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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Could transcranial direct current stimulation acutely enhance exercise capacity in patients with heart disease?

Artuur Neujens
Thibaut Nijs

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :
Prof. dr. Dominique HANSEN

COPROMOTOR :
dr. Felipe VILACA CAVALLARI MACHADO

BEGELEIDER :
De heer Tin GOJEVIC

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www.uhasselt.be
Universiteit Hasselt
Campus Hasselt:
Martelarenlaan 42 | 3500 Hasselt
Campus Diepenbeek:
Agoralaan Gebouw D | 3590 Diepenbeek

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Context of the master thesis

This master's thesis belongs to the physiotherapy category of internal rehabilitation, specifically cardiac rehabilitation. It fits in the research domain of “Clinical care paths & guidelines in rehabilitation.”

This master thesis aimed to establish whether a single dose of transcranial direct current stimulation (tDCS) can acutely enhance exercise capacity in patients with heart disease.

This master thesis serves as a pilot study of a large research project, the ATLAS (trAnscranial sTimuLation in heArt diSease) study It was initiated in January 2022 and was led by Prof. Dr. Dominique Hansen, the principal investigator. Dr. Felipe V. C. Machado played a crucial role as the executive researcher. The study was performed in the Revalidatie en Gezeondheidscentrum (ReGo) at Jessa Hospital, Hasselt, Belgium, and is financed by the Faculty of Rehabilitation (Hasselt University).

During the study, patients participated in an outpatient setting, undergoing baseline, second, and third cardiopulmonary exercise tests (CPET). Before the second and third CPET sessions, patients received either tDCS or sham stimulation. Due to the randomized cross-over design, all participants receive tDCS and sham stimulation. However, the order in which they receive these interventions has yet to be discovered. These CPETs were always guided and supervised by Prof. Dr. Dominique Hansen and Dr. Felipe V.C. Machado, who are part of the executive research team. The administering of the tDCS or sham was conducted by De heer Sybren Van Hoornweder.

In our thesis, we evaluated the acute effects of tDCS in a small cohort of eight patients with heart disease. The primary outcome measure was VO_{2peak}, which was assessed using CPET. However, these examinations did not consider the patient’s phenotype, psychological factors, and frailty. The extensive research project of Prof. Dr. Dominique Hansen will examine a total of 60 patients and will consider the three previously mentioned factors during the evaluation. Additionally, this research aims to explore the impact of tDCS based on the patient’s phenotype. The findings from both the master thesis and the extensive research could significantly impact the future rehabilitation of patients with heart disease.

Our research question, “Could transcranial direct current stimulation acutely enhance exercise capacity in patients with heart disease?” received approval from Dr. Felipe V. C. Machado. The promotor of our master’s thesis is Prof. Dr. Dominique Hansen. We closely worked with him and Dr. Felipe V. C. Machado during our scientific internship. While creating this master’s thesis, Dr. Felipe V. C. Machado provided invaluable guidance and support. Without his assistance, achieving our final result would not have been possible. We sincerely thank him for his unwavering support and expert advice.

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1. Abstract

Background: Cardiovascular diseases (CVDs) are the leading cause of premature mortality worldwide, making early detection and timely treatment crucial. Improving cardiorespiratory fitness (CRF) through exercise training is essential for reducing mortality. Significant symptoms are fatigue and dyspnea, which may facilitate a reduction in exercise capacity—exploring transcranial direct current stimulation (tDCS) as a possible tool to enhance rehabilitation programs for patients with heart disease by improving their exercise capacity (VO_{2peak}).

Objectives: In this study, we investigate the acute effects of tDCS on exercise capacity in patients with heart disease.

Methods: In this randomized cross-over study, eight patients with HF (mean age: 65 years) were evaluated. They received a baseline cardiopulmonary exercise test (CPET), including a medical safety check. Afterward, they were randomly assigned to either Group A, who received the first sham tDCS with CPET followed by tDCS with CPET one week later, or Group B, who received the sham and tDCS in the opposite order.

Results: The included participants have a mean BMI of 26.95 kg/m^2, and most of them suffer from dyslipidemia. Our analysis showed no significant improvement in VO_2 at the first ventilatory threshold (VT1), the second ventilatory threshold (VT2), and peak workload (Wmax). The mean difference in VO_2 between the sham and tDCS condition at VT1 is -0.02 ml/min/kg (p=0.844), and at VT2 -0.14 ml/min/kg (p=0.073). The mean difference in Wmax is -5 watt (p=0.458). Furthermore, it showed a significant difference of -0.19 ml/min/kg in VO_{2peak} (p=0.045) between sham and tDCS, indicating a reduction in VO_{2peak} in the tDCS condition.

Conclusion: We conclude that tDCS has an acute effect on exercise capacity by reducing VO_{2peak} utilization while the maximal workload remains unchanged. However, future research is necessary to assess the underlying mechanisms.

