Title

Cerebral Blood Flow Control in Women During a Ten Week, Two Paradigm Resistance Training Intervention: study protocol for a parallel group, equivalence randomized controlled trial.

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Abstract

Background: Resistance exercise training (RET) induces changes in blood pressure that challenge the cerebral vasculature to regulate cerebral blood flow (CBF). Resistance-trained individuals have higher blood pressure during RET, with no change in middle cerebral artery blood velocity (MCA*v*), an estimate of CBF. Most training interventions collect data at two points: pre- and post-intervention, providing limited insight into the time course of vascular adaptations – especially in women. Furthermore, it is unknown whether these adaptations are reversed upon cessation of training (detraining). Previous research has shown that detraining resulted in a reduction in peripheral arterial diameter below baseline levels. Yet, it remains unknown how the cerebrovasculature responds. Additionally, as RET intensity increases, arterial stiffness increases. Nonetheless, the literature is scarce regarding the effects of intensity on CBF regulation and adaptation. The purpose of this study is to investigate CBF regulation in women before, weekly, and after a RET intervention, comparing higher-load (HL) and lower-load (LL) groups. We hypothesize that CBF regulation will improve, detraining effects would occur, and that both groups would show similar control.

Methods: This study is a 10-week randomized, parallel-group, equivalence intervention trial in females. Participants will visit the lab weekly for supervised RET sessions, during which they are randomly assigned to one of two conditions: a higher load group completing 8-12 repetitions per set or a lower-load group completing 20-30 repetitions per set, with both groups working to volitional fatigue/failure. The study includes two intervention arms and no traditional control group. The design is not blinded as participants and researchers are aware of group assignments due to the nature of exercise interventions. Participants will have their peripheral vascular mechanics measured (including arterial stiffness, arterial distensibility, endothelial function, and global CBF) prior to the start of the intervention, at the end of the intervention, and two weeks post-intervention. CBF regulation, assessed during leg press and via a cerebrovascular reactivity test, will be measured throughout the intervention and 2 weeks post-intervention.

Discussion: Findings from this study will provide a foundational characterization of adaptation in CBF control over a short-term RET intervention in women. This study will address a critical knowledge gap regarding the intersection of RET and women's cerebrovascular health. This study will also provide insight into CBF control throughout an intervention, rather than only before and after, which assumes linear progression.

Trial Registration: Isrctn.com, ISRCTN38725877. Registered 29 July 2025, https://www.isrctn.com/ISRCTN38725877?q=cerebral%20blood%20flow&filters=&sort=&offset=4&totalResults=154&page=1&pageSize=10

Keywords

Resistance Exercise Training, Cerebral Blood Flow Control, Female Physiology

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	Cerebral Blood Flow Control in Women During a Ten Week, Two Paradigm Resistance Training Intervention .
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Name and contact information for the trial sponsor {5b}	n/a This study is investigator-initiated.
Role of sponsor {5c}	n/a This study does not have a sponsor.

Introduction

Background and rationale {6a}

During resistance exercise training (RET), oscillatory fluctuations in blood pressure(1) coincide with the eccentric and concentric contractions of the skeletal muscle(2). These extreme and rapid changes in blood pressure challenge the cerebral vasculature to regulate cerebral blood flow (CBF) through vasoconstriction and vasodilation. High intensity RET is associated with positive vascular adaptations such as greater resting arterial diameter(3), improved endothelial function, and nitric oxide production(4). However, RET has also been shown to significantly reduce arterial compliance(5,6)– a key regulator of dynamic cerebral autoregulation (i.e., the ability to control brain blood flow in the face of blood pressure changes)(7).

Compared to untrained adults, resistance-trained adults have higher cerebrovascular resistance, which could lead to better CBF regulation, potentially protecting the downstream microvasculature from the high pressures associated with RET (8,9). Resistance-trained individuals also showed increased blood pressure during RET, with no change in middle cerebral artery velocity (MCAv) – an estimate of CBF (10,11). This outcome could indicate better maintenance of cerebral blood flow in trained compared to untrained individuals and may be due to the stiffening effects of the vessels(10). However, understanding at what point during the training process these peripheral and cerebrovascular adaptations develop is less clear. Furthermore, it is unknown whether these adaptations are reversed when training is stopped and, if so, how long it takes for this to occur. Previous research mainly focuses on endurance detraining effects on the cardiovascular system (12–14). In one study focused on RET, it was found that 2 weeks of detraining resulted in a reduction in arterial diameter below pre-intervention baseline levels (15). Yet whether the brain vasculature also reverses adaptations following detraining is unknown.

The load used during RET is a major factor affecting the adaptations associated with the stimulus. When RET is performed using lower loads (50% of 1 repetition maximum), studies found that arterial stiffness was reduced(16). When performing RET at moderate intensity (60% of 1 repetition maximum), there was no change in arterial stiffness (17). Finally, when performing at high intensities (above 75% 1 repetition maximum (6)), individuals showed increased arterial stiffness (18). These studies did not have participants exercise until volitional failure and therefore load was indicative of intensity. Consequenctly, the literature is scarce regarding the effects of load on CBF and whether intensity matters when training to volitional failure. One study investigated the effects of endurance exercise intensity on cerebral blood flow (19). It was found that there are intensity-dependent effects on blood flow in the arteries that supply blood to the brain, with higher intensities resulting in a larger increase in blood flow in the internal carotid artery (19). However, this has not been investigated among resistance-trained individuals. Therefore, this study will also investigate whether the load of the RET affects CBF control and whether load affects the length and severity of detraining.

