participants were instructed in the same manner.

It has been suggested that a standardized exercise test is needed to eliminate variation in the intensity and duration of the exercise. This would also reduce the bias from the effort factor. The overall idea is that a standardized test may reduce the variation in post-exercise IMP and that the validity of the IMP criteria to indicate surgery is ensured. This idea is appealing, but the reality is that some patients develop the typical symptoms of chronic compartment syndrome from walking a short distance, while others are symptom free unless they run for more than an hour. It is generally believed that the exercise test should mimic the activity that usually elicits the CACS patient's symptoms. A set protocol may not reveal some patients' symptoms. This is probably why no consensus has been reached regarding a standardized symptom-provoking exercise protocol.

Comorbidity

Furthermore, the symptoms from comorbid leg disease may force the patient to quit the exercise test before pain and elevated IMP from a compartment syndrome occur. A lower IMP is expected if the exercise is discontinued due to comorbidity. Leg comorbidity is therefore not only a differential diagnosis in patients with leg pain. Common differential diagnoses and comorbidities include compartment syndrome in other compartments, medial tibial stress syndrome, stress fracture, popliteal artery entrapment syndrome and nerve entrapment (Burrus et al., 2014; Styf, 1988). A preliminary report suggests that comorbidity affects the measured IMP in patients with CACS (Styf & Nilsson, accepted abstract at ORS 2016).

Age

Age has been suggested to correlate with the measured IMP in patients with CACS (Nkele et al., 1988). No correlation was however found between age and IMP at rest after exercise or between age and the amplitude of the IMP oscillations in patients with CACS (Study III).

6.2 Methodological considerations

Recordings of IMP oscillations require a measurement system with high dynamic properties (Styf et al., 1986). This was the reason for measuring the amplitude of the IMP oscillations with a FOPT in Study I & II. The recording of the IMP transient following injection indicates low compliance of the FOPT (Figure 15). The results in Study I show that FOPTs may improve IMP measurement both in the clinical setting and in research. However, IMP systems used in a clinical environment need to be easy to handle and cost effective. The disposable transducers of the fiber-optic system were somewhat expensive. The participants in Studies III & IV were therefore not measured with the FOPT system.

6.2.1 Models of simulated compartment syndrome

The elevated IMP (simulated compartment syndrome) in Studies I & II was induced by venous obstruction of a casted leg. It elevated the IMP to abnormal levels by increasing the volume load in the restricted muscle compartment rather than by external compression. The idea behind this model is to induce elevated IMP by volume load to simulate the volume load seen in patients with compartment syndrome. The model may simulate acute and chronic compartment syndrome since it elicited sensory dysfunction, muscle weakness, a mild throbbing pain and oscillations in the IMP (Styf et al., 1998). In Studies I & II, the model was applied for only 10 minutes to elevate the IMP without provoking any other symptoms associated with compartment syndromes.

In Study IV, external compression was used, since this model may induce IMP values exceeding the systolic blood pressure, which is not possible with other models. Furthermore, patients with swollen legs following injuries are commonly treated with external compression before and after surgical treatment. External compression applies compressive forces and the volume of the leg may actually decrease instead of increase, as in the case of a real compartment syndrome (Styf et al., 1998). However, a difference in the amplitude of IMP oscillations was found between healthy subjects and patients with CACS in Study IV when exposed to this model. This indicates that the volume load induced by the preceding exercise was maintained to a greater extent in patients with CACS. The IMP decreased by 2 mmHg in patients and control subjects from the time before the cuff was inflated to the time when the cuff was completely deflated (Figure 24). This result indicates that external compression of the leg during the experiment did not reduce the volume load in the anterior compartment in either CACS patients or healthy subjects. The IMP returned to normal levels in all participants.

6.3 Subjects

Patients

CACS is usually described as an exercise-induced condition. Many studies have investigated competitive athletes and military personnel. The patients in Study III were mostly recreational athletes or non-athletes (60%), while 29% were competitive athletes at a regional level, and 11% were competitive athletes at elite/national level. Their mean age was about 30 years. Most of the patients had had symptoms for an extended period and had made many visits to health care. This concurs with other studies of CACS. The patients included in Studies III & IV are, however, not necessarily a representation of the whole population of patients with compartment syndrome.

Healthy control subjects

The age and BMI of the healthy control subjects in Studies I, II, III & IV were approximately the same as for those of CACS patients. The controls comprised roughly 50% women.

6.3.1 Non-invasive methods

Several non-invasive techniques have been evaluated as an option for IMP in diagnosing compartment syndrome. The techniques include ultrasound (Lee et al., 2013), quantitative muscle hardness (Steinberg et al., 2011; Steinberg, 2005), near infrared spectroscopy (Mohler et al., 1997; van den Brand et al., 2004; Zhang et al., 2012) and MRI (Litwiller et al., 2007; Ringler et al., 2013). However, none of the techniques has yet gained widespread clinical acceptance. For a non-invasive technique to be successful, it should measure a parameter that reflects the pathophysiology of compartment syndrome.

6.4 Limitations

One limitation of this thesis is that only the anterior compartment of the leg was investigated. The anterior compartment was selected since it is the most frequently affected. The anatomy differs between the anterior and other compartments. The amplitude of the IMP oscillations in other compartments is unknown and remains to be investigated.

Study I
In Study I, the influence of injections of saline was only investigated at the baseline level of the IMP. It is most likely that injections of the same volume would elevate the pressure even more in a muscle with abnormally elevated pressure due to the reduction in muscle compliance.