Keywords: Heart disease, transcranial direct current stimulation, exercise capacity, cardiac rehabilitation

2. Introduction

Cardiovascular diseases (CVDs) stand as the foremost cause of premature mortality worldwide, measured by Disability-Adjusted Life Years (DALYs), which amalgamate both mortality and morbidity [1], [2], [3], [4]. In 2019, 17.9 million people were victims of CVDs, standing for 32% of all global deaths. This high percentage of premature deaths can be prevented by addressing behavioral risk factors like tobacco use, harmful use of alcohol, high systolic blood pressure, dietary risks, elevated low-density lipoprotein cholesterol (LDL), high body mass index (BMI), and physical inactivity, which are playing pivotal roles in this context [1], [2]. With population expansion and aging, the prevalence of CVDs is anticipated to escalate. Inadequate control of previously mentioned risk factors significantly contributes to the global burden [3]. Early identification of individuals at high CVD risk and ensuring timely and appropriate treatment are crucial for averting premature mortality and burden [1]. Therefore, activating patients to more consistent physical activity (PA) levels is essential [5].

In patients with heart failure (HF), regular PA is essential; however, exercise often triggers symptoms like dyspnea and fatigue, leading to reduced exercise tolerance and diminished physical activity (PA) and resulting in a reduced quality of life (QOL). Exercise intolerance, an important cardinal symptom, is defined as “An impairment in the capacity to perform PA, accompanied by symptoms of significant dyspnea and/or fatigue” [5] and correlates with adverse clinical outcomes [6], [7]. Feelings of discomfort during PA may be one of the first symptoms and is an important reason why people seek medical help. Therefore, exercise intolerance is closely linked to the diagnosis of HF. Important limiting factors are the incapacity of the heart to augment the output to active musculature to meet the elevated oxygen demands, but also peripheral factors like abnormalities in endothelial function, vasodilatory capacity, and more anaerobically produced energy at the muscle level. These limiting factors contribute to exercise discomfort and symptoms like dyspnea and fatigue. Despite these adverse effects and challenges, enhancing cardiorespiratory fitness (CRF) through exercise training (ET) remains crucial in improving outcomes for individuals with CVD, mainly because physical inactivity emerges as a significant risk factor for coronary arterial diseases (CAD), with regular PA offering substantial preventive and therapeutic benefits [5].

As previously shown, improving CRF is essential. An enhancement of CRF is demonstrated with an augmentation of exercise capacity, as indicated as VO_{2peak}, by one metabolic equivalent is associated with a 12% reduction in premature mortality [8], [9], emphasizing the importance of robust CRF in decreasing all-cause mortality. VO_{2peak}, a measure of CRF, is the strongest predictor of life expectancy in healthy individuals and those with cardiorespiratory diseases [10], [11]. Notably, exercise training (ET) demonstrates significant enhancements in VO_{2peak}. Moreover, CRF is pivotal in prognostication, disease severity assessment, and outcome prediction. The cardiopulmonary exercise test (CPET) serves as the gold standard in these domains, aiding in risk analysis for safe treatment decisions and treatment effectiveness monitoring [12], [13], [14]. A CPET could detect abnormal ventilatory (VE/VCO_2 slope) and hemodynamic responses to exercise. A reduction in VO_{2peak} is correlated with dysregulation in cardiac output (CO), stroke volume (SV), and a lowered peak heart rate (HR) [12]. Despite the pronounced health benefits, individuals with HF often exhibit inadequate activity due to symptoms like fatigue and dyspnea, which diminish their exercise tolerance [15]. As a result, they cannot perform ET for an adequate duration, harming patient adherence to ET. [9], [13].

The duration of exercise programs correlates with the training effect [4], [6], [11], significantly impacting exercise adherence within cardiac rehabilitation (CR) [16], [17]. Despite evidence demonstrating ET's efficacy in improving clinical outcomes in CVDs, patient adherence to these programs remains inadequate [7], [17], [18]. Various reasons contribute to this phenomenon, including challenges associated with living with CVD, such as stress, anxiety, and depression; physical limitations like breathlessness, fatigue, fear, and uncertainty regarding future health; and most importantly, fatigue [19]. Thus, lifestyle behavior modification, especially regular exercise, remains challenging for patients with CVD [19].

Fatigue frequently accompanies PA in HF patients, potentially arising from both central and peripheral mechanisms. Distal to the neuromuscular junction, peripheral fatigue manifests as a decline in voluntary muscle activation during sustained exercise, impairing maximal force and/or power generation. Central or supraspinal fatigue implicates the brain's role in regulating muscular contractions through motor unit recruitment control [20]. Patients with chronic HF and CAD exhibit abnormal hemodynamics, with increased vascular resistance impeding adequate blood flow to active muscles due to the failure to enhance cardiac output

(CO). Consequently, this constriction results in inadequate blood flow, contributing to premature fatigue and exercise intolerance [20], [21]. ET has demonstrated beneficial effects on early fatigue, further highlighting its importance [22].