Objectives {7}

Although studies have shown that RET affects the vasculature (20), the time course of cerebrovascular adaptations during an RET intervention and following its cessation (i.e., detraining) is unknown. As well, it remains unknown whether RET intensity influences CBF control and whether detraining affects CBF control. The objective of this study is to investigate the effect of two resistance training paradigms (lower load vs higher load) on CBF control over the course of a ten-week intervention and two weeks post-training cessation (i.e., detraining) in women while working to volitional failure.

Trial design {8}

This protocol was developed in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and prospectively registered on https://www.isrctn.com (ISRCTN38725877). This trial is also a part of a larger study that was prospectively registered (ISRCTN95727228).

Methods: Participants, interventions, and outcomes

Study setting {9}

This study is a single-site, parallel-group, randomized controlled trial taking place at McMaster University in Ontario, Canada. The trial protocol will occur over 13 weeks: a baseline visit (week 0) to characterize the cardiovascular and cerebrovascular systems, a ten-week resistance training intervention with sessions twice per week, and a two-week detraining period. Specific measures will be evaluated at week 0, 1, 2, 3, 4, 7, 10, and 12.

Eligibility criteria {10}

We will recruit females aged 18-35 years. All females must be able to maintain a habitual diet and perform RET two times per week throughout the trial. Exclusion criteria includes pregnancy, mild-traumatic brain injury in the last year, any history of severe traumatic brain injury, cardiovascular, cerebrovascular, or neurological conditions, metabolic syndrome, history of syncope or light-headedness, history of migraines or chronic headache, respiratory illnesses, diabetes, claustrophobia, any current musculoskeletal injury that would make it difficult or unsafe to perform RET, major psychiatric conditions, dependence on alcohol or drugs within the past year, all of which will be determined from medical questionnaires. Participants must be free from the use of medications known to affect protein metabolism (i.e., corticosteroids, non-steroidal anti-inflammatory drugs (prescription or daily use of over-the-counter medication), or prescription-strength acne medications). Additionally, participants must not be taking anabolic steroids or other banned performance-enhancing substances as outlined by the Canadian Center for Ethics in Sport (https://cces.ca).

Who will take informed consent? {26a}

The team lead student investigator (V. Mizzi) will obtain all informed consent. Interested participants will be provided with a consent form to read alongside the lead student investigator, where they can ask questions. If they are eligible and decide to participate, they will be asked to sign the consent form and will receive a copy to keep, along with the original. For those who are ineligible and/or not interested, any information provided will be destroyed.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

n/a No specimens will be collected, and data or data will not be entered into a database for future research studies.

Interventions

Explanation for the choice of comparators {6b}

Based on previous research surrounding the intensity of resistance exercise (discussed in the introduction), two exercise intensities were chosen to compare. Participants will either perform exercise using a higher load (HL) where they will complete approximately 8-12 repetitions until volitional failure, or a lower load (LL) where they will complete anywhere from 20-30 repetitions until volitional failure,

Intervention description {11a}.

Testing Before the Start of the Ten-Week Intervention:

After being screened into the study, participants will come into the lab to have cerebrovascular and cardiovascular measures collected as a baseline, which will be compared with the same measures taken post-intervention and post-detraining.

At each data collection visit, participants must be fasted for at least 6 hours, free from caffeine and alcohol for 8 hours, and must not have engaged in any intense exercise at least 24 hours before their visit.

Participants will be tested on the leg press to determine their estimated 1-repetition maximum (1RM). Their height and weight will also be recorded. Prior to the start of the intervention, participants will be randomized to either the higher-load or lower-load group.

During the Ten-Week Intervention:

During the intervention, participants will train twice weekly under the direct supervision of our trained research team. Each RET bout will include either higher load (HL: ~80%1RM, 8-12 repetitions) or lower load (LL: ~30%1RM, 20-25 repetitions) RET. For the duration of the 10 weeks, participants will only perform either HL or LL. Each training session will consist of 3 supersets to keep workouts concise, with full-body muscles engaged. These consist of a bilateral machine leg press superset with machine chest press, a machine leg extension superset with machine seated row, and a machine shoulder press superset with machine lat pulldowns. Each superset will consist of three sets before moving on to the next pair of exercises. Sets will be separated by 2 minutes. Whereas when moving on to the next superset, participants will be given 3 minutes of rest. Each exercise is taken to volitional failure, and machine weight will be adjusted throughout the intervention so participants can obtain 8-12 repetitions at a higher load or 20-30 repetitions at a lower load. The twice-weekly training sessions must be separated by at least 48 hours.

In the tenth week of the intervention, participants will come to the lab for another characterization data-collection visit, during which both cerebrovascular and cardiovascular measures will be collected.

Testing Following the Ten-Week Intervention:

Following 10 weeks of resistance training, participants will refrain from weightlifting for 2 weeks, encompassing the detraining portion of the study.

The two post-testing visits will be a repeat of the data collection conducted in the tenth week of the intervention—a combination of the pre-testing data collection session and the testing prior to the training sessions. The only difference is that no exercise will take place after the single leg press set.

Criteria for discontinuing or modifying allocated interventions {11b}

Participants must complete at least 18 of 20 exercise sessions and attend at least one session per week. They cannot miss 7 days in a row. They will be excluded from the study is this occurs. Modifications have been made for individuals who unexpectedly left the country during the study timeframe. Their sessions were increased to 3 times per week. In this case, data collection days occurs on training session 1 (*week 1*), 3 or 4 (*week 2*), 5 or 6 (*week 3*), 7 or 8 (*week 4*), 13 or 14 (*week 7*), 19 or 20 (*week 10*), and two weeks post-intervention.

