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Effectiveness of short-term cycling interventions in older adults: a randomized trial of hypoxic, blood flow restriction, and eccentric cycling

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We evaluated whether a short-term cycling intervention in hypoxia, with blood flow restriction, or eccentric cycling induces greater health benefits than traditional cycling in older adults. Fifty-five individuals (68 ± 4 year, 25 females) performed supervised moderate-intensity intermittent training (MIIT) three times weekly for 4 weeks, assigned to one of four groups: HYP (hypoxic chamber, FiO_2 14%), BFR (thigh cuffs at ≈ 350 mmHg, deflated between sets), ECC (eccentric ergocycle), or CON (traditional ergocycle). Pre- and post-training assessments covered cardiovascular function, quality of life, cognition, aerobic fitness, skeletal muscle oxidative capacity, knee extensors and flexors strength, and thigh volume. Training interventions improved the 6-min cycling test average power output (9 ± 15%, $P < 0.001$), isokinetic at different speeds (10 ± 16 to 20 ± 26%, all $P < 0.001$) and isometric peak torques (14 ± 15%, $P < 0.001$), thigh circumference (1 ± 2%, $P = 0.008$), diastolic pressure (−3 ± 8%, $P = 0.021$), resting heart rate (−3 ± 7%, $P = 0.004$), digit span (9 ± 21%, $P = 0.031$) and TMT-B performance (−1 ± 51%, $P = 0.045$) in all groups. However, no significant differences were observed between groups. These results confirm the efficacy of MIIT in older adults and suggest that exercise per se is more important than the specific modalities. Short-term (4-week) MIIT programs promote healthy aging, regardless of the training modality, which may encourage older adults to take action.

Keywords Age, Elderly, Endurance, Old, Physical activity

The global elderly population is set to double by 2050. The over-65 age group faces higher chronic diseases rates, accounting for 40–50% of healthcare costs[1], straining resources. Finding strategies to prevent these diseases and financial burdens is crucial. Physical activity is a key intervention for healthy aging. Additionally, exercising in hypoxia (HYP)[2], with blood flow restriction (BFR)[3], or with eccentric actions (ECC)[4] show promise in enhancing exercise benefits.

HYP exercise involves training under reduced oxygen availability (lower ambient oxygen pressure), typically in a normobaric hypoxic chamber or by using a mask connected to a hypoxic generator (i.e., lower inspired pressure of oxygen). These devices enable precise control of oxygen levels and simulate hypobaric hypoxia (i.e., terrestrial altitude). Many benefits of HYP have been described in the literature: (i) Improved aerobic fitness through better oxygen delivery, mitochondrial efficiency and muscle oxygen diffusion; (ii) Metabolic benefits from enhanced glucose control and fat oxidation; (iii) Enhanced cardiovascular function, including lower blood pressure; (iv) Improvement in cognitive function supported by increased blood flow and neuroprotection[2]. All these physiological responses relevant for the elderly are mediated by different mechanisms, such as the activation of hypoxia-inducible factors, enhanced angiogenesis, and improved oxidative metabolism. Since these functions decline with age, HYP is a relevant tool for promoting healthy aging[5]. Moreover, exercising in HYP lowers mechanical load (i.e., decreased power output) while maintaining physiological strain (i.e., heart rate [HR]), making it potentially suitable for older adults with reduced mechanical tolerance or musculoskeletal constraints[6].

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BFR training involves exercising with pneumatic or elastic cuffs, placed around the proximal part of the limbs, and inflated to partially restrict venous return while maintaining arterial inflow. This method was shown to promote muscle hypertrophy and strength gains even with low-load resistance training[3]. BFR limits venous return, creating an ischemic muscular environment that, with mechanical tension, induces metabolic stress and promotes muscle adaptations[7]. Additionally, BFR training has been shown to enhance aerobic capacity[8] and vascular function[9]. The local ischemic/hypoxic environment created by BFR is thought to enhance vascular endothelial function by increasing the expression of hypoxia-inducible factors and vascular endothelial growth factor, while also stimulating nitric oxide synthesis[10]. BFR may also improve the benefits of exercise on cognitive function[11] by increasing lactate levels, which can cross the blood–brain barrier and serve as an energy source, stimulating brain-derived neurotrophic factor, and promoting angiogenesis in cerebral vessels[10]. The combination of stimuli makes BFR a potent strategy to induce peripheral (muscle, vascular) adaptations with minimal mechanical load, particularly relevant in aging populations with limited exercise tolerance. Another advantage of BFR training is its feasibility, providing substantial benefits for older individuals such as through home-based BFR programs.

ECC training focuses on the lengthening phase of muscle actions, which generates high mechanical stress at a low energy cost[12]. This effectively increases muscle mass and strength. Improvements in aerobic capacity have also been reported with ECC, though they tend to be less pronounced than those from CON training, when matched for power output and intensity[12]. Additionally, it may be beneficial for improving body composition in old populations[13]. The effects of ECC training are thought to be mediated through the expression of transcripts encoding factors involved in muscle growth, repair, and remodeling[13]. By minimizing cardiovascular strain[12], ECC is well-suited for older individuals with limited metabolic reserves. As such, it may offer a valuable strategy to combat sarcopenia and support independence in aging.

To compare their effects, we assessed a broad range of outcomes that capture the multidimensional impact of exercise in older adults. Cardiovascular measurements, including blood pressure, HR variability (HRV), and baroreflex sensitivity (BRS), were selected to assess autonomic function and cardiovascular health, key predictors of morbidity and mortality in older adults[14]. Blood pressure indicates arterial load and is a key marker of cardiovascular risk. HRV is an indirect way to assess the balance between the sympathetic and parasympathetic systems; a higher HRV generally reflects a more resilient autonomic nervous system[14]. BRS refers to the adjustment of HR in response to changes in blood pressure, serving as a mechanism for short-term blood pressure regulation; a higher BRS is associated with reduced cardiovascular risk and better overall autonomic function. Quality of life reflects the perceived benefits of training across physical, psychological, and social domains[15]. Cognitive tests were used because aging is associated with cognitive decline, and exercise has been proposed as a non-pharmacological strategy to maintain or improve cognitive function[16]. Aerobic fitness[17], strength[3], and leg hypertrophy[3] were assessed as they are critical for maintaining mobility, independence, and overall physical function in older adults. Together, these outcomes provide a comprehensive evaluation of the multifaceted benefits of exercise and offer a general picture of their relevance for healthy aging.

