University Outpatient Clinic Potsdam, Sports Medicine & Sports Orthopaedics International Master/PhD-Program

"Clinical Exercise Science"

Whole-body electrical muscle stimulation superimposed walking as training tool in the management of type 2 diabetes mellitus

Dissertation

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ABSTRACT

Background: The worldwide prevalence of diabetes has been increasing in recent years, with a projected prevalence of 700 million patients by 2045, leading to economic burdens on societies. Type 2 diabetes mellitus (T2DM), representing more than 95% of all diabetes cases, is a multifactorial metabolic disorder characterized by insulin resistance leading to an imbalance between insulin requirements and supply. Overweight and obesity are the main risk factors for developing type 2 diabetes mellitus. The lifestyle modification of following a healthy diet and physical activity are the primary successful treatment and prevention methods for type 2 diabetes mellitus. Problems may exist with patients not achieving recommended levels of physical activity. Electrical muscle stimulation (EMS) is an increasingly popular training method and has become in the focus of research in recent years. It involves the external application of an electric field to muscles, which can lead to muscle contraction. Positive effects of EMS training have been found in healthy individuals as well as in various patient groups. New EMS devices offer a wide range of mobile applications for whole-body electrical muscle stimulation (WB-EMS) training, e.g., the intensification of dynamic low-intensity endurance exercises through WB-EMS. This dissertation project aims to investigate whether WB-EMS is suitable for intensifying low-intensive dynamic exercises such as walking and Nordic walking.

Methods: Two independent studies were conducted. The first study aimed to investigate the reliability of exercise parameters during the 10-meter Incremental Shuttle Walk Test (10MISWT) using superimposed WB-EMS (research question 1, sub-question a) and the difference in exercise intensity compared to conventional walking (CON-W, research question 1, sub-question b). The second study aimed to compare differences in exercise parameters between superimposed WB-EMS (WB-EMS-W) and conventional walking (CON-W), as well as between superimposed WB-EMS (WB-EMS-NW) and conventional Nordic walking (CON-NW) on a treadmill (research question 2). Both studies took place in participant groups of healthy, moderately active men aged 35-70 years. During all measurements, the Easy Motion Skin® WB-EMS low frequency stimulation device with adjustable intensities for eight muscle groups was used. The current intensity was individually adjusted for each participant at each trial to ensure safety, avoiding pain and muscle cramps. In study 1, thirteen individuals were included for each sub question. A randomized cross-over design with three measurement appointments used was to avoid confounding factors such as delayed onset muscle soreness. The 10MISWT was performed until the participants no longer met the criteria of the test and recording five outcome measures: peak oxygen uptake (VO_2peak), relative VO_2peak (rel.VO_2peak), maximum walk distance (MWD), blood lactate concentration, and the rate of perceived exertion (RPE).

Eleven participants were included in study 2. A randomized cross-over design in a study with four measurement appointments was used to avoid confounding factors. A treadmill test protocol at constant velocity (6.5 m/s) was developed to compare exercise intensities. Oxygen uptake (VO_2), relative VO_2 (rel.VO_2) blood lactate, and the RPE were used as outcome variables. Test-retest reliability between measurements was determined using a compilation of absolute and relative measures of reliability. Outcome measures in study 2 were studied using multifactorial analyses of variances.

Results: Reliability analysis showed good reliability for VO_2peak, rel.VO_2peak, MWD and RPE with no statistically significant difference for WB-EMS-W during 10WISWT. However, differences compared to conventional walking in outcome variables were not found. The analysis of the treadmill tests showed significant effects for the factors CON/WB-EMS and W/NW for the outcome variables VO_2, rel.VO_2 and lactate, with both factors leading to higher results. However, the difference in VO_2 and relative VO_2 is within the range of biological variability of ± 12%. The factor combination EMS∗W/NW is statistically non-significant for all three variables. WB-EMS resulted in the higher RPE values, RPE differences for W/NW and EMS∗W/NW were not significant.

Discussion: The present project found good reliability for measuring VO_2peak, rel. VO_2peak, MWD and RPE during 10MISWT during WB-EMS-W, confirming prior research of the test. The test appears technically limited rather than physiologically in healthy, moderately active men. However, it is unsuitable for investigating differences in exercise intensities using WB-EMS-W compared to CON-W due to different perceptions of current intensity between exercise and rest. A treadmill test with constant walking speed was conducted to adjust individual maximum tolerable current intensity for the second part of the project. The treadmill test showed a significant increase in metabolic demands during WB-EMS-W and WB-EMS-NW by an increased VO_2 and blood lactate concentration. However, the clinical relevance of these findings remains debatable. The study also found that WB-EMS superimposed exercises are perceived as more strenuous than conventional exercise. While in parts comparable studies lead to higher results for VO_2, our results are in line with those of other studies using the same frequency. Due to the minor clinical relevance the use of WB-EMS as exercise intensification tool during walking and Nordic walking is limited. High device cost should be considered. Habituation to WB-EMS could increase current intensity tolerance and VO_2 and make it a meaningful method in the treatment of T2DM. Recent figures show that WB-EMS is used in obese people to achieve health and weight goals. The supposed benefit should be further investigated scientifically.

ZUSAMMENFASSUNG

Hintergrund: Die weltweite Prävalenz von Diabetes hat in den letzten Jahren zugenommen. Bis zum Jahr 2045 wird mit einer Prävalenz von 700 Millionen Patienten gerechnet, was zu einer wirtschaftlichen Belastung für die Gesellschaft führt. Diabetes mellitus Typ 2, der mehr als 95 % aller Diabetesfälle ausmacht, ist eine multifaktorielle Stoffwechselstörung, die durch Insulinresistenz gekennzeichnet ist und zu einem Ungleichgewicht zwischen Insulinbedarf und -angebot führt. Übergewicht und Adipositas sind die Hauptrisikofaktoren für die Entwicklung von Diabetes mellitus Typ 2. Die Änderung des Lebensstils durch eine gesunde Ernährung und körperliche Aktivität ist die wichtigste und erfolgreichste Behandlungs- und Präventionsmethode für Diabetes mellitus Typ 2. Probleme können bei den Patienten bestehen, den empfohlenen Umfang an körperlicher Aktivität zu erreichen. Die elektrische Muskelstimulation (EMS) ist eine zunehmend beliebte Trainingsmethode, die in den letzten Jahren in den Mittelpunkt der Forschung gerückt ist. Dabei wird von außen ein elektrisches Feld an die Muskeln angelegt, was zu einer Muskelkontraktion führen kann. Positive Effekte des EMS-Trainings wurden sowohl bei gesunden Personen als auch in verschiedenen Patientengruppen gefunden. Neue EMS-Geräte bieten eine breite Palette mobiler Anwendungen für das Ganzkörper-EMS-Training (WB-EMS), z.B. die Intensivierung von dynamischen Ausdauerübungen mit niedriger Intensität durch WB-EMS. In diesem Dissertationsprojekt soll untersucht werden, ob die WB-EMS zur Intensivierung von dynamischen Übungen mit geringer Intensität wie Walking und Nordic Walking geeignet ist.

Methodik: Zwei unabhängige Studien wurden durchgeführt. In der ersten Studie wurden die Zuverlässigkeit von Belastungsparametern während des 10-Meter-Inkremental-Penlde-Gehtests (10MISWT) unter Verwendung von überlagertem WB-EMS (Forschungsfrage 1, Unterfrage a) und der Unterschied in der Belastungsintensität zum konventionellen Gehen (Forschungsfrage 1, Unterfrage b) untersucht. Die zweite Studie beschäftigte sich mit Unterschieden in Belastungsparametern zwischen überlagertem WB-EMS (WB-EMS-W) und konventionellem Gehen (CON-W) sowie zwischen überlagertem WB-EMS (WB-EMS-NW) und konventionellem Nordic Walking (CON-NW) auf einem Laufband zu vergleichen (Forschungsfrage 2). Beide Studien wurden an Teilnehmergruppen von gesunden, mäßig aktiven Männern im Alter von 35-70 Jahren durchgeführt. Bei allen Messungen wurde das Niederfrequenz-Stimulationsgerät Easy Motion Skin® für WB-EMS mit einstellbaren Intensitäten für acht Muskelgruppen verwendet. Um die Sicherheit zu gewährleisten und Schmerzen und Muskelkrämpfe zu vermeiden, wurde die Stromintensität für jeden Teilnehmer bei jedem Versuch individuell angepasst. In Studie 1 wurden dreizehn Personen für jede Unterfrage einbezogen. Es wurde ein randomisiertes Cross-over-Design mit drei Messterminen verwendet, um Störfaktoren wie z. B. einen verzögert einsetzenden

Muskelkater zu vermeiden. Der 10MISWT wurde so lange durchgeführt, bis die Teilnehmer die Kriterien des Tests, das Erreichen des Kegels bis zum nächsten akustischen Signal, nicht mehr erfüllten. Fünf Ergebnisgrößen erfasst wurden: Spitzenwertmessung der Sauerstoffaufnahme (VO_2peak), relative VO_2peak (rel.VO_2peak), maximale Gehstrecke (MWD), Blutlaktatkonzentration und der Grad der wahrgenommenen Anstrengung (RPE). Elf Teilnehmer wurden in Studie 2 eingeschlossen. Um Störfaktoren zu vermeiden, wurde ein randomisiertes Cross-over-Design in einer Studie mit vier Messterminen verwendet. Es wurde ein Laufbandtestprotokoll mit konstanter Geschwindigkeit (6,5 m/s) entwickelt, um die Belastungsintensitäten zu vergleichen. Sauerstoffaufnahme (VO_2), relative VO_2 (rel. VO_2), Blutlaktat und der RPE wurden als Ergebnisvariablen verwendet. Die Test-Retest-Reproduzierbarkeit zwischen den Messungen wurde anhand einer Zusammenstellung absoluter und relativer Zuverlässigkeitsmaße ermittelt. Die Ergebnisgrößen in Studie 2 wurden mit Hilfe multifaktorieller Varianzanalysen untersucht.

Ergebnisse: Die Reliabilitätsanalyse zeigte eine gute Zuverlässigkeit für VO_2peak, rel.VO_2peak, MWD und RPE ohne statistisch signifikanten Unterschied für das WB-EMS überlagerte Gehen zwischen den beiden Messungen während des 10WISWT. Es wurden jedoch keine Unterschiede bei den Ergebnisvariablen im Vergleich zum konventionellen Gehen festgestellt. Die Analyse der Laufbandtests zeigte signifikante Effekte für die Faktoren CON/WB-EMS und W/NW für die Ergebnisvariablen VO_2, rel.VO_2 und Laktat, wobei beide Faktoren zu höheren Ergebnissen führten. Der Unterschied bei VO_2 und rel.VO_2 liegt jedoch im Bereich der biologischen Variabilität von ± 12 %. Die Faktorenkombination EMS∗W/NW ist für alle drei Variablen statistisch nicht signifikant. WB-EMS führte zu den höheren RPE-Werten, die RPE-Unterschiede für W/NW und EMS∗W/NW waren nicht signifikant.

Diskussion: Das vorliegende Projekt ergab eine gute Zuverlässigkeit bei der Messung von VO_2peak, rel.VO_2peak, MWD und RPE während des 10MISWT mit WB-EMS-Überlagerung beim Gehen, was frühere Untersuchungen zu diesem Test bestätigen. Der Test scheint bei gesunden, mäßig aktiven Männern eher technisch als physiologisch begrenzt zu sein. Er ist jedoch ungeeignet für die Untersuchung von Unterschieden in der Belastungsintensität bei überlagertem WB-EMS im Vergleich zum herkömmlichen Gehen, da die Stromstärkenintensität des WB-EMS zwischen Belastung und Ruhe unterschiedlich wahrgenommen wird. Für den zweiten Teil des Projekts wurde ein Laufbandtest mit konstanter Gehgeschwindigkeit durchgeführt, um die individuell maximal tolerierbare Stromintensität während der Belastung einzustellen. Der Laufbandtest zeigte eine signifikante Erhöhung der metabolischen Anforderungen während des WB-EMS überlagerten Gehens und des Nordic Walking durch eine erhöhte VO_2 und Blutlaktatkonzentration. Die klinische Relevanz dieser Ergebnisse bleibt jedoch umstritten. Die Studie ergab auch, dass WB-EMS-überlagerte Übungen als anstrengender empfunden werden als konventionelle Übungen. Während vergleichbare Studien zum Teil zu höheren VO_2-Werten führen, stimmen unsere Ergebnisse mit denen anderer Studien überein, welche dieselbe Stromfrequenz verwenden. Aufgrund der bisher fehlenden klinischen Relevanz ist der Einsatz von WB-EMS zur Trainingsintensivierung beim Gehen und Nordic Walking begrenzt. Die hohen Gerätekosten sollten berücksichtigt werden. Die Gewöhnung an WB-EMS könnte die Toleranz gegenüber der aktuellen Intensität erhöhen, die VO_2 weiter steigern und es zu einer sinnvollen Methode für die Behandlung von T2DM machen. Jüngste Zahlen zeigen, dass WB-EMS bei adipösen Menschen eingesetzt wird, um Gesundheits- und Gewichtsziele zu erreichen, der vermeintliche Nutzen sollte wissenschaftlich weiter untersucht werden.

1 BACKGROUND

1.1 Prevalence of diabetes

Diabetes in the majority of its forms is a serious, long-term condition with a major impact on the lives and well-being of individuals, families, and societies worldwide (Saeedi et al., 2019). Moreover, during the last few decades diabetes has become more and more prevalent in all parts of the world, reflected in a significant increase in the number of people affected. In 1995, the absolute number of diabetes patients worldwide was 135 million which resulted in a prevalence of 4.0% of the global population (King et al., 1998). Contrary to previous studies estimating a worldwide diabetes prevalence for the year 2025 of 300 million patients (King et al., 1998), a worldwide prevalence of 463 million people was already reached in the year 2019 (Saeedi et al., 2019). This represents 9.3% of the global population between 20-79 years. According to current evaluation, the International Diabetes Federation (IDF) prognosticate a worldwide diabetes prevalence for the year 2045 of 700 million patients. With a projected number of 9.5 billion people, this would mean 10.9% of the world's population (IDF, 2019).

Gender- and age-specific difference can also be seen in the prevalence of diabetes. In 2019, the estimated number of women suffering from diabetes is represented by 9.0% whereas 9.6% of the male population are diagnosed with the disease. With ageing, prevalence also increases, whereby 19.9% of people aged between 65-79 years have the disease (see figure 1) (IDF, 2019; Saeedi et al., 2019).

Diabetes is a phenomenon of the industrial and emergent countries (Guariguata et al., 2014). Compared to low-income countries (4.0%), the diabetes prevalence was 10.4% in the industrial or high-income countries (HIC), and 9.5% in the emergent or middle-income countries (MIC) in 2019. However, taking into account the higher population of MIC like China and India, the absolute number of 353.3 million diabetes patients is higher compared to HIC like the United States of America or Germany. For this group of countries, the figure is given as 95.2 million patients in 2019. Therefore, this worldwide increase in diabetes prevalence is mainly caused by an increase in prevalence in these groups of countries. In 2030, there is projected to be an estimated diabetes prevalence of 107.0 million people (11.4%) for HIC, and 449.6 million people (10.7%) for MIC respectively. These numbers will further increase to 112.4 million (11.9%) for HIC and 551.2 million (11.8%) for MIC by 2045 (IDF, 2019; Saeedi et al., 2019).

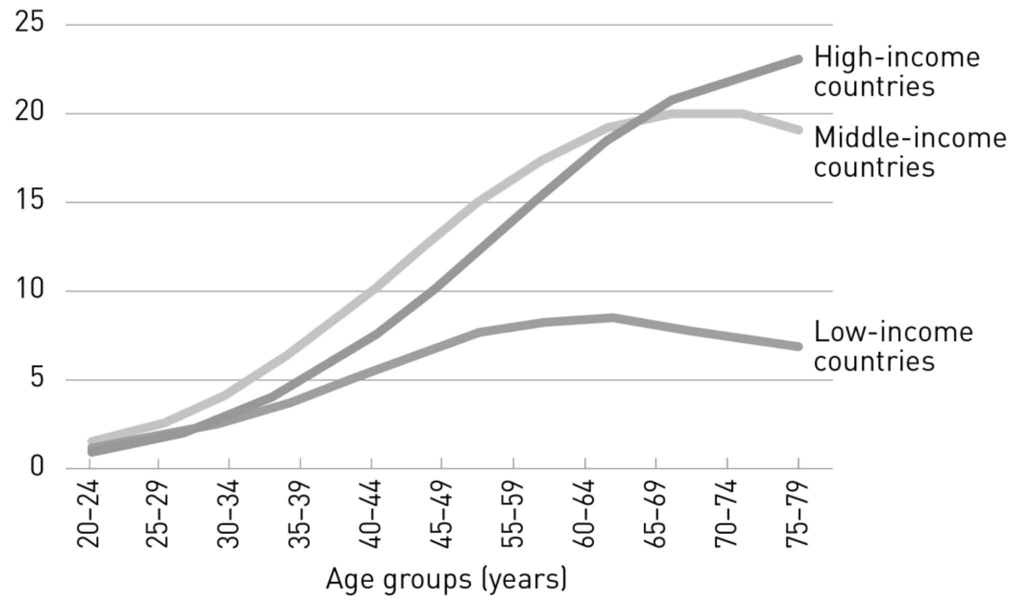

Figure 1: Diabetes prevalence in high-, middle- and low-income countries. Numbers are given in millions for 11 age groups in the age between 20 and 79 years; adapted from International Diabetes Federation 2019: "IDF Diabetes Atlas," November. Brussels, Belgium.

This is attributed to an estimated high number of undiagnosed diabetes patients, and patients in a pre-diabetic state (Dall et al., 2014a). In 2017, the estimated number of diabetes patients in the United States was recorded as 24.7 million people. In addition, the number of undiagnosed diabetes patients was estimated to be 7.5 million people, whereas 85.9 million people lives in a pre-diabetic state (Dall et al., 2019). Similar numbers have also been determined in China (Xu et al., 2013).

As can be observed worldwide, the number of diabetes patients are also increasing in Germany during recent years. While studies from 2013 assume a prevalence of diabetes in Germany of at least 4.6 million people (Heidemann et al., 2013) with an overall prevalence in the age group of 18-79-years old of 7.2%, recent studies already assume that 8.0 million people in Germany are suffering from type 2 diabetes mellitus (T2DM) and 340.000 adults suffer from type 1 diabetes mellitus (T1DM) . However, an unreported figure of 2 million people is assumed (Tamayo et al., 2014; DDG, 2020). The development of an increasing prevalence will continue in the coming years. A recent study from the German Federal Statistic Office projected the number of people with T2DM in Germany for the year 2040 (DDG, 2020). According to the results, the absolute number of T2DM patients will increase by 21% to 8.3 million people. However, considering different scenarios e.g., trends in incidence and mortality rates, the number might increase by 54 to 77% (approximately 10.7

to 12.3 million people) (Tönnies et al., 2019). The mean age of diagnosing diabetes in Germany is 61.0 ± 13.4 years (Jacobs et al., 2019).

As a result of the worldwide increase in diabetes prevalence, economic burdens are increasing. In the United States, the annual financial cost was estimated to be 218 billion dollars in 2007 (Dall et al., 2014b), increasing to an estimated 322 billion dollars in 2012 and was estimated at 404 billion dollars for 2017 (Dall et al., 2014b, 2019). This development can also be observed in Germany. Medical costs associated with diabetes in Germany reached €11.8 billion for the year 2010. Until the year 2030 an increase of 72% (€20.3 billion) is predicted (Waldeyer et al., 2013).

1.2 Pathology of type 2 diabetes mellitus

Beside gestational diabetes and some other specific forms of the disease, a distinction is made between two overarching forms of diabetes: type1 and type 2 diabetes mellitus. T1DM is a chronic organ-specific autoimmune disease, caused by a selective destruction of the insulin producing pancreatic beta-cells through the immune system which ultimately leads to an absolute insulin deficiency in the body (Atkinson et al., 2014; Thrower and Bingley, 2014). T2DM on the other hand, is a multifactorial chronic glucose (GLU) metabolic disorder without an absolute insulin deficiency. Due to a limited effectiveness of insulin on its target tissue, e.g., muscle cells, there is an imbalance between insulin requirements and its supply (Prana et al., 2019).

In many studies with different cohort groups, it could be shown independently that overweight and obesity are the main risk factors for the development of T2DM (Worede et al., 2017; Aldossari et al., 2018; Zatońska et al., 2020). Visceral adipose tissue (VAT) is increased in overweight and obese people. Contrary to earlier assumptions of storage tissue, adipose tissue is a secretory organ secreting a wide range of adipokines, such as tumor-necrosis-factor-alpha (TNF-α), interleukin-1beta (IL-1β) and interleukin-6 (IL-6). It is understood that these inflammatory markers are predictors of chronic low-grade inflammation in the body (Dinarello, 1996; Fonseca-Alaniz et al., 2007; Plomgaard et al., 2007; Odegaard and Chawla, 2013; Pereira et al., 2013) which is highly associated with insulin resistance (Spranger et al., 2003; Esser et al., 2014; Liu et al., 2016). Elevated blood glucose levels as a result of insulin resistance, in combination with low-grade inflammation could evoke a wide range of secondary diseases like hypertension, diabetic neuropathy, diabetic retinopathy, myocardial infarction, diabetic angiopathy or peripheral artery disease and stroke (see figure 2) (CDC, 2014; Canto et al., 2019).