Strategies to improve adherence to interventions {11c}

During the consent and screening visit (prior to the start of the intervention), interested volunteers will be walked through the details of the study, including the time commitment required, as outlined in the consent form they will receive. Emails are sent 24 hours prior to each data collection visit to remind participants, and calendar invites are sent at the time the visits are scheduled.

Relevant concomitant care permitted or prohibited during the trial {11d}

Participants must refrain from resistance training outside of the study. They can continue with any aerobic exercise as long as this is a constant in their routine prior to and during the intervention. No concomitant care is required during the trial.

Provisions for post-trial care {30}

Every effort will be made to minimize potential risks by evaluating preliminary information regarding your health and fitness and by careful observation during testing. Ensuring that all exercise is supervised at all times will also minimize the risks. Maximal resistance exercise will be performed on a leg press machine to mitigate potential mechanical risks associated with free-weight resistance exercise. We continuously monitor physiological data (e.g., heart rate and blood pressure). Additionally, juice and snacks will be on-site for participants who are fasting. Data will be de-identified, and only the consent forms and the study key will contain participants' first and last names. All other materials associated with individual participants will be linked to a unique study ID.

Outcomes {12}

The primary outcome measure of this study is directional sensitivity, which will require a Transcranial Doppler Ultrasound (TCD; Multigon Industries Inc.; Elmsford, New York, USA) and a non-invasive finger cuff (Human NIBP nano wrist unit; AD Instruments, Colorado Springs, CO, USA) for continuous blood pressure monitoring. This measure will be calculated using the maximum, minimum, and mean values of mean arterial pressure (MAP) and MCA*v*. Time to maximum and time to minimum will also be calculated.

The secondary outcome measures include arterial stiffness (measured by carotid-femoral applanation tonometry), endothelial vasodilatory function, intima-media thickness of the brachial artery, carotid distensibility, vertebral artery (VA) and internal carotid artery (ICA) blood flow, MCA*v*, and cerebrovascular reactivity. Systemic hemodynamic measures (e.g., blood pressure and heart rate) are also secondary outcomes.

The tertiary outcomes are fatigue-related measures, such as rating of perceived exertion (Modified Borg Scale), blood lactate concentration, and questionnaires (Profile of Mood States, Short Recovery and Stress Scale). Anthropometrics and strength testing will also be collected as outcomes.

Category	Variable	Measurements and Analyses
Primary Outcomes		
Cerebral Pressure Flow Relationship	*Directional Sensitivity*	Participants will perform one set of leg press until volitional failure at their calculated weight which will vary depending on their randomized grouping. As a note: this leg press set will count towards one of the three sets of leg press that will be done that day during the training itself. From this working set, we will analyze the cerebral pressure-flow relationship, including using a novel method to quantify directional sensitivity of the cerebral pressure-flow relationship. In brief, a time-adjusted ratio between MCAv and MAP changes is calculated for both increases and decreases in MAP during each repetition on the leg press. This is done by taking absolute changes in MCAv ($\Delta MCAv_T$) and MAP (ΔMAP_T) for each increase (from minimum to maximum) and decrease (from maximum to minimum) and adjusting for time intervals when the transitions in MCAv and MAP occur. Specifically, the changes in MCAv and MAP are divided by the duration of the transition (i.e., time interval between minimum to maximum or between maximum to minimum). The time adjusted changes in MCAv and MAP ($\Delta MCAv_T/\Delta MAP_T$) in both directions (increases and decreases in MAP) are then calculated for each individual. The ratios of increase over decrease are then averaged across repetitions. The ratios will also be compared amongst repetitions. Absolute Directional Sensitivity Increases and Decreases ($\Delta MCAv_T/\Delta MAP_T$) Relative Directional Sensitivity Increases and Decreases ($\%MCAv_T/\%MAP_T$)
Secondary Outcomes		
	Pulse Wave Velocity	We will measure arterial stiffness (Carotid-Femoral pulse wave velocity) for 30 cardiac cycles to make our data robust to any issues in signal acquisition. Carotid-Femoral pulse wave velocity will be measured using non-invasive applanation tonometry probes equipped with micromanometer-tipped pressure sensors on the surface of the skin at both the Carotid and Femoral arterial sites. Raw tonometry data will be used to calculate pulse wave velocity using the formula: (Carotid-Femoral pulse wave velocity = (0.8 × carotid-femoral distance)/carotid-femoral pulse transit time). Arterial augmentation index will be calculated using this formula: Augmentation Index (%) = (Pressure 2 – Pressure 1)/Pulse Pressure × 100.
	Flow Mediated Dilation	Endothelial function will be assessed by the flow mediated dilation test. We will begin the test by placing the pressure cuff on the lower arm and subsequently inflated to 200mmHg to reduce blood flow in the brachial artery for 5 minutes. Following the 5-minute brachial artery occlusion, the cuff will be released to elicit brachial artery endothelium-dependent dilation. We will use duplex ultrasonography to measure blood velocity and diameter changes (expressed as percent change) at the brachial artery. Images of diameter and blood velocity will be recorded at rest (before cuff inflation), during the last minute of cuff inflation, and continuously for 3 minutes following cuff-release. This will be calculated by: Flow Mediated Dilation (Diameter during Hyperemia – Baseline Diameter / Baseline Diameter).
Vascular Mechanics	*Distensibility*	Distensibility of the common carotid artery (CCA) will be assessed using 2 methods (the gold standard methods and the M-Mode method) described below. The gold standard method will occur at week 0 (prior to the start of the intervention), week 10 (end of the intervention), and week 12 (after a 2-week detraining period). The M-Mode method will occur throughout the intervention at week 1, 2, 3, 4, 7, 10, and after the detraining period (week 12). Gold Standard Method: To collect carotid arterial compliance, we will use the duplex Doppler ultrasound and Carotid artery tonometry simultaneously to measure arterial diameter and arterial blood pressure at the neck, respectively. This will assess the ability of the carotid artery to buffer pressures ejected from the heart over a duration of 30 seconds. We will then use a software to analyze and determine intima media thickness (mm). M-Mode: A similar process will be used. We will collect a proxy measure of resting carotid arterial compliance via M Mode Terason uSmart ultrasound to assess carotid arterial compliance. This will allow us to assess diameter and intima media thickness over time at a single point.

