Supervised exercise therapy for intermittent claudication: subgroups, gait and physical activity

Citation for published version (APA):

Document status and date:
Published: 01/01/2015

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:
- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Download date: 23 Aug. 2019
CHAPTER 10

Summary & general discussion
SUMMARY & GENERAL DISCUSSION

Intermittent claudication

Intermittent claudication (IC) is the most common manifestation of peripheral arterial disease (PAD) and may be considered as a locoregional expression of systemic atherosclerosis. IC is defined as muscle discomfort in a lower limb that is predictably evoked by exercise and relieved after a short period of rest. Most patients with IC develop a serious walking impairment during daily life.

Barriers and misconceptions regarding supervised exercise therapy

Supervised exercise therapy (SET) is the first-line symptomatic treatment for IC as stated in several contemporary international guidelines.\(^1\)\(^,\)\(^2\) In clinical practice however, SET is largely underused\(^3\) and most IC patients do not receive SET at all.\(^4\) There are three categories of reasons why this cost-effective treatment is not widely adopted yet (chapter 1).\(^5\)\(^,\)\(^6\) First, SET places a considerable burden on patients in terms of effort and responsibility rather than offering a ‘quick fix’ for their discomfort, so patient reluctance is understandable. A second category of reasons for SET resistance involves clinicians. Self-interest of doctors performing interventions that involve fee-for-service is most likely a contributor. Moreover, there is also misinterpretation of potential SET indications, for instance with regard to the efficacy of SET for IC due to aortoiliac stenosis.\(^7\) A third and possibly most important factor precluding a wider implementation of SET is lack of access and inadequate reimbursement.\(^8\) Therefore, even clinicians who fully endorse SET as the initial treatment for IC may end up performing invasive interventions as their patients cannot find a nearby qualified SET practitioner. This is even more bitter when the absence of budgetary restrictions regarding invasive procedures is considered.

It is IC patients who lose out

These three different types of resistance severely frustrate a universal implementation of SET as the standard care for patients with IC. Based on a 2009 invoice data analysis of a large Dutch health insurer (3.4 million members) it was demonstrated that only 14% of the IC patients actually did receive SET.\(^4\) An unknown portion of the remaining IC patients likely underwent a primary invasive revascularization, while most others may
have possibly been provided with a single 'go home and walk' advice. Consequently, IC patients are either unnecessarily exposed to the risks of an invasive intervention or received a truly inferior IC treatment, since general and unstructured exercise recommendations as prescribed by a physician do not lead to sufficient clinical benefit. Moreover, most physicians do not even recommend home-based walking exercise to patients with IC.

In the Netherlands, the tide may slowly be turning now as increased numbers of IC patients were referred for SET in 2011 (to be published, based on similar invoice data analysis). Great effort has been put into the implementation of a nation-wide network of physiotherapists (PT) providing SET in a community-based setting. ClaudicatioNet, founded in 2010, is a so-called open network which means that membership is attainable for every PT who fulfills a standard set of participation criteria. ClaudicatioNet strives to provide a stepped-care approach where all IC patients are initially referred to a SET program whereas invasive revascularization is exclusively considered for individuals not responding sufficiently to SET. This approach may be advantageous over a primary invasive intervention strategy as recent evidence indicated that a PTA is likely to be more cost-effective when combined with SET. These findings once again underscore the general benefits of any form of regular exercise.

Blueprint for implementation of SET
To date, ClaudicatioNet includes 1,552 fully trained PTs. These health care professionals provide information in a personalized portfolio on the network’s national website and attend mandatory educational courses. A web-based referral system is available to help patients find the ClaudicatioNet PT nearest in their community. This referral system guarantees that SET is initiated within 5 working days after diagnosis as PTs are instructed to contact a patient within 3 days. If a first PT fails to do so, a second other PT is automatically invited to contact this patient.