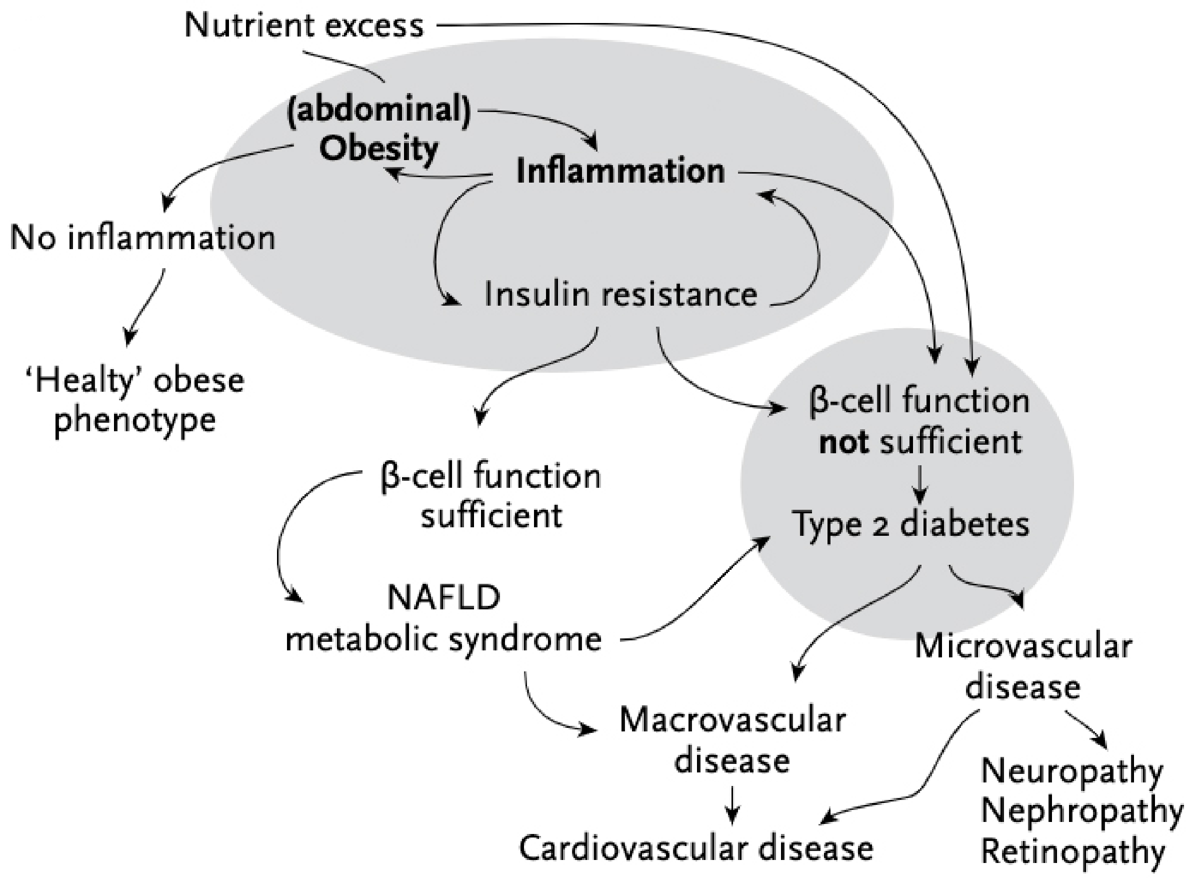

Figure 2: Schematic representation of the development of type 2 diabetes mellitus associated with obesity and its secondary diseases. Excess caloric intake leads to fat accumulation, which can result in a low-grade inflammatory response. This response leads to insulin resistance and attracts proinflammatory immune cells to adipose tissue. Insulin resistance causes normoglycemia with hyperinsulinemia, which is associated with dyslipidemia, hypertension, and ectopic fat accumulation. If insulin resistance worsens and b-cell secretion capacity declines, hyperglycemia and T2DM may develop, influenced by genetic and lifestyle factors. Adapted from **(Greevenbroek et al., 2013)**: Greevenbroek, M. M. J. van, Schalkwijk, C. G., and Stehouwer, C. D. A. (2013). Obesity-associated low-grade inflammation in type 2 diabetes mellitus: causes and consequences. The Netherlands journal of medicine 71, 174–187.

1.3 Relevance of physical activity in the management of T2DM

The first line of successful treatment, as well as prevention of T2DM is changing the patient's lifestyle (Fritsche and Stefan, 2011; Ried-Larsen et al., 2016; Landgraf et al., 2020), which can prevent or reduce reliance on pharmacological interventions (Matthaei et al., 2009; Landgraf et al., 2020). Evidence has shown that adopting a healthy lifestyle is associated with a substantially lower risk of T2DM (Zhang et al., 2020) and is the best intervention for prevention and management of T2DM (WHO, 2017; Zheng et al., 2018). Elements of this approach include maintaining or reaching a healthy body weight (BW), following a healthy diet, exercising daily for at least 30 min, avoiding smoking, and avoiding harmful alcohol consumption (Zheng et al., 2018). The goal is to reduce blood glucose and blood lipid levels, and to reduce blood pressure (Colberg et al., 2010). The reduction of body weight i.e., VAT and therefore, the reduction of low-grade inflammation, are the two main tools most commonly used to achieve these goals (Fayh et al., 2013; Lean et al., 2019).

The reduction of low-grade inflammation is not only achieved by reducing the VAT, but can also be accomplished via muscular pathways. In contrast to the pro-inflammatory effect of excessive VAT, the skeletal muscles also produce IL-6 in response to exercise (Pedersen, 2013). This exercise-induced secretion of IL-6 has a wide range of immune-regulatory effects. Human in-vivo studies showed that infusions with recombinant human IL-6 (rhIL-6) increased plasma cortisol, interleukin-1 receptor antagonist (IL-1ra), interleukin-10 (IL-10), soluble TNF-α receptors (sTNF-R), and C-reactive protein (CRP) (Steensberg et al., 2003; Pedersen, 2013). The plasma IL-1ra is increased after rhIL-6 infusion for one hour, and by diminishing the signal transduction through the interleukin-1 (IL-1) receptor, it attenuates the effect of the pro-inflammatory cytokine IL-1 (Pedersen, 2017). The increase in the plasma level of the anti-inflammatory cytokine IL-10 by rhIL-6 lasts twice as long, namely two hours. IL-10 has the ability to inhibit the lipopolysaccharide-stimulated production of several pro-inflammatory cytokines including TNF-α, IL-1α and IL-1β mediating insulin resistance in T2DM (Steensberg et al., 2002; Fischer, 2006; Plomgaard et al., 2007). It was shown that the combination of body weight reduction and physical activity leads to the highest impact in the management of T2DM (Hopps et al., 2011; Beavers et al., 2013).

A wide range of investigations have been conducted in the field of exercise and T2DM, whereby there is substantial evidence documenting the significant benefits of frequent, regular physical activity (PA) for the management of T2DM and glycemic control (Colberg et al., 2016; Kennerly and Kirk, 2018). However, in the literature there is a distinction between the terms “physical activity” and “exercise”. Colberg and his colleagues have defined both terms in the statement of the American Diabetes Association (ADA) (Colberg et al., 2016). PA includes all movements that require increased energy use, while exercise is a planned and structured physical activity. Commonly studied forms of exercise include balance training or related practices such as Yoga or Tai Chi, endurance training, and resistance training. Whilst positive effects like improvement in glycaemic control, lipid levels, and body composition in adults with T2DM are reported for Yoga and Tai Chi, the impact seems to be low (Innes and Selfe, 2016; Chao et al., 2018).

Endurance or aerobic exercise involves repeated and continuous movement of large muscle groups and is beneficial by increasing mitochondrial density, insulin sensitivity, oxidative enzymes, compliance and reactivity of blood vessels, lung function, immune function, and cardiac output (Garber et al., 2011; Colberg et al., 2016). The ADA recommends at least 150 min/week of aerobic exercise at moderate to vigorous intensities for most adults with T2DM. Activities such as cycling, running and swimming could be mentioned as examples of aerobic or endurance exercise. On the other hand, resistance training includes exercises with free weights, weight machines, body weight, or elastic resistance bands. It increases muscle mass, improves body composition, insulin sensitivity, blood pressure, lipid profiles, and cardiovascular health and is recommended 2-3 time/week for T2DM patients by the ADA (Garber et al., 2011; Grabert and Feito, 2013; Colberg et al., 2016). However, it is evident that a combination of aerobic exercise and resistance training has the highest benefit for diabetic people regarding disease management (Schwingshackl et al., 2014).

Different reasons could lead to physical inactivity of T2DM patients. People with diabetes were less likely to engage in physical activity at recommended levels than those without diabetes (Arnold-Wörner et al., 2008; Zhao et al., 2008). They are less likely to perform high impact exercise because of their impaired tolerance of physical capacity (Gusso et al., 2008), secondary diseases could be a cause for inactivity. Diabetic peripheral neuropathy (DPN) is one of the most common complications associated with diabetes, occurring in 30–50% of patients and causing dysfunction within peripheral nerves (Petrovic et al., 2016).

As already mentioned, aerobic activities such as running or bicycling should be performed at a moderate to vigorous intensity to obtain cardiovascular benefits (Colberg et al., 2010; Sénéchal et al., 2015). However, investigations in different cohorts of T2DM patients show that the recommendations for physical activity are not being achieved (Thomas et al., 2004; Zhao et al., 2008; Egan et al., 2013). Previous studies identified walking as the most popular and preferred exercise among patients with T2DM (Ford and Herman, 1995; Wanko et al., 2004). As a low-impact exercise, it has a variety of advantages compared to running and bicycling. For example, it can be done at a variety of speeds with different intensities, no specific skills are required nor any substantial pre-exercise evaluation, and there are comparatively minimal adverse effects (Qiu et al., 2014). Also, a lower injury risk is reported in walking activities, and fear of injury is known to be a barrier for T2DM patients when engaging in physical activity (Halali et al., 2016). A wide range of studies have examined the impact of walking on different outcome variables related to T2DM, such as glycemic control, BW reduction, blood pressure and blood parameters. A recent meta-analysis found a significant impact of walking on glycemic control, particularly a decreased HbA1c level, and body mass index (BMI) reduction in T2DM patients (Qiu et al., 2014). However, only minor beneficial metabolic effects for this patient group have been shown, indicating that the exercise intensity of normal walking might be insufficient (Karstoft et al., 2013). As a consequence, high-intensity interval training protocols have been evaluated (Tjønna et al., 2008). Recently, it was shown that high- intensity interval walking training leads to higher improvements in physical fitness, body composition, and glycemic control, compared to continuous walking training (Karstoft et al., 2013, 2014, 2017; Ried-Larsen et al., 2016).

Furthermore, Nordic walking represents another approach for exercise in T2DM patients. At a defined speed, Nordic-walking involves more muscles in various body segments and induces greater exercise intensity by means of higher oxygen uptake (VO_2) compared with conventional walking (Sugiyama et al., 2013). Different reviews examining the health benefits of Nordic walking confirm these results. Nordic walking exerts beneficial effects on resting heart rate, blood pressure, exercise capacity, maximal oxygen consumption, and quality of life in patients with various diseases and can thus be recommended to a wide range of people as both primary and secondary prevention (Tschentscher et al., 2013; Mathieson and Lin, 2014).

1.4 Cardiopulmonary exercise testing

The assessment of physical performance by exercise testing has a widespread application in research and clinical diagnosis. For example, it is used in the field of risk assessment and prognosis for patients (Members et al., 2002), in performance tests for athletes (Bosquet et al., 2002), to assess the cardiorespiratory fitness of patients and the metabolic demands of various activities (Macfarlane and Wong, 2011) and for exercise intensity prescription for rehabilitation and training. These training intensity prescriptions are an important tool for successful T2DM management through physical activity. Incremental ramp exercise (IRE); the most widely used cardiopulmonary exercise testing (CPET) protocol in clinical practice; is used to calculate the maximum volume of oxygen uptake (VO_2max), the aerobic threshold, respiratory compensation point, and peak work rate (WRpeak) or velocity (Yamamoto and Tabira, 2014).

Determination of VO_2max gives a representative value for the capacity of the pulmonary, cardiovascular and muscular system of the body to transport and utilize the inhaled oxygen volume (Poole et al., 2007). It is defined as the plateau of maximum oxygen uptake, which could not be increased by increasing the given workload or the running speed (Hill and Lupton, 1923). Derived from VO_2max, the maximum oxygen uptake relative to body weight (rel.VO_2max) is considered as the gold standard for exercise intensity description (Balducci et al., 2014). For T2DM patients, aerobic exercises like running or cycling at 40-60% of the individual VO_2max are recommended to balance the effort and motivation of the patient, and enhance metabolic impact (Balducci et al., 2014; Colberg and Sigal, 2015; Colberg et al., 2016). However, besides the clinical application of such tests for patient management, intensity assessment and training prescription are important for scientific work to make training interventions and their results comparable.

1.5 Electrical muscle stimulation and its application in training and therapy

Electrical muscle stimulation (EMS) is the electrical excitation and ultimately, the contraction of a muscle or a muscle group through an externally applied electric field (Banerjee et al., 2005). The application of these external electrical fields to the muscle or muscle group is carried out by wearing special vest, hip belt and belts for the lower arms and legs (see figure 3). A connection via a cable to a main station provides the power supply and the intensity setting.

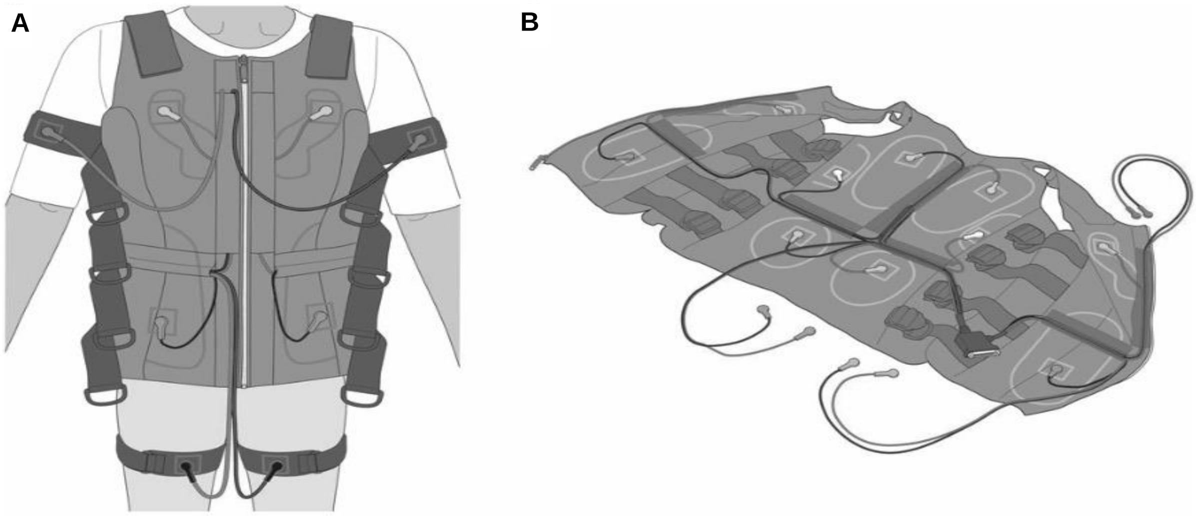

Figure 3: Setup for whole-body electrical muscle stimulation training Setup composed of trunk vest and belts for upper arms and legs. Adapted from (Buuren et al., 2015)**:** Buuren, F. van, Mellwig, K. P., Fründ, A., Bogunovic, N., Oldenburg, O., Kottmann, T., et al. (2013). [Electrical Myostimulation: Improvement of Quality of Life, Oxygen Uptake and Left Ventricular Function in Chronic Heart Failure.]. Die Rehabilitation. doi: 10.1055/s-0033-1358734.

EMS has been the focus of research for several years regarding different research questions. In patients with neurological injuries, EMS is able to simulate the physical adaptation of voluntary exercise (Poole et al., 2005). Previous investigations showed that an EMS application can increase heart rate, blood pressure and energy expenditure (EE) (Poole et al., 2005), increase cardiorespiratory fitness level (Rostrup et al., 2013), whole body GLU uptake during and after training sessions, and can significantly enhance GLU uptake compared to voluntary ergometry exercises (Hamada et al., 2003). Correspondingly, just a single bout of EMS training of the lower limb muscles induced significantly greater carbohydrate utilization than voluntary exercise at the same exercise intensity and duration (Hamada et al., 2004). It also seems that patients benefit due to an attenuation of postprandial hyperglycemia in middle-aged men with metabolic syndrome (Kimura et al., 2010) and T2DM (Miyamoto et al., 2012). Because of their larger nerve axons, glycolytic type 2 muscle fibers are preferentially activated during EMS training. This causes higher GLU and oxygen demand during EMS training, potential in its beneficial effects (Watanabe et al., 2014).

Currently, EMS training is very popular and is commonly implemented by combining external electrical muscle stimulation and voluntary muscle activation during strength and core stability workouts (see figure 4); often defined as a whole-body electrical muscle stimulation (WB-EMS) fitness workout (Buuren et al., 2013).

Figure 4: Examples for whole body electrical muscle stimulation (EMS) strength and core stability training. Adapted from www.easymotionskin.com/de/

These WB-EMS fitness workouts are well investigated in different groups of patients. Compared to a semi-active control group, the WB-EMS training significantly impacts total and regional muscle mass, increases muscle strength and could prevent elderly women from sarcopenia (Kemmler et al., 2013). Also, the effects on osteopenia patients were investigated (Stengel et al., 2015). WB-EMS has a significantly positive impact on overall and abdominal fat, and on strength parameters in a postmenopausal cohort (Kemmler et al., 2013) as well as a positive influence on body composition and strength compared to high-intensity resistance exercise training (HIT) (Kemmler et al., 2016b) and leads to a reduction of cardio-metabolic risk factors in untrained middle-aged males (Kemmler et al., 2016a). The effect of WB-EMS fitness training on glucose metabolism and glycaemic control in patients with T2DM has also already been investigated. After a 10-week intervention with WB-EMS training twice per week (overall 20 training sessions) significant improvements in fasting blood glucose and hemoglobin-A_{1c} (HbA_{1c}), a long-term marker for elevated blood glucose levels, were observed and therefore, a significant improvement in insulin resistance (Buuren et al., 2015).

EMS-devices have constantly been renewed and updated. Compared to the devices used in previous studies (Kemmler et al. 2016; Kemmler, Kohl, and Stengel 2016; van Buuren et al. 2013; van Buuren et al. 2015; Kemmler et al. 2013), which need a connection between the main station and vest and belts worn by the patient for power transfer via cable (see picture 4), newer EMS-devices work wirelessly via battery and apps for intensity adjusting (e.g. Easy Motion Skin®, see picture 3, www.easymotionskin.com). This new EMS-device offers a wide range of mobile application for WB-EMS training, e.g., WB-EMS superimposed walking or running. Therefore, the use of superimposed WB-EMS for intensification of dynamic exercises has become increasingly the focus of research (Wahl et al., 2014), producing contradictory results. Earlier studies had shown that superimposed WB-EMS is able to intensify voluntary body weight resistance training (Watanabe et al., 2019) and lead to a higher metabolic and respiratory response during its application in ergometer cycling (Mathes et al., 2017), as well as metabolic stress and hormonal response are increased (Wahl et al., 2015). In contrast, beneficial effects regarding strength and power parameters are debatable. Dynamic WB-EMS superimposed resistance training seems to provide minor or no benefits in comparison to dynamic resistance training alone (Micke et al., 2018). The combination of an easy and harmless aerobic exercise with this exercise intensity-stimulating device could be a new approach for weight management and glycemic control in T2DM patients.

2 RESEARCH PARADIGMS

Diabetes is one of the greatest challenges for public health and economic prosperity in all parts of the world (Bommer et al., 2017). Due to the higher prevalence of T2DM in comparison to T1DM, the implications of the disease for society and thus its negative impact are determined as significantly higher (Top et al., 2020).It is evident that physical exercise is, beside diet and medication, one of the three cornerstones in the treatment of T2DM (Pedersen and Saltin, 2015). Besides resistance exercise, aerobic exercise is the second pillar of physical exercise in T2DM management and prevention, and is supported by strong evidence for its benefits on blood pressure, systemic inflammation, cardiorespiratory fitness, and glycemic control, which is considered a primary outcome in the treatment (Delevatti et al., 2019).

However, T2DM patients mostly do not reach the recommendations for physical exercise (Zhao et al., 2008). Secondary diseases of T2DM, fear of injury risk or motivation problems, are reasons that patients do not regularly perform aerobic exercises like running or cycling (Halali et al., 2016). However, walking is the most performed leisure time activity in this patient group (Wanko et al., 2004). Nordic walking represents another approach for exercise in T2DM patients. Due to the use of the poles, additional muscle groups are involved in the movement compared to normal walking. Therefore, positive effects can be observed compared to walking (Mathieson and Lin, 2014).