		These measures will be quantified using the formulas: Compliance = [(End Systolic Diameter – End Diastolic Diameter)/End Diastolic Diameter]/[2(End Systolic Pressure – End Diastolic Pressure)] $\times \pi \times (D\ 0)^2$ CCA Strain ((Systolic Diameter – Diastolic Diameter)/ Diastolic Diameter) CCA Distensibility (1/[ln(SBP/DBP)/Strain $\times$ Intima Media Thickness]) CCA Pulsatility Index (Peak Systolic CCA v – End Diastolic CCA v / CCA v_{Mean})
Resting Cerebral Blood Flow	*ICA: flow, velocity, diameter*	A one-minute ultrasound measurement recording of the right and left internal carotid artery were taken to assess diameter, velocity of blood, and blood flow. This will then be used to calculate pulsatility index (PI = (ICA $v_{(systolic)}$ – ICA $v_{(diastolic)}$)/ICA v) and cerebrovascular damping factor (DF = PI_{ICA}/PI_{MCA}).
	VA: flow, velocity, diameter	A one-minute ultrasound measurement recording of the right and left vertebral artery were taken to assess diameter, velocity of blood, and blood flow. This will then be used to calculate pulsatility index (PI = (VA $v_{(systolic)}$ – VA $v_{(diastolic)}$)/VA v) and cerebrovascular damping factor (DF = PI_{VA}/PI_{MCA}).
	MCA: velocity	Middle cerebral artery velocity was collected using a Transcranial Doppler Ultrasound. This measurement will be used to calculate directional sensitivity (as described above), ICA and VA damping factor (as described above), cerebrovascular conductance index (CVCi = MCA v / MAP), cerebrovascular resistance index (estimated as MAP/MCA Vmean), and cerebrovascular pulsatility index (PI = (MCA $v_{(systolic)}$ – MCA $v_{(diastolic)}$)/MCA v).
Cerebrovascular Control	*Cerebrovascular Reactivity*	We will test for cerebrovascular reactivity using a Douglas bag filled with a fixed concentration of CO_2 (5%), O_2 (15-21%), and N_2 (74%). A valve will allow inspiratory gases to be switched from room air to the 5% CO_2 mixture for 3 minutes (using a 120-litre Douglas bag). After which, the valve will switch back to room air breathing. The duration of the test includes a 1-minute baseline recording, 3 minutes of breaking the 5% CO_2 mixture, and a 2-minute recovery period. For the entirely of the test, the right internal carotid artery will be imaged using the Duplex ultrasound. This will be calculated by: Cerebrovascular Reactivity (%ΔMCA v / $\Delta P_{ET}CO_2$).
Systemic Hemodynamics	*Heart Rate*	Heart rate will be collected using a 3-lead electrocardiogram.
	Blood Pressure	Blood pressure will be measured continuously using a small cuff placed on a finger (Finometer) which uses photoplethysmography. A blood pressure cuff placed will also be placed on the right arm to collect blood pressure measures in the brachial artery at the beginning of each data collection visit.
Tertiary Outcomes		
Fatigue Measures	*Rating of Perceived Exertion*	After completing the leg press set, one minute of recovery data will be collected, and participants will be asked to provide a rating of perceived exertion value using the Modified Borg Scale (1-10).
	Blood Lactate Concentration	To obtain blood lactate concentration, the Nova Biomedical Lactate Plus Meter and Lactate Plus Lactate Test Strips will be used. 0.7μL of capillary blood from the tip of the finger will be obtained. This blood is then processed in the Nova Biomedical Lactate Plus Meter Analyzer that produces immediate results regarding lactate concentration. This will be repeated a total of 2 times per data collection session – one before the leg press set and one 10 minutes following completion of the exercise. Blood will be drawn from the tip of the right index finger for pre-concentration values and from the right middle finger for post-concentration values. This will aim to understand peripheral fatigue.
	Questionnaires (POMS, SRSS)	Participants will be required to fill out 'The Profile of Mood States' questionnaire prior to each data collection visit to understand the participants' mood and feelings that day. As well participants will fill out 'The Short Recovery and Stress Scale' before each data collection session to get baseline measurements regarding recovery and stress data. The Profile of Mood States questionnaire will list a variety of emotions where participants will be asked to rate – on a scale from 0 = "Not At All" to 4 = "Extremely", the number that best describes how they feel right at that moment. The Short Recovery and Stress Scale contains 8 categories with 4 aspects relating to recovery and 4 aspects relating to stress. Participants will rate how they feel at the moment on a scale from 0 to 5, where 0 – "does not apply at all" and 5 = "fully applies".
Other Measures		
Strength Testing & Anthropometrics	*1RM Test*	A 1 repetition maximum test will be conducted prior to the start of the intervention to assess strength and provide an estimation of the starting weight to use on the semi-recumbent leg press machine when the intervention begins.

