Archives of Rehabilitation Research and Clinical Translation (2024) 6, 100331

ACRM AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Rehabilitation Research and Clinical Translation

Archives of Rehabilitation Research and Clinical Translation 2024;6:100331

Available online at www.sciencedirect.com

Original Research

Submaximal, Low-Dose Eccentric vs Traditional Cycling Exercise: Reduced Oxygen Uptake and Pulmonary Artery Pressure Assessed by Echocardiography in Healthy Middle-aged Adults. A Randomized Controlled, Crossover Trial

Julian Müller, MSc [a,b], Meret Bauer, MD [a,b], Simon R. Schneider, PhD [a,b], Laura Mayer, MD [a,b], Anna Titz, MD [a,b], Nico Sturzenegger[a,b], Esther I. Schwarz, MD [a,b], Christoph Bauer, PhD [c], Ekkehard Grünig, MD [d], Malcolm Kohler, MD [a,b], Mona Lichtblau, MD [a,b], Silvia Ulrich, MD [a,b]

[a] *Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland*
[b] *University of Zurich, Zurich, Switzerland*
[c] *University of Jyväskylä, Faculty of Sport and Health Science, Jyväskylä, Finland*
[d] *Thoraxclinic Heidelberg, Heidelberg, Germany*

List of abbreviations: CO, cardiac output; CON, concentric cycling exercise; ECC, eccentric cycling exercise; HR, heart rate; RER, respiratory exchange ratio; SV, stroke volume; TRPG, tricuspid regurgitation pressure gradient; TRV, tricuspid regurgitation velocity; $V'CO_2$, carbon dioxide output; V'E, minute ventilation; $V'E/V'CO_2$, ventilatory equivalent for CO_2; $V'E/V'O_2$, ventilatory equivalent for O_2; $V'O_2$, oxygen uptake; Vt, tidal volume.

Disclosures: Ekkehard Grünig has received fees for lectures and/or consultations from Actelion, Bayer/MSD, Ferrer, GEBRO, GSK, Janssen, and OMT. Research grants to his institution have been received from Acceleron, Actelion, BayerHealthCare, MSD, Bellerophon, GossamerBio, GSK, Janssen, Novartis, OMT, Pfizer, REATE, and United Therapeutics. Malcolm Kohler has received fees for lectures and/or consultations and/or travel from GSK, Deep Breath Intelligence, Novartis, and the ERS. Esther Irene Schwarz has received fees for lectures and/or consultations and/or travel from the Swiss National Science Foundation, Philips Respironics, ResMed, and the ERS. Silvia Ulrich has received fees for lectures and/or consultations and/or travel from the Swiss National Science Foundation, the Swiss lung League, OrPha-Swiss, Novartis, and Janssen. The other authors have nothing to disclose.

This study was financially supported by a grant of Janssen-Cilag GmbH.
Cite this article as: Arch Rehabil Res Clin Transl. 2024;000:100331

https://doi.org/10.1016/j.arrct.2024.100331

KEYWORDS
Cardiopulmonary exercise testing;
Eccentric cycling exercise;
Pulmonary hypertension;
Pulmonary vascular disease;
Rehabilitation

Abstract *Objective:* To investigate the ventilatory and circulatory differences between eccentric (ECC) and concentric (CON) cycling exercise at submaximal, low-dose intensity from onset to end-exercise in healthy middle-aged participants.
Design: Randomized controlled crossover trial.
Setting: The participants underwent 1 ECC and 1 CON test according to stepwise incremental exercise protocols at identical, submaximal intensities. Breath-by-breath analyses of ventilatory gas exchange and echocardiography were used to assess cardiopulmonary function during exercise.
Participants: 24 healthy middle-aged, untrained participants (14 women, 10 men, 50±14 years) were included.
Interventions: 1 ECC and 1 CON test at submaximal intensities.
Main Outcome Measure: The main outcome was oxygen uptake ($V'O_2$).
Results: The $V'O_2$ increase was reduced by -422 mL/min (-52%, 95% confidence interval: -513 to -292, $P<.001$) during ECC, as well as the ventilatory drive. Echocardiographic parameters, heart rate (-14%), cardiac output (-21%), stroke volume (-15%), and pulmonary artery pressure by tricuspid regurgitation pressure gradient (TRPG) (-26%) were also significantly reduced during ECC compared with CON at identical intensities. Participants reported significantly less dyspnea and unchanged perceived leg fatigue in ECC.
Conclusion: ECC was well tolerated, and significant reductions were observed in $V'O_2$, ventilation, and right ventricular load compared with CON, even at low intensity levels. This study, conducted on healthy middle-aged participants, did not raise concerns that would hinder further investigation of the effects of ECC in patients with severely limited cardiopulmonary disease, and it calls for further research on this topic.

