Title page:

1 Original project title

Is physiotherapy or fasciotomy the best treatment option for chronic exertional compartment syndrome in the anterolateral compartment of the lower leg? A randomized controlled trial.

This protocol including the statistical considerations/analysis plan (p. 19) was approved by the regional local ethical committee (H-18001263) on the 28th of May 2018.

Contact person for ethical application, primary investigator and clinical/medical/research responsible:

Simon Døssing, Senior Surgeon, MD, PhD
e-mail: simon.doessing.01@regionh.dk
Mobile phone: 27201311
Office phone: 38635042

Institute of Sports Medicine,
Bispebjerg Hospital, Building 8, 1st floor
Nielsine Nielsensvej 11
2400 Copenhagen NV

Index

2 Abbreviations

CECS: Chronic exertional compartment syndrome

EILP: Exercise induced leg pain questionnaire

PROM: Patient reported outcome measure

VAS: Visual Analogue Scale

ICP: Intracompartmental pressure

GRC: Global Rating of Change Score/Scale

SANE: Single Assessment Numeric Evaluation

MRI: Magnetic resonance imaging

NIRS: Near infrared spectroscopy

ACT: Anterior compartment thickness

DOMS: Delayed onset muscle soreness

3 Purpose

a. Hypothesis, endpoints and importance of the study

It is hypothesized that physiotherapy including a change in running landing pattern and surgical fasciotomy are equally good as treatment options for chronic exertional compartment syndrome (CECS) of the anterolateral compartment of the lower leg.

The endpoints/outcomes are:

Primary outcome:

Change from week 0 (start of study) to week 12 (completion of intervention) in: "Exercise induced leg pain Questionnaire" (EILP) a patient reported outcome measure (PROM).

Secondary outcomes are:

- Change from week 0 (start of study) to week 12 (completion of intervention) on Visual Analogue Scale (VAS) score after an "exercise provocation test": Before the intervention (week 0) the patients are asked to run on a treadmill until symptoms occur and pain reaches VAS ≥ 8. Running is performed at the patients approximated habitual running pace (prior to CECS symptoms). This exact same exercise provocation test (same distance and inclination) is repeated after the intervention 12 weeks later (week 12).
- Change in intracompartmental pressure (ICP) from week 0 (start of study) to week 12 (completion of intervention) following the exercise provocation test.
- Change in muscle compartment compliance from week 0 (start of study) to week 12 (completion of intervention) during the provocation test.
- Change from week 0 (start of study) to week 12 (completion of intervention), week 26 and week 52 in: Global Rating of Change Score/Scale (GRC), Single Assessment Numeric Evaluation (SANE) and questions: How far can you run without pain? Would you recommend this treatment to a friend?
- Change from week 0 (start of study) to week 26 and week 52 in: EILP.

The study is important because:

1) Results from recent studies suggest that physiotherapy represents a valid alternative to surgery for the treatment of CECS. Surgery is currently standard treatment and a change towards physiotherapy as primary treatment could potentially reduce both complication rates and costs.
2) Intracompartmental pressure (ICP) is gold standard for diagnosing CECS. However, the association between ICP and symptoms of CECS, both before and after physiotherapeutic and surgical treatment, as well as the association between ICP and muscle compartment compliance, has not been thoroughly investigated.

Background and literature

CECS of the lower leg is a condition of pain induced by exercise (Pasic, Bryant, Willits, & Whitehead, 2014; Stein & Sennett, 2005). CECS accounts for 14-33% of lower leg pain in athletes, evenly divided among males and females (Ab, Hansen, & Jessen, 2015; Aweid et al., 2012; Wilder & Magrum, 2010). Symptoms are described as a tight, cramp like ache that occurs at a well-defined and reproducible point in the exercise bout and increases if the training persists. Relief of symptoms typically occurs within 30 minutes of ending the activity (Pasic et al., 2014).

The anterior compartment is most commonly affected, followed by the deep posterior, the lateral and the superficial posterior compartment (Wilder & Magrum, 2010). Often more than one compartment in the same leg is involved, and the condition is reported bilateral in up to 95% of affected athletes (Ab et al., 2015; Aweid et al., 2012).

The pathophysiology of CECS is not fully understood. It is, however, generally agreed that exercise induces abnormal elevation in ICP, which interferes with tissue perfusion and cause painful ischemia affecting the nerves and impairing muscle function (Ab et al., 2015; Braver, 2016; Styf, 1987; Zhang, Rennerfelt, & Styf, 2012). A noncompliant muscle compartment, which is unresponsive to the expansion of muscle volume that occurs with exercise, offer a possible pathophysiological explanation for CECS (Bresler, Mar, & Toman, 2012; Wilder & Magrum, 2010). However, this view is challenged by a study reporting no difference in fascial thickness and stiffness between CECS patients and healthy controls (Dahl, Hansen, Stål, Edmundsson, & Magnusson, 2011). Furthermore, the thickness of the anterior compartment increased more with exercise in CECS patients relative to controls, questioning decreased compliance as the main pathophysiology in CECS (Rajasekaran, Beavis, Aly, & Leswick, 2013). The definition of a pathologically elevated ICP during exercise is important for the diagnosis of CECS and is currently debated (Aweid et al., 2012; Hislop & Tierney, 2011; Pasic et al., 2014; Touliopolous & Hershman, 1999). The criteria suggested by Pedowitz (Pedowitz, Hargens, Mubarak, & Gershuni, 1990) is used as standard by most clinicians for the diagnosis of CECS: 1) a pre-exercise pressure of 15 mmHg or greater, and/or 2) a 1-minute post-exercise pressure of 30 mmHg or greater, and/or 3) a 5-minute post-exercise pressure of 20 mmHg or greater (Robert a. Pedowitz & Gershuni, 1995). The precision and diagnostic value of these commonly used criteria is debated, due to a reported overlap in ICP readings between patients and healthy controls at certain time points (Aweid et al., 2012). Interestingly, in a small cohort of asymptomatic rollerskiers ICP was elevated, according to the Pedowitz criteria, in 100% of participants after 20 minutes of exercise (Woods, Petron, Shultz, & Hicks-Little, 2015). Despite these uncertainties, it is suggested that ICP measured 1-minute after ceasing exercise has the highest diagnostic value, as it most consistently display higher values in patients with CECS symptoms relative to healthy controls (Aweid et al., 2012). The different types of catheters (slid catheter, side-port, straight-needle) also clearly influence the absolute values of the measurements (Boody & Wongworawat, 2005; Hammerberg, Whitesides, & Seiler, 2012) and the catheter tip can be wrongfully placed outside the compartment by experienced health professionals in up to 21% of cases when positioned without ultrasound guidance (Winkes et al., 2016).

