UHASSELT

KNOWLEDGE IN ACTION

Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Pilot study: The application of transcranial direct current stimulation to acutely enhance exercise capacity in patients with heart disease: a randomized cross-over trial

Alex Mariën
Sarah Syroit

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

PROMOTOR :

Prof. dr. Raf MEESEN

BEGELEIDER :

De heer Sybren VAN HOORNWEDER

2022
2023

UHASSELT

KNOWLEDGE IN ACTION

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

UHASSELT

KNOWLEDGE IN ACTION

Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Pilot study: The application of transcranial direct current stimulation to acutely enhance exercise capacity in patients with heart disease: a randomized cross-over trial

Alex Mariën
Sarah Syroit

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

PROMOTOR :

Prof. dr. Raf MEESEN

BEGELEIDER :

De heer Sybren VAN HOORNWEDER

Research context

This master's thesis is situated in the field of technology-supported rehabilitation, as it aims to investigate whether transcranial direct current stimulation could be an intervention tool to acutely improve exercise capacity by suppressing fatigue in patients with diagnosed cardiovascular disease. If this suppression can be achieved, it would lead to the ability to exercise at greater volumes and intensities, which is beneficial in cardiac rehabilitation. As cardiovascular disease is one of the leading causes of death and disability worldwide, we wanted to explore the effects of tDCS on this specific patient population. Many studies on the effects of transcranial direct current stimulation have previously been done, but mostly in healthy populations.

Our study is a substudy of the ATLAS study (tr**A**nscranial s**T**imu**L**ation in he**A**rt di**S**ease) which is led by prof. dr. Dominique Hansen in collaboration with the research team of prof. dr. Raf Meesen. The ATLAS study is conducted at Jessa Hospital in Hasselt in collaboration with the Faculty of Rehabilitation Sciences (REVAL) and the Faculty of Medicine and Life Sciences (BIOMED) of Hasselt University located in Diepenbeek, Belgium.

The research question in this master's thesis was formulated in consultation with prof. dr. Raf Meesen and PhD student Sybren Van Hoornweder, who also guided us to the completion of this pilot study. We chose a research question that seemed interesting and feasible for us to investigate in this particular population. We adopted the ATLAS research question and modified it according to the goal of our substudy. The same applies to the study design.

Data acquisition for the study was difficult due to postponed commencement of patient recruitment. Once patient recruitment restarted, we noticed that it did not pick up pace. Therefore, Sarah helped with patient recruitment (we were not part of the patient recruitment process initially) because she was doing a clinical internship at the Jessa Hospital at the time.

We tried to make as much of our thesis as possible in collaboration. Alex was stronger in the statistical part and scientific writing, while Sarah already had more background knowledge about the discussed pathologies and cardiopulmonary exercise testing. We complemented each other nicely in this.

Abstract

Background: Cardiovascular disease (CVD) is one of the leading causes of death around the globe. Exercise-based cardiac rehabilitation programs result in less hospitalization, less premature death and better quality of life. However, many CVD patients fail to adhere to these programs. Reduced exercise capacity is often related to this adherence problem. Anodal transcranial direct current stimulation (tDCS) is able to acutely improve exercise capacity in healthy populations, but it remains unclear if CVD patients benefit from tDCS as an ergogenic aid.

Objectives: To investigate whether tDCS stimulation of the bilateral motor cortices can acutely improve exercise capacity in CVD patients by suppressing the sensation of fatigue. This would lead to the ability to exercise at greater volumes and intensities with a similar rate of perceived exertion, which could enhance (adherence to) exercise-based cardiac rehabilitation.

Methods: Six CVD patients participated in this study, performing three cardiopulmonary exercise tests (CPET): one baseline measurement, one preceded by sham tDCS and one preceded by verum tDCS (2 mA, 13 minutes). Each measurement was within seven days and sham-verum order was randomized. Peak workload (Wpeak) resembled exercise capacity.

Results: Mean Wpeak amounted to 203.5 ± 65.40 Watt at baseline, 215 ± 50.92 Watt for verum tDCS and 210.67 ± 54.38 Watt for sham tDCS. The mixed model, consisting of stimulation type, age, body mass index and all pairwise interactions, did not provide significant effects on Wpeak.

Conclusion: Anodal tDCS is not able to suppress fatigue and acutely improve exercise capacity in CVD patients, based on the current sample.

Keywords : Cardiovascular disease; (anodal) transcranial direct current stimulation; cardiopulmonary exercise test; exercise capacity; maximum workload

Introduction

On a global scale, the socioeconomic burden produced by cardiovascular disease (CVD) is immense. CVD is an umbrella term for diseases that concern the heart and circulatory system. CVD is one of the leading causes of death around the globe. (Amini et al., 2021; Lozano et al., 2012). In Europe, approximately 44% of all deaths are caused by CVD (Townsend et al., 2022). On top of that, the prevalence of CVD continues to rise over recent years (Virani et al., 2020). Therefore, it is crucial to detect, treat and follow-up CVD patients effectively to prevent premature death and avoid excessive burden on the healthcare systems.

According to Olvera Lopez et al. (2023), coronary artery disease (CAD) represents one third to one half of CVD cases, making it the most prevalent form of CVD. CAD is responsible for 20% of all mortality in Europe (Daponte-Codina et al., 2022). It is characterized by atherosclerotic narrowing in one or multiple coronary arteries of the heart (Fihn et al., 2012). Atherosclerosis refers to buildup of mainly cholesterol and fats in and on the artery walls (Falk, 2006). In the early stages of disease, CAD can be asymptomatic. Upon progression, CAD can lead to cardiac events such as angina pectoris (tightness or pain in the middle of the chest, feeling faint, shortness of breath) and myocardial infarction due to partially or fully restricted blood flow in the coronary arteries (Fihn et al., 2012). Over time, decreased myocardial perfusion attributed to CAD can cause functional or structural impairment of the heart muscle. When this leads to impaired filling or pumping function of the ventricles, it is called heart failure (HF). CAD is one of the many etiologies of HF (Ziaeian & Fonarow, 2016), but delving deeper into other etiologies is outside the scope of the current study. HF causes symptoms such as shortness of breath, fatigue, weakness and reduced exercise capacity (Heidenreich et al., 2022).

Numerous CVD risk factors, such as sedentary lifestyle, reduced physical fitness (i.e. exercise capacity), smoking, high blood cholesterol and overweight, have previously been identified (Virani et al., 2020). Exercise capacity is reduced in patients with CVD due to other risk factors and the pathofysiology of the disease itself (Gielen et al., 2015). Reduced exercise capacity in CVD patients correlates with an elevated hospitalization risk and premature death (Hung et al., 2014), providing a therapeutic opportunity. Exercise-based cardiac rehabilitation can improve physical fitness in CVD patients. It results in less hospitalization, less premature death and better health-related quality of life (Belardinelli et al., 2012; Hansen et al., 2022; Salzwedel et al., 2020; Taylor et al., 2019). Therefore, exercise-based cardiac rehabilitation is of utmost importance in patients suffering from CVD.