Each of these training modalities was shown to provide health benefits, targeting distinct physiological mechanisms that may provide a different stimulus and adaptation compared to traditional cycling, especially in older adults with limited exercise tolerance. However, they have never been directly compared in this population. Given that aging is marked by a multi-functions decline, comparing these modalities seems important, as each may preferentially target different age-sensitive function. By applying the same exercise intensity across all conditions, we aimed to isolate the specific effects of each method and determine their relative effectiveness. This study is the first to comprehensively assess various health and performance outcomes to evaluate whether a short-term moderate-intensity intermittent training (MIIT) combined with HYP, BFR, or ECC offers additional health-related benefits to older individuals compared to traditional cycling training. We hypothesized that HYP would enhance cardiovascular, metabolic, and cognitive outcomes, while ECC and BFR would primarily improve strength and muscle adaptations.

Methods

Ethics Approval

This clinical trial was approved by the Cantonal Ethics Committee for Research on Human Beings (CERVD: 2021-02135), was pre-registered at ClinicalTrials.gov (NCT05207501) on January 26, 2022, and conducted by the latest Declaration of Helsinki standards. All participants provided written informed consent before their inclusion.

Participants

A total of 55 older untrained individuals (68 ± 4 yr, 25 females and 30 males) took part in the study. Participants were required to be between 60 and 75 years old, have a body mass index < 35 kg/m^2, and were cleared for exercise by a medical doctor. Medication use included 11 on antihypertensives, 8 on cholesterol-lowering agents, 6 on anticoagulants, 4 on alpha-blockers, 4 on antidepressants, 2 on diabetes, thyroid, gastrointestinal, and heart medications each, and one each on psychostimulants, osteoporosis, rheumatology, hormonal therapies, breast cancer, HIV, hepatopathy, and asthma treatments. No changes were observed in participants' medications throughout the study. All sessions took place at the Institute of Sport Sciences, University of Lausanne.

Experimental protocol

Training

The training protocol overview is depicted in Fig. 1. All participants completed 4 weeks of supervised MIIT on a cycle ergometer, assigned to one of four distinct groups: HYP, BFR, ECC, or CON (control). The allocation of conditions was random, performed by the first author. Participants were matched based on sex and aerobic

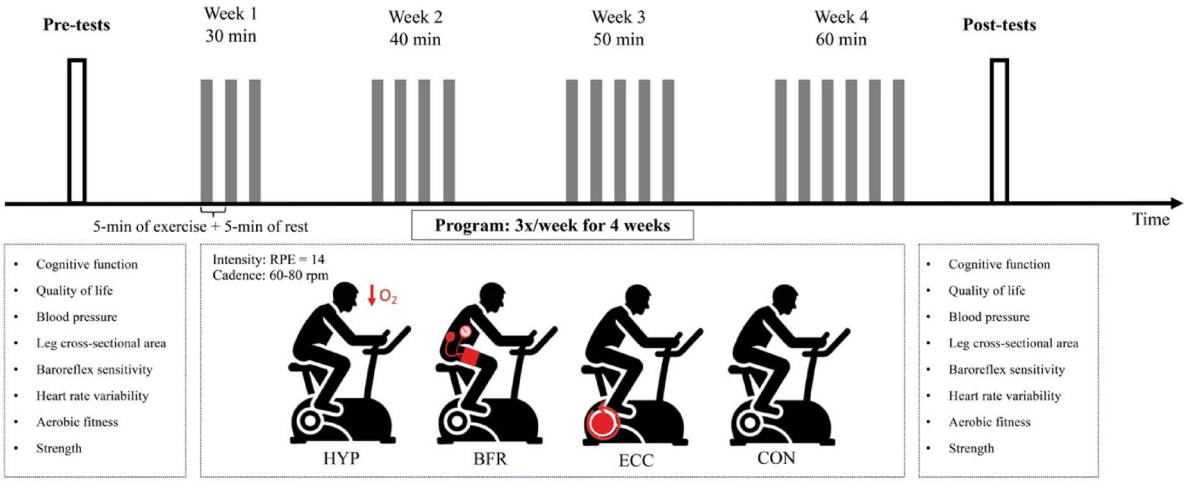


Fig. 1. Overview of the experimental protocol illustrating the random assignment of participants to four training modalities: hypoxic (HYP), blood flow restriction (BFR), eccentric (ECC), and control (CON).

level (as determined by the cycling test described below). Each week, participants exercised three times. Sessions in the first week comprised 3 sets of 5-min of exercise followed by 5-min of rest, with an additional set added each subsequent week to ensure a progressive and tolerable increase in duration. The pedaling cadence was freely chosen between 60 and 80 RPM, except in the ECC group, where it was 60 RPM. Exercise intensity was determined by a rating of perceived exertion (RPE) level of 14 on the 6–20 Borg scale. One key parameter is the matching of exercise intensity between the different interventions. Once ECC decreases cardiopulmonary demands but increases muscular strain[12], the use of power output was not relevant. Given that HYP[18] and BFR[19] increase cardiovascular and/or pulmonary demands, using HR was also irrelevant. Previous research[20] demonstrated that RPE reflects different constructs depending on muscle action type, distinguishing effort from exertion. This supports its use to capture the primary limiting factor across varied physiological stimuli. Therefore, prescribing exercise intensity based on RPE was considered the best approach. RPE reflects overall exertion by combining muscular and cardiopulmonary demands, allowing comparisons across protocols and practical application. Participants were familiarized with RPE during the pre-tests, where they rated their effort throughout an incremental warm-up (see details in the "Testing" section). They were instructed to rate their effort on the Borg scale based on what felt most limiting to them (cardiovascular, muscular, or otherwise) as this can vary between sessions, individuals, and training modalities. All training sessions were supervised by a qualified trainer who provided ongoing guidance and ensured consistent use of the scale.

The HYP group trained in a hypoxic chamber (ATS Altitude, Sydney, Australia) set at a F_iO_2 of 14% (simulating an altitude of ≈3370 m, considering the chamber's altitude of ≈372 m), aligning with established recommendations[21]. For each HYP participant, the hypoxic load [%HRmax / SpO_2 (%) × session duration (min)] per session was computed[22] and averaged over the training period. The BFR group had occlusion cuffs (BStrong, Park City, UT) placed around both thighs and sized according to the manufacturer's recommendations. Occlusion pressure was set at ≈350 mmHg according to preliminary tests[23]. The pressure was released between each set. Participants in all groups used an electrically braked cycle ergometer (Excalibur Sport, Lode BV, Groningen, The Netherlands), except for those in the ECC group who trained on an eccentric cycle ergometer (Cyclus 2, Cyclus GmbH, Leipzig, Germany), where they were instructed to resist the pedal movement.