In eccentric cycling exercise (ECC), the cyclist has to resist the backward movement of pedals on a special motor-driven ergometer. During this, the load on the pedals exceeds the torque generated by the lengthening muscle (negative work), while producing and storing elastic recoil energy.[1-3] ECC generates high forces but requires up to 80% less oxygen[4] than conventional concentric cycling exercise (CON) and is described as an effective training modality with low metabolic costs.[1,5,6] Exercise training over extended and regular periods induces chronic adaptation. Recently, ECC was found to be more effective than CON in enhancing muscle strength, hypertrophy, 6-minute walking distance, and, notably, maximum oxygen uptake ($V'O_{2max}$), especially in patients with cardiopulmonary disease.[7] Besides low metabolic costs, evidence shows reduced cardiac output (CO) during ECC compared with CON at the same intensity.[8] Therefore, it could be a promising addition to pharmaceutical treatment, especially for patients with severely limited exercise capacity due to cardiopulmonary diseases. In these patients, regular exercise and rehabilitation are recommended and have been considered effective and safe.[9] However, patients with severe cardiopulmonary disease are mostly unable to increase their $V'O_2$ during exercise. This results in low exercise intensities, making it difficult for them to achieve beneficial levels of exercise. Nevertheless, for this group, ECC might be an intriguing option.[10] Hence, ECC has been assessed in cardiopulmonary conditions such as coronary artery disease,[11] heart failure,[12] or chronic obstructive pulmonary disease.[13] In a few randomized controlled trials, ECC was reported to be well-tolerated with minimal cardiovascular stress. However, these studies are mostly constrained by small sample sizes[14,15] or included only stable patients with mild diseases. They were rated as having limited body of evidence in terms of study quality, as assessed by a systematic review.[16]

Before exposing patients with severe cardiorespiratory diseases, combined with low exercise capacity, to ECC, it is essential to investigate the effect of submaximal ECC on an age-adapted untrained control group. So far, studies with healthy participants have mainly focused on young, well-trained athletes. These studies often use higher intensity protocols and may also show sex imbalances, such as including only men participants.[2] Previously, a moderate load was applied at <65% of the maximum heart rate (HR). However, this method resulted in exercise intensities of up to 400-500 W in ECC.[14] This study focused on submaximal, low-dose exercise protocols suitable for severe patients without relying on %HR or $\%\dot{V}O_{2max}$ considerations. Furthermore, echocardiography represents a promising addition, offering a non-invasive, reliable, and widely available real-time tool, to assess heart function during exercise.[17]

The aim of this study was to investigate ventilatory and circulatory differences between ECC and CON, as well as to assess right heart function at submaximal, low-dose intensity from onset to end-exercise in healthy middle-aged participants.

Methods

Study design, randomization, allocation, and subjects

This was a randomized controlled crossover trial conducted at the University Hospital of Zurich from February to December 2022. Participants were recruited from the personal acquaintances and families of the hospital employees between October 2021 and April 2022. The sample size was calculated based on the primary outcome $V'O_2$, assuming a MCID of 30$\pm$ 30 mL/min[18] with a significance level of 0.05 and a power of 0.9. To account for dropouts, we aimed to include 24 participants. Randomization was completed using software-generated allocation sequences, employing block randomization with random computed block length. Allocation to different trial sequences was based on the participants' recruitment number and was performed by software to ensure random allocation. After data collection, participants' data underwent anonymization. We included healthy participants of all sexes, aged between 18 and 80 years, but preferably middle aged or older, with no diagnosed cardiopulmonary disease. Regular medication intake was not permitted.