Notably, many CVD patients fail to adhere to physical activity recommendations and

exercise training programs in the long run (Jackson et al., 2005). Tilgner et al. (2022) report that almost 50% of cardiac patients who entered a long term cardiac rehabilitation program, do not complete the program, nor do they achieve their rehabilitation goals. Reduced exercise capacity is often related to this adherence problem (Harlan et al., 1995; Lane et al., 2001; Resurrección et al., 2019).

Therefore, an intervention is needed to temporarily improve exercise capacity by acutely reducing the perception of physical exertion and subsequently break the vicious cycle. This intervention should be safe, feasible and able to temporarily overcome the problem of diminished motivation, to pave the way for CVD patients to benefit from the advantages of exercising. Considering the aforementioned necessary characteristics of an intervention for CVD patients, implementation of noninvasive brain stimulation could be beneficial.

Transcranial direct current stimulation (tDCS) is a form of noninvasive brain stimulation capable of modulating neuronal activity in the brain via low intense direct currents applied via scalp-electrodes (Yavari et al., 2018). This form of brain stimulation is able to induce changes in cortical excitability (Kiernan & Bostock, 2000; Priori, 2003; Stagg et al., 2018). Generally speaking, anodal stimulation facilitates cortical excitability, whereas cathodal stimulation inhibits cortical excitability (Vitor-Costa et al., 2015). Two aspects of tDCS are particularly relevant for our research purpose. Firstly, Tergau et al. (2000) demonstrated that fatigue of large muscles is related to changes in cortical excitability (indexed by cortical facilitation). Hence, anodal tDCS could diminish muscle fatigue during exercise. Secondly, tDCS has been shown to induce an analgesic effect when applied over the motor cortices (Antal & Paulus, 2010), which could lead to a diminished perception of fatigue.

Consequently, we hypothesize that, by combining the cortically facilitory and analgesic effects of anodal tDCS, exercise capacity in CVD patients can acutely be improved with anodal tDCS by suppressing fatigue during exercise. If true, it would lead to the ability to exercise at greater volumes and intensities with a similar rate of perceived exertion (RPE). However, it remains unclear if CVD patients benefit from anodal tDCS as an ergogenic aid.

Thus, this research could improve our understanding about the extent to which the brain contributes to an impaired physical performance in individuals with CVD. Also, this study may kickstart the implementation of a novel promising therapy to enhance (adherence to) exercise-based cardiac rehabilitation in the ever-increasing CVD population.

Methods

Population

The study design was prospective and cross-sectional. Data acquisition started in January 2022. Eight patients (pilot study), who were admitted at the cardiology department of the Jessa hospital, Hasselt, Belgium, were invited to participate and sign the informed consent, explaining the study and possible risks. The study was approved by the local medical ethical committee of Jessa Hospital (B2432022000006). Participants were included when diagnosed with CAD, HF or both, and aged between 40 and 80 years.

Individuals were excluded if they presented with one or more of the following phenomena: inability to exercise, significant electrocardiogram (ECG) and/or blood pressure abnormalities at the baseline cardiopulmonary exercise test (CPET) (ischemia, exercise hypertension, atrial fibrillation, significant ventricular arrhythmias), chronic obstructive pulmonary disease (medical history), renal failure that requires dialysis, cardiac resynchronization therapy pacemaker, cardiac resynchronization therapy defibrillator, neurostimulator, metallic implants, pregnancy, history of migraines, history of seizures, history of epilepsy, head injury in the past that resulted in loss of consciousness and required further examination, medical diagnosis of psychological or neurological disorders, adverse effects to previous tDCS or other brain stimulation techniques, scalp/skin condition, contact to the scalp is not possible (Glaab & Taube, 2022; Thair et al., 2017).

Study design

Figure 1 gives an overview of the study design. After signing the informed consent, participants underwent a clinical evaluation. Upon completion, every participant was invited to perform a maximal CPET on a bike. Within the following seven days, a second CPET was carried out directly after verum or sham tDCS. A third CPET was performed after the sham or verum tDCS within the next seven days, depending on what was applied in the prior session.

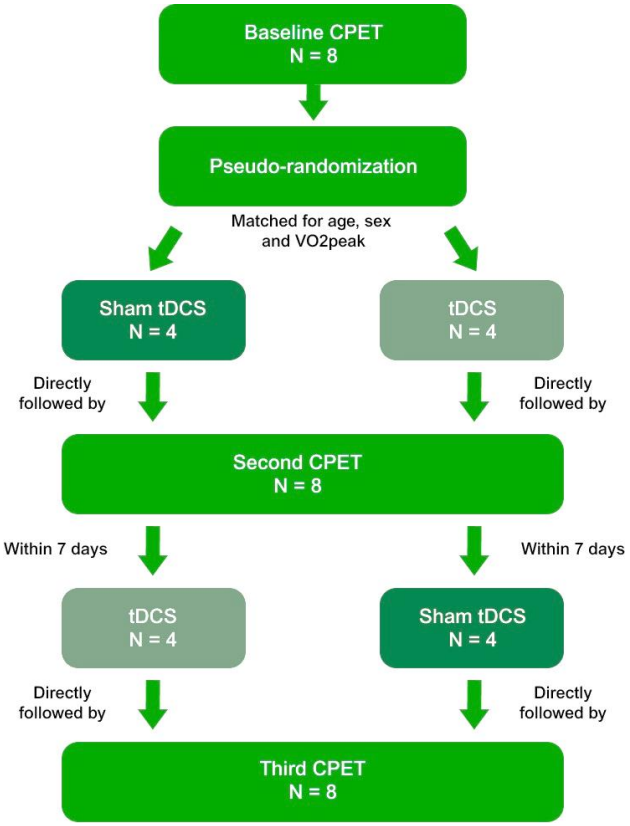


Figure 1. Study design
CPET: cardiopulmonary exercise test; tDCS: transcranial direct current stimulation

Assessments

Phenotype of the patient. A risk profile for cardiovascular disease was compiled before the first CPET takes place. This included determining whether hypertension, dyslipidemia, diabetes mellitus, obesity and/or smoking were present. The type of heart disease was also documented.

Via a wall-mounted Harpenden stadiometer (ICD 250 DW, De Grood Metaaltechniek, Nijmegen, The Netherlands), body height was measured barefoot with 10 mm precision. Participants stood on a digital-balanced weighing scale (Seca 770, Seca Hamburg, Germany) to determine their bodyweight with 100 gram precision. The body mass index (BMI) was calculated by dividing weight by height squared.