Non-invasive modalities such as magnetic resonance imaging (MRI) (Bresler et al., 2012), near infrared spectroscopy (NIRS) (Zhang et al., 2012) and ultrasound measurements (Rajasekaran et al., 2013) have been suggested as future adjuncts or alternatives for diagnosing CECS, but their diagnostic value remains to be established.

In summary, it is generally agreed that ICP measurements are important for diagnosing CECS, but several studies question current practice including the mentioned criteria and particularly the use of non-ultrasound guided catheter positioning.

Both conservative and surgical treatment options are suggested in the literature.

Conservative treatment, including physiotherapy, has been attempted with varying success and is generally believed by many to be insufficient for the long-term treatment of CECS (Brewer & Gregory, 2012; George & Hutchinson, 2012; Pasic et al., 2014). However, inducing muscle hypotrophy via injection of botulinum toxin, was efficient in reducing exercise induced pain in CECS patients, but also resulted in decreased muscle strength, although without measurable functional consequences (Isner-Horobeti, Dufour, Blaes, & Lecocq, 2013). Interestingly, changing the gait pattern in order to achieve a forefoot/midfoot strike during running, which potentially decrease pressure in the anterior compartment (Kirby & McDermott, 1983) and eccentric load of the anterior compartment muscles (Tweed & Barnes, 2008) has proven successful for treatment of anterior CECS (Breen & Foster, 2015; Diebal, Gregory, Alitz, & Gerber, 2012; Helmhout et al., 2015). These studies suggest a role for non-operative treatment of CECS, but to our knowledge, no randomized controlled studies exist regarding the effect of physiotherapy or other non-surgical interventions.

Surgical fasciotomy, with release of the compartment(s) with elevated intra-compartmental pressure, has been shown by many investigators to be effective using both open, mini-open and endoscopically assisted techniques (Biedert & Marti, 1997; Stein & Sennett, 2005). There are, however, considerable variations in the reported outcomes of surgery. In a large cohort, 45% had symptom recurrence after surgery and 16% experienced surgical complications including infection, neurological damage, and hematoma (Waterman, Laughlin, Kilcoyne, Cameron, & Owens, 2013). Moreover, the need for revision surgery can be as high as 11% (Pasic et al., 2014). Other groups report more successful outcome of surgery with patient satisfaction of 60 to 90% (Anthony A Schepsis, Fitzgerald, & Nicoletta, 2005; Waterman et al., 2013), including a retrospective follow-up study, in which operation was successful in 81% of patients and non-operative treatment successful in only 41% of patients (Packer et al., 2013). To our knowledge, no studies have compared surgical versus non-surgical treatment in a prospective or randomized designed study.

CECS is a common condition in athletes and although disagreements exist, the diagnosis is typically made based on a history of pain in the calf muscles during exercise that resolves within 30 minutes of ending the activity as well as a positive ICP reading. Typically the patients are offered fasciotomy if the symptoms persist.

To our knowledge, no studies have compared the effect of fasciotomy to any non-surgical treatment strategies in a randomized controlled setting. Moreover, correlation between symptom severity, ICP measurements, muscle compartment compliance, and effect of treatment is not fully elucidated. Finally, the possible effect of changing the landing pattern in combination with physical therapy has not been attempted in a randomized setting.

References

Ab, V., Hansen, R. L., & Jessen, P. T. (2015). Aktivitetsudløst kronisk kompartmentsyndrom i underbenet, 2–6.

Aweid, O., Del Buono, A., Malliaras, P., Iqbal, H., Morrissey, D., Maffulli, N., & Padhiar, N. (2012). Systematic Review and Recommendations for Intracompartmental Pressure Monitoring in Diagnosing Chronic Exertional Compartment Syndrome of the Leg. *Clinical Journal of Sport Medicine*, *22*(4), 356–370. https://doi.org/10.1097/JSM.0b013e3182580e1d

Barrett, E. J., & Rattigan, S. (2012). Muscle perfusion: Its measurement and role in metabolic regulation. *Diabetes*, *61*(11), 2661–2668. https://doi.org/10.2337/db12-0271

Beaton, D. E., Bombardier, C., Guillemin, F., & Ferraz, M. B. (2000). Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine*, *25*(24), 3186–3191. https://doi.org/10.1097/00007632-200012150-00014

Biedert, R. M., & Marti, B. (1997). Intracompartmental pressure before and after fasciotomy in runners with chronic deep posterior compartment syndrome. *International Journal of Sports Medicine*. https://doi.org/10.1055/s-2007-972650

Boody, A. R., & Wongworawat, M. D. (2005). Accuracy in the measurement of compartment pressures: a comparison of three commonly used devices. *The Journal of Bone and Joint Surgery. American Volume*, *87*(11), 2415–2422. https://doi.org/10.2106/JBJS.D.02826

Braver, R. T. (2016). C h ro n i c Ex e r t i o n a l C o m p a r t m e n t S y n d ro m e, *33*, 219–233.

Breen, D. T., & Foster, J. (2015). GAIT RE-TRAINING TO ALLEVIATE THE SYMPTOMS OF ANTERIOR EXERTIONAL LOWER LEG PAIN :, *10*(1), 85–94.