While the scale of this Dutch network is comparatively small, this concept could provide a blueprint for the implementation of structured SET programs throughout Europe and the US. As for the health care budget as a whole, the financial benefits of SET are considerable. A recent calculation of this stepped care approach (assuming a 80% referral rate) showed savings of up to 32M euro a year in the Netherlands alone. Efforts to expand SET implementation outside the Netherlands is of importance for IC patients.
in general, but also to anticipate to the current trend as observed in clinical trials which are mostly focusing on alternative IC exercising protocols (e.g., the value of home-based exercise programs). Unfortunately but not completely unexpected, large randomized controlled trials yielded mixed results on the efficacy of home-based protocols.\textsuperscript{15, 16} Moreover, the evidence that a conservative therapy is as effective as invasive alternatives is easily ignored.

Comparison of SET to alternative conservative exercise protocols

Further evidence for the efficacy of SET and its role as an alternative treatment tool was provided in a meta-analysis presented in chapter 2. The efficacy of four available conservative treatment options for IC (i.e. medical treatment, walking advice, home-based exercise, SET) was compared in the largest analysis to date (n=1,406 patients). A beneficial outcome of SET with significant effect sizes >0.8 was demonstrated at the 6 weeks, 3 and 6 months follow-up. SET resulted in superior walking distances compared to all other treatment options. A dose-response trend appeared present suggesting that grade of supervision was directly related to walking distances. Hence, supervision is necessary to optimally profit from the benefits of exercise in IC.

After 6 months of follow-up however, results following SET were not significantly different from a home-based protocol (HB). It therefore seems that the intensive supervision has its particular value during the first months of training. On the other hand, it may also be possible that ongoing improvement in maximal walking distance is not to be expected beyond the reported 50% to 200% increase.\textsuperscript{10} In addition, studies on the additional value of life-style interventions during SET have not been performed. These modifications probably make SET even more effective, both as reflected by an increased walking distance as in terms of altered morbidity and mortality as discussed later.

At the present time, a 3 months SET program is preferable, possibly followed by a combined ‘SET-HB’ program. Such a combined follow-up program may be more cost-effective due to the limited amount of supervision and use of training facilities. Moreover, these programs may be further optimized by future monitoring via novel eHealth and mHealth applications.\textsuperscript{8, 17}
Additional benefits of supervision

Intensive supervision at the start of an exercise program for IC may also have benefits when viewed from other perspectives. SET offers an opportunity for simultaneous motivational interviewing supporting IC patients in changing unhealthy habits including smoking, too high calorie of fat food intake and sedentary lifestyle. Evidence regarding the benefits of life style modification programs is growing. A lifelong habit of sedentary behavior due to reluctance to exercise aggravated by leg pain during walking or co-existing (multi-) morbidity can only be changed by simultaneous and prolonged efforts under professional supervision. A series of SET sessions evidently provide better opportunities for stimulating health-related behavioral changes than a single invasive intervention. Unfortunately, large studies on the effect of these interventions during SET are currently lacking, as previously stated. The potential positive influence on lifestyle adjustments however is just another argument for advocating SET. Another plea would be the positive influence of SET on the entire vascular system rather than on a portion thereof. The contralateral leg, which may not appear to be affected by symptomatic PAD yet, may also be trained. SET trains the entire cardiorespiratory system and improves overall fitness levels and by the same token significantly reduces long-term cardiovascular morbidity and mortality. Moreover, SET also allows to differentiate between (and further explore the influence of) comorbidities (e.g. osteoarthritis, chronic obstructive pulmonary disease). Last but not least, SET can be employed in a group setting, providing patients with a chance to share emotions and experiences. Such a group-based intervention also tends to increase the intrinsic motivation for exercise programs.