CPET. Participants performed the CPET on an electronically braked cycle ergometer (eBike, GE Medical Systems, Milwaukee, Wisconsin, USA), up to volitional exhaustion. The device was equipped with the Cardiosoft electrocardiography software (Cardiosoft 6.6, GE Medical Systems, Freiburg, Germany). Gas and volume calibrations were performed at the beginning of each test day. Throughout the course of the exercise test, an environmental temperature of 19 to 21 °C was maintained to ensure the test's reliability. The CPET followed a ramp protocol that

includes the following steps: a pre-exercise resting period of 30 seconds with the participant sitting upright on the bike, an unloaded warm-up cycling phase of one to two minutes, and the incremental exercise cycling period. The latter started with a workload of 10 to 60 Watt and increased with 5 to 40 Watt, depending on the clinical status of the participant (e.g. baseline exercise capacity, training status and history, medical history). The CPET lasted between 6 to 12 minutes for all participants. Throughout the test, the participant must maintain a cycling frequency of 60 to 70 revolutions per minute. Inability to maintain a frequency of 60 rounds per minute for more than 15 seconds signaled test cessation. To achieve the goal of maximal effort, participants were verbally encouraged during the CPET. To determine whether maximal effort had been achieved, two indicators were examined. Firstly, a respiratory exchange ratio (RER) equal to or more than 1.10 indicated maximal effort (Glaab & Taube, 2022; Triantafyllidi et al., 2022). Secondly, an experienced tester formed a subjective opinion about the matter by looking at features such as dyspnea, facial flushing, excessive sweating, clear unwillingness to continue and a sustained decrease in pedaling frequency (<60 rounds per minute) regardless of verbal encouragement. Heart rate (HR) was monitored and averaged per 10 seconds with the use of a 12-lead electrocardiography device (KISS^{TM} Multilead, GE Medical Systems, Freiburg, Germany). RER was measured every breath and averaged via a 10 second running-average procedure, using continuous pulmonary gas exchange analysis (Jaeger MasterScreen CPX Metabolic Cart, CareFusion Germany GmbH, Hoechberg, Germany). The peak workload (Wpeak) resembled the exercise capacity of the participants.

Intervention

tDCS protocol. Based on the work of Vitor-Costa et al. (2015) and Baldari et al. (2018), offline anodal tDCS of the bilateral primary motor cortices was used as the intervention. Offline tDCS involves a period of tDCS followed by a certain task, in this case the CPET. In other words, tDCS and CPET occur separately as shown in **Figure 1**. Offline tDCS is more practical, and is possible by the fact that tDCS of at least nine minutes results in changes in cortical excitability for an hour or more (Antal et al., 2022; Lefaucheur et al., 2017; Nitsche & Paulus, 2001). The electrodes were covered by saline-soaked sponges, with the anode (9 x 4 cm) placed over Cz in order to cover both C1 and C2 (in conformity with the international EEG 10-20 system), and the cathode (7 x 3 cm) placed over the protuberance of the occiput. Elasticated straps kept the electrodes in place and prevented disruption of the continuously needed contact between the

electrodes and the skin. The stimulation was applied for 13 minutes at an intensity of 2 mA. Prior to application on participants, the effect of the stimulation with this particular electrode configuration was simulated via SimNIBS (Thielscher et al., 2015). The magnitude of the resulting induced electric fields on the grey matter surface can be seen in **Figure 2**. For the sham condition, an identical electrode configuration was used. This condition only differs from the real tDCS by the fact that stimulation cessated after 30 seconds. After stimulation, the participants were asked whether the stimulation they just received is sham or verum tDCS.

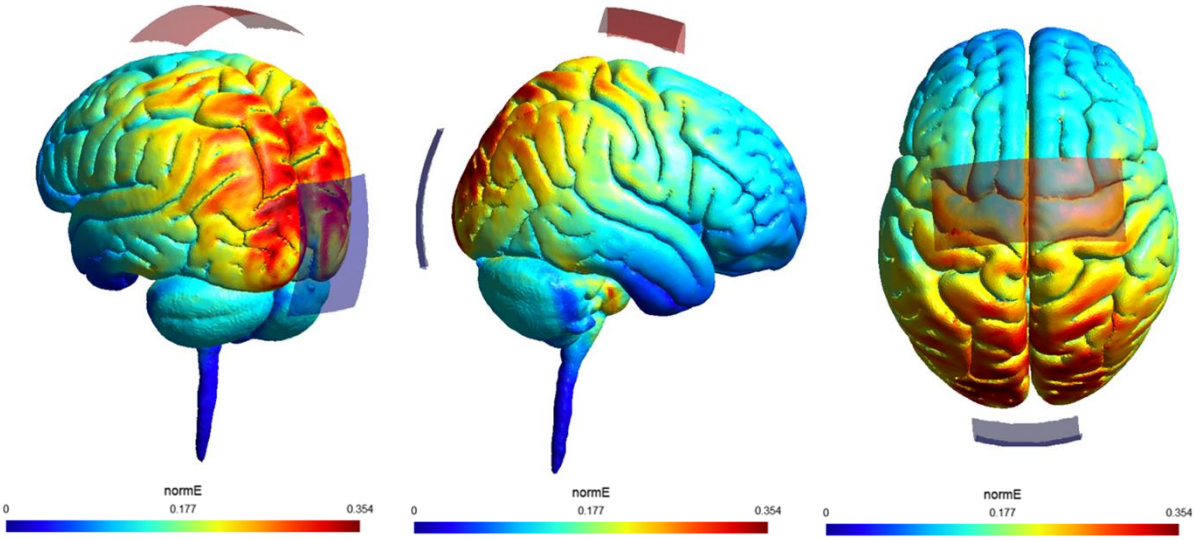


Figure 2. Induced electric fields
normE: magnitude of the electric field

Statistical analysis

Data were analyzed using JMP Pro for Windows (version 16.0). For the aforementioned parameters, averages and standard deviations were calculated to provide descriptive statistical information. Changes in Wpeak (primary outcome measure, dependent variable) as a result of tDCS were assessed by the use of mixed models. The fixed effects were type of STIMULATION (baseline (no stimulation), sham tDCS and verum tDCS), BMI, AGE. Pairwise interactions of these fixed effects were also included in the analysis. ID was included as the random effect. A p-value of <0.05 is considered statistically significant. Effect sizes were calculated for statiscally significant effects to provide information about the magnitude of the effects. Pairwise contrasts between all potential pairs were used to interpret significant effects. If STIMULATION turned out to be the only significant effect, paired t-tests and/or Wilcoxon signed-rank tests (based on sample size and normality) would be used to determine which stimulation type was significant and how it affected Wpeak (increase or decrease).

Results

Population and assessments

All results are shown as mean ± standard deviation, unless stated otherwise.

Phenotype of the patient. Eight CVD patients signed the informed consent and were included in the current study. Two out of eight participants later decided not to participate, which left the total at six participants. All participants were men and the average age was 63 ± 2.68. Six patients presented with CAD, zero with HF. The average height and weight were 1.76 ± 0.09 m and 83.83 ± 5.42 kg respectively. This resulted in an average BMI of 27.23 ± 2.79. **Table 1** provides an overview of participants' characteristics, including factors contributing to the risk profile.