Ethics and registration

Patients provided written informed consent. The study adheres to the Declaration of Helsinki, approved by local ethical authorities (KEK 2021-0132), and is registered on clinicaltrials.gov (NCT05185895).

Cycling exercise

Interventions were separated by a break of at least 2 hours to avoid carry-over effects. A familiarization session with the eccentric ergometer was conducted before the first experimental session to allow patients to learn the special movement and to prevent muscle soreness. Participants performed 2 submaximal, standardized, stepwise incremental cycling exercise tests, each consisting of cycling intervals lasting 5 minutes per step (15 min total), with pedaling rates of 55-65 rpm. One test was performed using a conventional ergometer,[a] and the other with an eccentric ergometer,[b] in a randomized order. The intensity began at 50 W and increased by 10 to 30 W per step, depending on the selected exercise protocol. The choice of the protocol was determined by participants' self-reported fitness levels, with 3 different increments (sedentary 10 Watts/step, average 20 Watts/step, very active 30 Watts/step). Subjects were connected to the flow sensor of a metabolic unit via a mouthpiece,[c] which was calibrated before each test to measured respiratory gas exchange. The primary outcome $V'O_2$, and secondary outcomes including tidal volume (Vt), breathing frequency, minute ventilation (V'E), carbon dioxide output ($V'CO_2$), respiratory exchange ratio (RER), and derived variables, were recorded breath-by-breath. Arterial oxygen saturation was continuously measured by finger clip pulse oximetry. HR was derived from a 12-lead ECG, and blood pressure was measured using automated arm-cuff measurements. After each test, participants reported outcomes the Borg CR10 scales for leg fatigue and dyspnea were assessed.

Echocardiography

Echocardiography was performed at rest and during exercise during the last 2 minutes of each step. Recordings were performed using a real time sector scanner[d] with an integrated color-, continuous wave- (CW), and pulsed wave (PW) Doppler system. Recordings and measurements were performed according to guidelines of the American Society of Echocardiography.[19] Maximal tricuspid regurgitation pressure gradient (TRPG) was calculated from maximal tricuspid regurgitation velocity (TRV) obtained with CW-Doppler using the modified Bernoulli equation: Δ Pressure=4 $\times$ TRV_{max}^2. CO was estimated by the Doppler velocity time integral method from the left ventricular outflow tract.

Data presentation and statistical analysis

To compare the main outcome between concentric and eccentric cycling at the end of each step, physiological values were averaged over the last 30 s of the 3 steps and compared. Data were summarized as means $\pm$ standard deviation. A linear mixed model was fitted to the data with intervention (ECC vs CON), period and intervention-period interaction as fixed effects and subject as random intercept, thus controlling for carry-over (treatment-period interaction) and period effects according to the standards of crossover trials. We tested if intervention-period interaction could be removed from the model. Model assumptions were tested by visual inspection of the homogeneity and normality of the residuals and the random effects.

Table 1 Patients' characteristics

Number of Participants	24
Women; men	14; 10
Age [years]	50 $\pm$ 14
Weight [kg]	71 $\pm$ 12
Height [cm]	173 $\pm$ 9
BMI [kg/m^2]	23.8 $\pm$ 3.2
Heart rate at rest [bpm]	77 $\pm$ 11
SpO_2 at rest [%]	97 $\pm$ 1
$V'O_2$ at rest [mL/min]	247 $\pm$ 89
$V'CO_2$ at rest [mL/min]	205 $\pm$ 72
Tidal volume [L]	0.76 $\pm$ 0.27
Breathing frequency [L/min]	14 $\pm$ 6
Minute ventilation [L/min]	10.4 $\pm$ 2.6
RER	0.84 $\pm$ 0.12
Echocardiography:	
Left ventricular ejection fraction [%]	65 $\pm$ 6
Fractional area change [%]	51 $\pm$ 8
Cardiac output [L/min]	6.3 $\pm$ 0.8
Tricuspid regurgitation pressure gradient [mmHg]	17 $\pm$ 3
Tricuspid annular plane systolic excursion [mm]	21.0 $\pm$ 3.8

NOTE. Data are presented as means $\pm$ standard deviations or absolute numbers.
Abbreviation: BMI, body mass index; SpO_2, oxygen saturation by pulse oximetry.