Concerns about safety of SET are unjust

Despite a nationwide coverage of community-based SET in the Netherlands and successful removal of some barriers (poor availability and limited access), there are still obstacles on the road to success. There is an ongoing uncertainty whether SET is sufficiently safe in IC populations as concomitant coronary artery disease is prevalent. For example, a cross-sectional survey among Dutch vascular surgeons and fellows found that respondents were reluctant to refer for SET in the presence of significant cardiopulmonary comorbidity. This concern is also found among physiotherapists as reflected in their 2003 guideline of the Royal Dutch Society for Physical Therapy (KNGF) recommending screening by
a cardiologist or exercise-physiologist prior to the start of SET.26 This guideline was only recently updated (2014).27 Although the onset of a cardiovascular event during exercise is not inconceivable, cardio-pulmonary screening prior to the initiation of SET may raise an additional unnecessary barrier. The prediction of a future severe cardiac event during exercise is difficult, if not impossible.28 Consequently, the use of cardiopulmonary exercise testing (CPET) as a screening tool for myocardial ischemia in people without known coronary artery disease is no longer recommended in the National Institute for Health and Care Excellence (NICE) guideline.29 Surprisingly, the 2015 guideline of the Society for Vascular Surgery still advocates screening for cardiopulmonary reserves to allow safe participation.1

In chapter 3 of this thesis, evidence was provided regarding the safety of SET in patients with IC. SET related complications were systematically studied on the basis of 74 articles, representing 82,725 hours of SET in 2,876 IC patients. Six adverse events of cardiac and two of non-cardiac origin were identified resulting in a very low 1 to 10,340 patient-hours all-cause complication rate. SET can therefore safely be prescribed to patients with IC. In line with current evidence but contrary to the SVS 2015 guideline, routine cardiac screening prior to initiation of SET is therefore not advised.

Caution is only required if one wants to generalize these safety findings, as our systematic review excluded IC patients with known major exercise-limiting comorbidities (e.g. poorly controlled hypertension, severe congestive heart failure). However, other studies too demonstrated the safety and benefits of exercise in these subpopulations.30 The risk of acute cardiovascular events was also low in patients with known coronary artery disease participating in a high-intensity exercise rehabilitation program.31 Moreover, exercise was superior compared to coronary angioplasty in improving exercise capacity and event-free survival in patients with coronary artery disease.32

In conclusion, patients with (cardiac) comorbidity should not routinely be excluded from SET in daily practice. These patients obviously require careful monitoring whereas exercise intensity should always be tailored to the patient's condition by a well-educated PT. Unfortunately, the benefits of such personalized exercise programs are difficult to scientifically evaluate as some form of standardization is needed. Based on our study, the previous recommendation on a mandatory cardiac screening was removed from the recently updated KNGF guideline for PTs in the Netherlands.27
Do women and men equally benefit from SET?

Gender-specific research on diagnostics and treatment in cardiology is very common but not in the field of peripheral arterial disease (PAD). This difference was also emphasized in a scientific statement of the American Heart Association. From a cardiovascular pathophysiologic perspective, however, true gender differences likely exist. For instance, smaller vessel size and dissimilar atherosclerotic plaque composition were demonstrated in females. Women were also found to suffer more from the consequences of PAD as they perceive a lower physical function and greater impact on daily activities. Moreover, women are less likely to receive antiplatelet and lipid-lowering therapy in the presence of cardiovascular diseases. One study also reported inferior patency rates following surgical lower-extremity revascularization in women.

Data on gender-specific SET outcomes are limited and conflicting. In chapter 4, a follow-up analysis on gender-specific response following SET was reported. A population of 113 men and 56 women who initially participated in a 2010 multicenter randomized controlled trial named ExercIse Therapy in Peripheral Arterial Disease (EXITPAD) study were again studied. The SET program was supervised by PT’s and included interval-based treadmill walking approximating maximal pain, combined with activities such as cycling and rowing. Patients usually started with three 30 minutes sessions a week, and training frequency was adapted during the following year on the basis of individual needs. At baseline, similar demographic characteristics (e.g., age, comorbidities, cardiovascular risk factors), maximal walking distances (men: 250 meters, women: 270 meters) and subjective walking impairment (expressed in terms of scored on a walking impairment questionnaire) were found. After 12 months of follow-up, both men and women demonstrated a significant increase in walking distance. However, men's maximal walking distances were significantly larger after 3 and 12 months of SET. A gender-difference of 95 meter (difference in median) after 12 months was found. Surprisingly, improvement in subjective walking impairment (as measured by the walking impairment questionnaire) was found to be similar in men and women.