As already mentioned, the brain has a significant role in fatigue. Current evidence suggests that a decline in excitability of the motor neuron pool or incapacity of cortical areas to compensate for the reduced neural drive to muscles is crucial in inducing fatigue [23]. Transcranial Direct Current Stimulation (tDCS) emerges as a potential and safe intervention to enhance brain function, reduce fatigability, and improve exercise performance [21]. tDCS involves extracranial delivery of a weak direct electric current, inducing increased excitability below the anode (depolarization) and decreased excitability below the cathode (hyperpolarization) [24].

In conclusion, individuals with CVDs experience heightened perceived effort during exercise, negatively impacting ET adherence. Therefore, exploring safe and feasible interventions to alleviate perceived effort temporarily becomes imperative. Brain stimulation techniques, like tDCS, present an intriguing avenue for consideration [25].

Current evidence shows inconsistent results regarding the use of tDCS due to the variety of applications. In addition, there is no research about the effect on patients with CVDs. This thesis aims to investigate whether tDCS can acutely enhance VO_{2peak} by mitigating the sensation of fatigue in patients with heart disease, seeing the gap of evidence in this specific population. This exploration seeks to (1.) provide evidence supporting the role of the brain or central fatigue in determining exercise capacity, a notion currently insufficiently established, and (2.) enable exercising at higher intensities or volumes with a similar subjective perception of effort.

3. Methods

3.1. Study design

This prospective cross-sectional study, initiated in January 2022, included patients with heart disease (coronary artery disease (CAD) and heart failure (HF)). Patients were recruited from the cardiology department at Jessa Hospital, Hasselt, Belgium, and were required to provide informed consent approved by the medical ethical committee. The study protocol included a maximal cardiopulmonary exercise test (CPET) on a bike. Subsequently, a second CPET was conducted either after sham-tDCS or tDCS within seven days, followed by a third CPET after the remaining intervention (sham-tDCS or tDCS) (see Figure 1).

To be eligible, patients must meet stability criteria examined by a cardiologist. A researcher investigated the following criteria: including stable body weight (<2 kg fluctuation), absence of dizziness or syncope, systolic blood pressure <140 mmHg, no cardiac arrhythmias at rest, no recent changes in cardioprotective medication, and no signs of angina pectoris or worsening dyspnea in the past two weeks.

Exclusion criteria encompass exercise impossibility, significant ECG and blood pressure abnormalities discovered during the initial CPET (exercise hypertension, ischemia, significant ventricular arrhythmias, atrial fibrillation), COPD (based on medical history), renal failure requiring dialysis, and the presence of a pacemaker, ICD, CRT-D, or neurostimulator.

Figure 1

Study Design

Note. First, execute a maximal cardiopulmonary exercise test (CPET) on a bike, followed by a second CPET directly after sham-tDCS or tDCS within seven days, followed by a third CPET after the remaining intervention (sham-tDCS or tDCS)

3.2. Assessments

3.2.1. Patient Phenotyping

In the postprandial state, participants' body height was measured with precision to the nearest 0.1 cm using a wall-mounted Harpenden stadiometer (ICD 250 DW, De Grood Metaaltechniek, Nijmegen, The Netherlands), with individuals being barefoot. Body weight (in underwear) was determined using a digital-balanced weighing scale accurate to 0.1 kg (Seca 770, Seca Hamburg, Germany). The Body Mass Index (BMI) was calculated from the obtained weight and height measurements (weight/height^2).

Additionally, as part of the clinical evaluation preceding the CPET, the patient's cardiovascular disease (CVD) risk profile was systematically compiled. This included an assessment of the presence of hypertension, dyslipidemia, diabetes mellitus, and the specific type of heart disease. Furthermore, details regarding medication intake were diligently recorded for comprehensive patient characterization.

3.2.2. Cardiopulmonary Exercise Test (CPET)

The CPET was conducted until voluntary exhaustion utilizing an electronically braked cycle ergometer (eBike, GE Medical Systems, Milwaukee, Wisconsin, USA), controlled by Cardiosoft electrocardiography software (Cardiosoft 6.6, GE Medical Systems, Freiburg, Germany). Each testing day was initiated with a gas and volume calibration following the manufacturer's guidelines. The ambient temperature was maintained at a stable 19-21 °C throughout the test. The exercise procedure followed a ramp protocol, encompassing a 30-second pre-exercise resting period while seated on the bike, a 1-to-2-minute unloaded warm-up cycling phase, and an incremental exercise cycling period. The workload started at 10-60 W, escalating by 5-40 W per minute based on the patient's clinical status, ensuring completion within 6-12 minutes. A cycling frequency of 60-70 revolutions per minute (rpm) was needed to be sustained during warm-up and incremental exercise. Termination occurred when the participant failed to maintain a pedal frequency of at least 60 rpm. Participants received verbal encouragement during testing to attain maximal effort, determined by a Respiratory Exchange Ratio (RER) ≥1.10 and the subjective assessment of an experienced tester. The tester evaluated features such as dyspnea, sweating, facial flushing, unwillingness to continue, or a sustained drop in