Bresler, M., Mar, W., & Toman, J. (2012). Diagnostic Imaging in the Evaluation of Leg Pain in Athletes. *Clinics in Sports Medicine*, *31*(2), 217–245. https://doi.org/10.1016/j.csm.2011.09.006

Brewer, R. B., & Gregory, A. J. M. (2012). Chronic lower leg pain in athletes: a guide for the differential diagnosis, evaluation, and treatment. *Sports Health*, *4*(2), 121–7. https://doi.org/10.1177/1941738111426115

Dahl, M., Hansen, P., Stål, P., Edmundsson, D., & Magnusson, S. P. (2011). Stiffness and thickness of fascia do not explain chronic exertional compartment syndrome. *Clinical Orthopaedics and Related Research*, *469*(12), 3495–3500. https://doi.org/10.1007/s11999-011-2073-x

Diebal, a. R., Gregory, R., Alitz, C., & Gerber, J. P. (2012). Forefoot Running Improves Pain and Disability Associated With Chronic Exertional Compartment Syndrome. *The American Journal of Sports Medicine*, *40*(5), 1060–1067. https://doi.org/10.1177/0363546512439182

George, C. a., & Hutchinson, M. R. (2012). Chronic Exertional Compartment Syndrome. *Clinics in Sports Medicine*, *31*(2), 307–319. https://doi.org/10.1016/j.csm.2011.09.013

Greis, C. (2011). Quantitative evaluation of microvascular blood flow by contrast-enhanced ultrasound (CEUS). *Clinical Hemorheology and Microcirculation*, *49*(1–4), 137–149. https://doi.org/10.3233/CH-2011-1464

Hammerberg, E. M., Whitesides, T. E., & Seiler, J. G. (2012). The Reliability of Measurement of Tissue Pressure in Compartment Syndrome. *Journal of Orthopaedic Trauma*, *26*(9), e166. https://doi.org/10.1097/BOT.0b013e3182673a3f

Helmhout, P. H., Diebal, a. R., van der Kaaden, L., Harts, C. C., Beutler, a., & Zimmermann, W. O. (2015). The Effectiveness of a 6-Week Intervention Program Aimed at Modifying Running Style in Patients With Chronic Exertional Compartment Syndrome: Results From a Series of Case Studies. *Orthopaedic Journal of Sports Medicine*, *3*(3), 1–10. https://doi.org/10.1177/2325967115575691

Hislop, M., & Tierney, P. (2011). Intracompartmental pressure testing: results of an international survey of current clinical practice, highlighting the need for standardised protocols. *British Journal of Sports Medicine*, *45*(12), 956–8. https://doi.org/10.1136/bjsports-2011-090368

Isner-Horobeti, M.-E., Dufour, S. P., Blaes, C., & Lecocq, J. (2013). Intramuscular pressure before and after botulinum toxin in chronic exertional compartment syndrome of the leg: a preliminary study. *The American Journal of Sports Medicine*, *41*(11), 2558–66. https://doi.org/10.1177/0363546513499183

Kirby, R. L., & McDermott, A. G. P. (1983). Anterior tibial compartment pressures during running with rearfoot and forefoot landing styles. *Archives of Physical Medicine and Rehabilitation*, *64*(7), 296–299.

Nauck, T., Lohrer, H., Padhiar, N., & King, J. B. (2015). Development and validation of a questionnaire to measure the severity of functional limitations and reduction of sports ability in German-speaking patients with exercise-induced leg pain, 113–117. https://doi.org/10.1136/bjsports-2012-091745

Packer, J. D., Day, M. S., Nguyen, J. T., Hobart, S. J., Hannafin, J. a, & Metzl, J. D. (2013). Functional outcomes and patient satisfaction after fasciotomy for chronic exertional compartment syndrome. *The American Journal of Sports Medicine*, *41*(2), 430–6. https://doi.org/10.1177/0363546512471330

Pasic, N., Bryant, D., Willits, K., & Whitehead, D. (2014). Assessing Outcomes in Individuals Undergoing Fasciotomy for Chronic Exertional Compartment Syndrome of the Leg. *Arthroscopy : The Journal of Arthroscopic & Related Surgery*, *31*(4), 1–7. https://doi.org/10.1016/j.arthro.2014.10.018

Pedowitz, R. a., & Gershuni, D. H. (1995). Pathophysiology and diagnosis of chronic compartment syndrome. *Operative Techniques in Sports Medicine*, *3*(4), 230–236. https://doi.org/10.1016/S1060-1872(95)80021-2

Pedowitz, R. a, Hargens, a R., Mubarak, S. J., & Gershuni, D. H. (1990). Modified criteria for the objective diagnosis of chronic compartment syndrome of the leg. *The American Journal of Sports Medicine*, *18*(1), 35–40. https://doi.org/10.1177/036354659001800106

Rajasekaran, S., Beavis, C., Aly, A., & Leswick, D. (2013). The Utility of Ultrasound in Detecting Anterior Compartment Thickness Changes in Chronic Exertional Compartment Syndrome : A Pilot Study, *23*(4), 305–311.

Schepsis, A. A., Fitzgerald, M., & Nicoletta, R. (2005). American Journal of Sports Revision Surgery for Exertional Anterior Compartment Syndrome of the Lower Leg. *Sports Medicine*, 1040–1047. https://doi.org/10.1177/0363546504271974

Schepsis, A. A., Martini, D., & Corbett, M. (1993). Surgical management of exertional compartment syndrome of the lower leg. Long-term followup. *Am J Sports Med*, *21*(6), 811–7; discussion 817. https://doi.org/10.1177/036354659302100609

Schepsis, a a, Gill, S. S., & Foster, T. a. (1999). Fasciotomy for exertional anterior compartment syndrome: is

lateral compartment release necessary? *The American Journal of Sports Medicine*, *27*(4), 430–435. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10424211

Stein, D. a., & Sennett, B. J. (2005). One-portal endoscopically assisted fasciotomy for exertional compartment syndrome. *Arthroscopy - Journal of Arthroscopic and Related Surgery*, *21*(1), 108–112. https://doi.org/10.1016/j.arthro.2004.09.023

Styf, J. (1987). I .., *69*(2).

