Study Title: The Effects of Exercise Training on Central and Peripheral Blood Flow Regulation in Individuals with Down Syndrome

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INFORMED CONSENT

Department of Physical Therapy

TITLE OF STUDY: The Effects of Exercise Training on Central and Peripheral Blood Flow Regulation in Individuals With Down Syndrome

INVESTIGATOR(S): Thessa Hilgenkamp

For questions or concerns about the study, you may contact Thessa Hilgenkamp at 702-895-1055**.**

For questions regarding the rights of research subjects, any complaints or comments regarding the manner in which the study is being conducted, contact **the UNLV Office of Research Integrity – Human Subjects at 702-895-2794, toll free at 888-581-2794 or via email at IRB@unlv.edu.**

Purpose of the Study

You are invited to participate in a research study. The purpose of this study is to evaluate the effects of an exercise program on regulation of blood pressure, blood flow, gait and balance, level of support and quality of life in individuals with Down syndrome compared to a control group without Down syndrome.

Participants

You are being asked to participate in the study because you fit the following criteria:

- You are between 18 and 35 years old
- You are generally healthy
- You have a low active or sedentary lifestyle
- You have Down syndrome

Procedures

If you volunteer to participate in this study, you will be asked to do the following:

1. You will visit a laboratory on UNLV Campus three times at the start, and another three times after 12 weeks. Each of those visits will take about 2-2.5 hours.
2. You will be selected to either participate in an exercise intervention for 12 weeks, or not participate in an exercise intervention.

During the visits to the Cardiovascular Research and Exercise Laboratory (CARE-Lab, BHS 112) on the UNLV Campus, we will start by non-invasively examine cardiac output (how much blood your heart can pump each minute) during a treadmill test. In addition, this study will examine the autonomic

response (how your body controls heart rate and blood pressure) and how blood vessels change during and after stimulation (handgrip exercise and lower body negative pressure [LBNP – this is where a small vacuum will be created around your legs]).

Over the phone or during the first visit, the researcher will review this consent form with you and answer any questions that you may have. If you agree to participate, you will be asked to sign this informed consent form.
If you agree, you will be randomized to either the 12-week exercise program or the 'control condition' which is 12 weeks of your usual daily routine without any changes. If you are assigned to the control condition, you will be offered the opportunity to participate in the exercise program once you have completed the data collection at the start and at the end of the 12 weeks of the 'control condition'.

Preparation for all visits
Twenty-four hours prior to each visit, you cannot participate in any exercise, and you are asked to not drink or eat anything with caffeine, or drink alcohol. You cannot eat anything 3 hours before the visit. If you do not refrain from these things prior to the visits, you will be asked to come back another day. Please wear comfortable clothes to exercise in at each visit. UNLV and the CARE-Lab follow state-issued COVID-10 guidelines with regards to face coverings and social distancing.

Visit #1

1. Questions, pregnancy test, measurements.
   We will ask some questions about your health, your physical activity level, any fear of falling, level of support and quality of life. You will also perform a few cognitive tests on an iPad. If you are a female, we will need to test your urine to see if you are pregnant. If you are pregnant, you will not be able to participate in this study. We will also measure around your waist and hip, and you will lay on a table to assess your body composition (how much fat, muscle, bone and tissue is in your body) with a DEXA (a machine that looks like an x-ray). Next, your heart function will be measured using cardiac ultrasound (a heart scan). This test will allow us to see an image of your heart on a computer screen. This is the same technology used to image babies while still in the womb. Some ultrasound gel (consisting of salt and water) will be placed on your chest. We will then place the ultrasound probe over your heart to help us obtain a clear image. We will measure how well your heart contracts and relaxes. We will also measure how stiff the arteries are by briefly holding a small sensor on the skin of your wrist, arm and neck.

2. Laboratory Tour
   We will give you a tour of our lab. You will get to see the facility and equipment we will use during the study and meet the researchers working there.

   Experience (practice) some of the study tests and procedures:
   - We will show you the treadmill test. You will have the chance to practice walking on the treadmill at a slow speed. When you are comfortable, you can try faster speeds, or walking uphill (at an incline). When you are comfortable with walking on the treadmill, you will stop walking for a minute. We will show you the breathing mask and you can

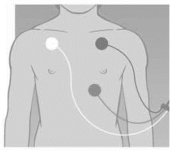
experience wearing it. When you are comfortable, we will practice walking on the treadmill with the breathing mask and while taking ultrasound measures.