pedaling frequency. Continuous pulmonary gas exchange analysis (Jaeger MasterScreen CPX Metabolic Cart, CareFusion Germany GmbH, Hoechberg, Germany) records breath-by-breath data, including oxygen uptake (VO_2), carbon dioxide output (VCO_2), minute ventilation (VE), and respiratory exchange ratios (RER), equivalents for oxygen uptake (VE/VO_2) and carbon dioxide production (VE/VCO_2) averaged every ten seconds. Heart rate (HR) was monitored with a 12-lead electrocardiography device (KISSTM Multilead, GE Medical Systems, Freiburg, Germany) and averaged every 10 seconds. Exercise tolerance was assessed through peak workload (Wpeak). Ventilatory thresholds (VT1 and VT2) were determined using the V-slope method, and this threshold was double-checked by establishing the nadir of the VE/VO_2 versus work rate relationship [26]. The initial ventilatory threshold, VT1, was ascertained using the V-slope method and subsequently corroborated by pinpointing the nadir of the VE/VO_2 versus work rate relationship [26]. This dual verification ensured accuracy in determining VT1, delineating the transition between light-to-moderate and moderate-to-high intensity effort domains. Subsequently, the second ventilatory threshold (VT2) was identified by analyzing the VE vs. VCO_2 plot. VT2 was located where VE exhibits disproportionate growth about VCO_2. This threshold was further validated to enhance reliability by establishing the nadir of the VE/VCO_2 versus the work rate relationship [26].VT2 is recognized as an indicator of critical power, representing the upper-intensity limit for prolonged aerobic exercise. The meticulous determination of these ventilatory thresholds involved collaboration between two independent observers, who cross-checked each other's findings. Further assurance was provided by a third independent observer, who systematically reviewed these thresholds in a randomly selected subset of patients.

3.3. Intervention

3.3.1. tDCS

Based on a systematic review of Marinus et al., we employed one tDCS protocol in our study [27]. The protocol involved offline anodal tDCS simulation of the bilateral primary motor cortices. Furthermore, the application of tDCS lasts less than 15 minutes, maintaining a mild current density and low charge density. This is in alignment with the insights derived from the aforementioned systematic review. The sham condition will replicate an identical electrode configuration, differing only in the cessation of stimulation after 30 seconds of tDCS.

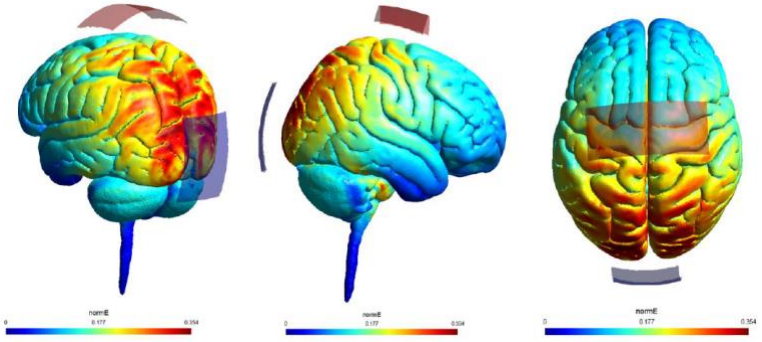
3.3.2. tDCS protocol

The tDCS protocol is developed based on the methodologies proposed by Vitor-Costa et al. [28] and Baldari et al. [29]. The procedural details are as follows: Saline-soaked sponges covered the electrodes, ensuring optimal conductivity. The anode, measuring 9 x 4cm, will be strategically placed over the Cz region following the international EEG 10-20 system, covering both C1 and C2. The cathode, with dimensions of 7 x 3cm, will be positioned over the occipital protuberance. During tDCS application, a current intensity of 2 mA will be administered for 13 minutes. The electric field induced by this electrode configuration has been meticulously simulated using SimNibs. [30]. The simulation results in Figure 2 offer insights into the anticipated effects. Extensive straps will be employed to maintain consistent contact between the electrodes and the skin throughout the experimentation process.

This comprehensive protocol ensures adherence to established methodologies and employs innovative approaches to optimize the effectiveness of tDCS in the designated research context.

Figure 2

Simulation of tDCS Protocol



Note. tDCS protocol with electrode placement with anode covering C1 and C2 and cathode over the occipital protuberance.

3.4. Statistical Analysis

Statistical analysis will be conducted using JMP Pro 17. Computation of averages and standard deviations will be performed and evaluated by the distribution (normal or no normal distribution) of data through Shapiro-Wilk tests. Standard deviation (SD) and mean are used if the sample is from a normal distribution. If in violation of this assumption, interquartile range (IQR) and median are used. Categorical variables are presented as absolute and relative values (Quantity (Percentage)).