Superimposed WB-EMS seems to be a tool, which is able to intensify aerobic exercises, e.g. cycling on an ergometer, as well as resistance exercise. An intensification via superimposed WB-EMS could be a new approach to increase the impact of low-intensive exercises like walking, on target health outcomes such as glycemic control in T2DM patients. However, there is a lack of knowledge describing whether WB-EMS leads to an intensification of walking in a healthy population, and whether measurements of the exercise intensity during WB-EMS walking can be carried out reliably.

Therefore, the aim of the present PhD-project was to investigate the effect of WB-EMS superimposed walking and Nordic Walking regarding exercise intensity. The primary research question was as follows: Is WB-EMS capable of intensifying conventional walking and Nordic walking? There is no information available on the reliability of stress intensity measurements using VO_2 during WB-EMS superimposed walking in the field test with an incremental walking protocol. Therefore, in a first study, the reliability of these measurements is determined as the basis for addressing the primary research question. It is hypothized that exercise intensity measurements using VO_2 during WB-EMS superimposed walking in the field test can be performed reliably. In a second research question of the first study, differences in stress intensity between WB-EMS superimposed walking and conventional walking are examined using VO_2 measurements. It is hypothesized that WB-EMS superimposed walking leads to higher exercise intensity compared to conventional walking.

In the second study, differences in exercise intensity of WB-EMS superimposed walking on the treadmill during a constant walking speed test are investigated. Additionally, Nordic walking, as an extension of walking with the involvement of the arms to a greater extent than in regular walking, is also examined. It is hypothesized that the superposition of WB-EMS will result in an increase in exercise intensity for walking and Nordic walking through VO2 measurements during a treadmill test at a constant walking speed.

2.1 Research Question

In agreement with the research paradigm described previously, the following main research questions and their respective sub questions are raised:

Research question 1 (RQ1; sub questions RQ1a, RQ1b)

> What influence does superimposed WB-EMS have on a low-level intensity activities like walking during an incremental walking test?
>
> > a) Can measurements of the oxygen uptake in a WB-EMS-superimposed walking protocol be conducted reliably, during an incremental walking test?
> >
> > b) During walking, does the superimposition of WB-EMS lead to an intensification of the task?

Research question 2 (RQ2)

> What influence does superimposed WB-EMS have on a low-level intensity exercise like walking and Nordic-walking, during an constant walking test on the treadmill?

3 MATERIAL AND METHODS

Two independent studies were planned and conducted to answer the scientific questions of this PhD project (see figure 5). The first study was designed as a test-retest (Study 1: WB-EMS-superimposed walking during the 10-meter incremental shuttle walk test), to assess the day-to-day reliability of peak VO_2 measurements (VO_2peak the highest oxygen uptake achieved during CPET but lower than VO_2max) during the 10MISWT using superimposed WB-EMS (RQ1a), and to investigate differences in VO_2peak between WB-EMS-W and CON-W during the 10MISWT (RQ1b). As a result of the first study, the test situation of the follow-up study was modified. The second study was conducted in a randomized cross-over design (Study 2: superimposed WB-EMS during a constant-speed treadmill test) and applied the WB-EMS during a constant-speed treadmill test. This study examined differences in VO_2 between WB-EMS-W and CON-W and between WB-EMS-NW and CON-NW (RQ2).

Ethical approval was obtained for both studies. The first study was confirmed by the State Medical Association of the state of Brandenburg (S 23(a)/2017), the second by the Ethics Committee of the University of Potsdam (19/2018).

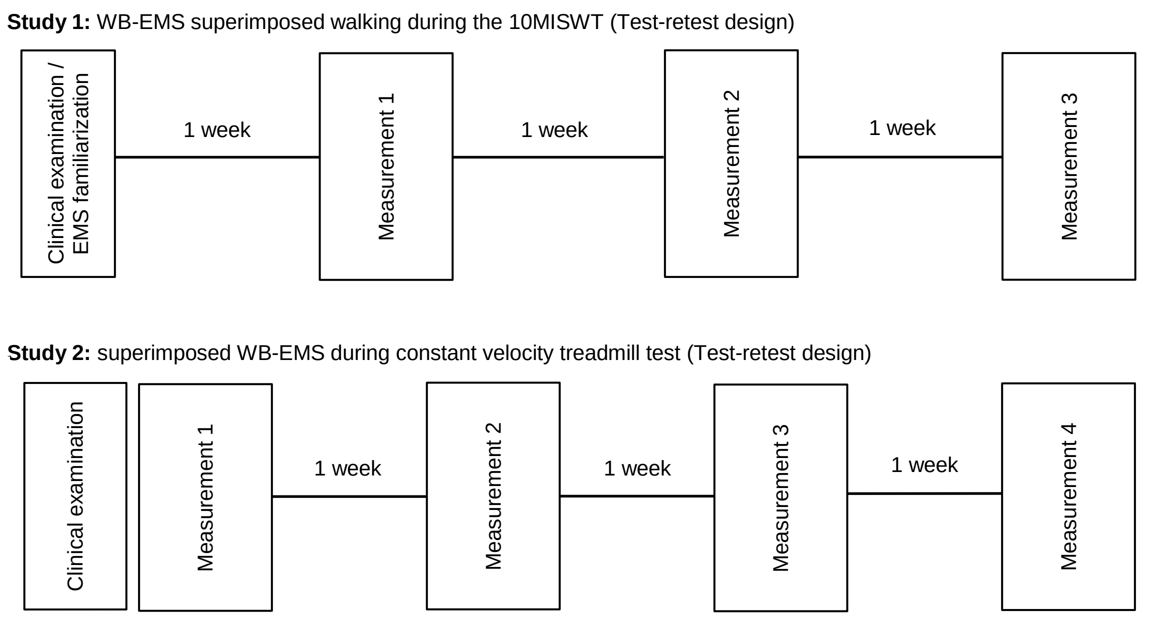

Figure 5: General structure of the research project and study designs of the two independent investigations. (WB-EMS: whole body electrical muscle stimulation; 10MISWT: 10-meter incremental shuttle walk test)

3.1 Walking test protocols

IRE protocols are the most commonly used CPET protocols in clinical practice. They are used to calculate important metrics such as VO_2max, anaerobic threshold (AT), respiratory compensation point, and WRpeak or speed (Yamamoto and Tabira, 2014). Field testing is often used in the clinical setting as a simpler, less costly alternative with lower staffing requirements compared to CPET on treadmills or cycle ergometers (Woolf-May and Meadows, 2013).

3.1.1 10-meter incremental shuttle walk test

A walking test may be a suitable alternative to CPET (Ekman et al., 2013). In addition to the widely used six-minute walk test (6MWT), the 10MISWT has also become an increasing focus of research in recent years. Originally developed for patients with chronic obstructive pulmonary disease (COPD) (Singh et al., 1992), the 10MISWT is now also recommended for the elderly and patient populations such as cardiac (Buckley et al., 2013) and heart failure patients (Green et al., 2001) and has already been used to assess physical performance in obese and T2DM patients (Sexton et al., 2014; Crowe et al., 2015).

Previous research has shown that VO_2peak is significantly higher with 10MISWT compared to 6MWT in both active older adults (Leone et al. 2016) and obese patients (Oliver et al., 2015) and is closer to patients' VO_2max. Maximum heart rate (HRmax) is also significantly higher in 10MISWT compared to 6MWT (Leone et al., 2016). The studies also showed a strong correlation between VO_2peak at the achieved level and maximal walking speed (Leone et al., 2016). The results of Jürgensen et al. 2015 showed that young obese women achieved a VO_2peak of ≈81% of the VO_2max obtained during treadmill CPET during a 10MISWT. In the same study, the VO_2peak values of the 10MISWT correlated significantly with the VO_2max during CPET in this patient group (Jürgensen et al., 2016). Excellent reliability of the 10MISWT has previously been demonstrated, for both maximal walking distance (MWD) in women with morbid obesity (Peixoto-Souza et al. 2015), and patients with chronic heart failure (Pulz et al., 2008). These results suggest that the 10MISWT could be an alternative to CPET for different patient groups.

The 10MISWT is an incremental, stepwise walking test. The test course consists of two cones spaced 9 meters apart. Walking around the cones results in an effective distance between the cones of 10 m (see figure 6). The individual stages each last one minute. The walking speed is indicated by an audio signal from the "Team beep test 20m software version 4.0". In each stage, the time by which the participant must have completed the distance between the two cones is shortened, thus increasing the walking speed. The test is terminated when the patient is unable to reach the cones three times in succession until the audio signal indicating the speed is heard (Woolf-May and Meadows, 2013).

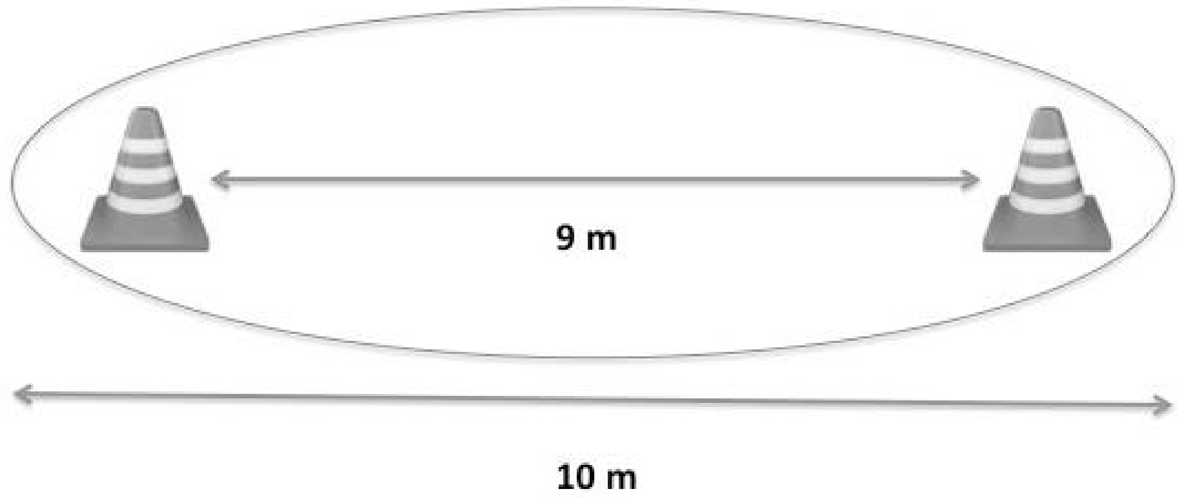

Figure 6: Setup for 10-meter incremental shuttle walk test. 10 m long round course (20 m per round), consisting of two cones placed at a distance of 9 m from each other.

Originally, the test consists of 12 stages. Starting with a speed of 0.50 m/s, which is increased by 0.17 m/s every minute, the final speed (step 12) is 2.37 m/s (Singh et al., 1992). An extension to 15 steps (final speed 2.88 m/s) is possible in a healthy study population (Dourado et al., 2013). Since the software was only programmed for the 20-meter shuttle run, a separate test setting had to be programmed for the 10MISWT. The run speed and number of runs per stage are shown in table 1. The MWD was calculated from the number of completed pendulum runs.

Table 1: 10-meter incremental shuttle walk test. Overview of the gradual structure of the test. The walking speeds and the number of runs per minute are given for each stage of the test. The walking speed in the first stage of the test is given as 0.5 m/s. The walking speed is increased by 0.17 m/s in each stage. The test is planned up to stage 15.

stage	velocity [m/s]	velocity [km/h]	runs per minute (adjusted)
1	0.5	1.8	3
2	0.67	2.41	4
3	0.84	3.02	5
4	1.01	3.65	6
5	1.18	4.25	7
6	1.35	4.86	8
7	1.52	5.47	9
8	1.69	6.08	11
9	1.86	6.70	11
10	2.03	7.31	12
11	2.20	7.92	13
12	2.37	8,52	14
13	2.54	9.14	16
14	2.71	9.76	16
15	2.88	10.37	17

3.1.2 Constant-walking treadmill test

To compare the results of an incremental walking test with those of a constant walking test, a test protocol for a treadmill test was designed. The results of previous studies on comfortable and maximum walking speed in different age groups, and on Nordic walking speed were used to calculate walking speed for the current study. The mean comfortable walking speed of the five age groups and the mean maximum walking speed of all age groups were averaged (Bohannon et al., 1996; Bohannon, 1997). As a result, a constant speed of 6.5 km/h (1.805 m/s) was set as the walking speed for the test. In view of the in-house common practice, the incline of the treadmill was set at 0.4% as an adequate substitution for the lack of air resistance in treadmill running compared to field tests (Meyer et al., 2003). During the study, the in-house hp cosmos® saturn 250/100 treadmill was used for all measurements.

3.2 Electrical muscle stimulation

In this project, the wireless WB-EMS-device from Easy Motion Skin® (EasyMotionSkin GmbH, Leipzig, Germany) was used. This is a commercially available device that is used in many studios. It consists of a vest, a waist belt and straps for the upper arms and thighs and was available in five different sizes for the study. Thus, it was possible to select a suitable vest, belt, and straps for each participant. In addition, participants wore only special EMS underwear during the test, which was cleaned for each test.

The vest is the central element of the EMS-device. Both the hip belt and the upper arm and thigh belts were connected to the vest via cables. The receiver box is also connected to the vest. This box served both as a battery, providing the electrical power for the EMS, and as a receiver of the intensity settings. The intensities for each muscle or muscle group were set on a tablet in the software provided by the manufacturer. This information was transmitted to the receiver box via Bluetooth. In the app provided by the manufacturer, the intensity of the stimulation current could be set individually for each subject and for each muscle group. These muscle groups were: upper arm, chest, shoulder, upper and lower back, abdomen, buttocks, hip area including pelvic floor and thighs. In preparation for each test, the vest and straps were sufficiently soaked with warm water to ensure optimal current transfer to the skin. The final fitting of participants with this WB-EMS vest and belts and spirometry mask is shown in figure 7.

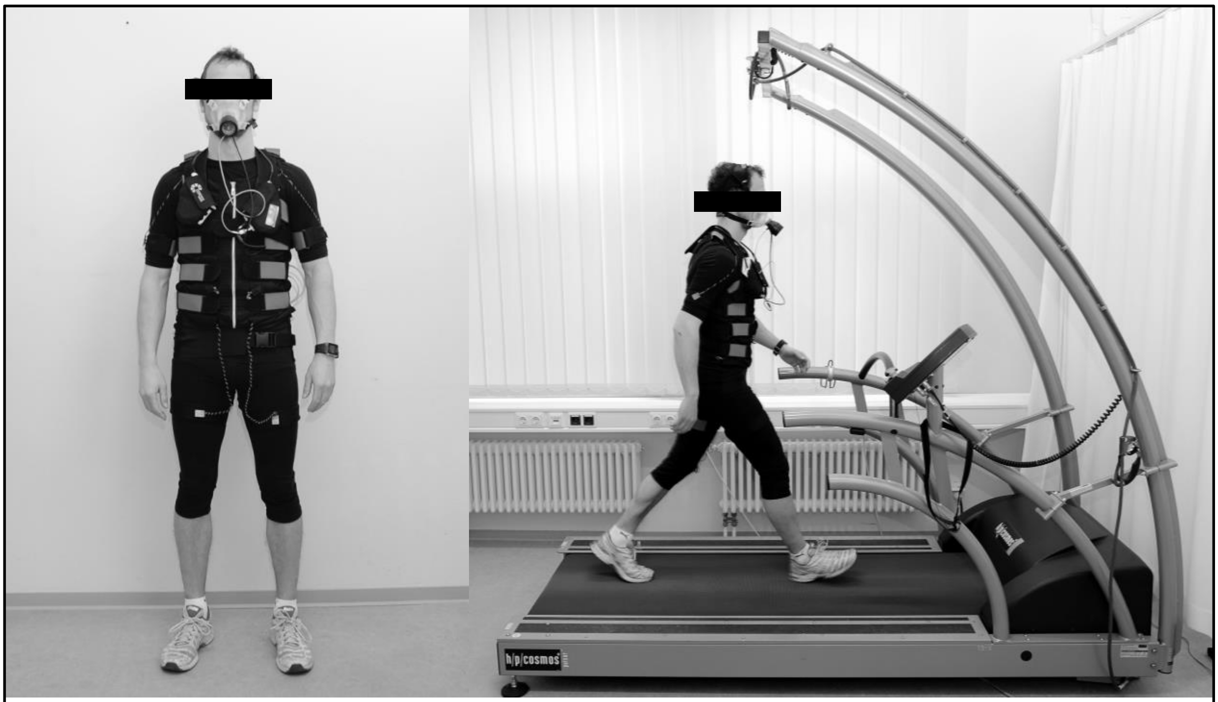

Figure 7: Final participants fitting with whole-body electrical muscle stimulation and spirometry devices. On the right, walking on the treadmill in final study fitting**.**

The device uses low frequency neuromuscular electrical stimulation. Depending on the current frequency, there are different training targets for EMS. While a current frequency of 7 hertz (Hz) is described by the manufacturer as effective for metabolism, a current frequency of 85 Hz triggers tetanic muscle contraction. The manufacturer did not have a suitable preinstalled training protocol. Therefore, it was necessary to program a new WB-EMS training protocol for the study. Unlike the fitness application of WB-EMS, walking is a continuous exercise. However, the software does not provide a mode for continuous muscle contraction with a current frequency of 85 Hz. Therefore, a training protocol was programmed with an interval stimulation pattern of 9 seconds 85 Hz and 1 second 7 Hz.

The perception of current intensity is very individual with WB-EMS. While some people can tolerate stronger currents without problems, others already report pain and cramps. Severe muscle injuries such as rhabdomyolysis as a result of excessive and overuse of EMS have also been described (Estes, 2018). Therefore, it is particularly important that the current intensity of WB-EMS is always adjusted individually and in consultation with the participant. In the first study, this was done during a familiarization phase; in the second study, it was done during a specific phase of the testing protocol. Participants should reach the maximum current intensity they can tolerate but should explicitly not feel any pain. Muscle cramps should also not have occured. The individual intensities were stored in the app and in the case report form. The current intensities are given as full numbers dimensionless in a range from 1 to 100 by the manufacture.

3.3 Measurements of oxygen uptake

The MetaMax3B® wireless portable breath-by-breath system from Cortex (Cortex Biophysik GmbH, Walter-Köhn-Straße 2d, 04356 Leipzig/Germany, www.cortex-medical.de) was used to determine VO_2 respectively VO_2peak in both studies. The MetaMax3B system measures volume using a bidirectional digital turbine. Inspiratory and expiratory volume and oxygen concentration were calculated using Metasoft version 3.9.5 analysis software. The measurement accuracy/current error of the MeatMax3B system is approximately ±2.2%. The analysis system was calibrated in preparation for each test with respect to volume, pressure, and the concentrations of oxygen and carbon dioxide using calibration gas. In the second study, air conditioning guaranteed consistent conditions throughout the test in the laboratory (standard temperature pressure dry (STPD)).

3.4 Rate of perceived exhaustion (Borg-scale)

The Borg-scale is an assessment method for grading the severity of subjectively perceived fatigue (rate of perceived exhaustion (RPE)), dyspnea, or pain and is used in many scientific fields such as sports science, cardiology, and pulmonology (Borg and Noble, 1974) . It is based on the assumption that the feeling of exertion is related to heart rate (Borg, 1982). This relationship applied not only to heart rate but also to power output and oxygen consumption during different exercises and in different cohorts (Garcin et al., 1998; Leung et al., 2003). The reliability of the Borg-scale has also been demonstrated in many areas of exercise science (Wilson and Jones, 1991; Pfeiffer et al., 2002).

The Borg-scale contains numerical values from 6 to 20, which also reflect the linear relationship between training intensity and heart rate, assuming a resting heart rate of 60 beats per minute. In addition, a description of the particular exertion is given for some values. These range from "no effort at all" for the value 6 to "maximum effort" for the value 20. The German version of the Borg scale can be found in the appendix (see figure 25).

Participants were asked to rate their perceived fatigue before and immediately after the test. The questionnaire before the start of the test was used to rule out any possible pre-existing stress on the part of the test subject that could influence the result. The questionnaire immediately after the test was used to determine the subjectively perceived stress during the test (Scherr et al., 2012).

3.5 Lactate measurement

The determination of blood lactate concentrations is a common method in science as well as in sports medicine performance diagnostics and training prescription/monitoring to determine load intensities during physical activity (Faude and Meyer, 2008).

In both studies, blood lactate concentration was determined by means of the analyzer used in-house (Biosen S-line®, EKF Diagnostic Sales, Magdeburg, Germany). This analyzer measures blood lactate concentration using the enzymatic-amperometric analysis method. With the help of the enzyme lactate oxidase, the lactate is biochemically converted into the substances pyruvate and hydrogen peroxide (H_2O_2). The hydrogen peroxide is then oxidized at an ion-selective electrode. The resulting electric current is directly proportional to the amount of lactate in the sample, allowing the blood lactate concentration to be determined. The device measures lactate in the range of 0.5-40 mmol/L, the coefficient of variation is 1.5% at a lactate concentration of 12 mmol/l.