Tobin, L., Simonsen, L., & Bülow, J. (2010). Real-time contrast-enhanced ultrasound determination of microvascular blood volume in abdominal subcutaneous adipose tissue in man. Evidence for adipose tissue capillary recruitment. *Clinical Physiology and Functional Imaging*, *30*(6), 447–452. https://doi.org/10.1111/j.1475-097X.2010.00964.x

Touliopolous, S., & Hershman, E. B. (1999). Lower Leg Pain. *Sports Medicine*, *27*(3), 193–204. https://doi.org/10.2165/00007256-199927030-00005

Tweed, J. L., & Barnes, M. R. (2008). Is eccentric muscle contraction a significant factor in the development of chronic anterior compartment syndrome? A review of the literature. *Foot (Edinburgh, Scotland)*, *18*(3), 165–170. https://doi.org/10.1016/j.foot.2008.06.005

Waterman, C. B. R., Laughlin, C. M., Kilcoyne, C. K., Cameron, K. L., & Owens, L. B. D. (2013). Surgical Treatment of Chronic Exertional Compartment Syndrome of the Leg. *The Journal of Bone and Joint Surgery. American Volume*, *95*, 592–596. https://doi.org/10.1016/S0021-9355(13)71677-1

Wilder, R. P., & Magrum, E. (2010). Exertional compartment syndrome. *Clinics in Sports Medicine*, *29*(3), 429–435. https://doi.org/10.1016/j.csm.2010.03.008

Winkes, M. B., Tseng, C. M., Pasmans, H. L., Cruijsen-raaijmakers, M. Van Der, Hoogeveen, A. R., & Scheltinga, M. R. (2016). The American Journal of Sports Medicine Accuracy of Palpation-Guided Pressure Measurements in Suspected Deep Posterior Chronic Exertional Compartment Syndrome of the Lower Leg, 2659–2666. https://doi.org/10.1177/0363546516652113

Woods, K. M., Petron, D. J., Shultz, B. B., & Hicks-Little, C. A. (2015). Lower Leg Anterior and Lateral Intracompartmental Pressure Changes Before and After Classic versus Skate Nordic Rollerskiing. *Journal of Athletic Training*, *50*(8), 150619105144009. https://doi.org/10.4085/1062-6050-49.03.101

Zhang, Q., Rennerfelt, K., & Styf, J. (2012). The magnitude of intramuscular deoxygenation during exercise is an unreliable measure to diagnose the cause of leg pain. *Scandinavian Journal of Medicine & Science in Sports*, *22*(5), 690–4. https://doi.org/10.1111/j.1600-0838.2011.01392.x

4 Method

a. Study design, timeline, interventions and outcomes

The study is a randomized controlled trial, designed to answer whether physiotherapy including a change in running landing pattern and surgical fasciotomy are equally good as treatment options for CECS of the anterolateral compartment of the lower leg. The study is observer blinded with regards to the primary and most secondary outcomes. The inclusion is limited to patients with bilateral anterior CECS, which will include the majority of CECS patients (Helmhout et al., 2015).

Inclusion is based on a history and a physical examination that clearly suggest bilateral anterolateral CECS, rather than on a positive ICP-measurement. We have chosen this approach due to the mentioned controversies and uncertainties regarding ICP-measurements in general. We do however measure ICP on all patients both before and after the intervention.

Patients are randomized into two groups:

1) Open fasciotomy of the anterolateral compartment + standard post-operative physiotherapy for 12 weeks.

2) Intensive physiotherapy for 12 weeks including a change to forefoot/midfoot strike during running.

Patients that fulfil the inclusion/exclusion criteria but have a strong preference with regards to the treatment, is invited to take part in an observational cohort.

Timeline of the study:

Location:

Inclusion, physiotherapy, surgery and intracompartmental pressure testing is performed at IOC Research Center Copenhagen: Center for Injury Prevention and Protection of Athlete Health, Bispebjerg or Hvidovre Hospital, and at Idrætssektoren, Aarhus Universitetshospital.

.

- 2 weeks	Inclusion, PROM, randomization into **A: Physiotherapeutic intervention group or** **B: Surgical intervention group**	
- 1 weeks	Running test including ICP testing and ultrasound measurement	
	PHYSIOTHERAPY	**SURGERY**
Day 1	Instructions by the physiotherapist with start of home training and change in running pattern	Operation of both legs by the surgeon
Day 14	Follow up by the physiotherapist including both running pattern and home training	Clinical follow up by the nurse including removal of sutures and referral to standard physiotherapy
Week 4	Follow up by the physiotherapist including both running pattern and home training	Clinical follow up by the surgeon
Week 12	PROM, ICP testing including running test and ultrasound, clinical follow-up and dismissal by the physiotherapist and the surgeon	
Week 26	PROMs via mail/letter	
Week 52	PROMs via mail/letter and the study ends	

Patients from both treatment groups that have not improved after the intervention will be offered the opportunity to cross-over and receive the other treatment modality (see later for statistical considerations regarding this group).

Interventions:

Physiotherapy in the physiotherapy group:

The aim of this intervention is to:

1: Change the running pattern to decrease load on the affected muscles of the lower leg (Helmhout et al., 2015), including the eccentric work performed by the tibialis anterior during the rear-foot strike (Tweed & Barnes, 2008).

2: Strengthen the major muscles of all lower leg compartments in order address any muscular imbalance/instability around the ankle joint, and to strengthen the main muscle groups responsible for alignment of the hip and knee.

Change in running pattern:

The patients are instructed in a midfoot running pattern by a physiotherapists, who is an expert in with running pattern analysis, treatment and prevention of running induced injuries. The patients are instructed to use their own running shoes.