Changes in VO_{2peak} (primary outcome), peak workload, and VO_2 at VT1 and VT2 will be investigated using a paired t-test if the normality assumption is fulfilled. If not, the Wilcoxon Signed Rank test will be used. A p-value <0.05 (two-tailed) will be considered statistically significant. These tests will uncover a possible considerable effect of tDCS in contrast with sham tDCS on the different outcome measures.

4. Results

4.1. Participants

Initially, 60 patients with heart disease, such as CAD and HF, were to be included in this study, with recruitment beginning in January 2022. While COVID-19 presented some challenges to the enrollment procedure, this thesis functioned as a pilot study. Further optimization of the study will be based on this work. Only ten patients were recruited, of whom eight were included in the analysis. For six patients, all measurements were conducted successfully.

Table 1 provides an overview of the baseline characteristics of the participants. All participants were male; their mean BMI was 26.95 kg/m^2, and their mean age was 64.75 years. Seven participants had a PCI, and only one had an endo-CABG. From the table, dyslipidemia was the most present cardiovascular risk factor, with seven participants suffering from this condition. The baseline CPET showed a mean maximal load of 199 watts and a median VO_{2peak} of 1.94 l/min.

Table 1

Baseline Characteristics

Characteristics (n=8)	
Characteristics of the sample	
Age	64.75 ± 7.19
Sex (m)	8 (100)
Height (cm)	176.63 ± 7.44
Weight (kg)	83.75 ± 8.55
BMI (kg/m^2)	26.95 ± 3.44
Indications CPET	
PCI	7 (84.5)
Endo-CABG	1 (15.5)
Baseline CPET	
Max load (watts)	199 ± 57
VO_{2peak}(L/min)	1.94 (1.57-2.19)
Cardiovascular risk factors	
Hypertension	4 (50)
Dyslipidemia	7 (87.5)
Obesity	3 (37.5)
Smoking	
Never	2 (25)
Former	5 (62.5)
Current	1 (12.5)
TC (mg/dl)	118 (98.25-132.75)
LDL (mg/dl)	56 (42-70.25)
HDL (mg/dl)	45.13 ± 12.3
HbA1c (%)	5.61 ± 0.2

Note. n = Number of participants; CPET = Cardiopulmonary Exercise Testing; m = male; PCI = percutaneous coronary intervention; endo-CABG = Endoscopic Coronary Artery Bypassing Grafting; TC = total cholesterol; LDL = low-density lipoprotein; HDL = high- density lipoprotein; HbA1c = hemoglobin A1c; According to normality: mean±SD or median (IQR 25% - 75%)

Table 2

Outcome CPET: Sham VS tDCS

		Sham	tDCS	tDCS-Sham	*p*
Load					
	Max (watt)	203 ± 50	203 ± 45	-5 ± 18	0.458
VO_2					
	Peak (L/min)	2.23 ± 0.66	2.09 ± 0.52	-0.19 ± 0.18	0.045*
	VT1 (L/min)	1.26 ± 0.32	1.31 ± 0.37	-0.02 (-0.18 - 0.22)	0.844
	VT2 (L/min)	2.00 ± 0.62	1.94 ± 0.51	-0.14 ± 0.15	0.073

Note. CPET = Cardiopulmonary exercise testing; VO_{2peak} = maximal oxygen consumption; VT1 = first ventilatory threshold; VT2 = second ventilatory threshold; According to normality: mean ± SD or median (IQR 25% - 75%)

4.2. Peak workload (Wmax)

Table 2 shows the results of the CPET during the sham and tDCS conditions. During the sham condition, the mean maximal load was 203 watts. The mean Wmax in the tDCS condition was also 203 watts with an SD of 45 watts. This means there is no difference in peak workload with tDCS brain stimulation.

As described in the statistics section, we used a paired t-test with the formula tDCS-sham. The p-value of this test (p= 0.458) is >0.05, which means that Wmax after tDCS is not statistically significantly higher than the Wmax with no tDCS.

4.3. Exercise capacity (VO_{2peak})

Table 2 shows a significant difference in VO_{2peak} between the sham (2.23 l/min.) and tDCS condition (2.09 l/min.). The P-value (p=0.045) of this paired t-test is <0.05, which indicates that the VO_{2peak} after the sham condition is statistically significantly higher than the VO_{2peak} after a CPET performed with tDCS-stimulation.

4.4. Exercise capacity at first ventilatory threshold (VO_2 at VT1)

For the VO_2 at VT1, a slight increase in VO_2 was detected in the tDCS condition. The mean VO_2 at VT1 in the sham condition was 1.26 l/min, and during the tDCS condition 1.31 l/min.

However, the Wilcoxon Signed-rank test did not show a statistically significant difference between the two groups at VT1 (P-value > 0.05). Based on the p-value of 0.844, we cannot conclude that tDCS results in a higher VO_2 at VT1.

4.5. Exercise capacity at the second ventilatory threshold (VO_2 at VT2)

From the results of Table 2, we can conclude a slight decrease in VO_2 at VT2 in the tDCS condition compared to the sham condition. Still, the paired t-test (p=0.073) indicates no statistically significant difference between the sham and the tDCS condition. Based on these results, we cannot conclude that tDCS results in a higher Vo2 at VT2 than the sham condition.