Sample collection was performed by an experienced person in both studies. Capillary blood samples were always taken from the same earlobe. The determination took place immediately after the end of the test (Feliu et al., 1999).

3.6 Methods – Reliability of VO_2 measurements using WB-EMS

3.6.1 Study design

The study comprised a total of four appointments. To avoid WB-EMS-induced delayed onset muscle soreness (DOMS) as an influencing factor on the test, an interval of one week was programmed between the first introductory appointment and the three actual measurements (Nosaka et al., 2002; Vanderthommen et al., 2012; Kemmler et al., 2015). The measurements took place between November 2017 and March 2018.

During the first appointment, the medical examination took place. During this examination, a physician ensured the participants' adequate fitness level for the study. It included a basic orthopedic and cardiopulmonary system check to clarify inclusion and exclusion criteria. Inclusion Criteria included male gender, aged 35-70 years, generally in good health, non-smoker with a moderate activity profile (less than three hours of physical activity per week, recorded via enquiry). Exclusion criteria included regular drug use, cardiac arrhythmias (Lown classification ≥ 3), heart failure (New York Heart Association (NYHA) ≥ II), and wearing an implantable cardiac device. A resting electrocardiogram (ECG) was performed to exclude cardiac symptoms. In case of acute infection, a blood sample was obtained to exclude severe systemic symptoms. Participants' anthropometric data (BW and height (BH)) were measured.

During the WB-EMS familiarization, the basic principles and handling of the WB-EMS device were explained to each participant. The individual sizes of the WB-EMS vest, waist belt and straps for upper arms and thighs were established. Subsequently, the subjects put on the WB-EMS underwear as well as the WB-EMS device. The current intensity levels were then adjusted individually. Starting with the shoulder muscle, followed by the upper arms, chest, upper back, lower back, abdominal muscles, glutes, hips including the pelvic floor, and thighs muscles, the individual maximum tolerated current intensity was set. Finally, each current intensity for each muscle group was checked a second time and adjusted if necessary. The results were stored for the actual testing.

During each of the three tests, participants had to complete the 10MISWT once. To assess reliability, the test was performed twice as WB-EMS superimposed walking (WB-EMS-W) and once as conventional walking (CON-W). The order was random, but the WB-EMS superimposed walks were consecutive. Randomization was carried out with a randomization software (www.randomizer.org). Nutritional status is known to have an effect on physical performance and VO_2max (Pendergast et al., 1996; Horvath et al., 2000). Changes in dietary habits in terms of meal composition could lead to changes in individual performance levels (Burke et al., 2004). Therefore, all participants were asked to log their food intake 24 hours prior to the first 10MISWT and repeat their intake in the 24 hours prior to the second and third 10MISWT. Identical footwear for all three tests was also required, so as to standardize the conditions of each test.

3.6.2 Participants

Finally, fifteen healthy men volunteered. All participants were informed in advance about the contents and objectives of the study and signed the written informed consent form One participant dropped out of the study because of injury after the first measurement, and another dropped out after the WB-EMS walk test. A third participant dropped out during the second WB-EMS test because of technical problems. An overview is shown in figure 8.

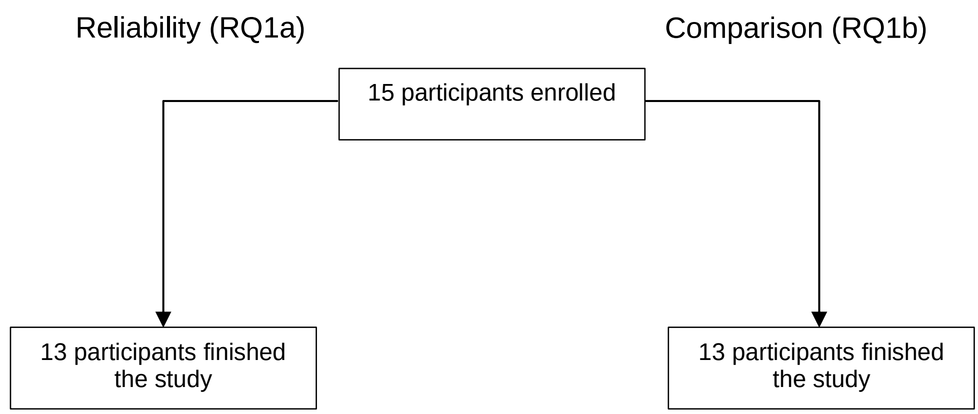

Figure 8: Flowchart of participants completion of the two research questions in the first study. Fifteen participants were enrolled in the first study. Both sub research questions were completed by 13 participants each (who did not fully match).

Thus, the two study cohorts differ with respect to the two study research questions. Anthropometric data for the two cohorts are shown in table 2 and table 3.

Table 2: Anthropometric data of 1st study participants for sub research question reliability (RQ1a). N represents number of participants. Age, body height, body weight and Body Mass Index (BMI) are presented descriptively as mean ± standard deviation.

N	age [years]	body height [cm]	body weight [kg]	BMI [kg/m^2]
13	49 ± 10	183 ± 8	88.2 ± 10.9	26.26 ± 2.80

Table 3: Anthropometric data of 1st study participants for sub research question comparison (RQ1b). N represents number of participants. Age, body height, body weight and Body Mass Index (BMI) are presented descriptively as mean ± standard deviation.

N	age [years]	body height [cm]	body weight [kg]	BMI [kg/m^2]
13	49 ± 10	183 ± 7	88.6 ± 11.2	26.52 ± 2.76

3.6.3 Test protocol

Each test began with measuring the participant's body weight, to allow for later calculation of the daily VO_2peak relative to the participant's body weight (rel.VO_2peak). Then, the participant was prepared with the WB-EMS setup and the spirometry device. The first blood lactate sample was collected, and the participant was also questioned about his RPE. In the next step, the WB-EMS current intensity already determined in the WB-EMS familiarization session were reproduced and the participant was asked about his comfort level regarding the current intensity. After adjusting the WB-EMS current intensity, the WB-EMS device was again placed in rest mode. A second lactate sample was taken to rule out any lactate increase due to the short WB-EMS period. Spirometric measurement then began with a two-minute rest period to allow for accurate rest measurements as a basis for further measurement, followed by restarting the WB-EMS device and beginning the test. Immediately after completion of the test, the WB-EMS device was turned off and the participant assessed for their RPE. The post-exercise lactate sample was collected and the spirometric measurement was terminated. In the case of the conventional 10MISWT, all steps regarding the WB-EMS were omitted, i.e., the application of the WB-EMS setup, the reproduction of the current intensity, and the WB-EMS steps during the 10MISWT. An overview of the test protocol is shown in figure 9.

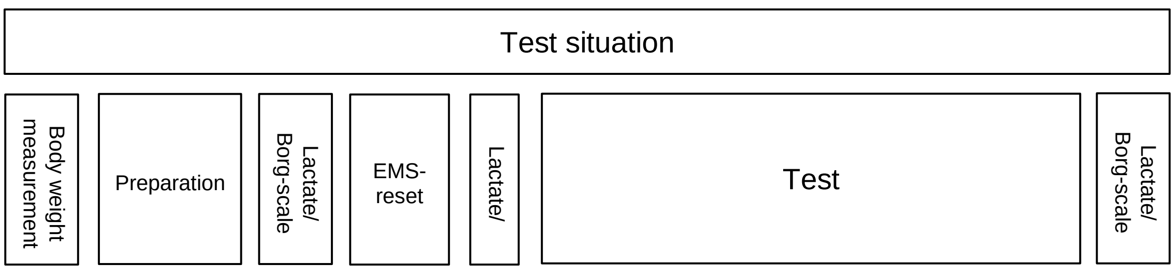

Figure 9: Test protocol of the 10-meter incremental shuttle walk test

Five outcome measures were of particular interest: VO_2peak, rel.VO_2peak, MWD, blood lactate, and the RPE. VO_2peak was defined as the mean of the five highest consecutive VO_2

values. The rel.VO_2peak was calculated by dividing the individual VO_2peak by the daily updated BW of each corresponding individual participant.

Usually, HRmax is also included in the assessment of exercise intensity. Due to the currents in the vest during WB-EMS, the measurement of heart rate by means of a watch and a corresponding pulse belt around the chest was not possible. However, corresponding watches should be able to measure the heart rate at the wrist. A corresponding in-house study with 18 test persons came to the conclusion that the measurement results of such a watch (GARMIN Fenix 5®) are not valid in comparison to a heart rate monitor with a pulse belt (POLAR V800®). Therefore, the HRmax was not used as an outcome measure.

3.6.4 Statistics

All collected data were transferred to a data matrix (Microsoft® Excel 2010). Data distributions with respect to a normal distribution were examined for all studies using the Kolmorogov-Smirnoff test. Calculations of mean and standard deviation (SD) were used to summarize data descriptively unless otherwise noted. A paired t test for interval-scaled data and a Wilcoxon signed-rank test were performed to examine statistically significant differences. The degree of inter-rater reliability was determined using coefficient of variation (CV), the intraclass correlation coefficient (ICC 2.1) for interval-scaled data, and Cronbach's alpha for ordinal-scaled data (Shrout and Fleiss, 1979; Cortina, 1993). Within-subject variability was assessed by Bland-Altman analysis (BA) with calculation of bias (systematic error) and limits of agreement (bias ± 1.96*SD; LoA) (Bland and Altman, 1986; Hopkins, 2000). Relative differences between measurements were assessed by calculating test-retest variability (TRV [%]: (| xi - yi | / 0.5 (xi + yi) * 100), where xi represents the corresponding values of M1 and yi represents those of M2 for subject i (König et al., 2013)). SPSS 23.0 statistical software was used for all tests, and a significance level of $\alpha=0.05$ was assumed.

3.7 Methods – superimposed WB-EMS during treadmill test

3.7.1 Study design

The study was conducted as a randomized cross-over design with a total of four measurement appointments. To avoid WB-EMS induced DOMS as a confounding factor on test performance (Nosaka et al., 2002; Mackey et al., 2008; Vanderthommen et al., 2012; Kemmler et al., 2015), an interval of one week between each of the four measurement appointments (M1-M4) was chosen. During the four measurements, the four test situations CON-W, WB-EMS-W, conventional Nordic walking (CON-NW), WB-EMS-superimposed Nordic walking (WB-EMS-NW)) were conducted in a random order. Randomization was carried out with a randomization software (www.randomizer.org). The measurements took place between November 2018 and April 2019.

At the beginning of the first measurements, the medical examination took place to ensure study eligibility. A physician performed the examination, which included a basic orthopedic and cardiopulmonary system check to clarify inclusion and exclusion criteria. A resting ECG was performed to rule out cardiac symptoms. In case of acute infection, a blood sample was obtained to exclude severe systemic complaints. Participants' anthropometric data (BW and BH) were measured.

Nutritional status has an impact on physical performance and VO_2max (Pendergast et al., 1996; Horvath et al., 2000). Changes in dietary habits related to meal composition could lead to changes in individual performance levels (Burke et al., 2004). Therefore, all participants were asked to record their food intake 24 hours before the first measurement and to repeat their intake in the 24 hours before subsequent measurements. In addition, identical footwear was required for all tests. This served to standardize the measurements as a basis for comparability across the four tests.

3.7.2 Participants

Healthy, non-smoking men aged 35-70 years with a moderate activity profile (less than three hours of physical activity per week, recorded via enquiry) were enrolled in the study. Regular drug use, cardiac arrhythmias (Lown classification ≥ 3), heart failure (NYHA ≥ II), and wearing an implantable cardiac device were exclusion criteria for the study. Finally, eleven healthy men volunteered. Anthropometric data are presented in table 4. After being informed about the background, aims, procedures, and risks of the study, participants signed the written informed consent.

Table 4: Anthropometric data of study 2 participants N represents number of participants. Age, body height, body weight and Body Mass Index (BMI) are presented descriptively as mean ± standard deviation.

N	age [years]	body height [cm]	body weight [kg]	BMI [kg/m^2]
11	52 ± 10	182 ± 6	85.9 ± 7.4	25.9 ± 2.2

3.7.3 Test protocol

Each measurement started by measuring the participant's body weight to calculate rel. VO_2peak. Afterwards, the participant was prepared with the WB-EMS and spirometry device. The initial blood lactate sample was taken, and the participant was also asked for his RPE. Depending on the test situation, the participant was prepared with the Nordic-walking sticks, which were adjusted relative to body height ($height_{sticks}$ = body height x 0.68).

Afterwards, the participant entered the treadmill and the spirometric measurement started with a two-minute rest phase, so that an accurate rest measurement could be carried out as a basis for further measurement. After a four-minutes warm-up at a walking velocity of 5 km/h, a one-minute break took place. A second lactate sample was taken to rule out an increase in lactate due to the short warm-up. Subsequently, the three-minute WB-EMS-adjusting period at a test velocity of 6.5 km/h and the ten-minute walking test at a constant velocity were performed. During the WB-EMS-adjusting phase, the intensities for the specific muscle groups and the whole body was adapted and increased until each participant's maximum tolerated amperage. Directly after finishing the test, the WB-EMS was switched-off and the participant rated his RPE. The post exercise lactate sample was taken and the spirometric measurement was stopped. An overview of the test protocol is given in figure 10.

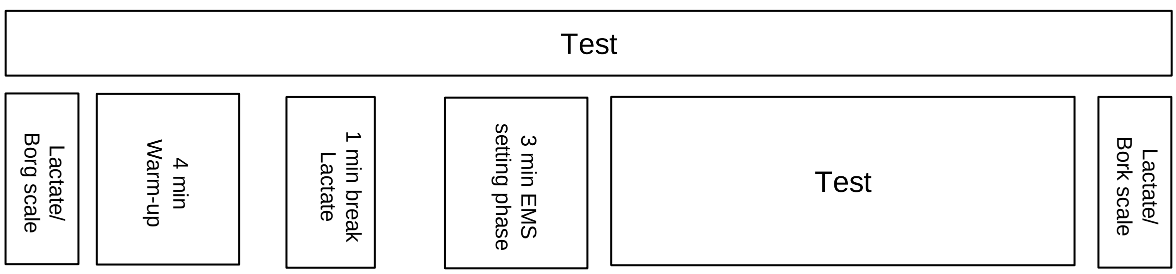

Figure 10: Test protocol for treadmill walking test.

Four outcome measures were of particular interest: mean VO_2, mean oxygen uptake relative to BW (rel.VO_2), RPE and the blood lactate concentration. Mean VO_2 was calculated over the entire measurement period of the 10-minute tests. The mean of rel.VO_2 was calculated by dividing the individual mean of VO_2 by the daily updated BW of the each of corresponding individual participant. As was the case with the 10MISWT in RQ1, the measurement of heart rate as an indicator of load intensity was not reported for this test for the reasons previously stated.

3.7.4 Statistics

All acquired data was transferred into a data matrix (Microsoft® excel 2010). Calculations of mean and SD were used to summarize the data descriptively, unless stated differently. The Kolmogorov–Smirnov test was used to test data for normality. Differences in outcome parameters between WB-EMS-W and CON-W and between WB-EMS-NW to CON-NW were presented relatively. BW differences between the four tests were analyzed using a one-factorial analysis of variances (ANOVA) test for repeated measures. To identify differences between WB-EMS-superimposed and CON-W respectively NW, two-factorial ANOVA with the single factors “WB-EMS application” (WB-EMS) and “gait W or NW” (W/NW) and its combination (WB-EMS∗W/NW) were performed. Paired t-test was used to identify differences in WB-EMS current intensities to the individual WB-EMS current intensities of the participants as well as in the mean current intensity of the eight muscle groups between the two measurement conditions. For all tests, the statistical software SPSS 23.0 was used, and a significance level of $\alpha=0.05$ was assumed.

4 RESULTS

4.1 Results superimposed WB-EMS during 10MISWT

The results of the two sub-questions of the first study are presented below.

4.1.1 Reliability of VO_2 measurements during 10MISWT using WB-EMS

All 13 subjects included in this sub-question successfully completed the measurements and were included in the data analysis. There were no dropouts and no missing data. Table 5 shows the descriptive results (mean ± standard deviation) of the outcome variables VO_2peak, rel.VO_2peak, MWD, RPE and lactate as well as the reliability analysis. Accordingly, M1 (measuring point 1) and M2 (measuring point 2) indicate the different measurement time points. The paired-samples t-test (Wilcoxon signed-rank test) revealed no statistically significant difference between M1 and M2 for the outcome variables. ICC and Cronbach's α ranged from 0.516 to 0.886 and, TRV from 6.20 ± 5.71 to 21.30 ± 15.19%.

Table 5: Results for RQ1a Descriptive statistics (mean ± standard deviation) and results of the reliability analysis for the outcome variables oxygen uptake (VO_2peak), relative oxygen uptake (rel.VO_2peak), maximum walking distance (MWD), rate of perceived exertion (RPE) and lactate measurements. Depending on the type of data, the p-value gives the results of paired t-test[1] or Wilcoxon-signed-rank-test[2]. Intraclass correlation coefficient (ICC) and Cornbach α indicate the reliability between measuring point 1 (M1) and measuring point 2 (M2) depending on the scaling of the variables (interval scaled, ordinarily scaled). Bland-Altman-Analyses (BA) gives values for bias ± limits of agreement (LoA, 1,96*standard deviation).

							BA	
	M1	**M2**	**p-value**	**ICC**	**Cronbachs α**	**TRV**	**Bias**	**LoA**
VO_2peak [l/min]	3.25 ± 0.92	3.36 ± 0.78	0.471[1]	0.886	---	12.54 ± 9.42	-0.12	1.07
rel. VO_2peak [ml/kg/min]	36.86 ± 10.09	38.07 ± 7.66	0.505[1]	0.869	---	12.36 ± 9.29	-1.21	11.95
MWD [m]	798 ± 89	821 ± 91	0.387[2]	---	0.809	8.42 ± 4.22	-23.08	140.58
RPE	14.4 ± 1.4	15.0 ± 1.6	0.099[2]	---	0.859	6.20 ± 5.71	-0.62	2.11
Lactate [mmol/L]	2.73 ± 0.37	2.98 ± 0.75	0.224[1]	0.516	---	21.30 ± 15.19	-0.25	1.32

Figures 11-15 use the BA diagram to make statements about the relationship between M1 and M2. A lot of information can be derived visually from the diagrams. On the x-axis is the mean value between M1 and M2 of each subject, and on the y-axis the corresponding difference between M1 and M2. The solid line represents the systematic error (bias) as the mean of the deviations between M1 and M2 for all subjects. The dashed lines show the limits of agreement. Furthermore, it is possible to check whether the data show a heteroscedastic distribution, whether the deviation of the methods or the dispersion of the deviation depends on the level of the measured values, and whether there are outliers in the data.

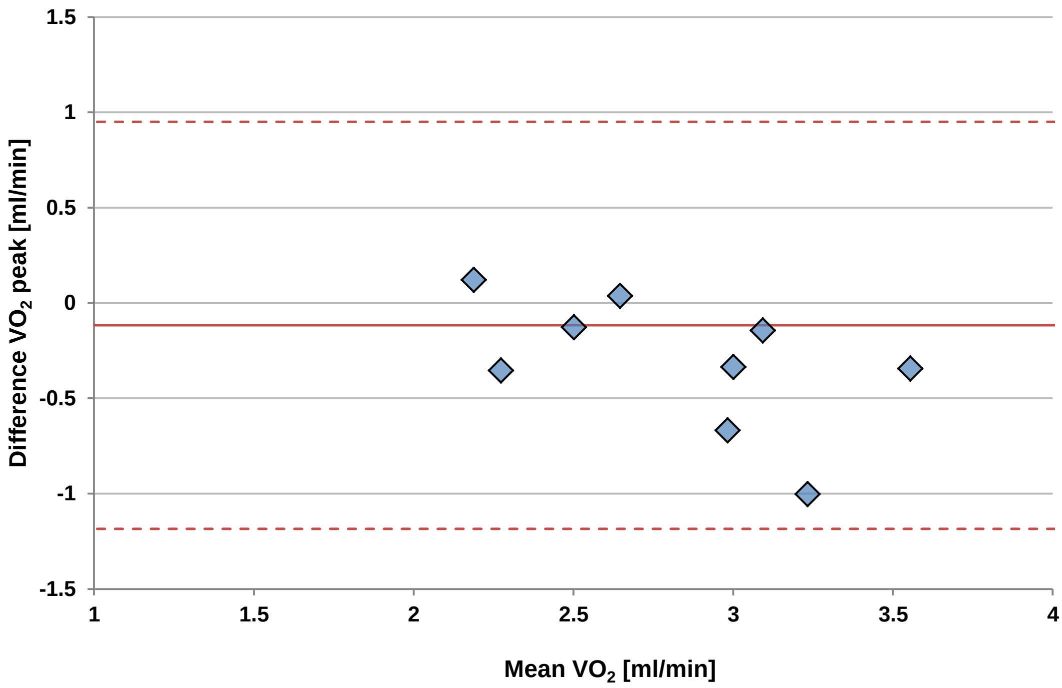

Figure 11: Bland-Altman-plot for VO_2peak measurements. The solid line represents the bias of the VO_2peak measurement, the mean of the differences between the two paired measurements. The upper dashed line represents the upper limits of agreement (bias + 1.96*SD), and the lower dashed line represents the lower limits of agreement (bias - 1.96*SD).