To avoid a placebo effect, subjects were informed that all experimental conditions could improve performance. To prevent a nocebo effect, they were informed that none of the modalities could cause any harm, despite discomfort related to the maneuver (e.g. BFR).

During every training session, several measurements were conducted. HR was recorded with a chest strap (H10, Polar Electro, Kempele, Finland) connected to a watch (M400). Peripheral oxygen saturation (SpO_2) was measured using a pulse oximeter (WristOx2 3150, Nonin Inc., Plymouth, Minnesota) with an ear clip sensor (8000Q2). Participants rated RPE on the 6–20 Borg Scale, and power output was recorded from the ergometers. HR was averaged over the entire session while SpO_2 was visually averaged for 30-s during the last minute of the last exercise bout. Muscular and cardiorespiratory exertion were reported on a 100 mm VAS 5 min after the training sessions. The level of muscle soreness was quantified 48-h after the first training session using a 100 mm VAS in which 0 indicated "no pain" and 100 represented "extreme pain". The participants marked the level of overall quadriceps muscular soreness perceived on the VAS immediately after performing a functional activity: slowly passing from a standing to sitting position (knee at -90°) with the upper limbs crossed over the chest.

Testing

A comprehensive assessment of various health and performance outcomes was performed before and after the training program, with the post-tests conducted 5 ± 2 days following the last training session. Primary outcomes include training parameters, cardiovascular function (e.g., blood pressure, BRS, HRV), aerobic fitness, knee strength, and cognitive function. Secondary outcomes include thigh cross-sectional area, quality of life, and

acceptability. These were assessed before and after the 4-week training intervention, with post-tests conducted 5 ± 2 days following the final training session. The tests were performed in the order presented below and were administered to all participants by the same investigators. Participants were instructed to keep their usual lifestyle during the training program (i.e., not replacing exercise sessions with other physical activities but rather performing them in addition to their regular activities). Additionally, they were asked to complete a questionnaire detailing their food intake over the preceding 24-h before the pre-tests and replicate it before the post-tests. Furthermore, participants were instructed to abstain from caffeine and alcohol 24-h before testing and avoid intense exercise 48-h before testing. During the pre-tests, height was measured using a stadiometer, weight was determined using a calibrated balance, and physical activity levels were recorded using a validated questionnaire designed for the older population[24]. The questionnaire categorized activity levels: < 9.4 = low, 9.4–16.4 = moderate, > 16.4 = high.

Cognitive function

The trail-making tasks A and B (TMT-A and TMT-B, respectively), the digit span, and the color Stroop tests were conducted using the Psychology Experiment Building Language software[25] to assess cognitive function.

The digit span task tests short-term and working memory. Participants were shown a series of increasing numbers, starting with three digits, and recalled them via keyboard. Each length had two trials, and the highest correctly recalled length determined the working memory score.

TMT-A evaluates processing speed and psychomotor skills. Participants were instructed to connect 25 numbered dots (1, 2, 3, etc.) as quickly as possible in numerical order. TMT-B adds cognitive flexibility by requiring participants to alternate between numbers and letters (1, A, 2, B, 3, C, etc.). The time taken to complete each part was directly recorded by the software.

The color Stroop test was used to assess selective attention and inhibition control. Participants are presented with color words printed in incongruent ink colors (e.g., the word "RED" printed in blue ink) and asked to identify the ink color while ignoring the word itself. An interference score was computed by subtracting the average reaction times of neutral words from incongruent words.

Blood pressure

Blood pressure was assessed using a validated[26] device (M3, Omron Healthcare, Kyoto, Japan) on the left arm of participants while they were seated. Systolic and diastolic pressures were measured after a minimum 5-min rest period, ensuring participants had an empty bladder, uncrossed legs, and rested arms and back. They were instructed to remain still and refrain from talking during the measurement.

Quality of life

Quality of life was measured with the validated[27] French version of the World Health Organization quality of life questionnaire for old people (WHOQOL-OLD). The WHOQOL-OLD consists of 24 items encompassing six domains: sensory abilities; autonomy; past, present, and future activities; social participation; death and dying; and intimacy. Responses are rated on a 5-point Likert scale, with some items reverse-scored for consistency. Raw total scores range from 24 to 120, with higher scores indicating a better quality of life.

Baroreflex sensitivity (BRS) and heart rate variability (HRV)

Spontaneous cardiovagal BRS and HRV were assessed during 6-min at rest in a supine position in a quiet room following a 10-min rest in the same position. Continuous blood pressure measurements were obtained from the index and middle fingers using a photoplethysmography device combined with a double cuff (NIBP100D, Biopac Systems Inc., Goleta, CA). Before each test, the device was automatically calibrated by measuring blood pressure on the participant's left arm. BRS assesses the change in HR in response to blood pressure variations, reflecting regulatory function. It was quantified using custom MATLAB routines (R2023b, The MathWork Inc, Natick, MA) based on the sequence method. Briefly, it identifies consecutive beats where changes in systolic blood pressure are followed by corresponding changes in inter-beat intervals. Criteria for a valid BRS sequence included a ≥ 1 mmHg change between consecutive systolic blood pressure peaks, a ≥ 5-ms change in inter-beat interval, and a correlation coefficient ≥ 0.85 between changes in systolic blood pressure and inter-beat interval. Additionally, at least five sequences per recording were required to validate BRS estimation.

HRV was derived from continuous blood pressure measurements, as pulse rate variability has demonstrated comparable reliability to traditional HRV assessments under resting conditions[28]. A custom MATLAB (R2023b, The MathWork Inc, Natick, MA) routine identified blood pressure peaks and computed HRV parameters, including mean HR, root mean square of successive differences (RMSSD), and power spectrum density in the low-frequency (LF), and high-frequency (HF) bands.

Thigh cross-sectional area

Thigh muscle-bone cross-sectional area (CSA) was measured based on thigh circumference and adipose tissue thickness measurements according to a method validated against magnetic resonance imaging[29]. Briefly, the right mid-thigh was assessed with the leg extended and relaxed. Circumference was evaluated with measuring tape seated at the midpoint of the right upper leg, positioned between the lateral condyle of the femur and the greater trochanter. Subsequently, participants were evaluated in a supine position for subcutaneous adipose tissue thickness at the midline of the thigh, both anteriorly and posteriorly. This evaluation was conducted using a linear Doppler ultrasound probe (L12-5L60N) connected to an ultrasonic beamformer (Telemed ClarUs-EXT) with EchoWave II software (version 3.4.4, Telemed Medical Systems, Telemed Ltd., Lithuania, Milano, Italy). The measurement sites were marked with a permanent pencil and retraced during training sessions to replicate placement during the post-tests. Distortion of tissue due to excessive compression was prevented

by applying a generous amount of water-soluble transmission gel and ensuring no movement of tissues occurred in the real-time ultrasonic image. The formula that was used to estimate the muscle-bone CSA was: $\left[CSA = \pi \left(\mathrm{r} - \frac{(\mathrm{QAT}+\mathrm{HAT})}{2}\right)^2\right]$; where r is the radius of the right thigh calculated as $\left[\frac{circumference}{2\pi}\right]$, and QAT and HAT are anterior and posterior thigh adipose tissue thickness, respectively.