Table 1. *Participants' characteristics*

	ID1	*ID2*	*ID3*	*ID4*	*ID5*	*ID6*
CVD	CAD	CAD	CAD	CAD	CAD	CAD
Sex	Male	Male	Male	Male	Male	Male
Age	69	55	69	55	63	67
Hypertension	No	/	No	Yes	Yes	Yes
Dyslipidemia	Yes	/	Yes	Yes	No	Yes
Diabetes Mellitus	No	/	No	No	No	No
Obesity (BMI)	No (24.6)	Yes (31.4)	No (27.2)	No (24.7)	No (26)	No (29.7)
Smoking	Former smoker	/	Current smoker	Former smoker	Never	Former smoker

ID: identification; CVD: cardiovascular disease; CAD: coronary artery disease; BMI: body mass index

CPET. **Figure 3** shows the Wpeak values per stimulation type for every participant. Five out of six participants completed all three CPET measurements. One participant did not complete the third CPET preceded by verum tDCS, as can be seen by the red line in **Figure 3**. However, the data of the other two measurements of this participant were still used in the analyses. Given the objective of the current work, it is useful to look at the mean Wpeak values for the different

stimulation types for interpretation. Mean Wpeak amounted to 203.5 ± 65.40 Watt at baseline, 215 ± 50.92 Watt for the verum tDCS condition and 210.67 ± 54.38 Watt for the sham tDCS condition. These values layed in close proximity to each other, so it is not surprising that the mixed model (discussed in *statistical analysis* paragraph below) did not show STIMULATION to have a significant effect on Wpeak. A slight mean increase of 11.5 Watt between verum and baseline was observed (as shown with the red line in **Figure 4**), but this was negligible.

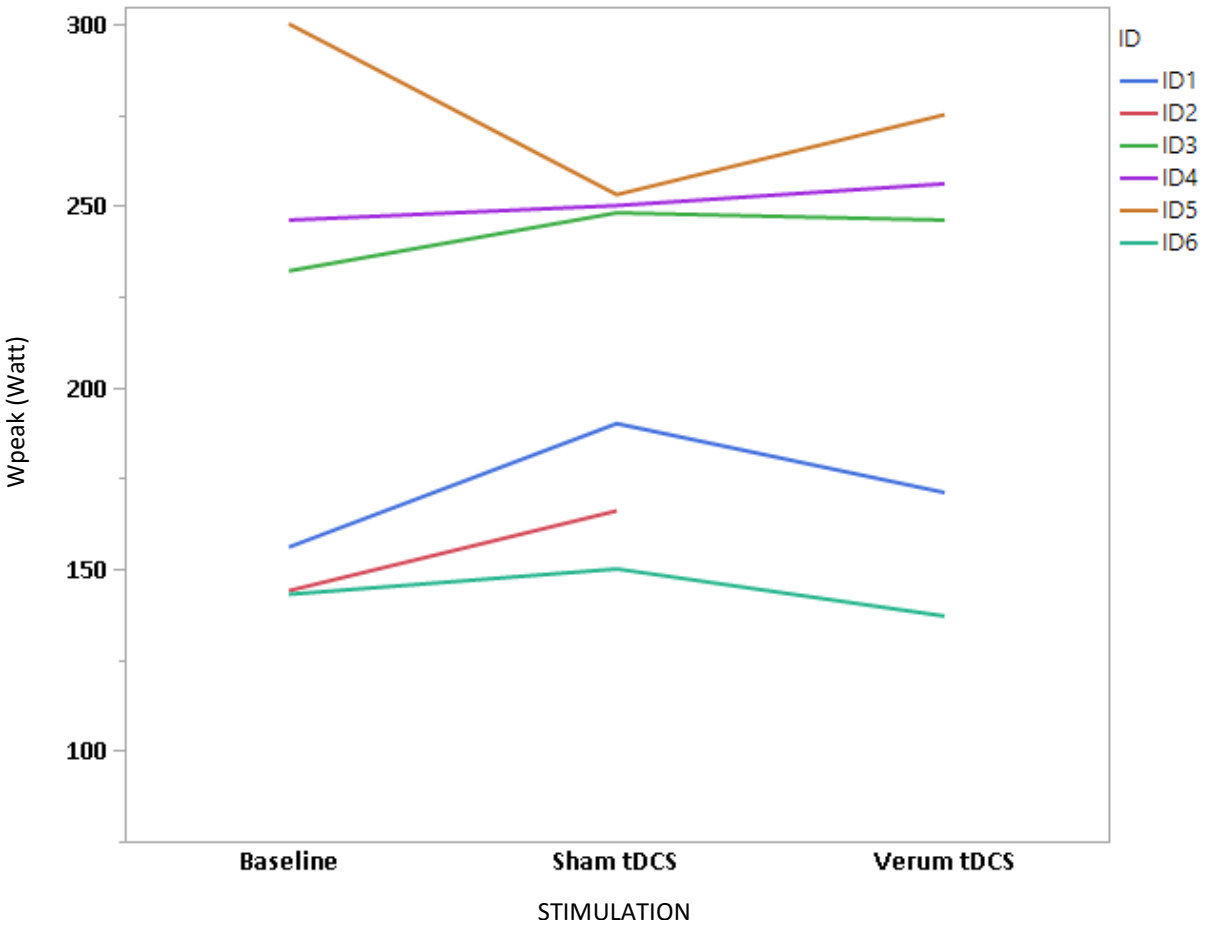


Figure 3. Wpeak vs. STIMULATION. Visualisation of the Wpeak measurements at the three conditions. Wpeak: peak workload; tDCS: transcranial direct current stimulation; ID: identification

Intervention

tDCS protocol. None of the participants reported discomfort or side effects during or after tDCS stimulation. Reports about the participants' ability to detect whether the stimulation they just received was sham or verum tDCS are as follows: one participant was able to correctly detect the sham tDCS, two participants wrongly identified verum as sham and two participants did not feel a difference. ID2 was not able to answer this question due to not receiving verum tDCS.

Statistical analysis

Figure 4 shows the general effect of verum tDCS as boxplots. Before simplifying the mixed model according to the rules of backward model building, the fixed effects and interactions were STIMULATION, BMI, AGE, STIMULATION x BMI, STIMULATION x AGE and BMI x AGE. The intraclass correlation for the initial model amounted to 0.959, which equates to a strong correlation between measurements of the same participant. None of the fixed effects and interactions had a significant p-value. Hence, STIMULATION x AGE was first removed from the model, chronologically followed by BMI x STIMULATION, BMI x AGE, STIMULATION and AGE. BMI was the last remaining effect in the model, with a p-value of 0.1943 and an F-ratio of 2.4147 with one degree of freedom in the numerator and four degrees of freedom in the denominator. Consequently, BMI was also removed, resulting in a final model with no fixed effects. Due to the model not providing significant effects, no effect sizes were calculated.

In conclusion, none of the fixed effects nor the interactions significantly affect Wpeak. Thus, anodal tDCS is not able to suppress fatigue and acutely improve exercise capacity in CVD patients, according to the current study.