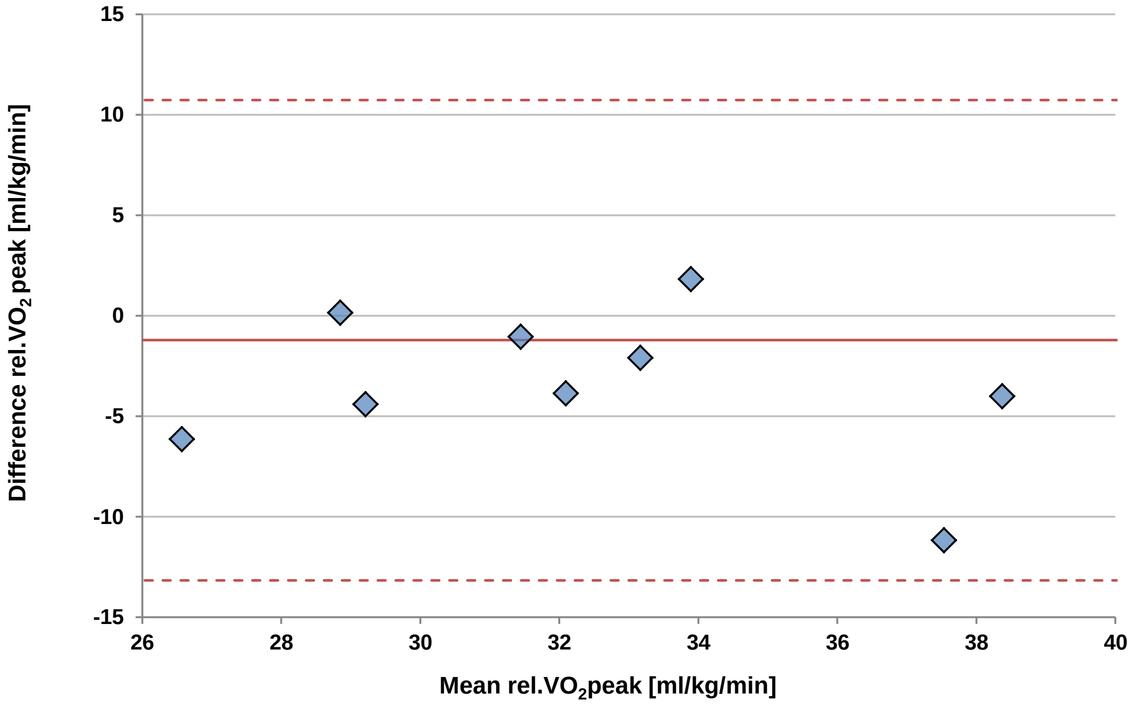

Figure 12: Bland-Altman-plot for rel.VO_2peak measurements. The solid line represents the bias of the rel.VO_2peak measurement, the mean of the differences between the two paired measurements. The upper dashed line represents the upper limits of agreement (bias + 1.96*SD), and the lower dashed line represents the lower limits of agreement (bias - 1.96*SD).

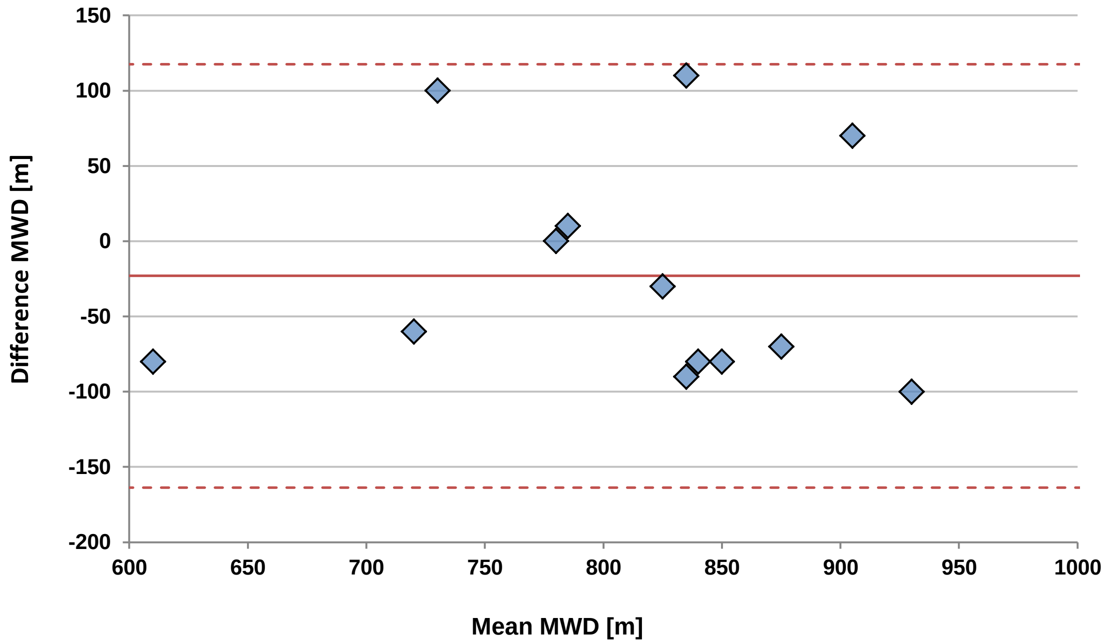

Figure 13: Bland-Altman-plot maximum walking distance (MWD) measurements. The solid line represents the bias of the MWD measurement, the mean of the differences between the two paired measurements. The upper dashed line represents the upper limits of agreement (bias + 1.96*SD), and the lower dashed line represents the lower limits of agreement (bias - 1.96*SD).

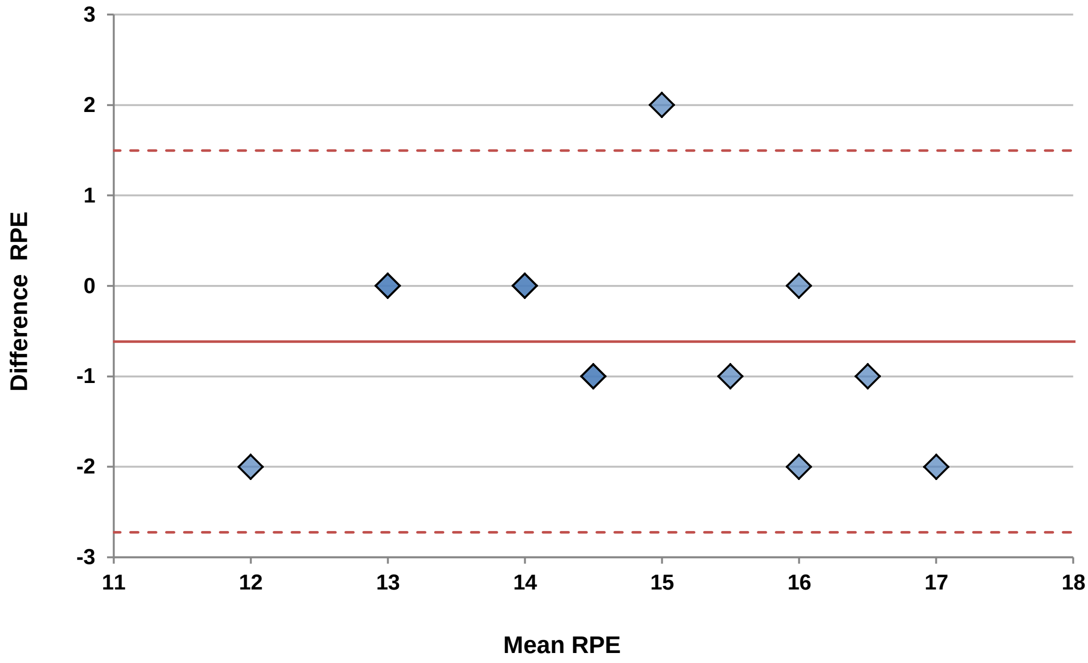

Figure 14: Bland-Altman-plot for measurements of rate of perceived exhaustion (RPE) measurements. The solid line represents the bias of the RPE measurement, the mean of the differences between the two paired measurements. The upper dashed line represents the upper limits of agreement (bias + 1.96*SD), and the lower dashed line represents the lower limits of agreement (bias - 1.96*SD).

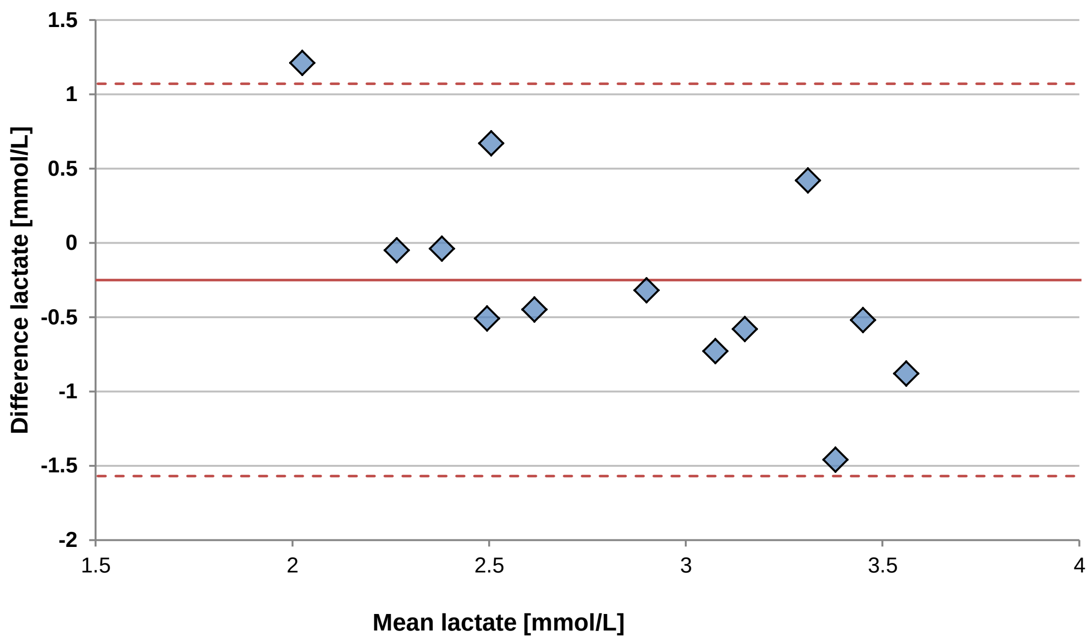

Figure 15: Bland-Altman-plot for measurements of lactate measurements. The solid line represents the bias of the lactate measurement, the mean of the differences between the two paired measurements. The upper dashed line represents the upper limits of agreement (bias + 1.96*SD), and the lower dashed line represents the lower limits of agreement (bias - 1.96*SD).

4.1.2 Differences between superimposed and conventional walking

All 13 subjects included in this sub-question successfully completed the measurements and were included in the data analysis. There were no dropouts and no missing data. Table 6 shows the descriptive results (mean ± standard deviation) of the outcome variables VO_2peak, rel.VO_2peak, MWD, RPE and lactate between the WB-EMS-W and CON-W. The paired-samples t-test and Wilcoxon signed-rank test revealed no statistically significant differences between M1 and M2 for the outcome variables.

Table 7 shows the mean VO_2peak values for all subjects for the WB-EMS-W and CON-W condition for each level of the 10MIWST, as well as the percent deviation between the two walking situations. The percentage deviation ranges from -1.22% to 4.98 %. Table 8 shows the mean rel.VO_2peak values for all subjects for the WB-EMS-W and CON-W for each level of the 10MIWST, as well as the relative difference between the two walking situations. The relative difference ranges from 0.42% to 8.89 %.

Table 6: Results of RQ1b: Descriptive statistics (mean ± standard deviation) for VO_2peak, rel.VO_2peak, maximum walking distance (MWD), rate of perceived exertion (RPE) and lactate for whole-body electrical muscle stimulation superimposed walk (WB-EMS-W) and conventional walk (CON-W). Paired t-test1 and Wilcoxon-signed rank test[2] (p-value) is given to identify statistical significance of differences

	WB-EMS-W	CON-W	p-Value
VO_2peak [l/min]	3.27 ± 0.79	3.15 ± 0.59	0.436[1]
rel.VO_2peak [ml/kg/min]	36.97 ± 8.38	35.81 ± 6.67	0.484[1]
MWD [m]	815 ± 98	805 ± 107	0.623[2]
RPE	14.8 ± 1.3	14.8 ± 1.8	0.680[2]
Lactate [mmol/L]	2.67 ± 0.44	2.81 ± 0.54	0.600[1]

Table 7: Mean VO_2peak-values during 10-meter incremental shuttle walk test. Values are given for whole-body electrical muscle stimulation (WB-EMS-W) superimposed and conventional walking (CON-W) for each walking velocity. Relative difference is given to state percentage difference between two walking conditions.

stage	walking velocity [m/s|	VO_2peak [l/min]		rel Diff. [%]
		WB-EMS-W	CON-W	
1	**0.5**	0.68	0.68	-0.06
2	**0.67**	0.82	0.78	4.98
3	**0.84**	0.92	0.91	0.19
4	**1.01**	1.00	0.98	1.79
5	**1.18**	1.12	1.11	1.66
6	**1.35**	1.29	1.27	1.69
7	**1.52**	1.53	1.49	2.92
8	**1.69**	1.84	1.82	0.84
9	**1.86**	2.19	2.16	1.11
10	**2.03**	2.64	2.59	1.91
11	**2.20**	3.13	3.17	-1.22
12	**2.37**	3.32	3.27	1.42

Figures 16 and 17 present VO_2 (figure 16) and rel.VO_2 (figure 17) as a function of walking speed during the 10MISWT. The light blue line shows VO_2peak and rel.VO_2peak, respectively, for WB-EMS superimposed walking and as a light red line for conventional walking. Both lines show an almost identical course in the graphs and thus again graphically support the results from tables 7 and 8.

Table 8: Mean relVO$_2$peak-values during 10-meter incremental shuttle walk test. Values are given for whole-body electrical muscle stimulation (WB-EMS-W) superimposed and conventional walking (CON-W) for each walking velocity. Relative difference is given to state percentage difference between two walking conditions.

stage	walking velocity [m/s]	rel. VO$_2$peak [ml/kg/min]		rel Diff. [%]
		EMS-W	CON-W	
1	0.50	7.73	7.66	0.99
2	0.67	9.22	8.75	5.35
3	0.84	10.32	10.28	0.42
4	1.01	11.30	11.07	2.05
5	1.18	12.67	12.44	1.84
6	1.35	14.57	14.34	1.60
7	1.52	17.40	16.80	3.58
8	1.69	20.71	20.55	0.79
9	1.86	24.73	24.43	1.24
10	2.03	28.06	27.56	1.83
11	2.20	34.89	32.04	8.89
12	2.37	35.69	34.60	3.16

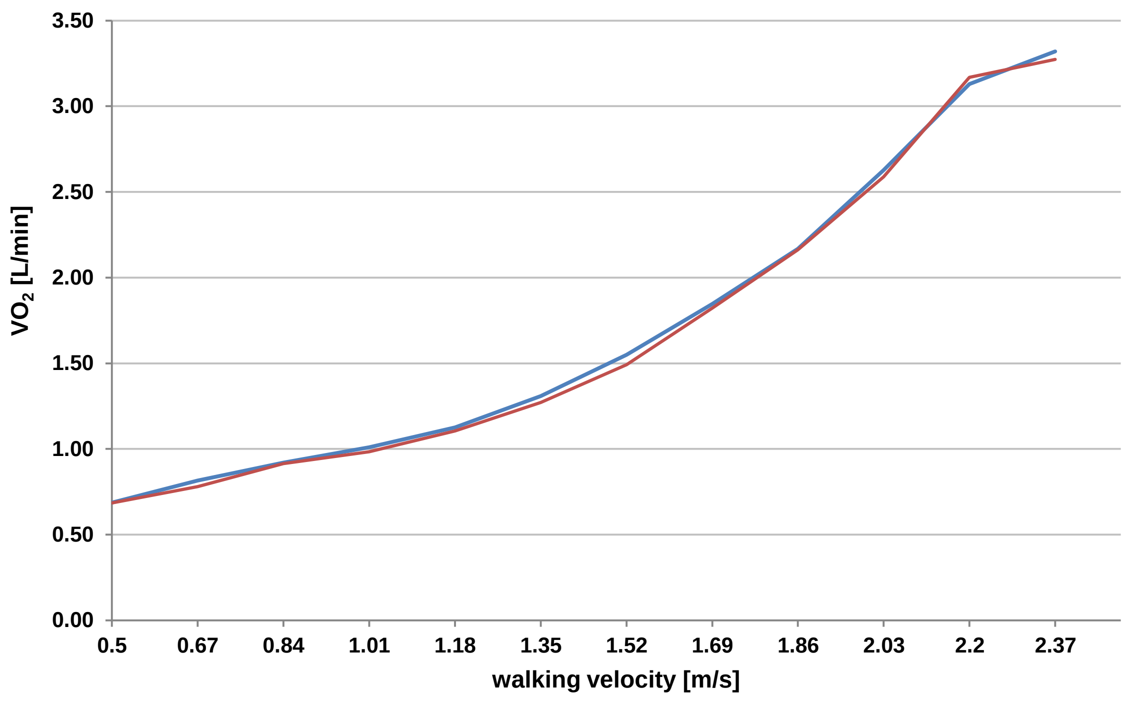

Figure 16: Oxygen uptake (VO$_2$) as a function of walking speed during 10-meter incremental shuttle walk test. WB-EMS superimposed walking (blue line) and conventional walking (red line)

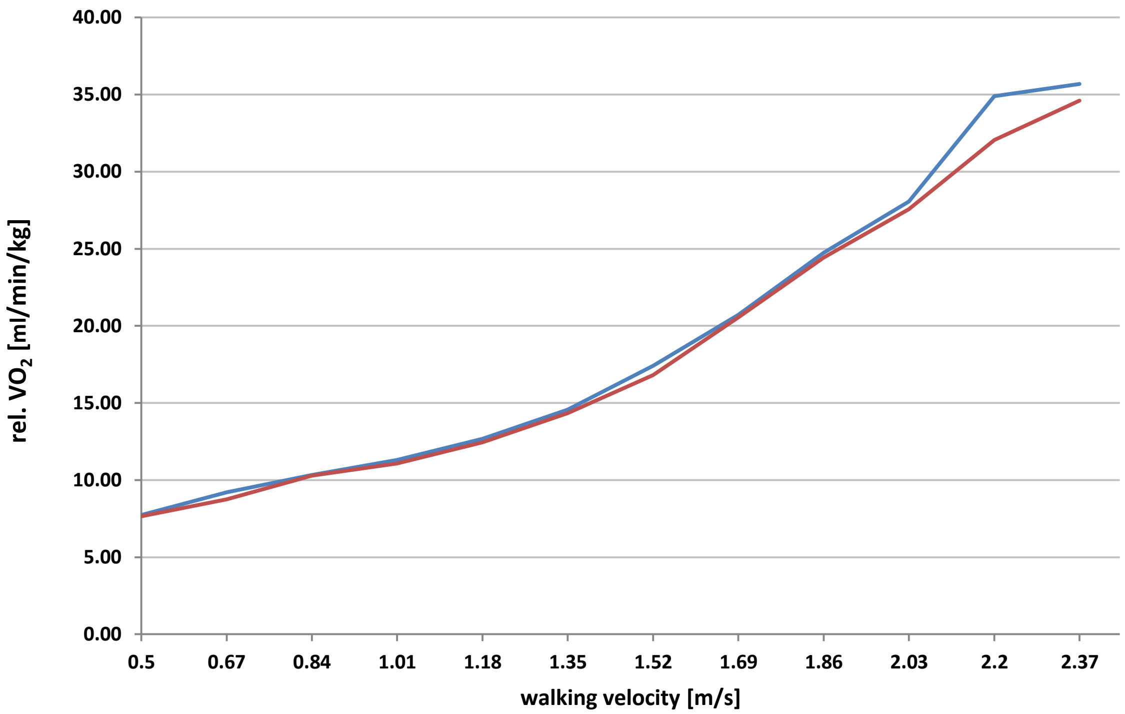

Figure 17: Relative oxygen uptake (rel.VO_2) as a function of walking speed during 10-meter incremental shuttle walk test. WB-EMS superimposed walking (blue line) and conventional walking (red line**)**

4.2 Results – WB-EMS during constant velocity treadmill test

All subjects completed the measurements successfully and were included for data analyses. There were no dropouts and no missing data. The results of body weight, the four outcome measurements, and results of the statistical analyses are presented in table 9. Repeated measures ANOVA test showed a p-value of 0.194 and revealed no statistically significant difference in BW between the four test situations. Results for mean VO_2 ranged from 1.72 ± 0.15 ml/min to 2.15 ± 0.21 ml/min with p-values of 0.006 (WB-EMS), 0.000 (W/NW), and 0.935 (WB-EMS∗W/NW). Mean values for VO_2 occurred in ascending order for CON-W, WB-EMS-W, CON-NW, WB-EMS-NW. Similar results can be seen for rel.VO_2 with mean values from 20.11 ± 1.05 to 25.18 ± 1.83 ml/min/kg and p-values of $p < 0.001$ (WB-EMS), $p < 0.000$ (W/NW), and 0.935 (WB-EMS∗W/NW).