Instructions take place while the patients are on a treadmill. The aim is to introduce an increase in cadence to approximately 180bpm, in order to activate the hamstrings and hip flexors and to create a circular motion of the leg. Changes in running pattern are followed-up after 2 and 4 weeks. All the patients are filmed during treadmill running before and after the interventions. Running cadence and landing pattern (rear-foot, mid-foot or forefoot) is determined. The effect of the intervention is determined based on the films by a blinded physiotherapist.

Strengthening exercises:

Details regarding each specific exercise are described below.

Exercise equipment: Patients perform part of the exercises standing or lying, working against the force of gravity with their own weight as well as the adjustable weight of water in bottles carried in a back-pack. The other part of the exercises is performed sitting on a chair using a sports rubber band with adjustable resistance.

Instruction and supervision of exercises: All patients are instructed in each specific type of exercise by physiotherapists very experienced within treatment of exercise induced musculoskeletal disorders.

Performance of exercises: The exercises are performed as home training based on the guidance of the physiotherapist. Patients train 3 times per week with a minimum of one rest day between the exercise days.

Adherence to exercise: All patients attend follow-up by the physiotherapist after 2 and 4 weeks (see details below). The patients are asked to record all exercises performed between

follow-ups in their exercise diary, which include recording of the number of repetitions and the level of resistance for each type of exercise. Adherence is calculated as the number of exercise sessions completed divided by the number of exercise sessions prescribed.

Determining load and progression of exercise program: Patient repetition maximum (RM) is estimated by the physiotherapist. 10-RM is determined for each type of exercise and used as guidance for training intensity. For each muscle group (se below) the patients are instructed to start training at 3x15 RM. The patients are instructed to contact the physiotherapist between follow-ups if the load is to high or to low. At follow-up after 2 and 4 weeks the progression in load is determined, and based on a new 10-RM measurement the program is adjusted accordingly. After the week 4 follow-up the load is increased to 3x12 RM for the remaining part of the 12 week training period.

Exercise replication at home: In addition to the described instructions, the patients are given specific detailed written instructions of each type of exercise with pictures to insure replication at home.

There are no planed non-exercise components such as coaching via telephone, other information material etc.

Adverse events: The patients will be asked to record any adverse events in their exercise diary. The physiotherapist will specifically ask and record any such events during the follow-ups.

Detailed description of the exercise intervention:

Week 1 and 2:

Peroneus: The patient is seated on chair with 30 degrees flexion in the knees. A sport rubber band between the feet is positioned at the forefoot of both feet. One at a time the feet are everted against resistance. Load is progressed by increasing the resistance of the sport rubber band used.

Tibialis posterior: The patient is seated on chair with 60 degrees flexion in knees and the feet flat on the floor. A sports rubber band fastened to a table is positioned at the forefoot. One at a time the feet are inverted against the resistance, with the fifth toe kept on the ground. Load is progressed by increasing the resistance of the sport rubber band used.

Tibialis anterior: The patient is seated on the floor with extended knees. A sports rubber band fastened to a table is positioned at the forefoot. One at a time the feet are dorsiflexed against the resistance. Load is progressed by increasing the resistance of the sport rubber band used.

Gastrocnemius: Patient stands on a step allowing maximum plantar- and dorsiflexion. Knees are extended. Heels are lifted on both feet to full plantar flexion and lowered to full dorsiflexion. Load is progressed by increasing the weight (i.e. water in bottles) in a back-pack.

Soleus: Patient stands on a step allowing maximum plantar- and dorsiflexion with knees flexed to 30 degrees. Heels are lifted on both feet to full plantar flexion and lowered to full dorsiflexion. Load is progressed by increasing the weight (i.e. water in bottles) in a back-pack.

Short-foot exercise: The patient stands with most of the weight on one foot. The arch of the foot is lifted without using the toes. Load is progressed by increasing the weight (i.e. water in bottles) in a back-pack.

Week 3-12:

In addition to the exercises described above, exercises with emphasis on optimizing alignment of the hip, knee and ankle are included from week 3 of the 12-week training period. Patients are instructed in strengthening exercises for the following muscle groups:

Gluteus medius: The patient is standing with a sports rubber band between both feet positioned around the ankles. One leg is extended/abducted, while the other hip/pelvic region is kept aligned. Load is progressed by increasing the resistance of the sport rubber band used.

Gluteus maximus and hamstrings: The patient is supine with the knees in 90-degree flexion and the feet flat on the ground. While activating the gluteus maximus muscle, the patient performs bridge exercise. Load is progressed by increasing the weight (i.e. water in bottles) in a back-pack positioned on the chest.

Alignment: The patient is instructed in a single leg squat, from 0 to 80 degrees of flexion, with focus on avoiding pelvic tilt and with the knee aligned over the central part of the foot. Load is progressed by increasing the weight (i.e. water in bottles) in a back-pack.

All the patients attend all the described elements of the exercise program (generic).

In addition to this program the patients are encouraged to do non-weight bearing cardiovascular training such as rowing, swimming, cross-trainer and cycle-ergometer. The patients are instructed not to stop the activity if lower leg pain or other symptoms of CECS occur. The time spent during these activities is recorded.

Exercise and physiotherapy in surgery group:

Patients are instructed to start weight bearing activities as tolerated after surgery and to keep the affected leg elevated when possible. Non-weight bearing plantar and dorsiflexion movements of the ankle joint and light non-weight bearing cardiovascular exercise such as rowing, cross-trainer and cycle-ergometer is allowed. The patients are instructed not to stop the activity if pain or other symptoms of CECS occur. The time spent during these activities is recorded.

The patients are referred to physiotherapy outside the centre, in accordance with the standard post-operative care for surgically treated CECS patients at our clinic. The number of exercise sessions (both supervised and non-supervised) that the patient has completed over the 12-week period is recorded.

After 2 weeks, following suture removal, the operated patients are allowed to start running gradually if tolerated without pain. The following program is suggested:

Week 3: 1-2 km x 2.

Week 4: 1-2 km x 3.