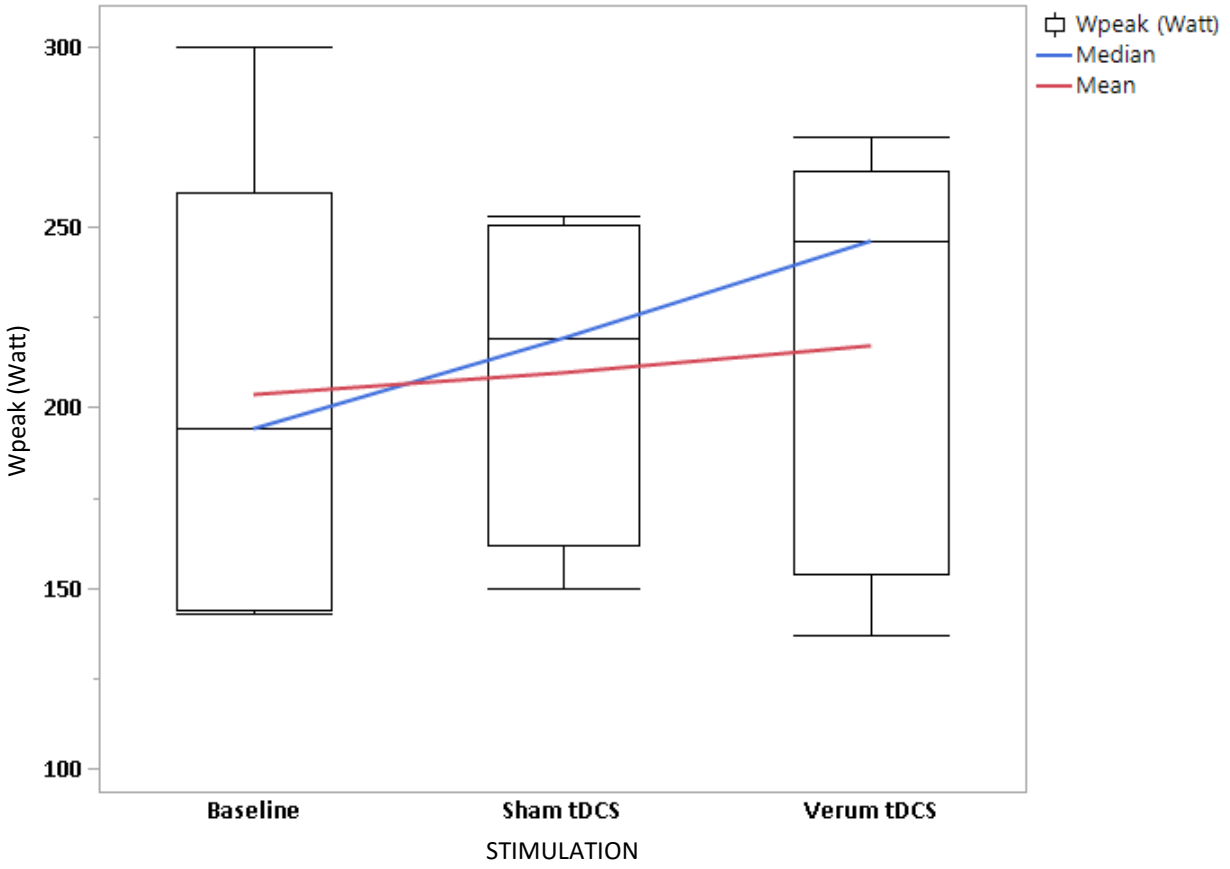


Figure 4. Wpeak vs. STIMULATION (basline, Verum tDCS) boxplots to show the general effect of verum tDCS. Wpeak: peak workload; tDCS: transcranial direct current stimulation

Discussion

In this randomized cross-over pilot study involving six participants, we hypothesized that stimulation of the bilateral motor cortices with anodal tDCS could acutely improve exercise capacity in CVD patients by suppressing the sensation of physical fatigue. Based on the current sample, we observed that anodal tDCS on bilateral motor cortices does not improve Wpeak and fails to acutely enhance exercise capacity.

To the extent of our knowledge, no research has been conducted regarding the impact of tDCS on exercise capacity in CVD populations. Therefore, comparing results with similar studies is not possible. However, several studies investigated the impact of tDCS on exercise capacity in healthy populations. A comprehensive systematic review by Machado et al. (2019) analyzed the effects of anodal tDCS on endurance performance and muscle strength. Regarding endurance performance (defined in the current study as Wpeak), they concluded that only half of the assessed parameters were improved by anodal tDCS. Eight endurance performance studies were included in this systematic review, all using offline 2 mA anodal tDCS as the intervention and 30 seconds stimulation as sham. Stimulation times ranged between 10 and 20 minutes, followed by a cycling exercise to measure endurance parameters. Half of the studies (Angius et al., 2018; Lattari et al., 2018; Okano et al., 2015; Vitor-Costa et al., 2015) reported significant endurance improvements, while the other half (Angius et al., 2015; Barwood et al., 2016; Holgado et al., 2019; Sasada et al., 2017) concluded that no endurance improvements took place after tDCS. The latter is in line with the results of the current study.

The inconsistency in results across different studies investigating tDCS effects on physical fitness may be attributed to inter-subject variety. On the other hand, inconsistencies in results between the current study and studies that found a significant impact of tDCS on exercise capacity, may be attributed to differences in samples.

Firstly, tDCS induced effects can vary between subjects. Wiethoff et al. (2014) showed that only 75% of individuals receiving anodal tDCS (2mA, 10 minutes) presented with cortical facilitation. Regarding the other 25%, anodal tDCS resulted in cortical inhibition. Another aspect of inter-subject variety is medication intake. McLaren et al. (2018) reviewed if and how medication impacts tDCS effects. They concluded that multiple classes of medication (e.g. sodium channel blockers, calcium channel blockers, medication influencing neurotransmitter systems) can impact the excitability effects of tDCS. Hence documenting medication of participants and considering different types of medication as exclusion criteria is important in tDCS studies. Medication documentation was done in the current sample as part of a larger study still in progress, but the

current pilot study dit not include certain types of medication as an exclusion criterium, nor was medication intake used in the analysis of results. Notably, in contrast with the 2 mA tDCS used in the current study, McLaren et al. (2018) only discussed studies using 1 mA tDCS.

Secondly, differences between samples can impact the potential of tDCS to affect exercise capacity across different studies. A meaningful difference between the current study and the studies included by Machado et al. (2019) was the population: (moderately) active, healthy men and women with ages ranging from 19 to 42. Two studies only included athletes. This population difference could be an explanation for them finding significant improvement in some parameters as a result of tDCS, in contrast with our insignificant findings. Hence, it is possible that tDCS can improve exercise capacity in young, healthy individuals, but not in inactive, sedentary populations with several comorbidities. Future research investigating tDCS effects in different pathologies and different patient phenotypes (preferably patients with low rates of physical activity, as most research is done in active populations) may provide clarification on this matter.

Lastly, some limitations of our study, possibly contributing to our insignificant findings, must be acknowledged. The small sample size, resulting in little statistical power, makes our study more prone to a type II error (i.e. higher likelihood of not rejecting the null hypothesis despite being false). The fact that this is a single center study exclusively investigating men affects the external validity (population validity) of the study as the sample is not a representation of the CVD population. This results in difficult interpretation of findings and makes generalization of results scientifically inappropriate. Furthermore, we only investigated the effects on Wpeak as a benchmark for exercise capacity, but other parameters such as maximal oxygen uptake, peak oxygen uptake, maximal HR and ventilatory thresholds are also indicative of exercise capacity. Analyzing other parameters of exercise capacity, as wel as other aspects of physical fitness such as muscle strength, could provide a different understanding of the effect of anodal tDCS on exercise capacity. Questioning participants about RPE throughout the CPET and their reason for exhaustion at the end of the CPET could provide more insight into how tDCS affects exercise capacity.