		Weight will be loaded in increments until participants can only complete one repetition. Adequate rest will be given between each repetition attempt. A maximum of 5 attempts are allowed.
	Height	Height was measured prior to the start of the intervention.
	Weight	Weight was measured prior to the start of the intervention.

Participant timeline {13}

Timepoints										
		Pre-Intervention Baseline		10-Week Intervention						Post-Intervention Detraining
	Week	*Week -1*	Week 0	*Week 1 (visit 1)*	*Week 2 (visit 3 or 4)*	*Week 3 (visit 5 or 6)*	*Week 4 (visit 7 or 8)*	*Week 7 (visit 13 or 14)*	*Week 10 (visit 19 or 20)*	*Week 12* (14 ± 1 day)
Enrollment										
	Eligibility screen	X								
	Informed consent	X								
	Randomization		X							
Category	Variable	Assessment								
Cerebral Pressure Flow Relationship	*Directional Sensitivity*			X	X	X	X	X	X	X
Systemic Hemodynamics	Heart Rate		X	X	X	X	X	X	X	X
	Blood Pressure		X	X	X	X	X	X	X	X
Vascular Mechanics	*Pulse Wave Velocity*		X						X	X
	Flow Mediated Dilation		X						X	X
	Distensibility		X	X	X	X	X	X	X	X
Resting Cerebral Blood Flow	*ICA: flow, velocity, diameter*		X	X	X	X	X	X	X	X
	VA: flow, velocity, diameter		X						X	X
	MCA: velocity		X	X	X	X	X	X	X	X
Cerebrovascular Control	*Cerebrovascular Reactivity*			X	X	X	X	X	X	X
Fatigue Measures	*Rating of Perceived Exertion*			X	X	X	X	X	X	X
	Blood Lactate Concentration			X	X	X	X	X	X	X
	Questionnaires (POMS, SRSS)			X	X	X	X	X	X	X
	1RM Test		X							

Strength Testing & Anthropometrics	*Height*		X								
	Weight		X								

Sample size {14}

Sample size calculations were performed for the primary objective of directional sensitivity. Based on previous work, exercise training modality does influence the directionality of the cerebral pressure-flow relationship and support the presence of a hysteresis-like pattern during 0.10 Hz repeated squat-stands in sedentary and endurance-trained participants, but not in resistance-trained individuals(11). Another study also found that resistance trained individuals had more effective cerebral autoregulation during acute reduction in blood pressure(10). Both studies had 12-15 participants per group. We also ran power simulations using SimR, and data (mean and SD values) from Roy *et al*'s paper(11). A sample size between 45 and 50 is required to reach 80% power with a calculated effect size of 0.17. We will recruit participants from the larger training study who is recruiting a sample size of 52.

Recruitment {15}

The larger study that is taking place (as mentioned in section 8 – Trial Design) aims to enrol 52 females from which we will recruit into our study. As with any study that relies on participant recruitment, finding eligible participants who are eager to join a study is difficult. Considering that this study is mainly non-invasive, we expect many participants to be open to participating. In the event that we do not recruit enough participants to have a fully powered study, this study will be deemed a pilot study to encourage future areas of research.

To increase recruitment efforts, we will post recruitment posters around McMaster University (Ivor Wynne Centre, David Braley Athletic Centre, student center), public libraries, off-campus gyms, and other areas in the community (e.g., Dundas community center). We will contact past participants in other ongoing study within the lab that gave permission to be contacted for future studies.

Assignment of interventions: allocation

Sequence generation {16a}

The randomization process for the intervention was completed using an online tool (www.sealedenvelope.com). We used the block randomization feature to ensure balanced allocation across groups. The system generated randomization codes, which were then used to assign participants accordingly.

Concealment mechanism {16b}

No concealment will be necessary as participants and researchers are not blinded to the training conditions of each participant.

Implementation {16c}

A team member of the larger, collaborating study will be responsible for assigning participants to the exercise conditions. Team leader (VM) will not be involved in this process.

Assignment of interventions: Blinding

Who will be blinded {17a}

There will be no blinding of participants or researchers throughout the intervention. As all participants will undergo exercise training and detraining, neither the participants nor the investigators will be blinded to these interventions. However, investigators conducting analyses (primary, secondary, and tertiary outcomes) and statistical analyses (all outcomes) will be blind to group and intervention week. The data collected and participants' study ID codes will be blinded to the lead investigator during data analysis. A password-protected study key with de-identified participant identification numbers will be used for blind analyses and will be revealed once analyses are complete.

Procedure for unblinding if needed {17b}

n/a Since blinding will not occur for this study, the unblinding procedure is not relevant.

Data collection and management

Plans for assessment and collection of outcomes {18a}

The protocols herein are piloted prior to study data collection. The study is approved by the Hamilton Integrated Research Ethics Board (HiREB). We will report participant anthropometric and other physiological characteristics (resting hemodynamics, 1-repetition maximum), including sex assigned at birth and age.

The primary outcomes of this study involve the use of transcranial Doppler ultrasound to obtain blood velocity data from the right MCA. Insonation depth and probe location will be documented for each participant each week to ensure reproducibility.

Carotid-femoral pulse wave velocity will be used to measure arterial stiffness (22) and is considered the gold standard for arterial stiffness assessment.