Week 5: 1-2 km x 4.

The number of runs and length of each runs is recorded.

Surgery/fasciotomy:

Senior surgeons perform the fasciotomies. The patients are positioned supine. A well-padded thigh tourniquet is applied, but not inflated unless an abnormal bleeder is present during surgery. A laryngeal mask airway or other anaesthesia is obtained. Standard sterile scrub, prep, and drape are performed. Two linear longitudinal skin incisions, each approximately 4 cm, are made allowing for excision of the fascia in full length. The most proximal incision is made approximately 10 cm distal to the lateral joint line, approximately 6 cm lateral to the tibial crest over the intermuscular septum that separates the anterior and the lateral compartments. The most distal skin incision is made approximately 10 cm proximal to the lateral malleolus, approximately 4 cm lateral to the tibial crest over the intermuscular septum that separates the anterior and the lateral compartments. Sharp dissection to the level of the subcutaneous tissues down to the layer of the overlying fascia is performed, and using a finger or blunt instrument, the subcutaneous tissue is swept away from the fascia, so that an unobstructed cut of the fascia can be performed. The fascias overlying the anterior and the lateral compartments are meticulously dissected under direct visualization and using either a Smillie knife or Metzenbaum scissors, holding the scissors open 1 cm and sliding the scissors along the fascia to cut it, the fascia is released approximately as far proximal and distal as the muscle belly is. The perimysium is spared.

The fascia is not sutured. Haemostasis is secured and standard one-layer skin closure is performed using 2.0 nylon sutures. The surgical site is dressed with sterile gauze and elastic bandages. Postoperative pain treatment includes paracetamol, ibuprofene and oxynorm when needed. Pain treatment is recorded. Bandage compression is used for the first 3-4 days.

This approach has proven successful and is well documented in the literature (Schepsis, Gill, & Foster, 1999)(Braver, 2016) and is used as standard in our clinic.

Outcomes

PROM

The primary outcome is 10-item uni-dimensional PROM, the "Exercise induced leg pain Questionnaire" (EILP) (Nauck, Lohrer, Padhiar, & King, 2015). Each item is scored on a five point Likert scale from 4 (no difficulty) to 0 (unable to do) with a total score of 40 points. This PROM is developed specifically to quantify the patients perceived severity of exercise induced lower leg symptoms and has a high validity and reliability. We have translated the original German version of the questionnaire into Danish for the purpose of the present study. The translation is in accordance with international standards (Beaton, Bombardier, Guillemin, & Ferraz, 2000) and have been approved by the authors of the original German version.

Intracompartmental pressure (ICP) testing

Following treadmill running until symptoms occur with pain reaching ≥ 8 on a visual analogue scale (VAS) the patients are positioned supine with a soft pad under the knee, and the knee in 10° flexion and the ankle relaxed in 30° plantar-flexion, confirmed with a goniometer. The catheter is inserted at a 90° angle with ultrasound guidance to insure correct positioning (Aweid et al., 2012; Hislop & Tierney, 2011). To save time, ultrasound is performed before exercise is begun to get the approximate position of the compartments, and the skin is anesthetised, specifically avoiding anesthetizing deep to the skin, using a 23g needle and 0.5% lidocain. Compartment pressure is measured immediately after exercise, after 1-minute and after 5 minutes (Aweid et al., 2012). We use the handheld Stryker Intracompartmental Monitor System with an 18g side-ported needle (Stryker®) as described by Braver (Braver, 2016). This equipment has proven both accurate and reliable (Boody & Wongworawat, 2005; Hammerberg et al., 2012; Wilder & Magrum, 2010)

Ultrasonic measurement of anterior compartment thickness (ACT)

The thickness of the anterior compartment is determined at rest and 0.5 min., 2.5 min., and 4.5 min after treadmill running (described above). The patients are positioned in the same supine position (see above). As described by Rajasekaran (Rajasekaran et al., 2013), ACT is measured at 20% of the distance from the head of the fibula to the lateral tip of the lateral malleolus. The site of measurement is located and marked on the skin prior to exercise provocation. Using Hitachi Avius ultrasound machine (Hitachi Aloka, Tokyo, Japan) with a linear array transducer and general musculoskeletal settings. The ultrasound probe is positioned at an approximated 90-degree angle to the anterior muscle group and parallel to the interosseous membrane. The thickness of the anterior muscle group is determined by measuring the shortest distance from the border of the interosseous membrane facing the anterior compartment and the interior border of the fascia adjacent to the subcutaneous fat.

b. Standard treatment

The standard treatment is currently surgical fasciotomy.

5 Statistical considerations

The trial is designed as a non-inferiority study. The goal is to conclude that physiotherapy (new treatment) not is appreciably worse than surgery (standard treatment), by rejecting the null hypothesis that physiotherapy is an appreciably worse treatment than physiotherapy. The difference in the effect of the physiotherapeutic intervention and the surgical intervention in PROM (see below) will be analysed using multivariate regression models and mixed models to evaluate primary and secondary outcomes, with the intention to treat principle. Non-parametric tests are used if the assumption of normality not is fulfilled. Data from patients that should choose to cross over to the other treatment group, as well as drop outs, are handled *per protocol* in according to guidelines for non-inferiority trials.

The level of significance will be set at $P < 0.05$.