Study II
One limitation in Study II was that the amplitude of the oscillations was not studied when the local perfusion pressure approached zero, as the model of simulated compartment syndrome only elevated the IMP to approximately 50 mmHg.

Study III
The measurement system had a 1 mmHg minimum resolution of the displayed amplitude of the IMP oscillations. To test the sensitivity and specificity of the amplitudes of the IMP oscillations, our inclusion criteria including absolute IMP values were used as a reference. Preferably, the reference should be a gold standard, independent of the tested parameter. In the case of compartment syndrome, the gold standard is clinical findings in combination with IMP measured at rest one minute after exercise.

Study IV
The tourniquet was inflated in steps of 40 mmHg. Smaller steps could have provided more detailed information. The somewhat large steps in cuff pressure were a trade-off for keeping the total time of compression to a minimum, since the IMP decreases gradually at rest after exercise. The number of participants limited the analysis. With a large number of subjects, subgroups could maybe have been created and analyzed.

6.4.1 Oscillations in diagnosing acute compartment syndrome

In patients who are at risk of developing an acute compartment syndrome, continuous IMP monitoring is ideal (McQueen et al., 2013; Whitney et al., 2014) and single readings should preferably be avoided (Collinge et al., 2010). Catheter patency must be ensured during long-term measurements of IMP. The injection of unnecessary surplus fluid should preferably be avoided, since the IMP is further increased by the added volume in the compartment, as shown in Study I. As long as pulse-synchronous IMP oscillations are recorded, no extra injection of fluid is necessary.

Using IMP measurement and a differential pressure criterion appears to have high sensitivity and specificity in diagnosing ACS (McQueen et al., 2014; McQueen et al., 2013). The oscillations may thus be most useful for the continuous validation of catheter patency.

One study showed that fascial oscillations measured by non-invasive ultrasound was a better predictor of abnormally elevated IMP than near-infrared spectroscopy during simulated acute compartment syndrome with IMP levels up to 70 mmHg (Lee et al., 2013). The studies in this thesis support the possibility of using non-invasive methods for estimating the reduced compliance and increased IMP by studying tissue oscillations.

7
Conclusions

7 CONCLUSIONS

7.1 Study I

The properties of the FOPT make it suitable for recording both the absolute IMP and the amplitude of pulse-synchronous IMP oscillations. The fluid injections used with needle-injection techniques are prone to influence the measured IMP. Even small amounts of saline (0.1 ml) constitute a measurement problem rendering an overestimated IMP reading. The FOPT had excellent dynamic properties and do not require injection of fluid to measure IMP. Fiber-optic techniques may therefore improve IMP measurements.

7.2 Study II

The amplitude of the pulse-synchronous IMP oscillations increased with increasing IMP levels during a model of abnormally elevated IMP (simulated compartment syndrome) in the human leg. Since the amplitude is correlated with the absolute level of the IMP, it may be an additional parameter both in research and in diagnosing compartment syndromes.

7.3 Study III

The amplitude of pulse-synchronous IMP oscillations exceeding 2 mmHg is a parameter with high sensitivity and specificity that may lend support when diagnosing CACS. The parameter is easily obtained during routine IMP measurements and it is related to the pathophysiology of CACS. In patients with CACS women had a significantly lower absolute IMP compared with men. However, no significant difference in the amplitude of the IMP oscillations was found between men and women. Continuous confirmation of catheter patency is ensured when oscillations of the IMP are recorded.

7.4 Study IV

The amplitude of the IMP oscillations varies with the absolute level of the IMP. The largest amplitudes were recorded when the level of the IMP was close to the level of the MAP and local perfusion pressure approached zero. The amplitude of the IMP oscillations was greater for the CACS patients compared with the control subjects. This indicates that the higher amplitude reflects the pathophysiology of volume load and/or reduced compliance of the muscle compartment in patients with CACS. The oscillations were observed in the entire IMP range commonly seen in patients with acute and chronic compartment syndromes. The oscillations of the IMP may therefore be an important parameter in diagnosing both acute and chronic compartment syndromes.

7.5 Overall conclusion

The measured IMP is assured when oscillations are measured, since they corroborate catheter patency continuously during IMP measurements. The amplitude of the pulse-synchronous IMP oscillations is a parameter that reflects the pathophysiological foundation in compartment syndromes. It has high sensitivity and specificity in identifying CACS patients. It may be an additional parameter in both research and diagnosing compartment syndromes.

8

Future perspectives

8 FUTURE PERSPECTIVES

IMP oscillations

The pulse-synchronous oscillations were only investigated in the anterior compartment of the leg. The amplitude of IMP oscillations in other compartments is unknown and remains to be investigated.

The IMP oscillations may also be present during isometric contraction of the muscle. This was, however, not investigated in the papers included in this thesis.

Model of elevated IMP

To further study the difference in amplitudes between CACS patients and healthy subjects, a model of simulated compartment syndrome that combines venous obstruction to create volume load and external compression to reach IMP exceeding MAP is of interest.

Diagnosis of chronic compartment syndrome

To improve the validity of IMP as a tool in diagnosing compartment syndrome, standardized recommendations for performing and reporting IMP should be developed. Standardized IMP measurements may produce IMP data that are easier to compare. This may improve our understanding of the underlying causes and the different etiologies of chronic compartment syndrome.

Opportunities for non-invasive techniques

The development of a reliable, non-invasive method for confirming the diagnosis of compartment syndromes would be a breakthrough. Based on the results of this thesis, techniques that measure fluid hydrostatic or tissue oscillations created by the elevated IMP and reduced compliance in the muscle compartment have a solid pathophysiological foundation.

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