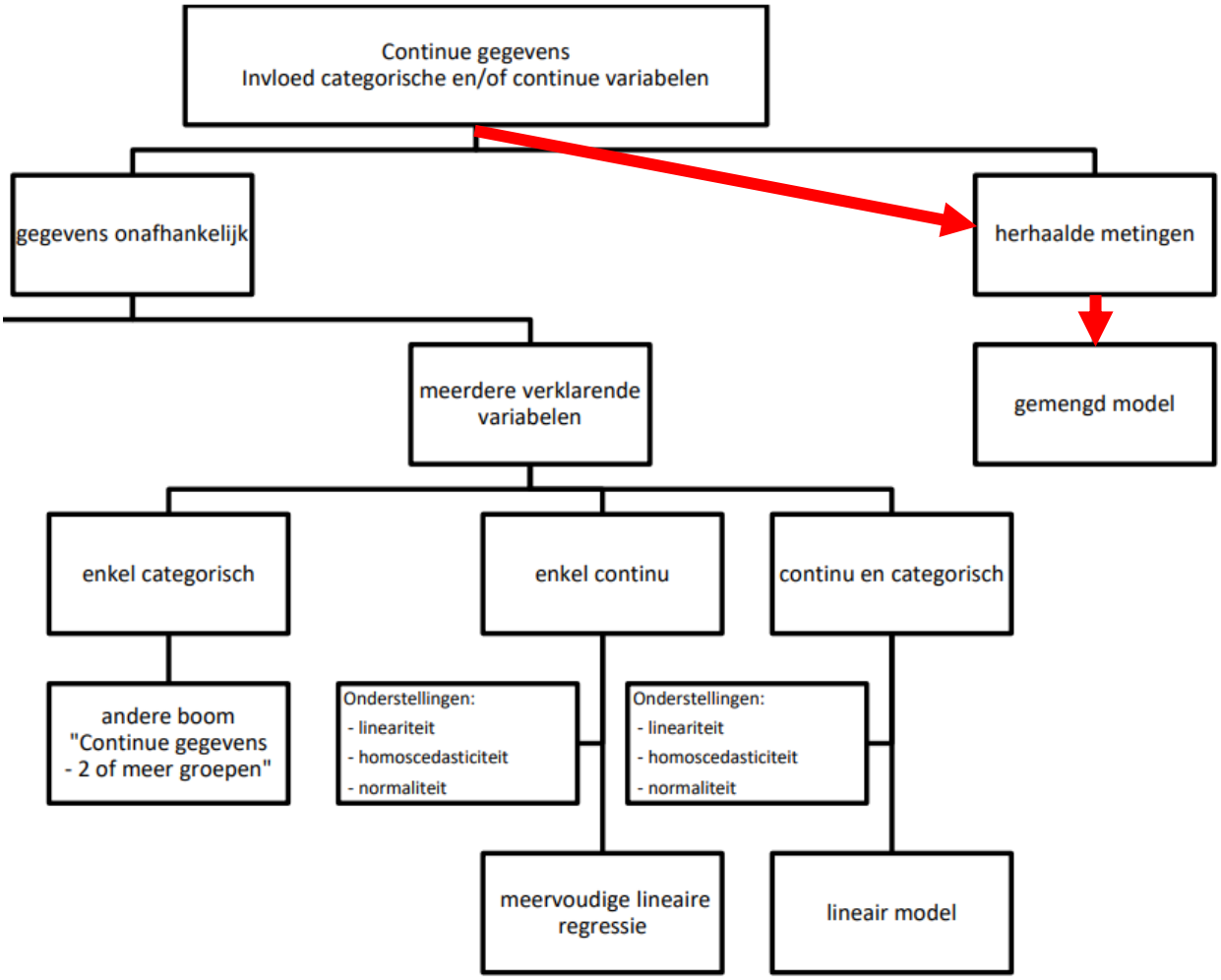
Future research will be important to further determine the exact regions of the brain on which stimulation via anodal tDCS can improve exercise capacity in CVD patients. We propose investigating the stimulation of different brain regions, recruiting participants from multiple centers, using larger sample sizes, compiling more diverse samples (sex diversity, variety of CVD types, other pathologies), categorizing participants based on daily physical activity rates and baseline exercise capacity, investigating the influence of different types of medication in CVD patients, analyzing different exercise capacity parameters (e.g. maximal oxygen uptake, ventilatory

tersholds), and not only analyzing peak parameters, but also the progression of parameters throughout the CPET. Investigating other aspects of physical fitness in CVD patients such as the effect on muscle (endurance) strength could bring new and interesting findings to light, because the literature (e.g. Machado et al. (2019)) provides more consistent results in terms of anodal tDCS improving muscle strength in healthy populations .

Conclusion

We analyzed the effects of anodal tDCS on fatigue suppression in CVD patients by applying stimulation on the bilateral motor cortices, to determine whether this intervention could acutely enhance exercise capacity in this population. We found no significant effect of anodal tDCS on the maximal workload during a CPET that is preceded by a 13 minute stimulation period. Thus, anodal tDCS is not able to suppress fatigue and acutely improve exercise capacity in CVD patients, based on the current sample.

Appendix A. **'Beslisboom' (dutch). Followed path indicated with red arrows.**



References

Amini, M., Zayeri, F., & Salehi, M. (2021). Trend analysis of cardiovascular disease mortality, incidence, and mortality-to-incidence ratio: results from global burden of disease study 2017. *BMC Public Health*, *21*(1), 401. https://doi.org/10.1186/s12889-021-10429-0

Angius, L., Hopker, J. G., Marcora, S. M., & Mauger, A. R. (2015). The effect of transcranial direct current stimulation of the motor cortex on exercise-induced pain. *Eur J Appl Physiol*, *115*(11), 2311-2319. https://doi.org/10.1007/s00421-015-3212-y

Angius, L., Mauger, A. R., Hopker, J., Pascual-Leone, A., Santarnecchi, E., & Marcora, S. M. (2018). Bilateral extracephalic transcranial direct current stimulation improves endurance performance in healthy individuals. *Brain Stimul*, *11*(1), 108-117. https://doi.org/10.1016/j.brs.2017.09.017

Antal, A., Luber, B., Brem, A. K., Bikson, M., Brunoni, A. R., Cohen Kadosh, R., Dubljević, V., Fecteau, S., Ferreri, F., Flöel, A., Hallett, M., Hamilton, R. H., Herrmann, C. S., Lavidor, M., Loo, C., Lustenberger, C., Machado, S., Miniussi, C., Moliadze, V., . . . Paulus, W. (2022). Non-invasive brain stimulation and neuroenhancement. *Clin Neurophysiol Pract*, *7*, 146-165. https://doi.org/10.1016/j.cnp.2022.05.002

Antal, A., & Paulus, W. (2010). [Transcranial magnetic and direct current stimulation in the therapy of pain]. *Schmerz*, *24*(2), 161-166. https://doi.org/10.1007/s00482-010-0899-x (Transkranielle repetitive Magnet- und Gleichstromstimulation in der Schmerztherapie.)