Patients will be stratified into surgery and physiotherapy respectively based on

1: Gender (male/female)

2: EILP (PROM) score (high >= 20/low < 20)

The power calculation has been done in collaboration with a statistician and is based on "Design and analysis of noninferiority trials" by SAS (http://support.sas.com/kb/48/616.html):

In order to do the calculations, data from the literature on the treatment effect was "translated" into a score on the PROM (EILP: 0-40 points), which is our primary outcome. Patients with compartment-syndrome typically score approximately 20 points on this scale, whereas healthy controls score approximately 40 points. Based on studies evaluating the treatment effect of physiotherapy (Breen & Foster, 2015; Diebal et al., 2012; Helmhout et al., 2015) using EILP and other PROMS, we estimated that patients would improve by 12 points on the EILP scale following physiotherapeutic treatment. Studies on the treatment effect of surgery (Gatensby, 2017; Howard, 2000; Packer et al., 2013; Schepsis, 1993) do not report the results as points in PROM's but e.g. as 90% of patients return to sport (Gatensby 2017), 68% pain relief (Howard 2000), 79% of patients were satisfied with the outcome, (Howard 2000), succes rate 81% (Packer 2013) and 96 % success rate (Schepsis 1993). This data is not easily "translated" into points on a PROM (to our knowledge, no groups have reported the results of surgery on a validated PROM) readily, and moreover, reports of success rates above 90% do not match our clinical experience. Based on this available data, and our clinical experience, we find that the effect of surgery is likely to be 14 points. The standard deviation (SD) for patients is 6.4 points on the EILP-prom. There is no available data on a potential SD on the difference between the two groups, however this will be smaller than SD for patients and 5 points is a reasonable estimate. Finally a clinical relevant difference was estimated as 5 points, which is 25% of the difference between patients with compartment syndrome (20 points) and subjects without symptoms (about 40 points), and almost 50% of the improvement seen with physiotherapeutic treatment.

The following program was run in SAS with power = 0.80

```
proc power;
         twosamplemeans
            test      = diff
            meandiff  = -2
            nulldiff  = -5
            sides     = u
            stddev    = 5
            power     = 0.8
            npergroup = . ;
         plot x=effect;
         run;
```

Resulting in N = 36 per group with a total of **N = 72**

6 Participants

a. Inclusion and exclusion criteria

Patients are recruited from the IOC Research Center Copenhagen: Center for Injury Prevention and Protection of Athlete Health at Bispebjerg and Hvidovre Hospital.

We perform ICP on all included patients in the present study before and after the intervention. Each patient is included after thorough clinical examination including the list of inclusion/exclusion criteria below. The list is adopted from Rajasekaran et al. (Rajasekaran et al., 2013) and translated into Danish for the purpose of including/excluding patients.

A "yes" to all questions/clinical examinations is required for inclusion.

Inclusion/exclusion criteria for patients with CECS	
Age between 18 and 50 years	yes/no
Symptoms for more than 3 months	yes/no
Symptoms from both legs	yes/no
Pain (cramp like, tight, burning or pressure) in the anterior part of the lower leg starting after approximately 10 minutes of exercise	yes/no
Pain worsened with prolonged lower extremity exertion	yes/no
Majority of pain relieved within 30 minutes of rest	yes/no
No previous fasciotomy in the lower leg	yes/no
No history of serious trauma involving the lower leg (fracture, muscle/tendon rupture)	yes/no
Not ASA (America Association of Anaesthesiologists Classification of Physical Health) > 2	yes/no
No clinical symptoms consistent with unilateral anterior CECS or lateral and posterior CECS	yes/no
No clinical symptoms consistent with lumbar spine radiculopathy	yes/no
No clinical symptoms consistent with periostit/shin-splint	yes/no
No clinical symptoms consistent with stress fracture	yes/no
No clinical symptoms consistent with popliteal artery entrapment syndrome	yes/no
No clinical symptoms consistent with isolated peroneal nerve entrapment	yes/no
No clinical symptoms consistent with muscle fascia herniation as primary problem	yes/no

7 Risks and adverse events

a. Risks and safety precautions

ICP:

This procedure is currently performed as standard for diagnosing CECS at our hospital. In the present project the participants are exposed to one additional post-treatment pressure testing of both legs. Thus participating in the project potentially increases the risk of complications related to this procedure. The procedure is performed using a standard "no touch technique" meaning that the skin is cleaned using alcohol in an 8 x 8 cm area, a sterile drape is applied, and the skin/drape is thereafter only touched with sterile instruments (see the methods section for the detailed description). No serious complications, such as infection or muscle herniation, are described in the literature (Boody & Wongworawat, 2005; Hammerberg et al., 2012; Wilder & Magrum, 2010). In our hands, mild discomfort during the procedure is reported. No complications have occurred.

Ultrasonic measurement of anterior compartment thickness:

No side effects are expected. The area of ultrasonic measurement is kept away from the area of insertion of needles during intracompartmental pressure testing, and sterile gel is used, to avoid infection.

Physiotherapy including a change in running landing pattern:

A certain level of delayed onset muscle soreness (DOMS) is to be expected following a change in exercise pattern. However, with the gradual increase in load of the muscles in this study, this is not likely to be a cause of pain, but rather mild soreness for 24-48 hours. A change in running/landing pattern can theoretically through a change in load introduce an injury in another region, such as the rear part of the foot and Achilles tendon. A change to forefoot landing in combination with the use of minimalistic running shoes is known to increase the risk of injury if not supervised. However, in this study we introduce a gradual and supervised change to a midfoot landing pattern using non-minimalistic shoes. This change has previously not resulted in any overload injuries in our hands, and no adverse events is described following this intervention in the literature.

Surgery/fasciotomy:

This approach is well described in the literature (Schepsis, Gill, & Foster, 1999)(Braver, 2016) and is used as standard surgical treatment for CECS in our clinics. Complications to fasciotomy of the lower leg include infection, neurological damage, and hematoma in up to 16% of patients (Waterman et al., 2013). Most complications are related to surgery in the deep posterior compartment, whereas surgery in the anteriolateral compartment, which is operated in the present study, typically has fewer complications.

Should any complications arise during the project the patient will be evaluated by an orthopedic surgeon. If deemed necessary, the participation will be stopped immediately and the patient will be excluded from the project. Participants will be informed immediately if new information about risks, side effects or complications should arise after the project has started, and should these risks or changes be ethically irresponsible the project will be ended. This project respects and meets the Helsinki Declaration II, along with the guidelines of the regional ethical committee.

b. Risk of exposure to radioactivity

There is no risk of exposure to radioactivity.