At the end of the first visit, all participants will be provided with an Actigraph and instructions to wear this device for 7 days.

Visit #2

1. The second visit you will perform the treadmill walking test. This test is performed to obtain maximal oxygen consumption (VO_2peak) (the best measure available for fitness/work capacity) and maximal heart rate. You will wear a mask over your mouth and nose so we can analyze the air you breathe out during the treadmill test. The start of the treadmill test will be at a comfortable speed for 4 minutes. Then, the incline (slope) will be increased to 2.5% (to simulate walking uphill) and you will continue walking at the same speed for the next 2 minutes. Then, the incline is increased to 5% and you will continue walking at the same speed. Then, the incline is increased with 2.5% every 2 minutes until 12.5% (to simulate a very steep hill), while you continue walking at the same speed. After that, the incline will be kept constant, but the speed will be increased with 0.5 mph (miles per hour) every minute until you get tired and/or cannot keep up with the speed anymore. If you can, you may be running in this last part. During this test, cardiac output (the amount of blood leaving your heart per minute) will be measured using ultrasound. We will do this by touching your skin with a pencil-like ultrasound probe (ped-off probe) for 30 seconds at the end of every 2-minute stage.

2. Experience (practice) some of the study tests and procedures:
   - **a.** We will show you how we measure heart rate. We will place three stickers (electrodes) on your skin on the upper body to measure the beating of your heart.

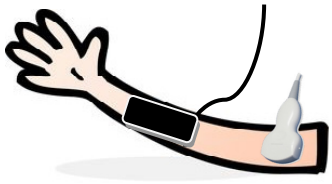


b. We will show you how we measure breathing. We will put a Velcro band around your upper body.

c. We will show you how we measure blood pressure. We put a small finger cuff around your middle finger to measure his/her blood pressure.

d. We will also show you how we measure blood pressure on your arm. During the treadmill exercise, we will measure your blood pressure with a cuff around your arm instead of on your finger.

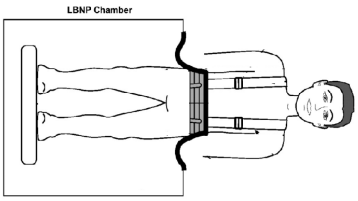
e. We will show you how we measure blood flow and oxygenation in the arm. We will use the ultrasound on the brachial (upper arm) artery to measure blood flow, and a device known as NIRS that sits on the forearm to measure oxygenation.



f. We will show you your heart rate, blood pressure, and brachial artery on the monitors.

g. We will show you the hand grip test. You will be asked to squeeze the hand grip device as hard as you can three times. After that, we will practice squeezing hard and squeezing a little to a rhythm.

h. We will show you the lower body negative pressure (LBNP) chamber. You will be asked to put your legs into the chamber. We will practice turning the chamber on to a very low pressure (-20 mmHg) so you can know how it feels.



Lastly, we will measure your gait and your balance with a number of different tests. We will look at the way you stand, the way you walk at different speeds, the way you walk stairs and make turns. Then we will look at how well you can keep your balance in different circumstance, such as reaching, closing your eyes, and standing on a moving platform. We will use a harness to prevent you from falling.
Once we are finished, we will discuss the next visit. We will provide you with information about how to prepare for the next visit.

Visit #3
Upon arriving to the lab, we will have you go to the bathroom before we start study procedures. Before and during the testing protocol in the lower body negative pressure (LBNP) chamber (at the end of the 5 min of resting before we start with the handgrip exercise) a total of approximately 6 tablespoons of blood will be drawn from a vein in your arm using a needle. This blood will be analyzed for biomarkers for a healthy heart and vascular system, inflammation and hormones, and we will also investigate if cardiovascular outcomes of this study are related to specific genetic variations.
We will start with the You will be asked to lie on your back in the LBNP chamber to perform arterial health assessments and handgrip exercise. Three electrode stickers will be put on your upper body to measure your heart rate. We will also attach a Velcro band around your chest to measure how much you breathe. We will attach a finger cuff around your middle finger of your left hand to measure your blood pressure, and an arm cuff on the right arm just for baseline measures. Lastly, a very sensitive pen-shaped microphone is placed on the wrist (radial artery). This microphone measures how stiff your radial artery is. After resting for 10 minutes, we will ask you to squeeze the handgrip as hard as you can to measure your maximal force. Then, you will perform different handgrip protocols:

1) Squeeze the handgrip 3 times for a single contraction at 20% of your hardest effort, 3 times for a single contraction at 40% of your hardest effort.
2) Perform rhythmic handgrip exercise at 15%, 30%, and 45% of your hardest effort for 5 minutes, with a 5-minute rest in-between

During this time, arm blood flow will be measured with ultrasound. In addition, forearm oxygen saturation will be measured by Near-infrared system on the palm side of the right forearm before and during handgrip exercise. A small near-infrared probe will be attached to your right forearm.