It may be concluded that female IC patients certainly benefit from SET but demonstrate less improvement in walking distance after 12 months. The reasons for this difference may be related to pathophysiologic dissimilarities (atherosclerotic plaques, vessel diameter), more common presence of atypical symptoms, different perception
of IC symptoms, more impaired lower extremity function and less leg strength in women.\textsuperscript{41, 42} However, if, how and to what extent these factors contribute to the gender-related difference in walking distance after SET is still unknown. Current results do not provide arguments for immediate initiation of gender-based exercise programs for IC. However, research on female aspects of cardiovascular care must be expanded as a previous study reported that IC women are more likely to present with further advanced disease, which is in line with the disparity in time-to-diagnosis and access-to-care between men and women with PAD.\textsuperscript{42}

**Does diabetic status influence the efficacy of SET?**

Diabetes mellitus (DM) is one of the strongest risk factors for the development of PAD\textsuperscript{43}, and a high prevalence of DM in IC is acknowledged.\textsuperscript{44} IC patients with DM tend to experience worse lower-extremity function than patients with IC alone\textsuperscript{45}, and it has been suggested that patients with DM have a reduced exercise tolerance.\textsuperscript{46} Others also advocated that IC patients with comorbidities might be less suitable for SET.\textsuperscript{47} The exact influence of diabetes on the effect of SET in IC is under debate, and this lack of knowledge may raise unjust barriers against commencing SET.

In chapter 5, current evidence regarding the effect of DM on the response to SET in IC patients was summarized. A total of three studies representing a total of 845 IC patients met inclusion criteria. All reported maximal walking distance outcomes, one study also included functional walking distance whereas the two other studies described pain-free walking distance. In general, IC patients with DM did improve in walking distance following a SET program. Nevertheless, conflicting results were found when diabetic and non-diabetic IC patients were compared. The largest study found no differences\textsuperscript{44}, whereas significant and nearly significant differences on maximal and pain-free walking distance were demonstrated by the other two studies.\textsuperscript{40, 48} In a subanalysis on gender, female diabetic IC patients responded poorest to SET and were a most vulnerable group.\textsuperscript{40} Similar results were found in a follow-up analysis as described in chapter 4 of this thesis. Although future studies are warranted to precisely elucidate the role of DM on SET outcomes, no arguments have been found to deny diabetic IC patients a form of SET.
How to adequately interpret effects of SET?

Outcome of SET is often evaluated in terms of (changes in) walking distance. Whether to measure walking distance on a treadmill or in a corridor by means of a 6-minute walking test was recently discussed. Both methodologies have limitations considering that the optimal test should directly correlate with patient-reported physical limitations. An outdoor measurement by a community-based global positioning system (GPS) was recently found to be a promising alternative compared to both indoor walking tests. Outdoor measurements are expected to reflect a real life situation, and it must be appreciated that GPS assessment has been found to correlate better with patient-reported measures of walking limitation. On the other hand, GPS revealed larger short-term walking capacity variability thereby limiting its test-retest reliability. Future studies are needed to determine the optimal functional outcome measure in IC.