8 Biologic material and bio-bank

No tissue biopsies or blood sampling is relevant to the current project.

9 Patient's journal

The patient's medical journal will be accessed as usual for any new patient entering the clinic. The assessment includes an evaluation of previous injuries as well as any co-morbidity, which may influence the treatment. Journals will not be accessed in order to perform recruitment.

10 Respect of integrity and privacy

This project will be reported to the Danish Data Protection Agency ("Datatilsynet") through the public data controller at the Capital Region. We will comply with the Danish law of processing personal data.
Data will be stored using an unidentifiable ID, and will thus be anonymised for everyone but the primary investigators project secretary. Therefore the material in this study is not depersonalized but encrypted. An ID-code document is filed electronically and locked according to the legislation from the Danish Data Protection Agency, so that only the primary investigators project secretary has access to the person identifiable code.

11 Economy

The initiative to this project was taken by Simon Døssing from the Institute of Sports Medicine at Bispebjerg Hospital, where the project will be carried out in collaboration with Hvidovre and Aarhus University hospitals. The project is self financed and there are no additional costs related to the project. No funding has been applied for. No conflict of interest exists.

12 Compensation

The included patients in this study will not receive financial or any other compensation for participating in this study, thereby insuring, that financial benefits are not a motivating factor for participation in the project in accordance with the committee law § 20, stk. 1, no. 3.

13 Recruitment process and informed consent

The patients are recruited from the IOC Research Center Copenhagen: Center for Injury Prevention and Protection of Athlete Health at Bispebjerg-Frederiksberg and Amager-Hvidovre Hospital and from Idrætssektoren, Aarhus Universitetshospital.

The patients are typically referred to the clinic from the general practitioner. Moreover, department of Ortopeadic surgery at Herlev-Gentofte Hospital, Køge Sygehus and Gildhøj Private Hospital will be notified of the project. As will department of nuclear and clinical physiology at Bispebjerg and Frederiksberg Hospital. Health professionals at these departments will be given the opportunity to refer relevant patients to our department.

At our departments the first contact is in the office at the outpatient clinics. If the patient is considered a potential candidate for participation a brief oral presentation of the study is provided together with the written information. If he/she is interested, the patient will be assessed in order to meet the inclusion and exclusion criteria, and if eligible, the patient is invited to an interview and is informed of her/his right to have a relative present. The interview takes place in the doctors office without interruptions and behind a closed door. The interview takes place no sooner than seven days after the initial presentation of the study. During this interview the patient's attention is called to the participant's right to have time for consideration, that their signature will stand for informed consent, that all personal information will fall into medical confidentiality, their right to access information about their own participation in this project but not information from other participants, the right to be informed about potential changes to the original project plan and finally the right of compensation if injuries were caused by methods applied in the project.
1-4 days after the interview the patient is contacted and if further participation is agreed upon, a new meeting is arranged. On this day written declaration of consent will be signed prior to any further progress in the study. Upon consent, the patient will be randomized and allocated to an intervention group.

The participants will always be able to contact the responsible researchers for more information, and they can at all times leave the project without further explanation and without the risk of affecting future relationships to neither the department nor the hospital itself in any circumstances.

14 Publication

When the project has finished, all patients who confirmed that they wanted to be informed about the study results through their written declaration of consent will receive written information regarding the results and overall conclusions from the study.
The achieved findings will be published in an anonymous form, just as the results presented in other professional context will be anonymous.
We will seek to publish all of the results, whether positive, negative or inconclusive in international peer reviewed journals, as well as presenting the data at national and international scientific conferences and meetings. However, if we are not able to publish our results in a journal, they will be made available to the public through www.clinicaltrials.gov and www.clinicaltrialsregister.eu
Lastly, the data will be presented locally in our department.

15 Ethical considerations

The project is based on voluntary participation. The participants will be informed about the study, the associated risks and their rights both orally and in written form. The participants will always be able to contact the responsible researchers for more information, and they can at all times leave the project without further explanation and without the risk of affecting future relationships to neither the department nor the hospital itself in any circumstances.

As described CECS is a common problem and a clinical challenge. Presently, there is a lack of agreement regarding the gold standard for diagnosis and treatment. This is problematic because exercise related injuries not only decrease the patients ability to perform health beneficial exercise in the short term, but also increase the risk of patients not returning to regular exercise at all.

We expect to find a similar treatment effect on CECS of physiotherapy and surgery.

On **the individual level**, the expected benefit with participation in the project is for the participants in the physiotherapy group a closely followed and supervised training protocol, with the potential to treat CECS and thus avoid surgery. For the surgically treated group the benefit is surgery by one of two highly specialized surgeons with special interest and experience in the treatment of these patients, in combination with a closer than usual follow-up including ICP measurements post-surgically.

On **the general population** level this study will give important information to guide the future treatment of CECS and the diagnostic value of ICP measurements.

As stated previously, we are using the inclusion/exclusion questionnaire and not ICP to include patients. This approach is in line with the clinical practise of several surgeons, who weight the patient history and examination over ICP for diagnosing CECS, due to the aforementioned uncertainties regarding the clinical value of ICP. In accordance with the protocol, patients with ICP that would be considered "normal" may be randomized to surgery. This may be considered controversial, but we believe that this approach can be justified by the lack of consensus regarding what should be considered a normal ICP and the lack of an association between symptoms, the effect of surgery and pressure measurements in the literature. Moreover, we find that this approach adds tremendous value to the study, because it allows us to make an association (or lack of) between ICP, symptoms and effect of treatment in a randomized setting.

Based on the described risks of participating in this project, it is considered responsible to perform. It is believed that the potential outcomes of this study's findings greatly outweigh the risks laid upon patients, and for that reason, the study is considered ethically justifiable.

16 Patient insurance

As all participants are patients, they will be covered by the regular patient insurance provided by Amager- and Hvidovre Hospital, Bispebjerg- and Frederiksberg Hospital and Aarhus University Hospital ("patientens forsikringsforanstaltning").