The analysis of the secondary outcomes followed the same procedure as above but included baseline characteristics as covariates in addition to minimize bias. Missing data were handled by the linear mixed model[20] and intention to treat analysis was used.

In all analyses, a 95% confidence interval that excluded the null-effect was considered evidence for statistically significance. Analyses were performed using R-Studio software Version 4.1.0.[e]

Results

Model assumptions of homogeneity and normality of the residuals and random effects were fulfilled, and there were neither carry-over nor period-effects.

Participants

A total of 24 participants (14 women, 10 men, 50±14 years) completed the trial by intention-to-treat and 23 per protocol. One participant discontinued ECC prematurely due to knee pain. Baseline characteristics are presented in table 1. The study flow chart is shown in figure 1.

Ventilation, gas exchange, and rating of exertion

The primary outcome, $V'O_2$, was statistically significantly lower by -422 mL/min (40%, 95% CI: -535 to -307 mL/min, $P<.001$) in ECC compared with CON (tables 2 and 3, fig 2).

$V'CO_2$, V'E, and Vt were lower during ECC compared with CON at end-exercise: -439 mL/min (44%), -12.9 L/min (38%), and -0.5 L (33%), all 3, $P<.001$, while breathing frequency was non-significantly lower during ECC.

Ventilatory equivalent for O_2 ($V'E/V'O_2$) was higher in ECC by 10% at step-I (P=.014) but remained unchanged thereafter during exercise. Ventilatory equivalent for CO_2 ($V'E/V'CO_2$) was higher during ECC by 4 (12%, $P<.001$) compared with CON. At end-exercise, the RER was lower during ECC compared with CON, by -0.08 (9%, $P<.001$) (for all 95% CI see table 3, fig 2). Oxygen saturation by pulse oximetry and Borg CR10 scale for leg fatigue were unchanged, while Borg CR10 scale for dyspnea assessed at end-exercise was reduced by -1.4 ($P<.001$) in ECC compared with CON.