Apart from the quest of the ideal method of measurement, adequate interpretation of currently applied outcome measures is important. To aid clinicians and researchers in determining what numerical change indicates a clinically meaningful change, the concept of a minimally important difference (MID) value was introduced as a means to define certain outcomes. In chapter 6, MID values were determined for treadmill-based walking distances in patients with IC. An anchor-based approach using longitudinal data of 103 IC patients who participated in a SET program was followed. Regarding the maximal walking distance after 3 months of SET, MIDs of 305 meters and 147 meters were found for improvement and deterioration, respectively. A positive value for deterioration implies that such a small increase in walking distance is apparently not satisfactory to the patient. This may not be surprising as SET demands a considerable patient’s investment of time and effort (chapter 1). Although the largest effects of SET were reported after 3 months of SET (chapter 2), it would be of interest to also determine MIDs for longer follow-up periods (i.e. 12 months). Inclusion of patient-reported outcome measures (PROMS, e.g. walking impairment questionnaire, vascular quality of life questionnaire) when evaluating treatment effects and patient satisfaction has been recommended. However, the current quality of disease specific PROMs for IC is alarmingly low.
Physical activity in IC, a novel outcome measure?

There is an ongoing debate regarding the value of physical activity (PA) and its essential role in ensuring health and well-being. A recent analysis found that acquiring the recommended minimum level of physical activity (from a level of ‘no activity’), led to an all-cause 19 percent mortality reduction. A dose-response relationship between degree of PA and early death was reported which is in line with the American Heart Association website’s statement saying that ‘Something is always better than nothing.’ Moreover, an increase in daily activity was just as strongly associated with reduced mortality as quitting smoking.

Unsurprisingly, equal trends regarding the benefits of PA have also been reported in PAD patients. For instance, higher levels of PA were associated with less functional decline and a lower all-cause mortality risk. Patients with IC exhibit lower daily PA levels compared to healthy controls and several barriers (e.g. personal, environmental) to refrain from being physically active were described. Therefore, benefits of increased PA are likely more substantial in IC. However, PA levels in IC populations are rarely questioned or objectively monitored in current clinical practice, in contrast to standardly used walking capacity tests. To explore whether commonly used physical exercise capacity (PEC) outcomes could serve as probably a surrogate marker for PA, a cross-sectional study was conducted in chapter 7. A total of 46 patients completed a set of PEC tests and wore a tri-axial accelerometer for seven consecutive days to determine actual PA levels. Overall, (very) weak to moderate correlations between PA and PEC indicate that the concepts PEC and PA, although overlapping, are distinct.

Achieving a higher level of PEC does therefore not necessarily mean that higher PA will follow. Notwithstanding, a higher exercise capacity that is often attained after prolonged training is permissive of greater physical activity (intensity and duration) in home and community environments. Previous assumptions are in line with a recent study which did not find an effect of SET on PA in patients with IC. These results, and the established correlation between PA and all-cause mortality, provide compelling arguments for focusing on PA as a distinct novel outcome measure for PAD patients (and possibly other populations as well). As it has recently been recognized that prolonged sitting (i.e. sedentarism), independent of overall physical activity levels, may be even more important to the all-cause mortality risk, it seems most appropriate to measure both active and sedentary PA components.
Classification of IC patients

The currently proposed PA measurement is only clinically relevant when it has a conceivable effect on the patient’s decisions and behavior. PA however is a complex endpoint that is influenced by a range of factors (e.g. personal; motivation, exercise-related, environment and policy). Current SET programs may be not specified (enough) for improving PA, as indicated by the lack of improvement in PA after SET. Nevertheless, promising results were reported regarding the effect of a brief psychological intervention on walking behavior. Two 1-hour sessions, 1 week apart at the patients’ homes, significantly improved the mean number of daily steps (Δ1,567 steps per day), as compared with a control group receiving standard care. Interestingly, this effect was maintained for 2 years. Such a psychological intervention could perfectly be incorporated into SET as provided by specialized PT’s trained in motivational interviewing, thereby probably extending the effectiveness and subsequent benefits of SET in regard to its effect on PA.