To assess cerebrovascular reactivity, participants will wear a non-rebreather mask and receive a gas mixture (5% CO_2, 15-21% O_2, balance N_2) delivered via a Douglas bag. This method is widely recognized in both clinical and research contexts as the gold standard for inducing hypercapnic conditions(23). The CO_2 challenge protocol has been thoroughly validated for safety and participant tolerability.

All subjective measures, such as the Borg Rating of Perceived Exertion scale, Profile of Mood States questionnaire, and Short Recovery and Stress Scale, have been validated in previous research (24–26).

The Nova Biomedical Lactate Plus analyzer will be used to measure blood lactate concentration prior to and after the leg press set. This tool has been proven to provide accurate and reproducible results(27).

Plans to promote participant retention and complete follow-up {18b}

A screening visit will take place where all expectations and a description of the study and requirements will be discussed with eligible participants. Participants will be able to ask questions to clarify and understand study expectations. This will improve intervention adherence and retention. To maintain participant retention during the study, participants must attend at least 18 of 20 exercise sessions, attend at least one session per week, and cannot miss 7 days in a row. Researchers will also remain in constant contact with participants through email and text message. A financial honorarium will be provided to participants upon completion of the trial. If a participant does not complete the entire trial, they will receive partial compensation, pro-rated to their level of involvement.

Data management {19}

We will store our data on our password-protected computers in encrypted folders and in a room with limited access. In the future, we may set up a server through McMaster's Research & High-Performance Computing department, where data will be backed up often and secured using McMaster's IT system. Furthermore, only people on the ethics application will have access to the raw data, and analyses will be conducted on the secure analysis computer rather than on individual laptops.

We will extract raw data and calculate variables (e.g. physiological variables, including blood pressure and middle cerebral artery blood velocity to calculate our outcome of interest - directional sensitivity) on the data as we collect it. All statistical analyses will be completed only after we finish recruitment. However, data extraction to acquire the calculated variables will be ongoing throughout the study.

Confidentiality {27}

Participant identifiable data will not be shared with anyone except with the participant's consent or as required by law. The consent forms, medical screening forms, and Physical Activity Readiness Questionnaire for Everyone (PARQ+) forms will be stored securely in Ivor Wynne Centre E113. All personal information will be removed from the data and anonymized using a unique study ID. A list linking the number with participant names will be kept in a secure place, separate from the other files. The data will be securely stored in a locked office. Data will be stored on a server located in Ivor Wynne Centre room e113. This data will be stored on our password protected computers in encrypted folders and in a room with limited access. If the study results are published, participant names will not be used, and no information that discloses identity will be released or published without specific consent to disclosure. We will keep de-identified data for 10 years. All data, including personal information (name, date of birth, email, phone number) will be destroyed at the completion of this study. De-identified data may be used by the principal investigator (BKA) for future studies. To ensure proper monitoring of the research study, representatives of HiREB, this institution, and affiliated sites may consult original (identifiable) research data to verify that the information collected for the study is accurate and in compliance with applicable laws and guidelines. By participating in this study, participants authorize such access.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

n/a No biological specimens will be collected, therefore there is no plan for evaluation and storage.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Descriptive statistics (means, standard deviations, and frequencies) and Q-Q plots of residuals will be used to test for normality and skewness and assess model assumptions. Linear mixed-effects models with fixed effects of time (fweek), group (higher and lower load), and their interaction (group × fweek), and random intercepts for participants (subject) will be used to assess training effects on primary and secondary outcomes using the following equation:

Primary or Secondary Outcome ~ group*fweek + (1 | subject).

The primary outcome of directional sensitivity will be calculated from the maximum and minimum MCA*v* values obtained from the right MCA, and the maximum and minimum MAP from the left middle finger using the NIBP during the single leg press set. The time to time to maximum and time to minimum for both MCA*v* and MAP will also be calculated. These will be the metrics considered in a linear-mixed effects model. The secondary outcomes: endothelial function, arterial stiffness, distensibility, global cerebral blood flow, and cerebrovascular reactivity will also be incorporated into the linear-mixed effects model. Pre-intervention strength, fitness levels, and age may be included as covariates in the linear-mixed effects model.

Interim analyses {21b}

Blinded interim analysis may be done after groups of participants have completed the intervention. No statistical interim analysis will be done, therefore there will be no need to establish stopping guidelines.

Methods for additional analyses (e.g. subgroup analyses) {20b}

This study will explore potential differences in cerebrovascular reactivity to hypercapnic (5% CO_2, balanced O_2 and N_2) gas compared to hypercapnic/ hypoxic (5% CO_2, 15% O_2, balanced N_2) gas.

This study will also explore potential menstrual cycle-phase effects on the multiple variables collected. The collaborating study will track menstrual cycle phase using ovulation kits and participant self-reporting.

This study will explore potential influences of strength levels (measured using the 1-repetition maximum test prior to the study), fitness levels (measured using the Global Physical Activity Questionnaire completed at the screening visit), and gender identity (collected using the GENESIS-PRAXY questionnaire at the screening visit).