Aerobic fitness

Aerobic fitness was assessed using a 6-min test on a cycle ergometer (LC6 Novo, Monark, Vansbro, Sweden). First, participants performed an incremental warm-up, beginning with an intensity of 25 W at 60 RPM. Each minute, the intensity increased by 15 W, and RPE was monitored with the 6–20 Borg scale. The warm-up stopped once the RPE reached a value ≥ 14. This warm-up routine not only prepared participants for the test but also established the test pre-set intensity and facilitated their comprehension of exertion levels on the Borg scale for subsequent training sessions. Standardized instructions were given, explaining that 6 reflects no exertion and 20 represents maximal effort.

Then, participants were instructed to produce their best performance possible over 6 min by changing independently the intensity or the RPM during the test. Standardized verbal encouragement that included the time left was given each minute while facing the participant.

Average power output was measured in addition to gas exchanges, cardiac parameters, muscle oxygenation (Total Saturation Index; TSI), SpO_2, and RPE. Gas exchanges were continuously monitored breath-by-breath using a metabolic cart (Quark CPET, Cosmed, Rome, Italy) calibrated before every test according to the manufacturer's instructions. Cardiac parameters (cardiac output, CO; HR; stroke volume, SV) were recorded continuously with a hemodynamic monitor (PhysioFlow®, Manatec Biomedical, Poissy, France) set up according to the manufacturer's guidelines. Muscle oxygenation was continuously measured in the vastus lateralis muscle by a NIRS device (Portamon, Artinis Medical Systems, Elst, The Netherlands). This device featured three dual-wavelength (760 and 850 nm) light transmitters–channels at a distance of 30, 35 and 40 mm, respectively, from the receiving optode. The NIRS probe was placed longitudinally over the belly of the right vastus lateralis muscle, ≈10 cm above the knee joint, and was firmly secured and protected from external light using an elastic bandage. The skin underlying the NIRS probe was carefully shaved and cleaned before initiating the experiment. SpO_2 was measured during the last minute and visually averaged using a pulse oximeter (WristOx2 3150, Nonin Inc., Plymouth, Minnesota) with an ear clip sensor (8000Q2).

Following the completion of the 6-min cycling test, skeletal muscle oxidative capacity was assessed using the repeated occlusion method[30]. This technique involves measuring post-exercise muscle oxygen consumption (mVO_2) recovery kinetics by NIRS. Immediately after exercise cessation, a series of 5-s intermittent arterial occlusions (5 separated by a 5-s cuff release, 5 separated by a 10-s release, and 5 separated by a 20-s release) were initiated. Arterial occlusion was achieved using a pneumatic cuff placed proximally on the thigh before cycling and connected to an automatic rapid inflation system (Hokanson E20 AG101, Bellevue, WA). For each intermittent arterial occlusion, the negative slope of TSI was fitted with a linear function to estimate relative mVO_2. This rate of deoxygenation, being inversely proportional to mVO_2, is reported as a positive value and subsequently fitted with a monoexponential function. From there, the mVO_2 exponential recovery rate constant (k, min^{-1}) was estimated using non-linear least-squares regression and served as an estimate of leg skeletal muscle oxidative capacity.

Knee extensors and flexors strength

About 20-min after the aerobic fitness assessment, dominant leg muscle strength was measured using a dynamometer (ConTrex MJ, CMV AG, Dubendorf, Switzerland). The seat positions were recorded to ensure reproducibility during post-tests. To avoid compensatory movements, belts were firmly fixed to the tested thigh and the trunk, the contralateral leg was maintained in a flexed position, and participants were instructed to hold the trunk belt. Before each test (except the last one), a familiarization was implemented by performing the same protocol at submaximal intensity. Isometric knee extensor strength was first assessed at a knee angle of 80°. The rate of force development was calculated on the isometric test over a 50-ms window with custom MATLAB (R2023b, The MathWork Inc, Natick, MA) routines. Subsequently, isokinetic concentric knee extensor and flexor strength were assessed at angular velocities of 30°/s, 90°/s, and 180°/s by recording the best peak torque generated over 3 repetitions. Endurance strength was then assessed during 30 repetitions at 180°/s and calculated as recommended[31]: $Fatigue = 100 - [(Total\ power\ output \div Ideal\ power\ output) \times 100]$. For all tests, participants were instructed to produce maximal force, as quickly as possible (especially for the rate of force development). Strong verbal encouragements were provided throughout, and visual feedback was withheld.

Acceptability

A custom-designed survey of 12 questions, rated on Likert scales, was used to evaluate participants' subjective perceptions of their respective training modalities at the post-tests. It focused on perceived difficulty, discomfort, enthusiasm towards the sessions, perceived worthiness, ease of execution, and satisfaction with quantity, duration, and intensity. It also measured the likelihood of continuing and recommending the program, as well as perceived safety.

Data and statistical analysis

The study was adequately powered, as it aligns with established guidelines[32] indicating that 13–20 participants are typically sufficient to detect meaningful changes in the 6-min walking test distance among older adults.

Due to technical issues, adipose tissue thickness (and consequently, cross-sectional area) data were missing for 17 participants. A two-way ANOVA was conducted to assess the effects of training, group, and their interaction.

Group	*HYP*	*BFR*	*ECC*	*CON*	Group effect
Sample size	15	14	13	13	
Female/male	7/8	7/7	4/9	7/6	0.654
Age (years)	69 ± 3	68 ± 4	67 ± 2	68 ± 4	0.348
Weight (kg)	75 ± 11	72 ± 11	77 ± 11	70 ± 11	0.441
Height (cm)	170 ± 10	170 ± 12	173 ± 8	170 ± 8	0.728
Physical activity score	13 ± 5	14 ± 6	12 ± 8	14 ± 7	0.868

Table 1. Participant characteristics. Values are mean ± SD and p-value in "Group effect" column. HYP, Hypoxia; BFR, blood flow restriction; ECC, eccentric; CON, control.