In the present thesis, measurements of both PEC and PA parameters are suggested, as this information allows for a novel classification of IC patients (figure 1). It is expected that a number of factors contribute to the category in which a patient actually belongs. For instance, an IC patient with a very good response to SET (high PEC) who leads a very sedentary life (low PA) fits into category C. A detailed characterization (e.g. demographics, motivation, health status, environment, etc.) of the patients in these four categories may facilitate an improved understanding of the underlying determinants for a certain type of PA behaviour. This may eventually aid in optimizing intervention strategies and employment of personalized medicine. Thus, the purpose is not to move patients from one category to the other, but to gain insight in the patients’ characteristics in order to provide ‘tailor-made’ therapy.
Altered gait patterns in IC

Spatio-temporal changes of gait pattern were previously described in IC patients. IC patients were found to walk slower, have a lower cadence (i.e. steps per minute), and have a shorter step length.\(^{69, 70}\) Moreover, oxygen uptake during pain-free ambulation was higher when compared to age-matched controls indicating that IC patients exhibit a poorer walking economy.\(^{71, 72}\) Walking economy (i.e. cost of transport) progressively decreased following the onset of claudication pain. In addition, poorer walking economy correlated with diabetic status\(^{73}\), probably explaining the poorer response to SET of diabetic IC patients (chapter 5). However, since oxygen uptake is already higher in pain-free ambulation, factors other than IC pain have to be responsible, and adaptations of the gait pattern might therefore be a contributor.\(^{72}\)
Previous research revealed that SET conferred no effect on altered gait pattern in patients with IC.\textsuperscript{74} Lack of improvement in gait after SET may be due to insufficiently tailored SET programs to elicit significant improvement. Additional research into detailed muscle and biomechanical adaptations may provide new insights to improve the effects of SET.\textsuperscript{74} Besides, previous research based their conclusions on just a couple of steps, while it has been recommended to include at least 20 to 30 strides.

In chapter 8 and 9 of this thesis, different aspects of gait pattern of IC patients were studied using a treadmill-based protocol. Continuing analysis during treadmill walking allows for assessment of a large number of steps. In addition, this novel methodology permitted for data capturing immediately after the pain threshold was reached, thereby excluding confounding factors potentially due to recovery processes.

A first analysis of spatio-temporal parameters in 28 IC patients and 28 healthy age-matched controls was conducted (chapter 8). IC patients walked at a self-selected 3.3 km/h pace, whereas controls walked a significantly 1.2 km/h faster. Most evident differences between IC patients and controls were found in the foot contact phase and toe off (i.e. propulsion) phase. A 14\% shorter propulsion and a 17\% longer foot contact phase were demonstrated in IC patients. Moreover, the ankle-brachial index (a measure for disease severity and atherosclerotic occlusion) was correlated with both walking speed and decrease in propulsion during ischemic pain. IC patients seem to 'discontinue' walking for a longer period during every step. These adoptions might be intuitive as arterial blood inflow and supply of oxygen to the skeletal muscles takes place during this relaxation phase.\textsuperscript{75, 76} This may explain why IC patients take fewer rather than shorter steps when claudication pain develop as also suggested by a previous study.\textsuperscript{77}

Based on these spatio-temporal results (chapter 8) it was hypothesized that IC patients use a longer contact phase to enable muscle relaxation to occur for a prolonged period of time, as the relaxation phase is known to be the largest moment of arterial blood inflow. Chapter 9 described the subsequent analyses to test this hypothesis. Lower limb joint kinematics and muscle activity by means of surface electromyography (EMG) were determined during similar self-selected comfortable walking speed. The study population consisted of 22 IC patients and 22 healthy age-matched controls. The kinematic analysis showed a significantly smaller ankle displacement (-28\%) in IC patients, most evidently in the propulsion phase. Therefore, joint angle data supported the hypothesis. The
EMG data however demonstrated no differences in muscle activity duration of tibialis anterior and medial gastrocnemius muscles suggesting that IC patients use these muscles, considered main actuators of the ankle, for a similar amount of time during the gait cycle. Duration of muscle activity was expressed in percentages of the gait cycle in order to correct for the differences in walking speed between both groups.