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Participants who complete less than 90% of the training sessions or miss more than 7 days of training will be excluded from data analyses. Missing data will be analyzed to assess for systematic or random error, such as cross-referencing within lab data collection notes to better understand the reason for the missing data. Any missing data across weeks will be handled in the linear mixed models.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The full protocol is being made public through this open-access publication and our trial pre-registration (www.isrctn.com, identifier: ISRCTN38725877). Participant data will be shared with researchers from reputable institutions upon reasonable request made to the principal investigator (B.K.A). These data will be presented at conferences and disseminated via manuscript publication.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

Our team comprises an interdisciplinary group of experts in cerebrovascular physiology, skeletal muscle health, metascience, and neuroimaging. VM, BKA, and EYA will oversee the day-to-day facilitation of the trial including recruitment, eligibility screening, and data collection, management, and analysis. The collaborating lab is responsible for randomizing participants to the HL or LL group. All research team members have contributed to trial design and will be involved in the writing of manuscripts that arise from this trial.

Composition of the data monitoring committee, its role and reporting structure {21a}

n/a There is no data monitoring committee for this trial.

Adverse event reporting and harms {22}

Adverse events will be reported by the research team leader or the Principal Investigator (B.K.A) using the adverse events protocol provided by and submitted to HiREB.

Frequency and plans for auditing trial conduct {23}

n/a There will be no audits for this trial.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

All protocol modifications will be formally submitted to HiREB as a protocol amendment before any modifications are actioned. Following approval, protocol modifications would be communicated to study participants currently enrolled and, if necessary, to those who have completed their data collection.

Dissemination plans {31a}

Findings from this trial will be disseminated via peer-reviewed journal articles and presented at academic conferences.

Discussion

As mentioned various times throughout this manuscript, this study is working in collaboration with another study (registered at https://www.isrctn.com/ISRCTN95727228?q=derrick%20van%20every&filters=&sort=&offset=1&totalResults=1&page=1&pageSize=10). This study and the collaborating study are investigating different questions: one relating to CBF control and the other hypertrophy and strength gain, respectively. However, both studies use the same resistance training intervention format. This format involves supervised resistance training twice per week, with one group training at a lower load and the other at a higher load. Therefore, although the focus may differ across studies, the intervention and the group being studied are the same. Utilizing the same participants in both studies eliminates extra costs and time and allows resources to be used appropriately and efficiently.

Trial status

Full research ethics board approval was received on April 30th, 2025. The approved protocol document is version 4 (as of October 7, 2025). Participant recruitment began in May 2025, and recruitment is expected to be completed by January 2026.

Abbreviations

CBF

cerebral blood flow

CCA

common carotid artery

CO_2

carbon dioxide

CVCi

cerebrovascular conductance index

DBP

diastolic blood pressure

DF

damping factor

HiREB

Hamilton Integrated Research Ethics Board

HL

higher load

ICA

internal carotid artery

LL

lower load

MAP

mean arterial pressure

MCA*v*

middle cerebral artery velocity

NIBP

non-invasive blood pressure

NSERC

Natural Sciences and Engineering Research Council of Canada

N_2

nitrogen

O_2

oxygen

PARQ+

Physical Activity Readiness Questionnaire for Everyone

$P_{ET}CO_2$

partial pressure of end-tidal carbon dioxide

PI

pulsatility index

RET

resistance exercise training

SBP

systolic blood pressure

TCD

transcranial doppler

VA

vertebral artery

1RM

1 repetition maximum

Declarations

Acknowledgements

Not applicable.

Authors' contributions {31b}

BKA is the Principal Investigator. Conception: BKA, VM. Design: BKA, VM, EYA, SMP, JJW, MC. First draft of manuscript: BKA, VM. All authors have read and approved the final manuscript.

Funding {4}

This trial is funded through the Natural Sciences and Engineering Research Council of Canada (NSERC). This funding body will have no role in the design, data collection, analyses, interpretation or writing of manuscripts or presentations related to this trial.

Availability of data and materials {29}

All members of the research team will have access to the final anonymized dataset to ensure transparency and efficiency during data analysis and reporting. We will store data on our password protected computers in encrypted folders and in a room with limited access. In the future, we may set up a server through McMaster's Research & High-Performance Computing department, where data will be backed up often and secured using McMaster's IT system. Furthermore, only people on the ethics application will have access to the raw data, and analyses will be conducted on the secure analysis computer rather than on individual laptops.

Ethics approval and consent to participate {24}

This study protocol has received full and final ethics approval by the Hamilton Integrated Research Ethics Board (HiREB #18711). All protocol modifications, if any, will be approved by the HiREB, and participants may be asked to re-consent to the study if deemed necessary by the ethics board.

Consent for publication {32}

Not applicable.

Competing interests {28}

The authors declare that they have no competing interests.

References

1. Perry BG, Lucas SJE. The Acute Cardiorespiratory and Cerebrovascular Response to Resistance Exercise. Sports Med Open. 2021 May 27;7(1):36.

2. Vincent HK, Sharififar S, McLaren C, May J, Vincent KR. Acute and chronic cardiovascular responses to concentric and eccentric exercise in older adults with knee osteoarthritis. BMC Sports Science, Medicine and Rehabilitation. 2023 Aug 1;15(1):95.

3. Zoeller RF, Angelopoulos TJ, Thompson BC, Wenta MR, Price TB, Thompson PD, et al. Vascular remodeling in response to 12 wk of upper arm unilateral resistance training. Med Sci Sports Exerc. 2009 Nov;41(11):2003–8.

4. Silva JKTNF, Menêses AL, Parmenter BJ, Ritti-Dias RM, Farah BQ. Effects of resistance training on endothelial function: A systematic review and meta-analysis. Atherosclerosis. 2021 Sept;333:91–9.

5. Miyachi M. Effects of resistance training on arterial stiffness: a meta-analysis. Br J Sports Med. 2013 Apr;47(6):393–6.