Group	HYP	BFR	ECC	CON	Group effect	*N*
Power output (W)	107 ± 3	116 ± 35	218 ± 73[ab]	123 ± 34[c]	**< 0.001**	55
SpO_2 (%)	90 ± 3	99 ± 1[a]	99 ± 1[a]	99 ± 1[a]	**< 0.001**	55
Heart rate (bpm)	112 ± 9	118 ± 11	105 ± 7[b]	122 ± 12[c]	**< 0.001**	55
Rate of perceived exertion (a.u.)	14.0 ± 0.0	13.9 ± 0.5	13.7 ± 0.6	13.9 ± 0.4	0.356	55
Cardiorespiratory exertion (a.u.)	5 ± 2	3 ± 1[a]	2 ± 1[a]	5 ± 2[c]	**< 0.001**	55
Muscle exertion (a.u.)	2 ± 2	3 ± 1	4 ± 1[a]	4 ± 2	**0.048**	55
Soreness 48 h post session 1 (cm)	0.2 ± 0.5	0.3 ± 0.6	2.2 ± 2.2[ab]	0.3 ± 0.5[c]	**< 0.001**	44

Table 2. Training parameters averaged over the 12 sessions. Values are mean ± SD. $P < 0.05$ for differences with [a] hypoxia (HYP), [b] blood flow restriction (BFR), [c] eccentric (ECC). SpO_2, peripheral oxygen saturation, CON, control. Signficance values are in bold.

In case of missing value, a mixed-effect model was utilized. Subsequently, post-hoc comparisons between group means were performed using the Tukey multiple comparison test. All statistical analyses were carried out using GraphPad Prism software (version 9.5.0, San Diego, CA), and statistical significance was set at $P \leq 0.05$.

Results

Table 1 presents the participants' characteristics, for which no differences were observed between groups.

Table 2 displays the parameters monitored during training averaged over the 12 sessions. While exercising at equivalent RPE, some training parameters varied significantly between modalities. Power output was higher in ECC compared to the other groups. SpO_2 was lower in HYP compared to the other groups. HR was lower in ECC compared to BFR and CON. Cardiorespiratory exertion was higher in HYP compared to BFR and ECC and in CON compared to ECC. Muscle exertion was higher in ECC compared to HYP. Soreness was higher in ECC compared to the other groups. The hypoxic load per session in HYP was 35 ± 4 min^{-1} on average.

Table 3 presents the parameters measured at pre-tests and post-tests. Improvements were observed across all domains: cardiovascular, cognitive, aerobic capacity, muscle strength, and muscle volume. Specifically, diastolic pressure and resting HR decreased, and digit span score and TMT-B scores improved. Power output and VO_2 increased, SpO_2 and leg TSI decreased, all strength parameters (excluding RFD) improved, and thigh circumference increased.

A group effect was noted for TMT-A time (BFR < ECC and BFR < CON at pre-tests; BFR < ECC, BFR < CON, and BFR < HYP at post-tests) and quality of life (HYP < CON at pre-tests).

Only SV and isokinetic flexor strength at 90°/s showed an interaction effect, with no significant differences in multiple comparisons for both cases ($P \geq 0.276$ for both).

Figure 2 illustrates the most significant metrics measured pre- and post-tests, displaying group results.

There were no significant differences among the training modalities in terms of perceived difficulty, discomfort, enthusiasm towards the sessions, perceived worthiness, ease of execution, satisfaction with quantity, duration, intensity, likelihood of continuing and recommending the program, as well as perceived safety.

Discussion

This is the first study to comprehensively compare the effects of a short-term (4 weeks) cycling MIIT combined with HYP, BFR, or ECC training versus traditional cycling on various health parameters in older adults. Our findings demonstrate multiple improvements underscoring the efficacy of MIIT for promoting healthy aging. However, we found no evidence that one modality outperformed another, suggesting that 4 weeks of training are enough to yield meaningful benefits, but a greater stimulus (e.g., a longer training period or higher intensity) may potentially differentiate between modalities.

Effects of training

The training intervention led to improvements in cardiovascular health, cognitive function, aerobic fitness, muscle strength, and muscle volume. These improvements are all relevant for disease prevention and successful aging, as discussed in detail below.

			PRE	POST	Change (%)	Training effect	Group effect	Inter-action effect	*n*
Cardiovascular function	Systolic pressure (mmHg)		132 ± 17	129 ± 18	−2 ± 9	0.145	0.744	0.399	55
	Diastolic pressure (mmHg)		83 ± 10	81 ± 11	−3 ± 8	**0.021**	0.390	0.776	55
	BRS (ms/mmHg)		25 ± 16	23 ± 14	−2 ± 45	0.247	0.083	0.326	53
	Resting heart rate (bpm)		61 ± 7	59 ± 7	−3 ± 7	**0.004**	0.173	0.855	55
	RMSSD (ms)		50 ± 16	52 ± 16	9 ± 36	0.588	0.914	0.807	52
	Low-frequency (ms^2)		692 ± 979	738 ± 1307	51 ± 147	0.420	0.654	0.928	54
	High-frequency (ms^2)		633 ± 532	736 ± 674	43 ± 125	0.275	0.870	0.668	54
Cognitive function	Digit span score		5.9 ± 1.3	6.3 ± 1.3	9 ± 21	**0.031**	0.551	0.465	54
	TMT-A time (s)		58 ± 15[ab]	59.16[abc]	3 ± 29	0.992	**0.002**	0.753	51
	TMT-B time (s)		112 ± 51	96 ± 33	−1 ± 51	**0.045**	0.172	0.802	51
	Stroop interference (ms)		260 ± 273	194 ± 312	−192 ± 1922	0.224	0.372	0.397	54
	Quality of life		96 ± 16[d]	99 ± 10	1 ± 6	0.529	**0.025**	0.412	55
Cycling test	Mean power output (W)		122 ± 35	131 ± 38	9 ± 15	**< 0.001**	0.948	0.266	55
	Mean VO_2 (ml/min/kg)		24 ± 5	26 ± 6	9 ± 20	**< 0.001**	0.900	0.216	55
	Net efficiency (%)		0.24 ± 0.05	0.25 ± 0.05	4 ± 22	0.565	0.196	0.792	55
	Mean cardiac output (L/min)		15 ± 3	15 ± 3	5 ± 26	0.316	0.927	0.062	55
	Mean stroke volume (mL)		111 ± 21	113 ± 18	4 ± 19	0.368	0.819	**0.037**	55
	Mean heart rate (bpm)		136 ± 17	137 ± 16	1 ± 8	0.706	0.169	0.683	55
	SpO_2 (%)		99 ± 1	98 ± 4	−1 ± 4	**0.011**	0.775	0.622	55
	Mean leg TSI /%)		68 ± 6	66 ± 7	−3 ± 5	**< 0.001**	0.649	0.358	55
	Leg oxidative capacity (min^{-1})		1.7 ± 1.2	1.8 ± 1.3	10 ± 45	0.694	0.617	0.467	54
Knee strength	Extensors	Isometric strength (Nm)	110 ± 40	123 ± 41	14 ± 15	**< 0.001**	0.671	0.947	55
		RFD ($N\ s^{-1}$)	469 ± 300	514 ± 267	27 ± 47	0.110	0.446	0.449	55
		Isokinetic 30°/s (Nm)	99 ± 38	113 ± 37	18 ± 17	**< 0.001**	0.494	0.261	55
		Isokinetic 90°/s (Nm)	96 ± 34	109 ± 33	17 ± 20	**< 0.001**	0.170	0.764	55
		Isokinetic 180°/s (Nm)	82 ± 26	88 ± 26	10 ± 14	**< 0.001**	0.113	0.937	55
	Flexors	Isokinetic 30°/s (Nm)	76 ± 25	86 ± 26	15 ± 21	**< 0.001**	0.725	0.760	55
		Isokinetic 90°/s (Nm)	56 ± 19	65 ± 20	20 ± 26	**< 0.001**	0.478	**0.038**	55
		Isokinetic 180°/s (Nm)	60 ± 18	65 ± 19	10 ± 16	**< 0.001**	0.502	0.229	55
		Endurance strength (%)	23 ± 6	24 ± 6	9 ± 40	0.321	0.271	0.774	55
Thigh	Volume	ATT (mm)	12 ± 7	12 ± 7	−3 ± 9	0.077	0.313	0.836	38
		Circumference (cm)	52 ± 3	53 ± 3	1 ± 2	**0.008**	0.357	0.392	55
		Cross-sectional area (cm^2)	168 ± 31	170 ± 35	2 ± 7	0.140	0.059	0.570	38