Next, the LBNP portion of the test will begin. The LBNP will be turned on to a low negative pressure (-20 mmHg) for 5 minutes. The same rhythmic handgrip exercise described in 2) above will be repeated.

Please wear loose and comfortable clothes and shoes that are suitable for working out.

Exercise Intervention

If you are selected to the group that will receive an exercise intervention, you will be participating in online 3 exercise sessions a week of 1 hour each. The exercise sessions will be offered as a remote exercise program, which means that all sessions will take place online through a HIPAA compliant Zoom platform. The program is specifically developed for individuals with Down syndrome based on the Mann Method PT Principles. The MMPT Principles TM focus on different exercises designed to improve cardiovascular fitness, strength and balance to address the unique needs of individuals with Down syndrome. This program has been developed and successfully implemented in Down syndrome activity centers across the country. The trainer is part of the research team and will be a certified PT or a Personal Trainer certification with at least a bachelor degree in Exercise Science of Kinesiology. In the exercise sessions, you will work on your strength, balance and aerobic endurance. Each session consists of 10 min of strength exercises, 10 min of hip exercises, 10 min of balance exercise, and 20 min of aerobic exercise, and starts with a warming up and ends with stretching/cooling down. Each new exercise will be introduced in easy steps and practiced until you are comfortable executing it. After a 5 min. warm-up, you will perform 20 min of aerobic exercise at a heart rate of 65% of your maximum heart rate, which increases to 65-85% during the later weeks of the program. The resistance exercise part will include all major muscle groups, both upper and lower body. Balance training will include exercises such as standing on one leg and standing on different surfaces, walking in different speeds and walking with obstacles. The caregiver does not need to be present during the exercise sessions.

If you are selected to the group that does not receive the exercise intervention, you will not have any exercise sessions to attend.

All participants will be fitted with footwear with good support before starting the exercise program.

Blood Banking

We would like to save any blood that is left over after we have completed analyzing it for this research study so that it could be used in future research about cardiovascular disease. Upon completion of the study, any remaining samples will be de-identified so that there is no link to your identity. The samples will be stored indefinitely at UNLV in the freezers located in the Translational Biomarker Unit. These de-identified samples could be used for future research studies or distributed to other investigators for future research studies. If you agree to bank your leftover samples, you may withdraw

your consent at any time **before** study completion by contacting Dr. Hilgenkamp at 702-895-1055. You will not be able to withdraw your consent **after** study completion (when the samples are de-identified) because we will not know which samples are yours.

☐ **I agree** to allow my blood samples to be kept by Dr. Hilgenkamp in the UNLV Translational Biomarker Unit for use by other researchers for future research to learn more about how to prevent, detect, or treat **cardiovascular disease**.
Initials _____.

☐ **I do NOT agree** to allow my blood samples to be kept by Dr. Hilgenkamp in the UNLV Translational Biomarker Unit for use by other researchers for future research to learn more about how to prevent, detect, or treat **cardiovascular disease**.
Initials _____.

☐ **I agree** to allow my blood samples to be kept by Dr. Hilgenkamp in the UNLV Translational Biomarker Unit for use by other researchers for future research to learn more about how to prevent, detect, or treat **other health problems**.
Initials _____.

☐ **I do NOT agree** to allow my blood samples to be kept by Dr. Hilgenkamp in the UNLV Translational Biomarker Unit for use by other researchers for future research to learn more about how to prevent, detect, or treat **other health problems**.
Initials _____.

Participating in Future Studies

As an optional part of this study, we would like to bank (indefinitely store) your contact information to contact you in the future about participating in other research studies about cardiovascular health and Down syndrome. If you agree, Dr. Hilgenkamp will keep the following information: your name, address, phone number, e-mail address, date of birth, age, race, sex, weight and height, and whether you are a control subject or have Down Syndrome. Access will be limited to her alone. You may withdraw your consent at any time in the future by contacting Dr. Hilgenkamp directly at 702-895-1055.