5. Discussion

To the best of our knowledge, this is the first study to evaluate the acute effects of a single-dose tDCS application on maximal exercise capacity in patients with heart disease. Contrary to our hypothesis and other studies, the current research shows that VO_{2peak} is reduced with tDCS. Results show a significant p-value (0.045) in favor of the control group, which suggests that tDCS acutely reduces the percentage used of the maximal exercise capacity in patients with heart disease. Importantly to note is that the other studies differ in methodology, sample size, and population.

5.1. Comparison with other studies

5.1.1. tDCS as a modulator of the autonomic nervous system (ANS)

The aim of the study of Okano et al. (2013) was to evaluate the effects of tDCS on various physiological and performance metrics during incremental exercise tests in trained cyclists. It specifically focused on exercise performance, heart rate (HR), heart rate variability (HRV), and RPE. Hypothesizing that anodal tDCS over the temporal cortex (TC) could enhance parasympathetic activity, thereby improving exercise tolerance by reducing RPE and enhancing exercise performance [31].

Ten trained cyclists were included as participants. The duration of stimulation was 20 minutes of anodal tDCS over the left TC. Sham stimulation served as the control condition. The primary outcomes measured during a maximal incremental cycling exercise test were RPE, HR, and R–R intervals (a measure of ANS) and obtaining peak power output (PPO) at the end of the test [31].

The results demonstrated several critical findings with anodal tDCS. Peak power output was 4% higher with tDCS. The parasympathetic vagal withdrawal was delayed, resulting in a lower HR at submaximal load. Additionally, RPE values were lower during exercise following anodal tDCS application [31].

The brain has an essential function in exercise performance. ANS can be associated with the induction of fatigue in patients with diseases. Anodal tDCS over the TC influences the ANS by stimulating the parasympathetic branch of the nervous system [31].

Building on the findings from Okano et al. (2013), the reduction in VO_{2peak} in our study can be compared to the reduced HR in combination with a slower increase in RPE at submaximal workloads. This hypothesis could account for the lower VO_{2Peak} after tDCS compared to the sham condition. The underlying mechanism may involve a lower percentage of VO_{2Peak} required to achieve the same maximal workload, indicating more efficient oxygen utilization by stimulating the parasympathetic nervous system (PNS) [31].

5.1.2. tDCS' role in central and peripheral fatigue

Based on the work of Angius and Crisafulli (2020), the lower VO_{2peak} levels observed in our thesis following tDCS interventions could be attributed to its influence on fatigue, impacting the vasodilatory capacity of working muscles and oxygen delivery. A peripheral reflex may induce a lower percentage of VO_{2peak} through tDCS, which enhances vasodilation and oxygen delivery to working muscles. In connection with this, patients with HF suffer from an overactivated sympathetic nervous system. tDCS interventions could stimulate the PNS, thereby acutely reducing the percentage of VO_{2peak} required to exercise at the same maximal workload. While acute tDCS interventions may not be sufficient to enhance VO_{2peak} significantly due to HF's significant influence on muscle functioning, structure, and metabolism, it may help reduce perceived exertion in strenuous exercise by utilizing a lower fraction of the VO_{2peak}. One possible reason for the lack of enhancement in VO_{2peak} could be the necessity for longer interventions, possibly in combination with exercise. This could help overcome chronic changes in skeletal muscle metabolism, functioning, composition, and architecture in patients with chronic heart failure (CHF). Cardiovascular irregularities often induce exercise intolerance, which is linked with an overactivity of feedback from muscle afferents. In conditions such as CHF and CAD, augmentation in mean arterial pressure (MAP) is achieved by increased systemic vascular resistance (SVR). Therefore, tDCS could affect SVR by stimulating the PNS, thus enhancing vasodilation. This could result in lower oxygen demand due to increased blood flow to active muscles, counteracting the exaggerated increase in SVR and arteriolar constriction and compensating for the inability to increase stroke volume (SV).

The arteriolar constriction restricts muscle perfusion, contributing to the early development of fatigue and exercise intolerance observed in CHF patients. By applying tDCS, we may influence this restriction in muscle perfusion by activating the PNS and initiating vasodilation. This vasodilation enhances blood flow to active muscles, delaying early fatigue, as indicated by a lower percentage of VO_{2Peak} utilized during CPET with tDCS compared to sham condition [32].