6. Miyachi M, Kawano H, Sugawara J, Takahashi K, Hayashi K, Yamazaki K, et al. Unfavorable effects of resistance training on central arterial compliance: a randomized intervention study. Circulation. 2004 Nov 2;110(18):2858–63.

7. Tzeng YC, Ainslie PN. Blood pressure regulation IX: cerebral autoregulation under blood pressure challenges. Eur J Appl Physiol. 2014 Mar 1;114(3):545–59.

8. Korad S, Mündel T, Perry BG. The effects of habitual resistance exercise training on cerebrovascular responses to lower body dynamic resistance exercise: A cross-sectional study. Exp Physiol. 2024 June 18;109(9):1478–91.

9. Thomas HJ, Marsh CE, Naylor LH, Ainslie PN, Smith KJ, Carter HH, et al. Resistance, but not endurance exercise training, induces changes in cerebrovascular function in healthy young subjects. American Journal of Physiology-Heart and Circulatory Physiology. 2021 Nov;321(5):H881–92.

10. Korad S, Mündel T, Perry BG. Larger reductions in blood pressure during post-exercise standing, but not middle cerebral artery blood velocity, in resistance-trained versus untrained individuals. Exp Physiol. 2024 Dec 25;

11. Roy MA, Labrecque L, Perry BG, Korad S, Smirl JD, Brassard P. Directional sensitivity of the cerebral pressure–flow relationship in young healthy individuals trained in endurance and resistance exercise. Experimental Physiology. 2022;107(4):299–311.

12. Neufer PD. The Effect of Detraining and Reduced Training on the Physiological Adaptations to Aerobic Exercise Training. Sports Med. 1989 Nov 1;8(5):302–20.

13. Barbieri A, Fuk A, Gallo G, Gotti D, Meloni A, La Torre A, et al. Cardiorespiratory and metabolic consequences of detraining in endurance athletes. Front Physiol [Internet]. 2024 Jan 22 [cited 2025 Feb 20];14. Available from: https://www.frontiersin.org/journals/physiology/articles/10.3389/fphys.2023.1334766/full

14. Giada F, Bertaglia E, De Piccoli B, Franceschi M, Sartori F, Raviele A, et al. Cardiovascular adaptations to endurance training and detraining in young and older athletes. International Journal of Cardiology. 1998 July 1;65(2):149–55.

15. Stebbings GK, Morse CI, McMahon GE, Onambele GL. Resting Arterial Diameter and Blood Flow Changes With Resistance Training and Detraining in Healthy Young Individuals. Journal of Athletic Training. 2013 Apr;48(2):209.

16. Okamoto T, Masuhara M, Ikuta K. Effect of low-intensity resistance training on arterial function. Eur J Appl Physiol. 2011 May 1;111(5):743–8.

17. Yoshizawa M, Maeda S, Miyaki A, Misono M, Saito Y, Tanabe K, et al. Effect of 12 weeks of moderate–intensity resistance training on arterial stiffness: a randomised controlled trial in women aged 32–59 years. 2009 Aug 1 [cited 2025 Feb 22]; Available from: https://bjsm.bmj.com/content/43/8/615.long

18. Cortez-Cooper MY, DeVan AE, Anton MM, Farrar RP, Beckwith KA, Todd JS, et al. Effects of High Intensity Resistance Training on Arterial Stiffness and Wave Reflection in Women. American Journal of Hypertension. 2005 July 1;18(7):930–4.

19. Moir ME, Corkery AT, Miller KB, Pearson AG, Loggie NA, Apfelbeck AA, et al. The independent and combined effects of aerobic exercise intensity and dose differentially increase post-exercise cerebral shear stress and blood flow. Experimental Physiology. 2024;109(10):1796–805.

20. Korad S, Mündel T, Perry BG. The effects of habitual resistance exercise training on cerebrovascular responses to lower body dynamic resistance exercise: A cross-sectional study. Experimental Physiology. 2024;109(9):1478–91.

21. Koep JL, Weston ME, Barker AR, Bailey TG, Coombes JS, Lester A, et al. The within- and between-day reliability of cerebrovascular reactivity using traditional and novel analytical approaches. Experimental Physiology. 2022;107(1):29–41.

22. Wilkinson IB, Mäki-Petäjä KM, Mitchell GF. Uses of Arterial Stiffness in Clinical Practice. Arteriosclerosis, Thrombosis, and Vascular Biology. 2020 May;40(5):1063–7.

23. Shephard RJ. Open-circuit respirometry: a brief historical review of the use of Douglas bags and chemical analyzers. Eur J Appl Physiol. 2017 Mar;117(3):381–7.

24. Stamford BA. Validity and Reliability of Subjective Ratings of Perceived Exertion During Work. Ergonomics. 1976 Jan;19(1):53–60.

25. Terry PC, Lane AM, Fogarty GJ. Construct validity of the Profile of Mood States — Adolescents for use with adults. Psychology of Sport and Exercise. 2003 Apr 1;4(2):125–39.

26. Kölling S, Schaffran P, Bibbey A, Drew M, Raysmith B, Nässi A, et al. Validation of the Acute Recovery and Stress Scale (ARSS) and the Short Recovery and Stress Scale (SRSS) in three English-speaking regions. J Sports Sci. 2020 Jan;38(2):130–9.

27. Hart S, Drevets K, Alford M, Salacinski A, Hunt BE. A method-comparison study regarding the validity and reliability of the Lactate Plus analyzer. BMJ Open. 2013;3(2):e001899.