Table 3. Testing parameters. Values are mean ± SD. PRE and POST values are averages of hypoxia (HYP), blood flow restriction (BFR), eccentric (ECC) and control (CON) modalities. [a] BFR < ECC, [b] BFR < CON, [c] BFR < HYP, [d] HYP < CON. BRS, baroreflex sensitivity; RMSSD, root mean square of successive differences; TMT, trail-making task; VO_2, oxygen consumption; SpO_2, peripheral oxygen saturation; TSI, total saturation index; RFD, rate of force development; ATT, adipose tissue thickness. Signficance values are in bold.

Cardiovascular function

Training improved cardiovascular health as evidenced by the decrease of 3 ± 8% in diastolic blood pressure and 3 ± 7% in resting HR. Reductions of 2.4 mmHg ($P < 0.01$) for systolic and 1.6 mmHg ($P < 0.001$) for diastolic blood pressure have been reported with endurance training in a meta-analysis[33]. Small changes, as reported for the diastolic blood pressure, are crucial for health once a 2 mmHg decrease correlates with ≈10% decrease in stroke mortality and a ≈7% decrease in mortality from ischemic heart disease[34]. Mechanistically, the decreased blood pressure observed with exercise has been attributed to a decrease in peripheral vascular resistance[35].

The decreased resting HR is in line with the 5.2% decrease reported in a meta-analysis[36], and has been attributed to a decrease in intrinsic HR[37]. This parameter is inversely related to life expectancy and its improvement underscores the benefits of exercise. BRS and HRV remained unchanged with training, yet large SDs indicated considerable variability, possibly obscuring statistical significance.

Cognitive function

Cognitive function (i.e., digit span and TMT-B) improved with training, aligning with previous research on older individuals[16]. Conversely, there were no changes in TMT-A and Stroop interference. The large improvements observed in TMT-B contrast with the absence of such changes in TMT-A. This suggests that cognitive flexibility, required specifically in TMT-B, was improved with the training intervention, while the processing speed and psychomotor skills necessary for both TMT-A and TMT-B remained unchanged. Interestingly, TMT-B is also the task that leads to the largest performance variability. In comparison, previous studies investigating exercise