5.1.3. tDCS' role in exercise tolerance

The recent study by Ministro et al. (2022) provides evidence of the efficacy of tDCS in enhancing cardiovascular and respiratory parameters in patients with resistant hypertension. Applying tDCS improved heart rate recovery (HRR) and VO_{2peak}. Furthermore, this study also reported attenuated ventilatory variability and central and peripheral blood pressure. These factors collectively contribute to an improvement in exercise tolerance. This, in turn, increases the likelihood of completing a rehabilitation program [33]. The findings of Ministro et al. (2022) are contrary to ours. Our study found a reduced VO_{2peak}, whereas Ministro et al. (2022) found an increase in VO_{2peak}. This discrepancy can be attributed to differences in stimulation protocols. Ministro et al. (2022) performed a tDCS stimulation for 20 minutes with the anode placed on the primary motor cortex (unilateral) and the cathode on the right supraorbital region [33]. In our study, we performed an offline anodal stimulation for 13 minutes over the bilateral primary motor cortices. The cathode was placed over the occipital protuberance. Based on our findings, clinicians should approach tDCS as an intervention for enhancing exercise capacity in patients with heart disease with caution. Further research is necessary to investigate the underlying mechanisms.

5.1.4. Single- versus multi-session tDCS

A recent systematic review (SR) by Maudrich et al. (2022) performed a subgroup analysis specific to review the influence of a single administration of anodal tDCS on sport-specific performance. The study compared a cohort of 258 trained athletes engaged in diverse sporting disciplines. The researchers categorized the sports into three categories and compared the stimulation of different brain regions [34]. Drawing from 19 studies, Maudrich et al. (2022) conclude that a single dose of anodal tDCS significantly enhances visuomotor skills, not endurance and strength. Furthermore, the best effects were obtained when the M1

region was stimulated.

Contrary to our study, this study was performed in trained athletes and not in patients with heart disease. Our research found no increase in VO_{2peak} after a single dose of anodal tDCS. The absence of endurance and strength improvements could be attributed to the so-called “ceiling effect”, which states that it’s challenging to augment sport-specific parameters, such as endurance and strength, in well-trained athletes. Furthermore, the non-improvement of stimulating other brain regions can be attributed to using different tDCS methods in the studies included in the SR [34]. Our study only used tDCS ones, 10 minutes preliminary to the CPET. The systematic review of Maudrich et al. (2022) suggests that multi-session tDCS could have more effect as a stand-alone intervention or as priming before exercise to enhance athletes' performance [34].

As we found contradictory results based on our hypothesis, Isis et al. (2023) found similar outcomes. They tested the effects of tDCS on the maximum power, RPE, and time to exhaustion in healthy non-athletes. They concluded that applying tDCS on M1 (primary motor cortex) or T3 (left temporal cortex) did not enhance maximal performance. However, it demonstrated an improvement in performance during low-intensity exercises. These findings can significantly benefit ET in patients with heart disease, where exercise capacity and intensity are lower than in the healthy population [35]. Isis et al. (2023) suggest that the maximal exercise capacity is not reached in a non-athletic population due to other limiting factors, such as muscular fatigue, resulting in a strong feeling of perceived exertion [35]. This statement is proven by Okano et al. (2015), who state that the RPE of trained cyclists increases more slowly during exercise due to tDCS stimulation [31]. Also, lack of motivation in this population could result in an early ‘switch-off’ of the central nervous system and loss of drive to active muscles. As discussed in the study of Maudrich et al. (2022), Isis et al. (2023) also suggest that a single session of tDCS is insufficient as a stand-alone treatment. Several consecutive sessions of tDCS may lead to a cumulative effect, resulting in performance benefits [34], [35].

5.1.5. tDCS parameters

Another hypothesis for our inconsistent findings is presented in the study of Giordano et al.

(2017). They state that the basic mechanisms of tDCS need to be better understood, particularly in pathological populations. Meta-analysis has shown inconsistent effects of the use of tDCS in different pathologies (e.g., stroke). This failure could be described as insufficient knowledge about the parameters of tDCS, like the number of electrodes, location, size, polarity, and stimulation intensity and duration. Further research is needed to detect the working mechanisms behind tDCS and its influence on brain function, circuits, and networks. By understanding the mechanisms behind the tDCS parameters, it could be possible to define which types of patients would benefit from this intervention [36].

5.1.6. Exercise and heart failure

In March 2003, the American Heart Association Committee (AHA) released a statement regarding exercise, rehabilitation, and prevention in patients with HF. Based on 15 studies, Piña et al. concluded that exercise training improves exercise tolerance due to an improvement in VO_{2peak}. Most of these enhancements manifest by the third week, yet they may continue to accrue for up to six months if adherence to the training program is present. Fatigue and dyspnea manifest during exercise and contribute to an elevated RPE are possible factors for reducing adherence to an exercise program [37]. Because of this, Piña et al. suggest that using tools that evaluate these symptoms is essential to detect favorable responses to an intervention. Furthermore, based on seven studies, they conclude that exercise training results in an improvement in exercise capacity, as well as an improvement in QOL [37]. In our research, we did not use a tool to evaluate the QOL and symptoms, but based on this statement, the evaluation of RPE and symptoms could be of great benefit.

5.2. Strengths

This study has several strengths. One of the primary strengths of this study is that it is double-blinded. This implies that both the participants and the researchers are unaware of the tDCS conditions (sham or tDCS). Due to its cross-over design, all participants receive both sham-tDCS and tDCS, but the order remains to be discovered. The random order of administration helps minimize bias.