Post-exercise RPE ranged from 11.09 to 12.64 with similar results for CON-W and CON-NW, and for WB-EMS-W and WB-EMS-NW. EMS had an influence on these values, resulting in a statistically significant difference ($p = 0.035$). However, W/NW ($p = 0.370$) and the factor combination EMS∗W/NW ($p = 0.857$) revealed no significant difference. The results for blood lactate concentration are in line with the results for VO_2 and rel.VO_2 with a range of the mean values from 1.14 to 2.39 mmol/L, statistically significant results of the 2-factorial ANOVA for

EMS (p = 0.003) and W/NW (p = 0.003), and a statistically non-significant result for EMS∗W/NW (p = 0.117).

Table 9: Results for the outcome variables body weight, absolute (VO_2) and relative (rel.VO_2) oxygen intake, rate of perceived exhaustion (RPE; Borg-scale) and post exercise blood lactate concentration. Results are given as mean and standard deviation (SD), and p-value for [1] ANOVA for repeated measures, [2] two-factorial ANOVA

			CON-W	WB-EMS-W	CON-W	WB-EMS-NW
Body Weight [kg]		Mean ± SD	85.9 ± 7.4	85.7 ± 6.8	85.0 ± 7.0	85.5 ± 7.2
		p-value[1]	0.194			
VO_2 [l/min]		Mean ± SD	1.72 ± 0.15	1.89 ± 0.14	1.98 ± 0.22	2.15 ± 0.21
		Confidence interval	(1.608–1.841)	(1.770–2.003)	(1.862–2.095)	(2.034–2.267)
		rel. Diff. [%]	9.41		8.69	
	p-value[2] (effect size)	EMS	0.006 (0.736)			
		W/NW	< 0.001 (0.870)			
		EMS*W/NW	0.935			
rel.VO_2 [ml/min/kg]		Mean ± SD	20.11 ± 1.05	22.07 ± 1.17	23.27 ± 1,74	25.18 ± 1.83
		Confidence interval	(19.16–21.06)	(21.12–23.02)	(22.32–2.095)	(24.23–26.13)
		rel. Diff. [%]	9.77		8.20	
	p-value[2] (effect size)	EMS	< 0.001 (0.850)			
		W/NW	< 0.001 (0.937)			
		EMS*W/NW	0.952			
RPE post		Mean ± SD	11.09 ± 1.44	12.27 ± 1.60	11.64 ± 1.43	12.64 ± 1.82
		Confidence interval	(10.08–12.10)	(11.26–13.28)	(10.63–12.65)	(11.63–13.65)
	p-value[2] (effect size)	EMS	0.035 (0.613)			
		W/NW	0.370			
		EMS*W/NW	0.857			
Lactate post [mmol/L]		Mean ± SD	1.14 ± 0.47	1.50 ± 0.46	1.49 ± 0.61	2.39 ± 0.88
		Confidence interval	(0.74–1.54)	(1.10–1.90)	(1.09–1.89)	(1.99-2.79)
	p-value[2] (effect size)	EMS	0.003 (0.771)			
		W/NW	0.003 (0.764)			
		EMS*W/NW	0.177			

CON-W, conventional walking; WB-EMS-W, whole-body electrical muscle stimulation superimposed walking; CON-NW, conventional Nordic-walking; WB-EMS-NW, whole-body electrical muscle stimulation superimposed Nordic-walking; WB-EMS, factor whole-body electrical muscle stimulation; W/NW factor walking vs. Nordic walking.

VO_2 over the duration of the 10-minute test on the treadmill for the four test situations is shown graphically in Figure 18. The values were averaged for 10 second intervals and are shown in the solid line. The dashed line shows the average value over the entire test period for each test situation. Figure 19 shows the same plot for rel. VO_2.

A graphical comparison between the mean values for VO_2 and rel. VO_2 is shown in Figures 20 and 21. This form of presentation is intended to particularly illustrate whether there are differences in a supposed influence of the WB-EMS during walking or Nordic walking.

Similarly, Figure 22 is intended to demonstrate graphically an influence of WB-EMS on a supposed difference in the rate of perceived exertion during walking or Nordic walking compared with the non-EMS conditions.

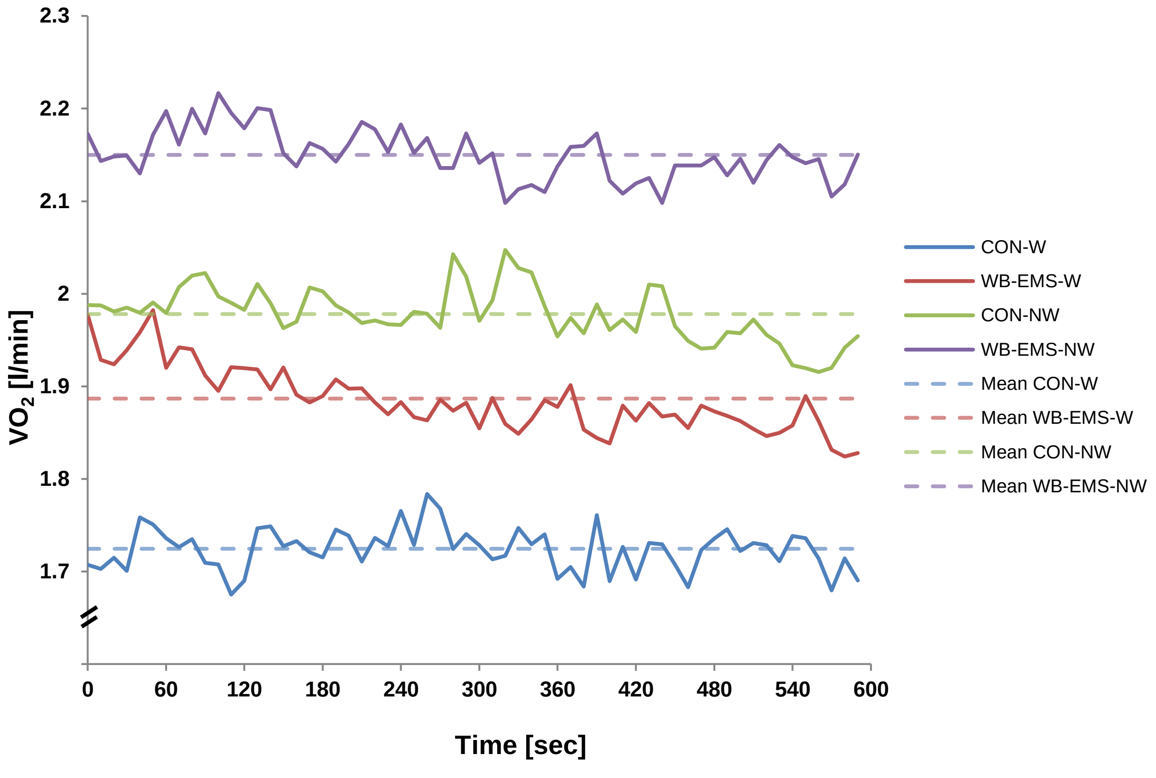

Figure 18: Oxygen uptake (VO_2) during the ten-minute treadmill test for the four different test situations. The solid line represents the mean of the 10-second intervals for all subjects, the dashed line represents the mean for all subjects over the 10-minute measurement period.

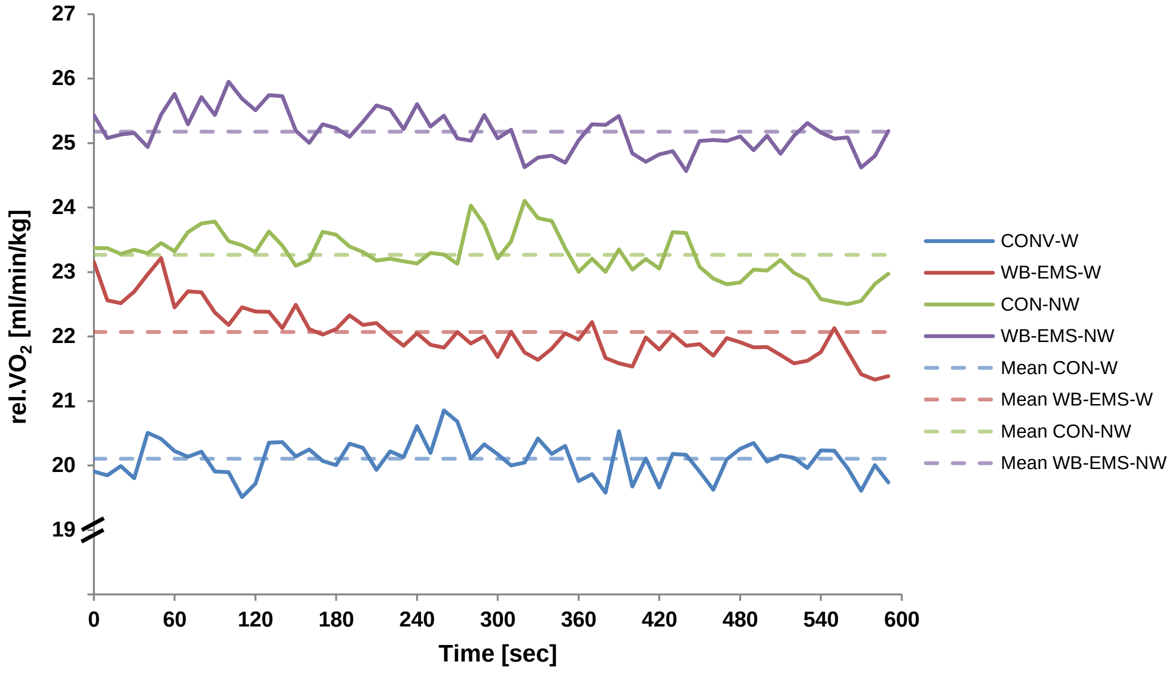

Figure 19: Relative oxygen uptake (rel. VO_2) during the ten-minute treadmill test for the four different test situations. The solid line represents the mean of the 10-second intervals for all subjects, the dashed line represents the mean for all subjects over the 10-minute measurement period.

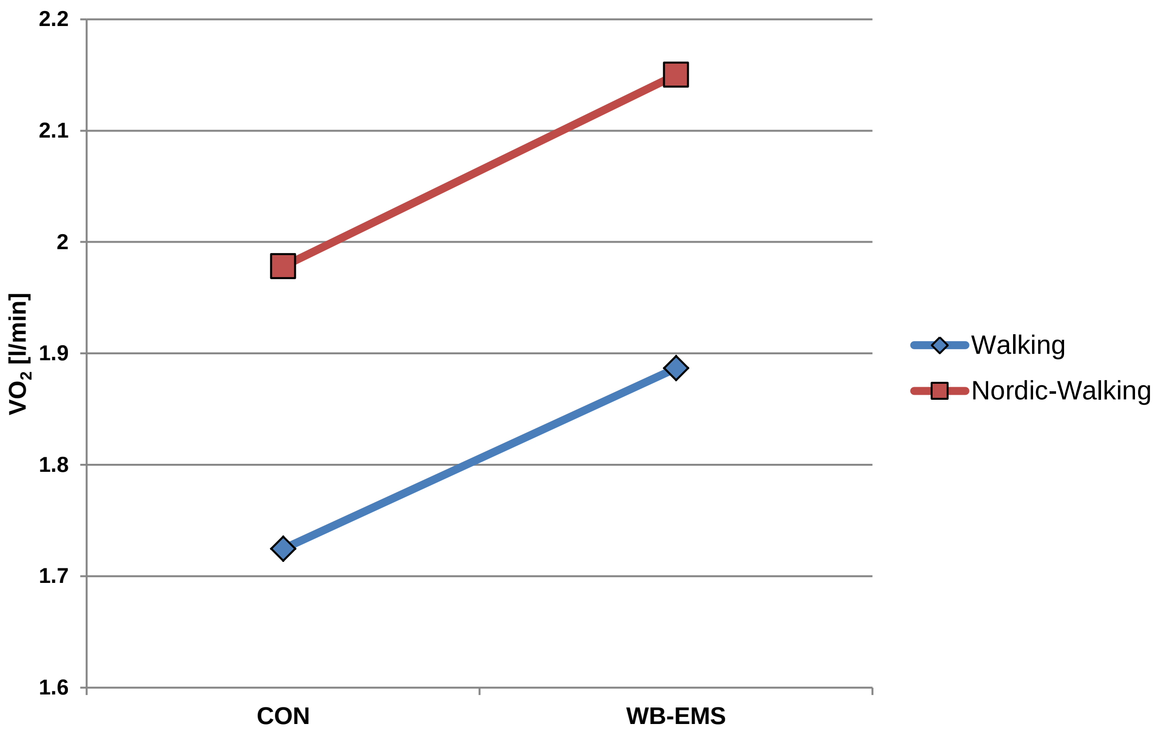

Figure 20: Mean oxygen uptake (VO_2) comparison for the four test situations.Karos indicate the mean values of walking for conventional (CON) and whole-body electrical muscle stimulation (WB-EMS), in both the walking and Nordic walking condition.

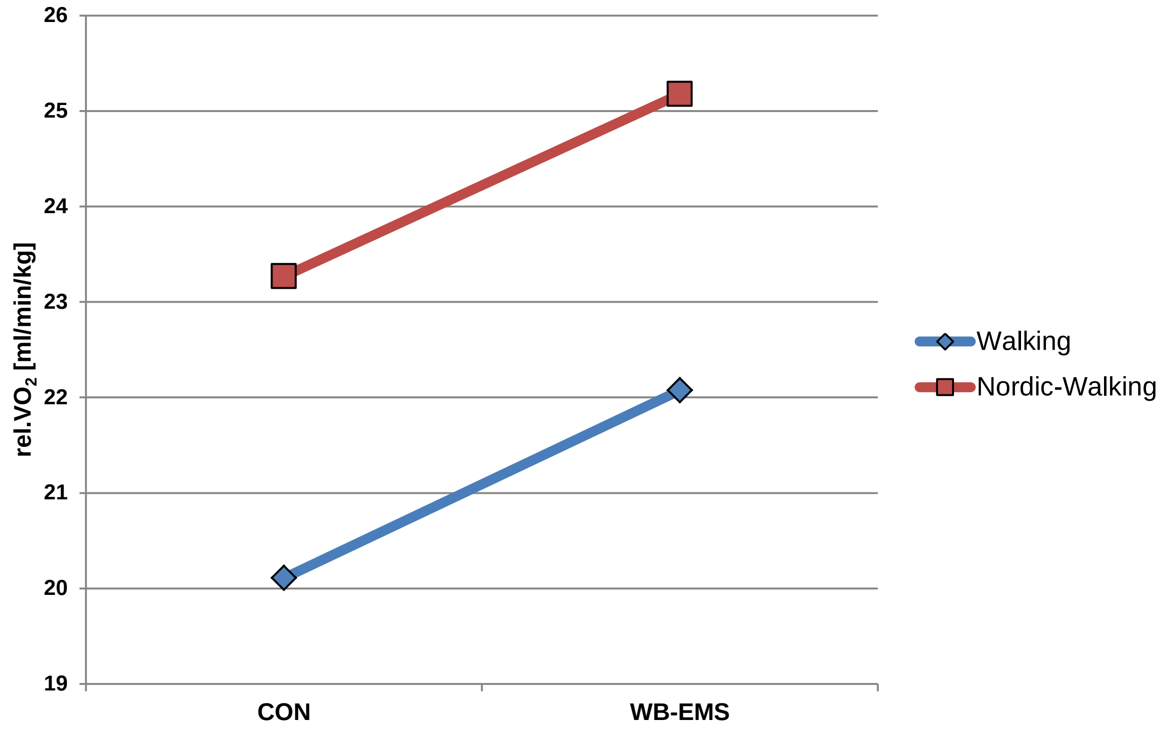

Figure 21: Mean relative oxygen uptake (rel.VO_2) comparison for the four test situations. Karos indicate the mean values of walking for conventional (CON) and whole-body electrical muscle stimulation (WB-EMS) superimposed walking, squares for CON and WB-EMS Nordic walking, respectively.

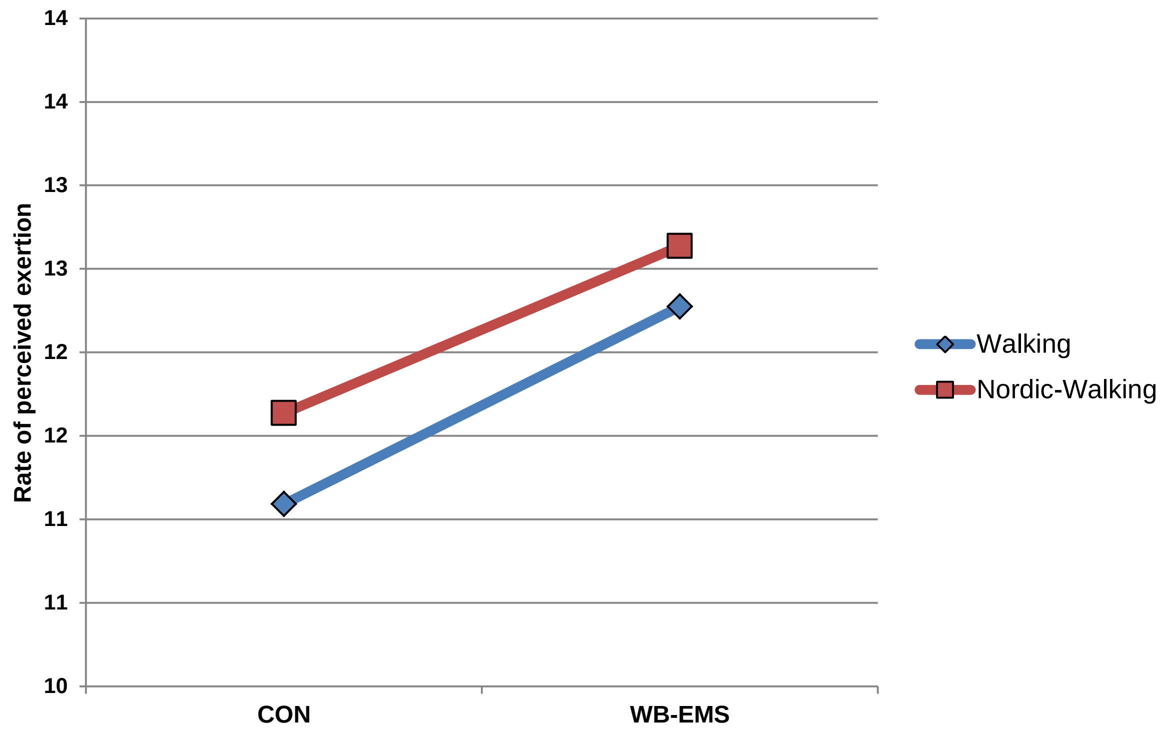

Figure 22: Mean rate of perceived exertion comparison for the four test situations. Karos indicate the mean values of walking for conventional (CON-W) and whole-body electrical muscle stimulation (WB-EMS) superimposed walking, squares for CON and WB-EMS Nordic walking, respectively.

Table 10 shows the mean lactate values at the beginning (pre1) of the test and after the five-minute warm-up (pre2) for the four test situations as well as the results of the respective t-test for paired samples. The lactate values range from 0.89 ± 0.36 mmol/ml to 1.32 ± 0.67 mol/l, with the lactate values for pre1 being higher than for pre2 for both CON-W and WB-EMS-W. This difference is statistically significant at p=0.007 for CON-W and p=0.039 for WB-EMS-W. For both CON-NW and WB-EMS-NW, there is no statistically significant difference in lactate values between pre1 and pre2. Figure 23 compares the results of the lactate measurements graphically between the four test situations at the three measurement timepoints.

Table 10: Results of pre-test lactate measurements. Values Blood lactate concentration pre1 (before warm-up) and pre2 (after warm-up) for the four test conditions. Results are given as mean ± standard deviation. Paired t-test was used to identify statistical differences.