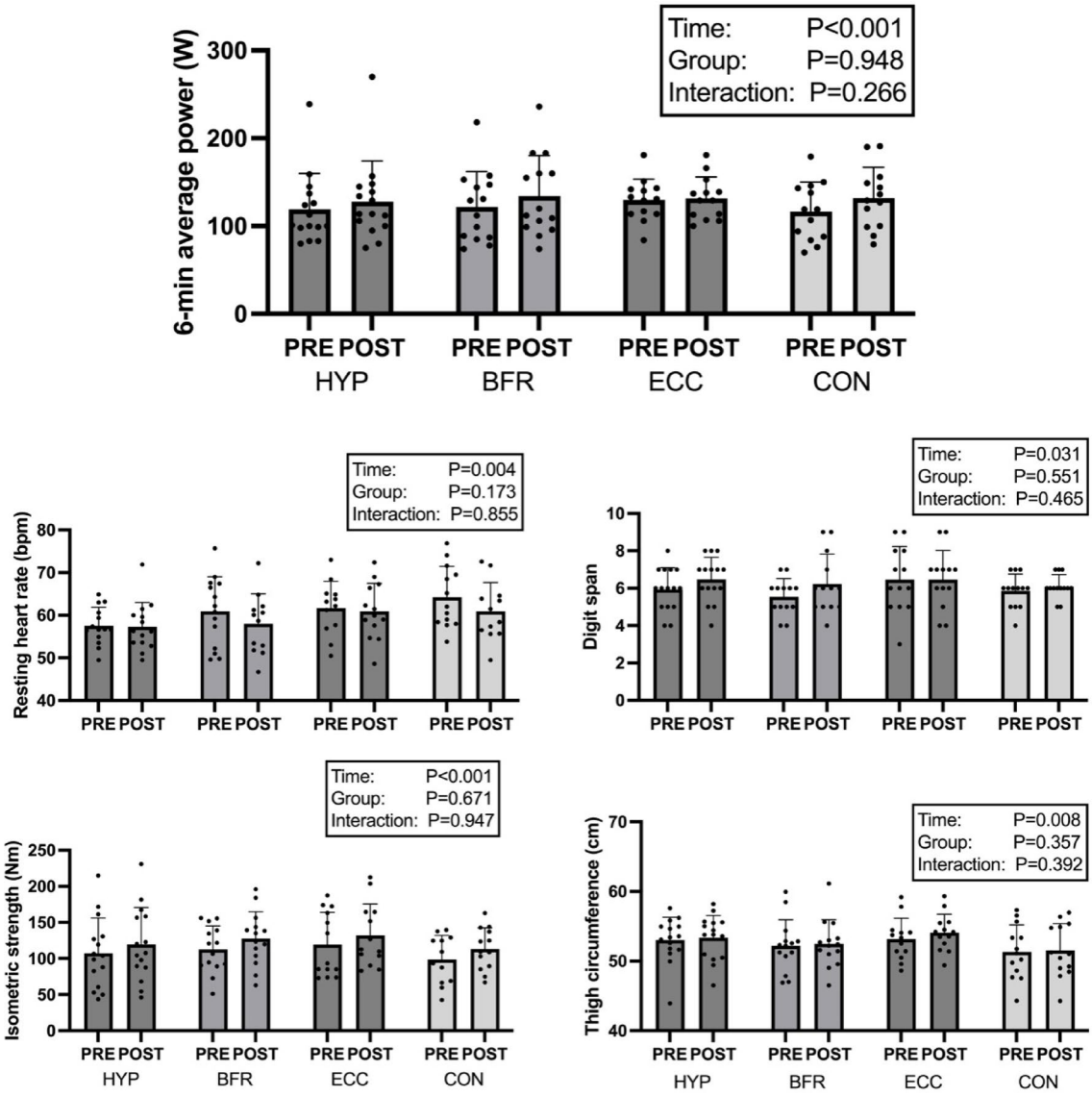


Fig. 2. Key parameters measured pre- and post-training in the four different training modalities: hypoxia (HYP), blood flow restriction (BFR), eccentric (ECC), and control (CON), expressed as mean ± SD.

training reported improved TMT-A[15,38] and digit span[15,39], but also unchanged TMT-A[39], TMT-B[38], digit span[38], and Stroop interference[39] in older individuals. This suggests variability in findings, but that the cognitive functions required for these tests may all be enhanceable with training.

Quality of life

The quality of life did not show significant changes with training, aligning with previous findings[40] but not with other findings of increased quality of life with training[41]. At baseline, participants reported a high quality of life (96 ± 16), which exceeded international reference values (88 ± 13) but aligned closely with Swiss reference values (93 ± 10)[42]. The elevated quality of life observed among our Swiss population may have blunted the potential increase in perceived quality of life induced by short-term training, suggesting that longer training periods might yield more pronounced improvements.

Aerobic fitness

Improvements in aerobic fitness were observed with training, as evidenced by the significant 9% increase in average power output during the 6-min cycling test. Additionally, the observed increase in VO_2 further supports the enhancement of aerobic fitness. Meanwhile, TSI decreased, aligning with the literature[43], but cardiovascular parameters (i.e., cardiac output, stroke volume, and HR) remained unchanged. This indicates that the improvements in aerobic fitness may have been primarily driven by peripheral adaptations within the muscles (i.e., increased muscle oxygen extraction and utilization) rather than improvement in cardiac function. This observation aligns with previous findings indicating that aerobic training results in more peripheral adaptations

in older individuals compared to younger individuals while younger individuals experience more central adaptations, driven by an increase in maximal cardiac output, than older individuals[44].

Skeletal muscle oxidative capacity
While the muscle oxygen extraction capacity may have been improved (as indirectly shown by the decreased TSI), the skeletal muscle oxidative capacity remained unchanged following training. This suggests that training had a negligible effect on the mitochondrial function. These results contradict previous research indicating improvement in muscle oxidative capacity with training[45], or in individuals with higher training levels[46], as well as its positive correlation with VO_2peak[47]. Despite high baseline values compared to highly active older adults[48], previous studies reported improvement independent of age[49] and after only 3 weeks of endurance training in individuals with higher baseline values[45].

Knee extensors and flexors muscles strength and thigh volume
Isometric and all isokinetic strength improved with training. This confirms that not only resistance training can induce strength gains[50]. Maintaining these qualities is paramount as their decline is associated with frailty and low quality of life and represents one of the strongest risk factors for falling[51]. The increase in strength at high angular velocities is particularly relevant for older individuals once it faces more pronounced declines with age and is considered a hallmark of aging[52]. Mechanistically, the enhanced strength is partially attributed to hypertrophy, as indicated by the increased circumference. Neural adaptations are also recognized for their important role, particularly in early-phase training[53], but they were not directly assessed here and it remains hypothetical.

Acceptability
Regarding the acceptance of the training modalities, participants consistently rated the difficulty, discomfort, enthusiasm, perceived worthiness, ease of execution, satisfaction with quantity, duration, intensity, likelihood of continuing and recommending the program, and perceived safety similarly across all groups. These findings suggest a uniform experience among participants regardless of group affiliation and that all training modalities were positively accepted by our older individuals.

Comparison of the training modalities

The present study demonstrated that all training interventions induced benefits, but we did not find evidence supporting the superiority of one modality over another for any parameter measured. Several physiological and methodological factors should be considered: (i) Training characteristics: the moderate intensity (RPE of 14) and short duration (4 weeks) may have limited the extent of adaptations. Still, the 9% increase in average power output is in line with previously reported improvements in 6-min walking distance: 6.8–21% with ECC[54,55], 9% with BFR[56], and 12.5% with HYP[57], all of which reported significant differences compared to control; (ii) Training status: although participants were untrained, their average physical activity level was classified as moderate[24], making it unlikely that low baseline fitness led to large nonspecific gains that could have masked modality-specific effects; (iii) Age-related responsiveness: aging is associated with a general decline in exercise responsiveness, including anabolic resistance to training stimuli[58]. Beyond this overall dampening, older adults may also exhibit modality-specific limitations with decreased adaptation to HYP (attenuated HIF-1α activation[59], lower EPO response[60]), strength and hypertrophy gains with BFR[61], and gene expression in ECC[62]; (iv) Modality-specific dosing: hypoxia severity or cuff pressure could theoretically be raised. However, higher hypoxia levels tend to impair performance and reduce training effectiveness[21]. And our cuff pressure was already high, and excessively high pressure has been shown to increase discomfort without added benefit[63], so we used parameters validated in our pre-tests[23]; (v) Study design: The absence of a non-exercise control group limits our ability to isolate the specific effects of each modality.

Hypoxic training
Surprisingly, HYP did not induce larger improvement in any of the parameters measured, while we hypothesized a larger positive effect on aerobic power[64,65], cognitive function[17,65,66], blood pressure[67], and HRV[68] when compared to CON. Superior improvement in aerobic power[69,70] or blood pressure[69,70] with HYP is nevertheless not consistently observed. In line with the literature, HYP was not more beneficial for muscle mass gain[70,71], strength[72], or quality of life[66]. The inconsistencies may arise, in addition to the reasons discussed earlier for all modalities, from variations in individual responses and HYP protocols. Older adults may not exhibit the same physiological responses to HYP and/or hypoxemia when compared to their younger counterparts, as shown in microvascular responsiveness to vascular occlusion followed by hyperemia[73]. Additionally, hypoxic dose (i.e., severity, duration, frequency, and type) seems to determine the efficacy of the intervention[18].