Furthermore, all participants were randomly assigned to receive either sham-tDCS or tDCS initially. This helps diminish potential confounding factors. Secondly, the standardized

administration of tDCS and sham-tDCS is an additional advantage. In the sham condition, tDCS automatically stops after 30 seconds for all participants. Another strong point is the utilization of a standardized CPET protocol. Each participant followed the same protocol, which was adjusted according to their clinical status.

5.3. Limitations

Our study has two primary limitations. The first limitation is the small number of participants included in the study. Currently, only eight participants performed both CPETs. Our power calculation indicates that a minimum of 50 patients should be included in the study to achieve 80% statistical power, and to compensate for potential dropouts, a goal of 60 participants was set. However, we currently have only 13.33% of the required total sample size with only eight participants. Due to the low number of participants, there is a low statistical power. This implies that our test has a slight chance of detecting actual effects, resulting in false negatives, or that random and systematic errors may influence the results.

Our statistical analysis showed a contradictory effect of tDCS, lower VO_{2peak}, on maximal exercise performance in patients with heart disease. These findings could be attributed to the study's low statistical power. Including a minimum of 50 participants may yield different results than our current findings. These remarks underscore the importance of preceding the research and testing more patients with heart failure, which would enhance statistical power and increase the likelihood of detecting accurate and positive effects.

The second limitation of our study is that we used a heterogeneous study population without considering phenotyping. This has primarily two adverse effects. Firstly, heterogeneity within our study population introduces the possibility of effect modification [42]. This implies that the intervention effect of tDCS may vary across different subgroups within the population. For instance, tDCS might exhibit a more pronounced effect in patients with specific phenotypes than others. Given this possibility, future research should consider investigating the effects of tDCS in a more extensive and diverse population encompassing multiple phenotypes. This would make it possible to compare tDCS effects across different phenotypes. Secondly, the presence of heterogeneity also impacts the generalizability of our findings [43]. It becomes challenging to apply the results to specific subgroups or other populations.

It's also possible that tDCS may have other effects or benefits beyond exercise capacity that were not captured in this study. As already discussed, tDCS could impact the subjective feelings of patients. The study by Okano et al. (2015) provides evidence that the RPE increases more slowly during exercise, but there is no difference in maximal RPE after tDCS stimulation. The slower increase in RPE allows patients to extend their efforts. By doing this, ET will have a more significant influence on their symptoms and health condition. Furthermore, future research must investigate the underlying mechanisms of tDCS in patients with heart disease. Lastly, longitudinal investigations and personalized tDCS protocols could provide deeper insights into optimizing exercise capacity while managing and rehabilitating heart disease patients.

5.4. Future directions

Future research into tDCS should focus on several key areas to fully understand and harness its potential. One promising application of tDCS is during CPET, where preliminary findings suggest that anodal tDCS could significantly increase VO_{2peak}. Stimulating specific brain regions, such as the prefrontal cortex (PFC), warrants exploration. However, the precise parameters for effective tDCS interventions still need to be clarified, highlighting the need for comprehensive studies to standardize aspects like stimulation type, duration, and location. Multi-session tDCS, in particular, requires further investigation to determine its potential for more substantial effects. Additionally, patient phenotyping emerges as a crucial factor in determining the appropriateness of brain stimulation interventions and identifying the subgroups of patients likely to benefit from them. As such, future studies should aim to elucidate these mechanisms more comprehensively and explore patient-specific factors to optimize the clinical application of tDCS in the context of CVDs.

As this thesis only included four outcome measures, future studies should utilize a broader range better to understand the effects of tDCS across various domains. An important parameter to consider is the respiratory exchange ratio (RER), which can be used in two ways: (1) to assess if the CPET is performed maximally and (2) to check if the VT2 is placed correctly (RER around 1.0) [38], [39], [40]. VE/VCO_2 can also be an essential parameter to consider. VE/VCO_2 is used as a prognostic value [40], [41]; the steeper it is, the more severe the HF [38]. In addition to its prognostic function, VE/VCO_2 can also detect VT2 [39]. Cardiac functioning

can be assessed by the end-tidal CO_2 partial pressure (PETCO2) [39], [40]. In patients with CAD, it could be helpful to measure HRR as it can detect changes in autonomic function [39].
Understanding the role of the brain in the termination of physical efforts is another critical research direction. The perception of effort often leads to suboptimal performance, and tDCS could be a game-changer by altering neural activity to resist fatigue and enhance exercise performance. However, the mechanisms behind this potential benefit still need to be clarified, necessitating further research to validate and understand these effects.

6. Conclusion

In conclusion, our study found that using tDCS in patients with heart disease significantly influences acute exercise capacity, as indicated by VO_{2peak}. Exercise capacity is enhanced, measured by reduced VO_{2peak} utilization, while the maximal workload remains unchanged.

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8. Appendix

Appendix A

Decision tree statistics