Baldari, C., Buzzachera, C. F., Vitor-Costa, M., Gabardo, J. M., Bernardes, A. G., Altimari, L. R., & Guidetti, L. (2018). Effects of Transcranial Direct Current Stimulation on Psychophysiological Responses to Maximal Incremental Exercise Test in Recreational Endurance Runners. *Front Psychol*, *9*, 1867. https://doi.org/10.3389/fpsyg.2018.01867

Barwood, M. J., Butterworth, J., Goodall, S., House, J. R., Laws, R., Nowicky, A., & Corbett, J. (2016). The Effects of Direct Current Stimulation on Exercise Performance, Pacing and Perception in Temperate and Hot Environments. *Brain Stimul*, *9*(6), 842-849. https://doi.org/10.1016/j.brs.2016.07.006

Belardinelli, R., Georgiou, D., Cianci, G., & Purcaro, A. (2012). 10-year exercise training in chronic heart failure: a randomized controlled trial. *J Am Coll Cardiol*, *60*(16), 1521-1528. https://doi.org/10.1016/j.jacc.2012.06.036

Daponte-Codina, A., Knox, E. C., Mateo-Rodriguez, I., Seims, A., Regitz-Zagrosek, V., Maas, A., White, A., Barnhoorn, F., & Rosell-Ortiz, F. (2022). Gender and Social Inequalities in Awareness of Coronary Artery Disease in European Countries. *Int J Environ Res Public Health*, *19*(3). https://doi.org/10.3390/ijerph19031388

Falk, E. (2006). Pathogenesis of atherosclerosis. *J Am Coll Cardiol*, *47*(8 Suppl), C7-12. https://doi.org/10.1016/j.jacc.2005.09.068

Fihn, S. D., Gardin, J. M., Abrams, J., Berra, K., Blankenship, J. C., Dallas, A. P., Douglas, P. S., Foody, J. M., Gerber, T. C., Hinderliter, A. L., King, S. B., 3rd, Kligfield, P. D., Krumholz, H. M., Kwong, R. Y., Lim, M. J., Linderbaum, J. A., Mack, M. J., Munger, M. A., Prager, R. L., . . . Williams, S. V. (2012). 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*, *60*(24), e44-e164. https://doi.org/10.1016/j.jacc.2012.07.013

Gielen, S., Laughlin, M. H., O'Conner, C., & Duncker, D. J. (2015). Exercise Training in Patients with Heart Disease: Review of Beneficial Effects and Clinical Recommendations. *Progress in Cardiovascular Diseases*, *57*(4), 347-355. https://doi.org/https://doi.org/10.1016/j.pcad.2014.10.001

Glaab, T., & Taube, C. (2022). Practical guide to cardiopulmonary exercise testing in adults. *Respir Res*, *23*(1), 9. https://doi.org/10.1186/s12931-021-01895-6

Hansen, D., Mathijs, W., Michiels, Y., Bonné, K., Alders, T., Hermans, A., Copermans, K., Swinnen, H., Maris, V., Timmermans, I., Vaes, J., Govaerts, E., Reenaers, V., Frederix, I., Doherty,

P. J., & Dendale, P. (2022). Phase III multidisciplinary exercise-based rehabilitation is associated with fewer hospitalizations due to adverse cardiovascular events in coronary artery disease patients. *Eur J Prev Cardiol*, *28*(18), e17-e20. https://doi.org/10.1093/eurjpc/zwaa038

Harlan, W. R., Sandier, S. A., Lee, K. L., Choi Lam, L., & Mark, D. B. (1995). Importance of Baseline Functional and Socioeconomic Factors for Participation in Cardiac Rehabilitation. *The American Journal of Cardiology*, *76*(1), 36-39. https://doi.org/https://doi.org/10.1016/S0002-9149(99)80797-8

Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M., Deswal, A., Drazner, M. H., Dunlay, S. M., Evers, L. R., Fang, J. C., Fedson, S. E., Fonarow, G. C., Hayek, S. S., Hernandez, A. F., Khazanie, P., Kittleson, M. M., Lee, C. S., Link, M. S., . . . Yancy, C. W. (2022). 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*, *145*(18), e876-e894. https://doi.org/10.1161/cir.0000000000001062

Holgado, D., Zandonai, T., Ciria, L. F., Zabala, M., Hopker, J., & Sanabria, D. (2019). Transcranial direct current stimulation (tDCS) over the left prefrontal cortex does not affect time-trial self-paced cycling performance: Evidence from oscillatory brain activity and power output. *PLoS One*, *14*(2), e0210873. https://doi.org/10.1371/journal.pone.0210873

Hung, R. K., Al-Mallah, M. H., McEvoy, J. W., Whelton, S. P., Blumenthal, R. S., Nasir, K., Schairer, J. R., Brawner, C., Alam, M., Keteyian, S. J., & Blaha, M. J. (2014). Prognostic value of exercise capacity in patients with coronary artery disease: the FIT (Henry Ford ExercIse Testing) project. *Mayo Clin Proc*, *89*(12), 1644-1654. https://doi.org/10.1016/j.mayocp.2014.07.011

Jackson, L., Leclerc, J., Erskine, Y., & Linden, W. (2005). Getting the most out of cardiac rehabilitation: a review of referral and adherence predictors. *Heart*, *91*(1), 10-14. https://doi.org/10.1136/hrt.2004.045559

Kiernan, M. C., & Bostock, H. (2000). Effects of membrane polarization and ischaemia on the excitability properties of human motor axons. *Brain*, *123*(12), 2542-2551. https://doi.org/10.1093/brain/123.12.2542

Lane, D., Carroll, D., Ring, C., Beevers, D. G., & Lip, G. Y. H. (2001). Predictors of attendance at cardiac rehabilitation after myocardial infarction. *Journal of Psychosomatic Research*, *51*(3), 497-501. https://doi.org/https://doi.org/10.1016/S0022-3999(01)00225-2

Lattari, E., de Oliveira, B. S., Oliveira, B. R. R., de Mello Pedreiro, R. C., Machado, S., & Neto, G. A. M. (2018). Effects of transcranial direct current stimulation on time limit and ratings of perceived exertion in physically active women. *Neurosci Lett*, *662*, 12-16. https://doi.org/10.1016/j.neulet.2017.10.007

Lefaucheur, J. P., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B., Marangolo, P., Mylius, V., Nitsche, M. A., Padberg, F., Palm, U., Poulet, E., Priori, A., Rossi, S., Schecklmann, M., . . . Paulus, W. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol*, *128*(1), 56-92. https://doi.org/10.1016/j.clinph.2016.10.087

Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., Abraham, J., Adair, T., Aggarwal, R., Ahn, S. Y., Alvarado, M., Anderson, H. R., Anderson, L. M., Andrews, K. G., Atkinson, C., Baddour, L. M., Barker-Collo, S., Bartels, D. H., Bell, M. L., . . . Memish, Z. A. (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, *380*(9859), 2095-2128. https://doi.org/10.1016/s0140-6736(12)61728-0