☐ **I agree** to allow the researchers to contact me about future research.
Initials _____.

☐ **I do NOT agree** to allow the researchers to contact me about future research.
Initials _____.

Benefits of Participation

There may not be direct benefits to you as a participant in this study. However, we hope to learn whether exercise can improve the regulation of blood pressure and blood flow in individuals with Down syndrome, and how we can use this knowledge in motivating and supporting individuals with Down syndrome in an active lifestyle.

Risks of Participation

There are risks involved in all research studies. We consider this research to have minimal risk for the participants because any harm or discomfort anticipated in the research are not greater than in daily life or during the performance of routine physical examinations or tests in the doctor's office or physical therapist's office.

1. You may feel uncomfortable providing personal information in the questionnaires. You will be instructed to skip any questions they do not wish to answer.
2. To address possible anxiety caused by a laboratory setting, techniques that have been successful in our lab will be used previously to familiarize the participants will be employed.
3. Blood pressure will be measured using a cuff around the finger and around the arm. You may feel some tingling on the finger and some squeezing on the arm.
4. Skin redness may appear where the electrodes (patches) are placed on the skin for heart rate measurements.
5. Aerobic capacity test: The treadmill testing may result in muscle soreness, feeling tired, or out of breath. The soreness should go away in a few days. You may also feel dizzy, faint, trip, fall, or sprain an ankle during the testing. Spotters will be used during the test. A mouthpiece will be worn to measure breathing so participants may feel uncomfortable. You may feel warm during the test. Ambient temperature will be kept at a comfortable temperature between 22-24 degrees Celsius. Additional fans will be provided, as needed, to keep you cool and comfortable. You will be instructed that you can stop the test at any time. Other rare, but serious, risks associated with a peak exercise test include: rapid or irregular heart rhythms, chest pain, heart attack, and very rarely death.
6. Adverse events and injuries during the exercise testing might occur. Your physical response of will be monitored throughout the test by trained research staff. There have previously not been any problems with adverse events and injuries when the research is performed by experienced personnel, but, in the instance of an adverse event, the PI will report the event to the IRB.
7. Risk of loss of privacy or confidentiality of information. To reduce the risk, all data will be stored coded.
8. You may experience mild pain, bleeding or bruising at the site of the blood draw. You may also faint or get a mild infection at the site of the draw.
9. You may also feel dizzy or light-headed during the tilt-table testing.
10. Your hands may get tired squeezing during the hand grip exercise.
11. There are no known risks with ultrasound and all efforts will be made to maintain your modesty. The gel used during the ultrasound may feel cool and sticky and is hypoallergenic (not likely to cause an allergic reaction) and washes off easily.

Cost /Compensation

There will not be any financial cost to you to participate in this study. The study will take 14 hours or your time for the study visits to the laboratory, and an additional 36 hours in exercise sessions if you are randomized to the exercise intervention. You will be compensated for your time with $25 for each of the 6 study visits to the laboratory at UNLV Campus. All research-related tests and the exercise intervention will be performed free at no cost to the subjects.

We will do our very best to prevent any injury from happening to you. However, UNLV may not provide compensation if unanticipated injury occurs in the course of the research.

Confidentiality

All information gathered in this study will be kept as confidential as possible. Participants will be asked to provide their mailing address and date of birth for compensation purposes. These identifiers will not be linked to the study data and destroyed upon the completion of the study. No reference will be made in written or oral materials that could link you to this study. All records will be stored in a locked facility at UNLV for 7 years after completion of the study. After the storage time the information gathered will be destroyed.

Voluntary Participation

Your participation in this study is voluntary. You may refuse to participate in this study or in any part of this study. You may withdraw at any time without prejudice to your relations with UNLV. There is no penalty if you withdraw from this study. You are encouraged to ask questions about this study at the beginning or any time during the research study.

Participant Consent:

I have read the above information and agree to participate in this study. I have been able to ask questions about the research study. I am at least 18 years of age. A copy of this form has been given to me.

_____ _____

Signature of Participant Date

_____

Participant Name (Please Print)

_____ _____

Signature of Parent / Legal Authorized Representative (LAR) of Participant Date

_____

Printed Name of Parent / LAR of Participant

Describe relationship to subject including the legal authority this individual has to act on behalf of the subject. (Check one below)

☐ Parent
☐ Medical Power of attorney/representative
☐ Health care surrogate
☐ Other; specify _____