	CON-W	WB-EMS-W	CON-NW	WB-EMS-NW
pre1 [mmol/ml	1.32 ± 0.76	1.04 ± 0.36	1.15 ± 0.41	1.25 ± 0.42
pre2 [mmol/ml	0.97 ± 0.45	0.89 ± 0.36	1.20 ± 0.41	1.27 ± 0.71
p-value	0.007	0.039	0.469	0.939

CON-W, conventional walking; WB-EMS-W, whole-body electrical muscle stimulation superimposed walking; CON-NW, conventional Nordic-walking; WB-EMS-NW, whole-body electrical muscle stimulation superimposed Nordic-walking

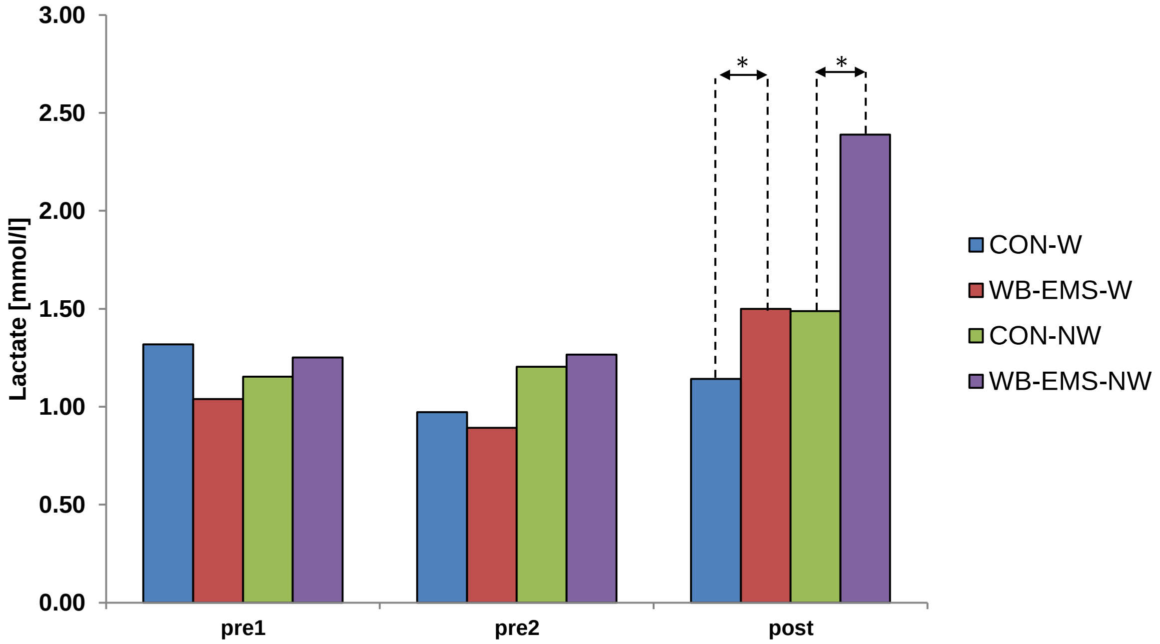

Figure 23: Bar chart for the lactate measurements. The results of the lactate measurements for the four test situations are grouped for the three measurement time points (before the start of the measurement (pre1), after the end of the warm-up (pre2), after the end of the test (post)). The four test situations with the corresponding colors can be found in the legend. * indicates a statically significant difference (p < 0.05)

A graphical comparison between the mean values for blood lactate concentration is shown in figure 24. This form of presentation is intended to particularly illustrate whether there are differences in a supposed influence of the WB-EMS during walking or Nordic walking.

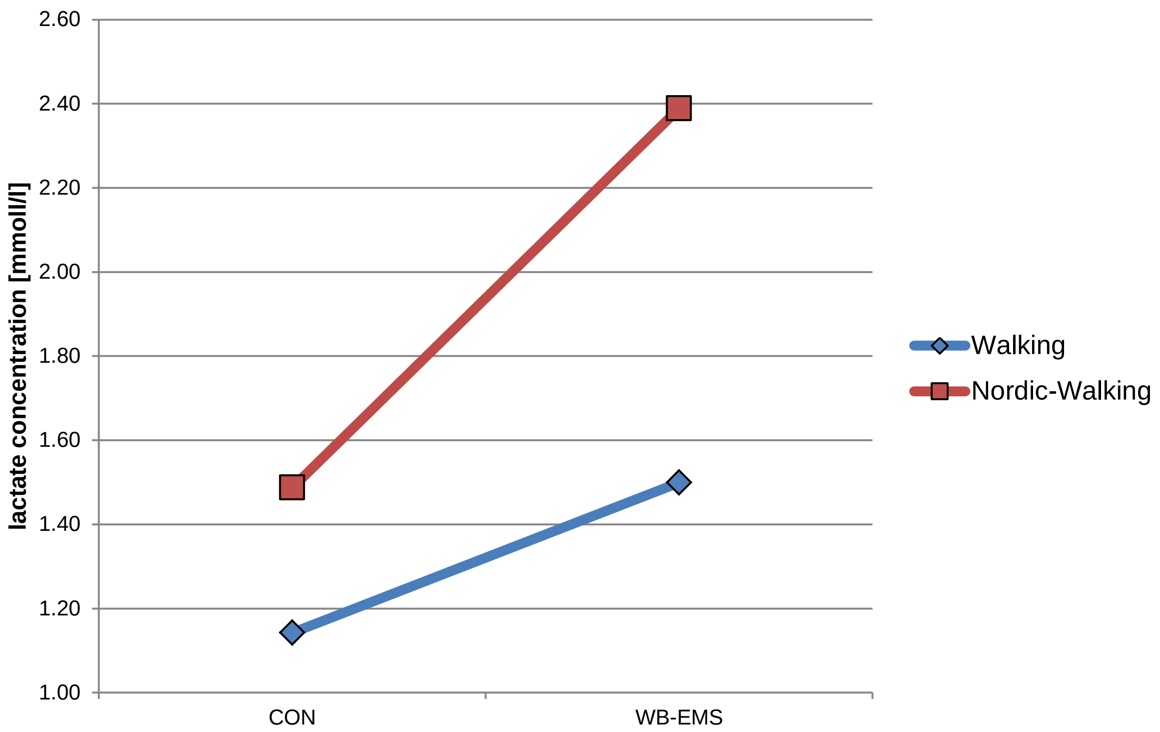

Figure 24: Mean post exercise blood lactate concentration comparison for the four test situations. Karos indicate the mean values of walking for conventional (CON-W) and whole-body electrical muscle stimulation (WB-EMS) superimposed walking. Squares indicates mean values for CON and WB-EMS Nordic walking, respectively.

Results of WB-EMS current intensity analysis are given in table 11. The individual WB-EMS current intensity of participants ranged dimensionless from 19.9 to 29.8 with a mean ± SD of 24.7 ± 3.4 for walking, and from 19.5 to 32.8 with a mean ± SD of 27.7 ± 3.8 for Nordic walking. The t-test revealed no significant difference between these values ($p = 0.100$). The muscle group WB-EMS current intensity related to the whole subject group ranged from 15.6 to 43.7 with a mean ± SD of 24.7 ± 8.4 for walking and from 15.6 to 46.6 with a mean ± SD of 25.7 ± 3.8 for Nordic walking. The t-test revealed no significant difference between these values ($p = 0.054$). The WB-EMS current intensity of the upper arms, which are the only muscle group in the WB-EMS-NW to experience significantly more involvement in the overall movement than in the WB-EMS-W according to the preliminary considerations, ranged within the subject group from 15 to 22 with a mean ± SD of 18.5 ± 2.4 for WB-EMS-W. For WB-EMS-NW it ranged from 17 to 26 with a mean ± SB of 20.5 ± 2.9. The t-test revealed a significant difference between these values ($p = 0.002$).

Table 11: Whole-body electrical muscle stimulation (WB-EMS) intensity. Values are given without dimension by the system. Panel A: Mean participants (represented by ID) individual current intensity for both conditions, walking (W) and Nordic walking (NW) as well as conditions mean and standard deviation (SD). Paired t-test revealed no statistical difference between the two conditions (p=0.100). Panel B: Mean ± SD of current intensity for the eight muscles/muscle groups of all participants for both conditions, W and NW. Paired t-test revealed no statistical difference between the two conditions (p=0.054)

A

ID	**W**	**NW**
01	22.4	20.6
02	22.6	29.0
03	21.5	23.9
04	29.8	29.6
05	26.4	25.5
06	27.3	27.3
07	29.8	32.8
08	19.9	19.5
09	20.8	25.3
10	24.8	27.0
11	22.4	22.4
mean ± SD	24.7 ± 3.4	27.7 ± 3.8

B

	W	**NW**
Chest	15.6 ± 4.1	15.6 ± 3.0
Upper arm	18.5 ± 2.4	20.5 ± 2.9
Abdominal	22.2 ± 4.9	23.5 ± 5.9
Upper legs	43.7 ± 5.3	46.6 ± 6.5
Shoulder	19.5 ± 5.3	21.8 ± 5.6
Upper back	28.7 ± 6.5	28.5 ± 6.2
Lower back	20.2 ± 7.7	20.7 ± 6.4
Gluteal region	28.9 ± 5.2	28.4 ± 5.4
mean ± SD	24.7 ± 8.4	25.7 ± 8.8

5 DISCUSSION

The aim of this research project was to investigate the effect of superimposed WB-EMS on walking and Nordic walking in terms of training intensity. The research question was whether WB-EMS could intensify conventional walking and Nordic walking. Previous studies on superimposed WB-EMS have mainly focused on static and/or dynamic fitness training with and without additional equipment in various age groups. However, these results were based on an exercise situation that does not occur in the everyday life of the selected patient group. Therefore, in the present research project, a test situation was proposed aiming to apply WB-EMS during everyday movement or physical activity of the patient group to examine the added value for the users.

To answer the formulated research questions, two separate empirical studies were conducted. Three main findings can be deduced from the results. Firstly, measurements of the intensity of stress using VO_2 during WB-EMS superimposed walking can be reliably performed. Secondly, for an effective current intensity of WB-EMS, it must be adjusted during the movement to the intensity that can be maximally tolerated by the participants. Thirdly, WB-EMS during walking and Nordic walking on a treadmill with a constant walking speed leads to a statistically significant increase in training intensity. However, the clinical benefit needs to be discussed and requires further investigation.

The results of the two studies are discussed in detail below.

5.1 Discussion - superimposed WB-EMS during 10MISWT

In the present project, the superimposition of physical activity with WB-EMS was used for the first-time during walking. Therefore, the first part of the study investigated the question of whether measurements of training intensity can be reliably performed during WB-EMS superimposed walking (RQ1a). For this purpose, the 10MISWT was selected as a well-researched and valid test in different patient groups as well as in healthy subjects during conventional walking (Singh et al., 1992; Green et al., 2001; Buckley et al., 2013; Sexton et al., 2014; Crowe et al., 2015). The outcome variables VO_2peak and rel.VO_2peak, MWD, RPE and lactate measurements have already shown to be reliable in different patient groups. For the assessment of training intensity, measurements of relative VO_2max or rel. VO_2peak derived from VO_2max/VO_2peak measurements are considered the gold standard (Balducci et al., 2014). In the second part of the study, to answer the second sub-question (RQ1b), differences in exercise intensity between WB-EMS-W and CON-W during the 10MISWT were investigated using the outcome variables already mentioned.

5.1.1 Reliability of VO_2 measurements during 10MISWT using WB-EMS

The main result of the first part of the study regarding sub question RQ1a was good reliability for the measurements of VO_2peak, rel. VO_2peak, MWD, as well as RPE used to assess exercise intensity during the 10MISWT with WB-EMS superimposition. The hypothesis according to the reliable measurement of exercise intensity based on VO2 during WB-EMS-superimposed walking in the field test is accepted. Earlier studies have previously investigated the reliability of VO_2peak measurements during the 10MISWT in different populations.

Jürgensen et al. investigated the test-retest reliability of maximal oxygen uptake in 15 obese women aged 18-46 years whilst performing the 10MISWT (Jürgensen et al., 2015). They found excellent reliability for the VO_2peak measurements with an ICC of 0.900 and good reliability for the rel. VO_2peak measurements with an ICC of 0.890. The results for the rel. VO_2peak measurements are thus comparable to the present results of an ICC of 0.869, while the ICC for the VO_2peak is higher compared to our investigated results. However, when comparing the findings, it should be noted that the subjects in the study only achieved a MWD of 463 ± 92 m and 467 ± 99 m, respectively (Jürgensen et al., 2015). These values are significantly lower than those achieved by participants in the present study. According to feedback from the participants, it can be assumed that the 10MISWT seems to be technically rather than physiologically limited in a group of healthy, moderately active men. This fact underlines the accuracy of the present results compared to results from a group of subjects who reached maximal workload during the 10MISWT and did not avoid technical limitations.

The measurement of oxygen uptake is subject to natural biological day-to-day variability. Bagger et al. (2003) reported the biological variability of VO_2max and VO_2submax measurements to be ±10.7% and ±14.3%, respectively (Bagger et al., 2003). This means that, for example, VO_2max measurements in the context of maximum exercise can fluctuate by this amount for one subject on two separate measurement days despite the achievement of maximum exercise capacity, i.e. values can be higher or lower between sessions. For the present group of test persons, it was possible to determine a coefficient of variation of ±12.06% for the VO_2peak measurements and a coefficient of variation of ±11.46% for the rel.VO_2peak measurements. The TRV for VO_2peak (12.54%) and rel.VO_2peak (12.36%) is also within the range of the biological variability stated by Bagger et al.. Considering that the 10MISWT appears to be technically limited in the group of healthy, moderately active men, the results for VO_2peak and rel.VO_2peak evaluated in the present study are consistent with the biological day-to-day variability of both parameters, and support the accuracy of measuring exercise intensity during WB-EMS-W during the 10MISWT with the Cortex MetaMax3B.

Another performance measure in the present study was the MWD. Jürgensen et al. found excellent reliability (ICC=0.926) for the MWD (Jürgensen et al., 2015), while results revealed a good reliability (Cronbach's α=0.806) in present study. Pulz et al. investigated the reliability of MWD measurements in a cohort of heart failure patients (Pulz et al., 2008). Bland-Altman analysis showed a deviation ± limits of agreement of 8 ± 45 m. With a deviation of -23 m and limits of agreement of ± 140 m, the systematic and random errors in the present study are higher. The results of Peixoto-Souza et al. showed excellent reliability for the MWD (ICC=0.91) in a cohort of women with morbid obesity (Peixoto-Souza et al., 2015).

Looking at the studies from Jürgensen et al. (2011), Pulz et al. and Peixoto-Souza et al. an important difference should be noted. Compared to the present study, the studies were conducted on patient groups. The 10MISWT was originally developed for COPD patients and has recently been used in older and overweight people. Compared to COPD patients or overweight people, there was no physiological limitation during the 10MISWT in healthy men in the present study. This methodological limitation has also been reported in previous studies. Jürgensen et al. evaluated a reference equation for predicting MWD based on demographic and anthropometric parameters in a group of older Brazilian adults (Jürgensen et al., 2011). In contrast to the definition of the 10MISWT as a maximal exercise test (Green et al., 2001), participants achieved only 78% of their predicted maximal heart rate. This is consistent with the present study, in which participants reported being technically unable to run faster and had no physiological limitations that led them to drop out of the test. It is therefore not possible to rule out a learning effect of the participants in terms of running technique leading to better results on the MWD in the second test. This learning effect, represented by the bias of -23 m (MWD_{M1} - MWD_{M2}), is consistent with previously reported results (Singh et al., 1992; McKeough et al., 2011; Probst et al., 2012). Although, the differences in MWD between the first and second test were not statistically significant, an influence on VO_2peak or rel.VO_2peak and thus on the results of the reliability analysis could not be excluded. This could possibly explain the lower ICC values and higher systematic and random errors displayed in our reliability analyses. Dourado et al. conducted a reliability analysis for 10MISWT with a healthy population and found an excellent ICC of 0.973 for MWD (Dourado et al., 2013). However, compared to the present study, participants had to perform the 10MISWT three times within one day.

The rate of perceived exertion using the Borg scale has been shown to be a valid and cost-effective tool for monitoring exercise intensity in different groups of subjects (Scherr et al., 2012). Statistical analysis showed good reliability of RPE with a Cronbach's α of 0.859. However, Wallman et al. determined excellent reliability (ICC=0.970) for RPE, but on a different test (Wallman et al., 2003). They determined the reliability of the Aerobic Power Index, a submaximal fitness test, in a non-sedentary population. Even though the Aerobic Power Index is a submaximal test, the exercise intensity could still be higher compared to the exercise intensity in healthy, moderately active men during the 10MISWT. This could explain the higher reliability for RPE, as already discussed for VO_2peak and rel.VO_2peak, respectively. TRV for MWD and RPE range from 5.12 to 8.42% and are lower than the CV and TRV values for VO_2peak and rel. VO_2peak. However, no comparative values were found in the literature.

In contrast to the good reliability for VO_2peak, rel. VO_2peak, MWD and RPE measurements, the blood lactate measurement does not seem to be reliable for the assessment of training intensity in WB-EMS walking during the 10MISWT. With a reported Cronbach's α of 0.512, only moderate reliability of blood lactate measurements was found. However, with a CV of 16.47% and a TRV of 21.30%, our results are consistent with the measurements of blood lactate concentration after submaximal exercise in the study by Bagger et al. that investigated biological variability in exercise-related variables (Bagger et al., 2003).

The present study has limitations that should be considered. Compared to previous studies of VO_2peak/rel.VO_2peak reliability during the 10MISWT (Jürgensen et al., 2015) or studies to determine reference values for the 10MISWT (Probst et al., 2012), we did not perform spirometry to test lung function during the medical examination and enrolment of participants in the study. Therefore, impaired lung function of study participants cannot be excluded, and could have had an impact on the outcome variables. Although, none of the participants reported lung impairment or discomfort during study enrolment.

Another limitation of the present study is the fact that not all participants were familiar with WB-EMS. Kemmler et al. compared the influence of WB-EMS on body strength and fitness compared to high-intensity resistance training in a group of middle-aged men over a training period of 16 weeks (Kemmler et al., 2016b). After a conditioning phase of five WB-EMS sessions, the current intensity was individually adjusted in consultation with the participants. Compared to this long-term WB-EMS application, the present study participants used the WB-EMS a total of three times. First during the WB-EMS familiarization session, which served to adjust current intensity, and then twice during the two 10MISWT. Long-term habituation of participants to the WB-EMS may have had an impact on outcome variables and reliability assessment. Also, introducing subjects to the 10MISWT over the long term through repeated practice of the test could possibly reduce the systematic difference in MWD between M1 and M2 by reducing the learning effect of the participants.

As a conclusion of the study, it can be stated that measurements of training intensity via VO_2preak or rel.VO_2peak during WB-EMS-W can be reliably performed, using the example of the 10MISWT in a cohort of healthy, moderately active men aged between 35 and 70 years. The MWD and RPE could be used as a further performance parameter of the 10MISWT, as these could be reliably evaluated and are therefore suitable. However, the results of the blood lactate measurements must be viewed critically and are not appropriate for determining the load intensity during WB-EMS-W during the 10MISWT. As a consequence of the present study, the measurement of exercise intensity by measuring VO_2peak and rel.VO_2peak can be used in further investigations of WB-EMS assisted walking as a new approach for intensifying an endurance exercise in a group of healthy men aged 35-70 years.

5.1.2 Differences between superimposed and conventional walking

The results regarding RQ1b show that there is no difference in exercise intensity between EMS-W and the CON-W in the group of healthy male subjects aged 35-70 years. There is no statistically significant difference in any of the four outcome variables (VO_2peak, rel. VO_2peak, MWD, RPE). The hypothesis according to which WB-EMS-superimposed walking leads to a higher training intensity compared to conventional walking is rejected. The agreements for VO_2peak and rel.VO_2peak between EMS-W and CON-W are not only shown in the maximum achieved values, but also in the values of the individual levels of the 10MISWT. The relative differences range from -1.22% to 4.98% for VO_2peak and from 0.42% to 5.35% for rel. VO_2peak. Both ranges are well within the expected biological variability for VO_2 measurements of ±12% mentioned in the previous section. Blood lactate as an outcome variable is not relevant in this approach due to its low reliability.

In this study, the current intensity of the WB-EMS was adjusted in a separate phase before the start of the actual 10MISWT to the maximum tolerable intensity for the participants. One of the reasons for this was that two influencing variables could not be changed during the 10MISWT. This would have made it difficult to clearly determine whether the increase in VO_2 resulted from the increasing load due to the increased walking speed, or from the increase in WB-EMS current intensity.

After the test, participants reported that they felt the WB-EMS increasingly less during the 10MISWT. While they perceived the WB-EMS at the maximum tolerable threshold before the start of the test, the intensity perception decreased with the onset of voluntary muscle contraction through walking. In most cases the WB-EMS was no longer noticeable at all at the end of the test and was only registered again when the test was stopped. Based on this subjective perception by the participants, it is assumed that the perception of the WB-EMS current intensity and thus also the individual maximum tolerable intensity depends on the degree of voluntary movement of the test persons. The higher the degree of voluntary movement of the test persons, the higher the individual maximum tolerable intensity of the WB-EMS.

Other studies took a different approach to adjusting WB-EMS current intensity. Kemmler et al. (2012) adjusted WB-EMS current intensity in 19 male recreational athletes at the start of 20 minutes of dynamic commercial WB-EMS training and then adjusted it after 2, 8 and 13 minutes (Kemmler et al., 2012). Perez-De-Arrilucea-Le-Floc'h et al. (2022) followed this approach in their study of EE and the respiratory exchange ratio in the supine position and during uphill walking in a group of 10 healthy and recreationally active men (18-25 years old) (Perez-De-Arrilucea-Le-Floc’h et al., 2022). They adjusted the WB-EMS current intensity to the participant's maximum tolerance during the first 2 minutes of the 6-minute application time. As already described, such a form of WB-EMS adjustment was not possible in the present scientific approach.