Machado, S., Jansen, P., Almeida, V., & Veldema, J. (2019). Is tDCS an Adjunct Ergogenic Resource for Improving Muscular Strength and Endurance Performance? A Systematic Review. *Front Psychol*, *10*, 1127. https://doi.org/10.3389/fpsyg.2019.01127

McLaren, M. E., Nissim, N. R., & Woods, A. J. (2018). The effects of medication use in transcranial direct current stimulation: A brief review. *Brain Stimul*, *11*(1), 52-58. https://doi.org/10.1016/j.brs.2017.10.006

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, *57*(10), 1899-1901.

https://doi.org/10.1212/wnl.57.10.1899
Okano, A. H., Fontes, E. B., Montenegro, R. A., Farinatti Pde, T., Cyrino, E. S., Li, L. M., Bikson, M., & Noakes, T. D. (2015). Brain stimulation modulates the autonomic nervous system, rating of perceived exertion and performance during maximal exercise. *Br J Sports Med*, *49*(18), 1213-1218. https://doi.org/10.1136/bjsports-2012-091658
Olvera Lopez, E., Ballard, B. D., & Jan, A. (2023). Cardiovascular Disease. In *StatPearls*. StatPearls Publishing
Copyright © 2023, StatPearls Publishing LLC.
Priori, A. (2003). Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. *Clinical Neurophysiology*, *114*(4), 589-595. https://doi.org/https://doi.org/10.1016/S1388-2457(02)00437-6
Resurrección, D. M., Moreno-Peral, P., Gómez-Herranz, M., Rubio-Valera, M., Pastor, L., Caldas de Almeida, J. M., & Motrico, E. (2019). Factors associated with non-participation in and dropout from cardiac rehabilitation programmes: a systematic review of prospective cohort studies. *Eur J Cardiovasc Nurs*, *18*(1), 38-47. https://doi.org/10.1177/1474515118783157
Salzwedel, A., Jensen, K., Rauch, B., Doherty, P., Metzendorf, M. I., Hackbusch, M., Völler, H., Schmid, J. P., & Davos, C. H. (2020). Effectiveness of comprehensive cardiac rehabilitation in coronary artery disease patients treated according to contemporary evidence based medicine: Update of the Cardiac Rehabilitation Outcome Study (CROS-II). *Eur J Prev Cardiol*, *27*(16), 1756-1774. https://doi.org/10.1177/2047487320905719
Sasada, S., Endoh, T., Ishii, T., & Komiyama, T. (2017). Polarity-dependent improvement of maximal-effort sprint cycling performance by direct current stimulation of the central nervous system. *Neurosci Lett*, *657*, 97-101. https://doi.org/10.1016/j.neulet.2017.07.056
Stagg, C. J., Antal, A., & Nitsche, M. A. (2018). Physiology of Transcranial Direct Current Stimulation. *J ect*, *34*(3), 144-152. https://doi.org/10.1097/yct.0000000000000510
Taylor, R. S., Long, L., Mordi, I. R., Madsen, M. T., Davies, E. J., Dalal, H., Rees, K., Singh, S. J., Gluud, C., & Zwisler, A. D. (2019). Exercise-Based Rehabilitation for Heart Failure: Cochrane Systematic Review, Meta-Analysis, and Trial Sequential Analysis. *JACC Heart Fail*, *7*(8), 691-705. https://doi.org/10.1016/j.jchf.2019.04.023
Tergau, F., Geese, R., Bauer, A., Baur, S., Paulus, W., & Reimers, C. D. (2000). Motor cortex fatigue in sports measured by transcranial magnetic double stimulation. *Med Sci Sports Exerc*, *32*(11), 1942-1948. https://doi.org/10.1097/00005768-200011000-00019
Thair, H., Holloway, A. L., Newport, R., & Smith, A. D. (2017). Transcranial Direct Current Stimulation (tDCS): A Beginner's Guide for Design and Implementation. *Front Neurosci*, *11*, 641. https://doi.org/10.3389/fnins.2017.00641
Thielscher, A., Antunes, A., & Saturnino, G. B. (2015). Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? *Annu Int Conf IEEE Eng Med Biol Soc*, *2015*, 222-225. https://doi.org/10.1109/embc.2015.7318340
Tilgner, N., Nehls, D., Lichtmess, C., Kober, A., Küsel, C., Radloff, L., & Gabrys, L. (2022). Adherence to exercise and fitness following exercise-based outpatient cardiac rehabilitation: a cross-sectional survey for Germany. *BMC Sports Sci Med Rehabil*, *14*(1), 191. https://doi.org/10.1186/s13102-022-00585-0
Townsend, N., Kazakiewicz, D., Lucy Wright, F., Timmis, A., Huculeci, R., Torbica, A., Gale, C. P., Achenbach, S., Weidinger, F., & Vardas, P. (2022). Epidemiology of cardiovascular disease in Europe. *Nat Rev Cardiol*, *19*(2), 133-143. https://doi.org/10.1038/s41569-021-00607-3
Triantafyllidi, H., Birmpa, D., Benas, D., Trivilou, P., Fambri, A., & Iliodromitis, E. K. (2022). Cardiopulmonary Exercise Testing: The ABC for the Clinical Cardiologist. *Cardiology*, *147*(1), 62-71. https://doi.org/10.1159/000520024
Virani, S. S., Alonso, A., Benjamin, E. J., Bittencourt, M. S., Callaway, C. W., Carson, A. P., Chamberlain, A. M., Chang, A. R., Cheng, S., Delling, F. N., Djousse, L., Elkind, M. S. V., Ferguson, J. F., Fornage, M., Khan, S. S., Kissela, B. M., Knutson, K. L., Kwan, T. W., Lackland, D. T., . . . Tsao, C. W. (2020). Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation*, *141*(9), e139-e596. https://doi.org/10.1161/cir.0000000000000757
Vitor-Costa, M., Okuno, N. M., Bortolotti, H., Bertollo, M., Boggio, P. S., Fregni, F., & Altimari, L. R. (2015). Improving Cycling Performance: Transcranial Direct Current Stimulation Increases Time to Exhaustion in Cycling. *PLoS One*, *10*(12), e0144916.

https://doi.org/10.1371/journal.pone.0144916
Wiethoff, S., Hamada, M., & Rothwell, J. C. (2014). Variability in response to transcranial direct current stimulation of the motor cortex. *Brain Stimul*, *7*(3), 468-475. https://doi.org/10.1016/j.brs.2014.02.003
Yavari, F., Jamil, A., Mosayebi Samani, M., Vidor, L. P., & Nitsche, M. A. (2018). Basic and functional effects of transcranial Electrical Stimulation (tES)-An introduction. *Neurosci Biobehav Rev*, *85*, 81-92. https://doi.org/10.1016/j.neubiorev.2017.06.015
Ziaeian, B., & Fonarow, G. C. (2016). Epidemiology and aetiology of heart failure. *Nat Rev Cardiol*, *13*(6), 368-378. https://doi.org/10.1038/nrcardio.2016.25