In conclusion, IC patients demonstrate predictable spatio-temporal and kinematic changes during walking, even before the onset of claudication pain. This strategy however did not result into longer muscle relaxation periods, as duration of lower-limb muscle activity was similar in both groups. There are several ways to explain these results. Surface EMG solely measures muscle activity but not muscle force. It has been described that a minimal level of intensity (i.e. above 50% of the maximum voluntary contraction force) is needed to cause a reduction in calf muscle blood flow. As a consequence, it might be the amount of muscle force rather than the duration of contraction which really determines arterial blood inflow. This idea is substantiated by previous research which demonstrated a reduced propulsion force and a decreased ability of the ankle plantar flexors in IC patients. On the other hand, spatio-temporal and kinematic changes can also be due to a reduced muscle force, instead of an intended strategy to cope with the disease related arterial obstruction. This could also explain the unfavourable reduced metabolic efficiency in IC patients, which in fact adds to a reduced walking speed and walking capacity.

Implications for clinical practice and suggestions for future research

Serious effort should be put into effective measures overcoming the problem of a limited access of SET allowing its routine implementation in clinical practice. The success of the community-based ClaudicatioNet network proves that significant financial investments are not required. However, the mere availability of a nation-wide network of SET facilities is not enough, since it essentially only provides a sound infrastructure. After establishing a network, structural funding should be secured by incorporating SET in standard health care budgets. In addition, continuous education on IC related issues is required to motivate doctors, PT’s as well as patients.

Further research should focus on identifying the optimal contents of a modular package of SET that is tailored to subgroups of IC patients. The possibility of incorporating
lifestyle-changing techniques into standard SET sessions requires exploring. Lifestyle-changing interventions fit perfectly into the suggested addition of PA measurement in daily clinical routines and its subsequent aim to improve PA in patients with IC. As it is very hard to change deep-rooted behavior of an IC patient, a second focus should be on gaining more insight into the type of factors determining this behavior. A classification as proposed in figure 1 may aid in categorizing IC patients and may allow for the identification of specific categories sharing certain characteristics.

Third, the effect of specific lower-limb muscle strength training on walking distance and gait patterns should be investigated. Limb muscle strength is an important contributor to both walking speed and balance (i.e. risk of falling), and it seems therefore logical to add strength training to a SET program. This is in line with the current trend of providing a variety of exercises during SET. Longitudinal EMG registration (baseline measurement followed by an intervention and follow-up measurement) may be suggested to study the effect of muscle strength training on the gait pattern, as for paired EMG measures, amplitudes can be interpreted as muscle force.

The data in this thesis provide evidence for specific changes regarding contact time and propulsion phase during walking in IC. As these changes were related to walking speed, the fourth focus of future research should be on the effect of improving gait speed during SET.
Conclusions of this thesis

1. Supervised exercise therapy (SET) is a safe treatment in patients with intermittent claudication (IC).

2. SET leads to a longer walking distance when compared to other conservative treatment options.

3. Women with IC tend to benefit less from SET in terms of absolute walking distance.

4. Patients with IC and diabetes mellitus do profit from SET.

5. The ‘minimally importance differences’ (MID) of treadmill-based maximal walking distance for improvement and deterioration are 305 and 147 meters, respectively. The positive MID value for deterioration indicates that a minor improvement in walking distance apparently is not satisfactory in the patients’ eyes.

6. Correlations between physical exercise capacity (PEC) and daily physical activity (PA) of patients with IC are weak to moderate indicating that the concepts PEC and PA, although overlapping, are distinct.

7. Patients with IC walk slower and present with less propulsion and ankle range of motion during walking compared to healthy controls. No difference in electromyographic muscle activity duration is present between IC patients and controls. However, painful walking in IC did result in significantly higher electromyographic muscle activity.
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