The conclusion from this result is that although the 10MISWT is an established and well-studied walking test in different patient groups as well as in a healthy population, it is unsuitable for investigating differences in exercise intensities using the superimposed WB-EMS. This is due to the different perception of WB-EMS current intensity at rest and during voluntary exercise. For the goals of this project, it was therefore necessary to conduct a treadmill test at constant walking speed. This allowed for adjustment of the individual maximum tolerable WB-EMS current intensity of the participants after a warm-up at the walking speed ultimately applied during testing. Thus, higher and more impactful WB-EMS current strengths could be achieved for the research question and the influence of the superimposed WB-EMS on the load intensity during walking could be investigated more adequately. The test situation was therefore adapted for the second part of the project.

5.2 Discussion - WB-EMS during constant velocity treadmill test

The major finding of the second part of the project regarding RQ2 was that superimposed WB-EMS affects metabolic demand during walking and Nordic walking significantly. VO_2 uptake was higher in both WB-EMS-W and WB-EMS-NW when compared with conventional exercise. In addition, WB-EMS leads to higher blood lactate concentrations when applied to exercise. The hypothesis according to which the superposition of WB-EMS leads to an increase in exercise intensity by VO_2 measurements during walking and Nordic walking during a treadmill test with constant walking speed is accepted. However, clinical relevance for VO_2 uptake and blood lactate concentration remains debatable. The second finding of the study was that WB-EMS-superimposed exercises are perceived as more strenuous compared with conventional exercise.

At the time the measurements were carried out, this project represented one of the first investigations of a possible intensification of low-intensity exercises through superimposed WB-EMS. However, a wide range of studies already showed that WB-EMS has the potential to increase the metabolic demands of different types of exercise, whether limited to a single muscle or related to the whole body (Buuren et al., 2015; Mathes et al., 2017). Measuring oxygen uptake relative to body weight during exercise represents the gold standard for measurements of exercise intensity. However, different outcome measures can be useful in defining metabolic demands and metabolic stress to identify the intensification potential of WB-EMS.

As a prerequisite for evaluating the relative oxygen uptake, body weight difference of the participants between the four measurement appointments were analyzed. ANOVA for repeated measures resulted in a p-value of 0.94 being synonymous with a statistically non-significant body weight differences between the four measurement appointments. Therefore, it can be concluded that reported differences in rel.VO_2 can be explained by differences in VO_2 and not by variations in body weight. Amaro-Gahete et al. (2018) investigated performance-related parameters in runners and concluded that six weeks of WB-EMS training, coupled with a reduction in running endurance training, improved rel.VO_2max (Amaro-Gahete et al., 2018). While VO_2max did not improve after the intervention period, body weight reduction during that time was statistically significant. Therefore, the conclusion of a rel.VO_2max improvement through WB-EMS training implementation compared with the control group training conventionally with non-significant differences in VO_2 and body weight is worth challenging. Based on the BW data in the present study, the effect of WB-EMS-W/NW on rel.VO_2 is proven and not a result of different BW.

Regarding WB-EMS-superimposed cycling, several studies support the present findings regarding exercise intensification through WB-EMS. Wahl et al. (2012) investigated the physiological responses and perceived exertion during an incremental cycle ergometer test. Compared to the present study, EMS was just applied to the thigh and calf muscles (Wahl et al., 2012). However, they found higher metabolic stress at 75% of peak power, respectively, 100% of peak power output when superimposed EMS was applied. In a further study, they found similar results during a 60 min constant workload test on the cycle ergometer (Wahl et al., 2014). Mathes et al. (2017) investigated the chronic effects of superimposed WB-EMS during ergometer cycling. Participants in the WB-EMS superimposed cycling group performed the training sessions during a four-week training intervention, which resulted in a significantly higher VO_2peak (7% higher) compared with the cycling group (Mathes et al., 2017). Even though participants performed more demanding exercise for the metabolic and respiratory system with applied WB-EMS, a 4-week training intervention of WB-EMS superimposed cycling exercise did not result in superior improvements of endurance capacity than cycling alone did. This outcome is in line with the current results that an increase of 9.41% (VO_2) and 9.77% (rel.VO_2) for WB-EMS-W, and 8.69% (VO_2) and 8.2% (rel.VO_2) for WB-EMS-NW is within the range of biological day-to-day variability of ±12% for VO_2 measurements (Bagger et al., 2003). Therefore, regardless of the fact that the obtained differences are statistically significant (WB-EMS as factor of 2-factorial ANOVA), the intensification of CON-W and CON-NW through WB-EMS seems to be clinically irrelevant for this population. However, the results for combined factor analyses (WB-EMS∗W/NW) of the 2-factorial ANOVA test indicate that WB-EMS does not have a different impact on VO_2 between WB-EMS-W/NW. This result contradicts our hypothesis that due to the higher muscle recruitment in various body segments during Nordic Walking, superimposition of WB-EMS has a higher impact on Nordic walking compared with walking.

This conclusion is also confirmed by the results of the WB-EMS current intensity analysis. Even though the analysis of WB-EMS current intensity for the upper arms demonstrated a statistically significant higher current in this muscle group, concerning all eight muscle groups, no statistically significant difference in WB-EMS current intensity between WB-EMS-W and WB-EMS-NW could be observed. Neither the individual mean across all participants for all eight muscle groups ($p = 0.100$), nor the mean of muscle group-specific averages across all participants ($p = 0.054$), showed statistically significant differences. Hence, it was evident that the additional use of the arms during Nordic Walking, incorporated into the overall movement, did not lead to a heightened influence of WB-EMS through the stimulation of an additional muscle group. Various studies recommend WB-EMS familiarization for a higher tolerance of the WB-EMS current intensity by the participants, and correspondingly a higher impact of the WB-EMS (Kemmler et al., 2016b, 2018; Teschler and Mooren, 2019). Since none of the study participants had any prior experience with WB-EMS, we did not do this familiarization to investigate the acute impact of WB-EMS. A more extended period of familiarization to WB-EMS can potentially lead to a higher tolerance to WB-EMS current intensity in the context of superimposed walking and Nordic walking, subsequently exerting a more pronounced effect on VO_2. Further investigations are required concerning this research question.

In addition to the use of superimposed WB-EMS in endurance training, it is also commonly applied as an intensification tool in strength training. Watanabe et al. (2019) investigated the metabolic differences of WB-EMS, voluntary exercise, and its combination during body weight resistance training (Watanabe et al., 2019). They found an increase in relative VO_2 of ≈23% during WB-EMS superimposed body weight resistance training. Compared to the difference for VO_2 obtained during WB-EMS-W and WB-EMS-NW compared to CON exercises in the present study, the VO_2 increase during WB-EMS-superimposed resistance training seems to be clinically relevant. One reason for this discrepancy might be differences in the focus of the participants on the exercise. During the WB-EMS resistance training, training was programmed to 4s of exercise and 4s rest intervals, whereas WB-EMS was just applied during continuous dynamic exercise. Therefore, it might be possible that participants were more focused on their muscle contraction during the 4s intervals compared with the ongoing walking tasks on the treadmill, and a higher WB-EMS intensity was tolerable leading to a higher VO_2 increase.

Since the data collection and publication of partial results of this project (Verch et al., 2021), further studies on the topic of WB-EMS superimposed physical activities have already been published. Perez-De-Arrilucea-Le-Floc'h et al. (2022) studied different stimulation frequencies of EMS during WB-EMS superimposed uphill walking in a group of ten healthy and recreationally active men (18-25 years old) with EE as the primary outcome variable (Perez-De-Arrilucea-Le-Floc'h et al., 2022). They reported an increase in EE of 38.1% at 2 Hz, of 43.56% at 6 Hz and of 33.94% at 8 Hz stimulation frequency compared to unstimulated uphill walking. These results are significantly higher than the present results and may be due to the low stimulation frequency range of the WB-EMS used in the present study or the differences between ground level W or NW and uphill walking. For example, a higher effort during uphill walking could be the reason for the stronger efficacy of WB-EMS compared with walking without a significant incline.

In contrast, there were studies whose results did not show such a large increase in the outcome variables after using the superimposed WB-EMS for different activities. Stephan et al. (2022) investigated the influence of superimposed WB-EMS during a maximal treadmill test in a group of 22 healthy men aged 18 to 35 years (Stephan et al., 2022). They compared the oxygen uptake of three incremental treadmill test with three different test situations, two-times WB-EMS superimposed running tests (35 Hz, 85 Hz) and one conventional run test. As a result, they could only find significant differences between the two frequencies for individual speeds during the incremental test, whereby the speeds between the two frequencies were not congruent.

In another study, Watanabe et al. (2021) examined the acute of voluntary exercise intensity on metabolic responses during voluntary pedaling exercise with and without superimposed WB-EMS (Watanabe et al., 2021). After an exercise tolerance test on a cycle ergometer to determine the exercise intensity at the ventilatory threshold 2 (VT2) and peak oxygen consumption for each participant, the participants performed pedaling exercise on a cycle ergometer at four different workloads: 50%, 75%, 100%, and 125% of VT2. The results showed that, among others, oxygen consumption increased after superimposing WB-EMS on voluntary pedaling exercises at different exercise intensities. Moreover, the increases in oxygen consumption due to the superimposition of WB-EMS were decreased as the intensity of voluntary exercises increased, thus the influence of WB-EMS decreased. Since the absolute results for VO_2 are only presented graphically, or in relation to the VO_2peak from the exercise test, the relative increase of VO_2 by the superimposed WB-EMS is not explicitly determined and thus not comparable with our results. However, it can be seen that the influence of WB-EMS is higher for low-level activities, such as walking and Nordic walking.

In a follow-up study, Watanabe et al. investigated the effect of voluntary exercise intensity on metabolic responses during the combined application of voluntary pedaling exercise and WB-EMS (Watanabe et al., 2022). During a training intervention of 7.5–10.5 weeks, the participants trained with a leg pedaling ergometer once or twice a week (total of 17 training sessions). The participants were randomly divided into two groups, the vigorous intensity voluntary exercise group (at 100% of VT2) and the one training with moderate-intensity voluntary exercise (at 75% of VT2) with superimposed WB-EMS. Before and after the training intervention, participants performed an exercise tolerance and submaximal exercise test. As a result, VO_2peak during the exercise tolerance test was found to be significantly increased after the training intervention compared to baseline in both groups. VO_2peak during the exercise tolerance test was not significantly different between both groups. Thus, the superimposed WB-EMS training at moderate intensity had the same positive effect as the vigorous intensity voluntary exercise training without additional WB-EMS.

The difference in VO_2 between walking and Nordic walking is another interesting result of the present study. The present investigation obtained a 15.12% higher VO_2 for CON-W compared with CON-NW, whereas the VO_2 for EMS-NW was 13.76% higher compared to CON-NW. For relative VO_2, differences were 15.71% (CON) and 14.09% (WB-EMS superimposed). Nordic walking has been the subject of research in previous studies, for example, Schiffer et al. (2006) investigated differences in VO_2 between walking and Nordic (Schiffer et al., 2006) . In contrast to present results, they found a VO_2 difference between walking and Nordic walking of 8% for a similar velocity of 1.8 m/s (≈ 6.48km/h). In contrast, Church et al. (2002) found a ≈20% higher VO_2 during a 1,600m walking field test at selfselected walking speed. Figard-Fabre et al. (2009) investigated the impact of a four-week learning period of the Nordic waling technique on VO_2 intake during a 5 min treadmill test (v= 4 km/h walking) (Figard-Fabre et al., 2009). In line with the present results, they found an initial difference of ≈12.2% in VO_2 between Nordic walking and walking, and beyond an increase of ≈17.6% after the learning period. Participants of the present investigation were only familiar with the Nordic walking technique at a basic level. Therefore, it could not be excluded that a familiarization of the participants with the Nordic walking technique might have enlarged the difference in VO_2 intake between walking and Nordic walking. It can only be speculated about a stronger WB-EMS impact after a Nordic walking technique-learning period. However, a longer period of Nordic walking with additional WB-EMS might increase the VO_2 and rel.VO_2.

In addition to the measurable differences in exercise intensity, the RPE is an important factor during the investigation of new training methods. Results of the present investigation suggest that both WB-EMS superimposed exercises, walking and Nordic walking, were perceived as being more exhausting compared to the CON exercise. The application of WB-EMS during exercise seems to be a significant influencing factor regarding RPE. In contrast to this, Wahl et al. (2012) found conflicting results for EMS superimposed cycling on an ergometer. While there were no differences in a first examination, another study concluded that EMS superimposed cycling was perceived as more strenuous than cycling alone (Wahl et al., 2014). Therefore, an evaluation of our results is difficult. It is different from the comparison between walking and Nordic walking for both CON and WB-EMS superimposed. In line with previous studies, results of the present investigation did not find a statistically significant difference in RPE between the two exercises for both test situations. Barberan- Garcia et al. (2015) reported that Nordic walking generates a higher exercise intensity at the same RPE compared with standard walking (Barberan-Garcia et al., 2015). They investigated VO_2 uptake and RPE (using the modified Borg scale) in a group of chronic obstructive pulmonary disease patients and compared the results of two 6 min walking tests, one time during a standard walking test and additionally during Nordic walking. Participants did not report any differences in RPE between walking and Nordic walking. Figard-Fabre et al. (2011) investigated RPE between walking and Nordic walking in a group of obese middle-aged women, and results confirmed similar findings for RPE between walking and Nordic walking.

Lactate measurements represent another tool for exercise intensity evaluation. As a result of this investigation, it could be shown that WB-EMS-W/NW leads to higher lactate concentration in the blood compared with CON exercise. However, it is debatable whether the extent of this increase is relevant or not. This result supports the assumption that EMS primarily excites type 2 muscle fibers, which have a higher lactate formation compared to type 1 muscle fibers. In line with the present results, Wahl et al. (2012, 2014) also found that WB-EMS superimposed cycling leads to a significantly higher lactate formation compared with cycling alone during a 60 min constant workload and an incremental test. Due to the additional non-selective recruitment pattern of primarily fast-twitch motor units, they concluded that an intensifying impact of WB-EMS on low-intensity endurance exercise could be a result of the mild eccentric work induced by the simultaneous activation of agonist and antagonist, directly through the electrical stimulus and not via pathway brain-nervous system-muscle, during the cycling movement. Further research seems to be necessary to investigate the impact and type of contraction modes of WB-EMS during dynamic exercises.

There are some limitations of the current study. The high variability in the age of the included participants within this sample could be stated as a limitation of the study with regard to the results, since it would be expected this would produce a large range of outcomes, especially regarding VO_2 and relative VO_2. The decision for this inclusion criterion was based on an assessment of the age of a manifestation of T2DM (35 years) and the occurrence of accompanying diseases (70 years), which could influence the outcome measures. However, the low SD in the examined variables suggests that age should not be regarded as an influencing factor. This could be attributed to the fact that the chosen WB-EMS current intensity for both walking and Nordic walking, both with and without superimposed WB-EMS, can be considered relatively low due to the participants' limited experience with WB-EMS. Consequently, the age and age-related VO_2 capacity of the subjects had little influence on the results.

The results of the study show that the use of WB-EMS to intensify exercise is limited, at least in the present sample group. An influence of the WB-EMS on exercise intensity is statistically shown but is below the threshold for clinical relevance. Therefore, the high cost of acquiring the device should be considered when using WB-EMS in different patient groups, such as T2DM. However, habituation of the subjects with the WB-EMS and the presumed higher tolerance to the current intensity of the WB-EMS and associated higher intensification may still change this cost-benefit consideration and indicate WB-EMS-W or Nordic walking as an effective training method in different patient groups such as T2DM. This assumption is also supported by recent figures on WB-EMS usage behavior of different population groups. According to these figures, WB-EMS is widely used in the obese group. 18.5% of participants reported using WB-EMS to improve their health, while 81.5% reported reducing their body weight as a goal (Rodrigues-Santana et al., 2022). The supposed benefit should be further investigated scientifically.

6 CONCLUSION

The results of the first study of this PhD-Project showed that measurements of exercise intensity using VO_2peak or relative VO_2peak during the 10MISWT could be reliably performed in a cohort of healthy, moderately active men aged between 35 and 70 years. Additionally, MWD, another performance parameter of the 10MISWT, as well as RPE, could also be reliably evaluated. As a consequence of the results, the measurement of exercise intensity by measuring VO_2peak and relative VO_2peak can be used in further investigations of WB-EMS superimposed walking.

However, it was found that an intensification of walking by superimposed WB-EMS could not be detected during the 10MISWT. This is partly due to the characteristics of the test, which is an incremental test from complete rest, and the fact that the current intensity of the WB-EMS is perceived as more intense at rest than in motion. In conclusion, investigations of WB-EMS superimposed walking as well as other WB-EMS superimposed dynamic exercises should be performed with a physically active phase of WB-EMS current intensity adjustment and not at rest.

The results of the second part of the PhD-project indicated that both walking as a low-intensive exercise and Nordic walking can be significantly intensified by superimposed WB-EMS. This could be demonstrated both ventilatory, through increased oxygen uptake, and metabolic, through higher lactate values. The intensification was relatively equal in the WB-EMS-NW compared to the CON-NW, despite the greater arm input, as well as in the WB-EMS-W compared to the CON-W. Despite the significant intensification in both the WB-EMS-W and the WB-EMS-NW, the clinical relevance remains unclear. If subjects are untrained in Nordic walking and WB-EMS, CON-NW appears to be a more intense training method than WB-EMS-superimposed walking.

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10 LIST OF ABBRIVIATIONS

6MWT .... six-minute walking test

ADA .... American Diabetes Association

ANOVA .... analysis of variances

AT .... anaerobic threshold

BA .... Bland-Altman analysis

BH .... body height

BMI .... body mass index

BW .... body weight

CON-NW .... conventional Nordic walking

CON-W .... conventional walking

COPD .... chronic obstructive pulmonary disease

CPET .... cardiopulmonary exercise testing

CRP .... C-reactive protein

CV .... coefficient of variation

DOMS .... delayed onset muscle soreness

DPN .... Diabetic peripheral neuropathy

ECG .... electrocardiogram

EE .... energy expenditure

EMS .... Electrical muscle stimulation

GLU .... glucose

H_2O_2 .... hydrogen peroxide

HbA_{1c} hemoglobin-A1c

HIC .... high-income countries

HIT .... high-intensity resistance exercise training

HRmax .... Maximum heart rate

Hz .... Hertz

ICC .... intraclass correlation coefficient

IDF .... International Diabetes Federation

IL-1 .... interleukin-1

IL-10 .... interleukin-10

IL-1ra .... interleukin-1 receptor antagonist

IL-1β interleukin-1beta

IL-6 .... interleukin-6

IRE .... incremental ramp exercise

LoA .... limits of agreement

M1 .... measuring point 1

M2 .... measuring point 2

MIC .... middle-income countries

MWD .... maximal walking distance

NYHA .... New York Heart Association

PA .... physical activity

rel.VO_2 .... mean oxygen uptake relative to body weight

rel.VO_2max .... maximum oxygen uptake relative to body weight

rel.VO_2peak .... peak oxygen uptake relative to body weight

rhIL-6 .... recombinant human IL-6

RPE .... rate of perceived exhaustion

RQ1 .... Research question 1

RQ1a .... sub research questions 1a

RQ1b .... sub research question 1b

RQ2 .... Research question 2

SD .... standard deviation

sTNF-R .... soluble TNF-α receptors

STPD .... Standard Temperature Pressure Dry

T1DM .... type 1 diabetes mellitus

T2DM .... type 2 diabetes mellitus

TNF-α .... tumor-necrosis-factor-alpha

TRV .... test-retest variability

VAT .... visceral adipose tissue

VO_2 .... oxygen uptake

VO_2max .... maximum volume of oxygen uptake

VO_2peak .... peak measurements of oxygen uptake

VT2 .... ventilatory threshold 2

WB-EMS .... whole-body electrical muscle stimulation

WB-EMS-NW ....whole body electrical muscle stimulation superimposed Nordic walking

WB-EMS-W .... whole-body electrial muscle stimulation superimposed walking

WRpeak .... peak work rate

11 APPENDIX

Borgskala

6	überhaupt keine Anstrengung
7	
	extrem locker
8	
9	sehr locker
10	
11	locker
12	
13	ein wenig hart
14	
15	Hart
16	
17	Sehr hart
18	
19	extrem hart
20	maximale Anstrengung

Figure 25: Borg scale (German version)

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Prof. Mayer, reporting to you: CES3 from 2012 - mission completed!

13 AFFIDATIVS

According to the doctoral degree regulations (§ 4 (2), sentences No. 4 and 7) of the Faculty of Human Sciences, University of Potsdam:

I hereby declare that this thesis entitled "Whole-body electrical muscle stimulation superimposed walking as training tool in the management of type 2 diabetes mellitus" is the original work of the author. I did not receive any help or support from commercial consultants. All sources and/or materials applied are listed and specified in the thesis. All parts or single sentences, which have been taken analogously or literally from other sources, are identified as citations. Furthermore, I declare that this thesis or parts of the thesis have not yet been submitted for a doctoral degree to this or any other institution neither in identical nor in similar form.

Place, Date

Ronald Verch