HYP was shown to induce similar benefits to normoxia but at a reduced relative intensity[6]. However, in our study, no significant differences were observed between HYP and CON in terms of HR or power output during training sessions.

Blood flow restriction training
BFR did not show superiority for any of the parameters measured. In comparison, a meta-analysis reported greater improvements in strength and muscle mass with BFR in older populations[3]. The superiority of BFR on aerobic fitness has been also reported in some studies[41] but not in all[56,74,75]. In terms of blood pressure, a meta-analysis showed decreased systolic blood pressure using low-load BFR in older individuals[76]. Despite the theoretical benefits of BFR for cognitive function[11], previous studies did not observe additional benefits with BFR[41,77].

The discrepancy with our findings could be attributed to our short-term training. Additionally, BFR shows superior improvements in muscle mass and strength when compared at low loads, but high load is still superior to BFR at low load. The moderate intensity applied in this study may explain the absence of difference. BFR has been suggested as an option to induce positive adaptations without high mechanical loads, which is suitable for older individuals[78]. However, in this study, while BFR matched CON in benefits, no differences in intensity (HR or power) were observed.

Eccentric training

ECC did not improve further any parameters aligning with a recent meta-analysis reporting that isometric knee strength, 6-min walking test, and thigh circumference do not improve significantly more compared to CON in older adults[4]. These results suggest that while ECC training holds promise in theory, its practical benefits are not systematically observed in older individuals. In line with previous research[79], ECC caused significantly more muscle soreness 48-h after the first session, a drawback to consider when incorporating eccentric training.

Methodological considerations

Limitations should be considered. Group sizes (n = 13–15) limited power for subtle between-group effects. Comparing four strategies across various outcomes offers valuable insights, but limits sample size. Lack of significant differences suggests that any modality-specific effects are likely small compared to the overall benefits of exercise. Larger, single-modality studies are needed to confirm and refine these findings.

To our knowledge, matching training intensity on RPE offers the most reliable option across experimental conditions, as it accounts for varied cardiovascular, respiratory, and perceptual strains. For example, neither HR (higher in hypoxia and BFR) nor power output (higher with eccentric training) would provide a consistent measure due to these differences. RPE has strong correlations with physiological markers of exercise intensity[80], yet it could be moderated by factors such as fitness levels[80] or having no previous experience with the scale. To limit this, groups were matched by fitness, the Borg scale was introduced during pre-tests, and training was supervised by a qualified trainer.

While the present study focused on enabling a rigorous comparison of four cycling exercise modalities under controlled conditions with multidimensional assessments, future studies should build on these findings by evaluating longer-term adaptations and their persistence after training cessation. Also, incorporating a non-exercise control group would enable to isolate the effects of exercise from potential confounding variables or spontaneous changes. This would have ensured that improvements observed on post-training were due to the exercise training, in comparison with a control group. However, in these untrained aging individuals (who did not change their diet and lifestyle), it seems very unlikely that these improvements may be due to another cause than exercise.

CSA measured by anthropometry in combination with ultrasound may be influenced by variations in adipose tissue thickness across different anatomical locations. Nevertheless, this method has been shown to provide a reliable and accurate for assessing muscle hypertrophy when compared to magnetic resonance imaging[29].

NIRS measurements could potentially be affected by adipose tissue thickness. However, since our study involves participants being compared to their own baseline values and TSI being a ratio where both the numerator and denominator are impacted similarly, it's unlikely that our results were affected by this factor.

While we assessed multiple health-related functions, our physical performance outcomes focused specifically on knee strength and cycling performance, specific to the cycling intervention. We acknowledge that including functional measures (e.g., gait speed, balance, or activities of daily living) would have provided additional insights on geriatric-relevant generalized benefits.

The gender ratio was imbalanced in the ECC group (9 men and 4 women) due to logistical constraints. Additionally, participants may require several sessions to become familiar with the eccentric ergometer and the unconventional backward pedaling motion, potentially impeding immediate training adaptation. However, this adjustment period reflects real-world scenarios and thus still represents the typical learning curve expected in practical applications.

It is known that aerobic testing could potentially influence subsequent neuromuscular performance. However, all participants followed the same testing order at both pre- and post-tests, so any residual fatigue would have affected both time points equally.

Finally, recruiting older adults for research may introduce selection bias, as volunteers may represent higher-performing individuals. However, participants averaged moderate physical activity for their age group.

Conclusions

In conclusion, the absence of discernible differences between the training modalities (HYP, BFR, ECC, and CON) suggests that comparable effects on health outcomes may be expected when implementing these modalities over 4 weeks. This supports the development of evidence-based exercise recommendations to promote healthy aging. Consideration of individual preferences and health limitations is recommended. For example, HYP and BFR are contraindicated in individuals with certain preexisting medical conditions, such as cardiovascular diseases and related risk factors[81,82]. Additionally, the potential for muscle damage and delayed onset muscle soreness associated with ECC should be carefully considered when designing training programs. While ECC training is possible without delayed onset muscle soreness[83], this requires familiarization and lower training intensities.

While further research is needed to explore the potential benefits of HYP, BFR, and ECC in older adults, this study demonstrates that training programs as short as 4 weeks can significantly promote healthy aging. Notable improvements were observed in various health parameters, including cardiovascular health, aerobic fitness, strength, muscle volume, and cognitive function, which should encourage older adults to take action.

Several perspectives emerge for future research. Longer training durations may reveal differences among conditions not evident in this 1-month study. Additionally, follow-up assessments could offer valuable insights into the sustainability and delayed benefits of various training modalities, as has been previously reported for BFR[84] and ECC[85].

Overall, this clinical trial highlights the need for an individualized approach, potentially combining modalities while prioritizing participant enjoyment, as adherence is key to the success of any training intervention[86].

Data availability

Data is provided within the manuscript or supplementary information files.

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Author contributions

Conceptualization: TC, GRM, and GPM; data collection: TC, GRM, MC, KH, and DP; data analysis: TC and MC; writing – original manuscript preparation: TC; reviewing, editing, and revising the paper: TC, GRM, and GPM. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

This clinical trial received approval from the local ethics committee (CERVD: 2021–02135).

Patient consent

All participants provided written informed consent before their inclusion.

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Not applicable.

Clinical trial registration

This clinical trial was pre-registered at ClinicalTrials.gov (NCT05207501).

Additional information

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