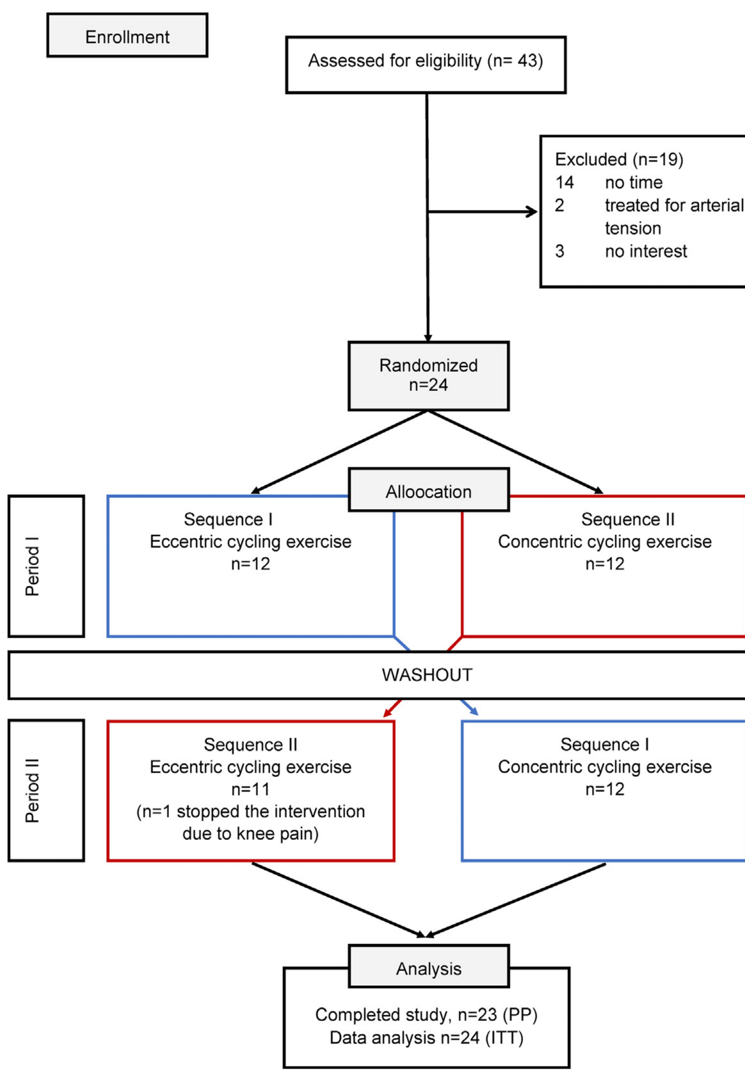

Fig 1 The patients flow. N, number of participants; PP, per protocol; ITT, intention to treat.

Table 2 Increase of the main outcome $\dot{V}O_2$

V'O$_2$ [mL/min]	Concentric	Eccentric			
Baseline at Rest	247±89	247±89			
	Mean Increase	Mean Increase	Mean Difference	95% CI	*P* Value
End step I - rest	562 ± 261	254 ± 261	-308 (55%)	-378 to -235	**<.001**
End step II - rest	680 ± 262	345 ± 261	-335 (49%)	-428 to -241	**<.001**
End step III - rest	818 ± 263	396 ± 261	-422 (52%)	-513 to -292	**<.001**

NOTE. Data are presented as means ± standard deviations, mean differences (plus percentage change (%)) and corresponding 95% confidence intervals.

Circulation and right heart function

At end-exercise, the pulmonary artery pressure assessed as TRPG was significantly lower by -9 mmHg (26%, *P*=.009) during ECC compared with CON, while TAPSE remained unchanged. CO, stroke volume (SV) and HR, were all lower at end-exercise in ECC, showing a significant mean reduction by -1.8 L/min (21%, *P*<.001), -12.2 mL (15%, *P*=.014), and -16 bpm (14%, *P*<.001) compared with CON. This resulted in a statistically significant TRPG/CO ratio until end-exercise.

DBP was increased at end-exercise during ECC by +17 mmHg (21%, *P*<.001), while SBP remained unchanged (table 4, fig 3).

Table 3 Ventilation, gas exchange, and rating of exertion

Step I — 4:30-5:00 min	Concentric	Eccentric	Mean Difference	95% CI	*P* Value
Watts	50	50	NA	NA	NA
V'O$_2$ [mL/min]	809 ± 293	501 ± 294	-308 (38%)	-380 to -236	**<.001**
V'CO$_2$ [mL/min]	704 ± 277	421 ± 278	-283 (40%)	-344 to -221	**<.001**
V'E [L/min]	25.8 ± 8.3	17.6 ± 8.3	-8.2 (32%)	-10.4 to -5.9	**<.001**
Vt [L]	1.3 ± 0.4	0.9 ± 0.4	-0.4 (31%)	-0.5 to -0.3	**<.001**
Bf [1/min]	20 ± 6	19 ± 6	-1 (5%)	-3 to 1	**.431**
V'E/V'O$_2$	31 ± 6	34 ± 6	3 (10%)	1 to 4	**.014**
V'E/V'CO$_2$	36 ± 6	40 ± 6	4 (11%)	2 to 6	**<.001**
RER	0.87 ± 0.08	0.84 ± 0.08	-0.03 (3%)	-0.07 to 0.01	.082
SpO$_2$ [%]	95 ± 2	95 ± 2	-0.3 (0%)	-1 to 1	.349
Step II — 9:30-10:00 min					
Watts	60-80	60-80	NA	NA	NA
V'O$_2$ [mL/min]	927 ± 294	592 ± 295	-335 (36%)	-429 to -240	**<.001**
V'CO$_2$ [mL/min]	848 ± 278	507 ± 279	-341 (40%)	-425 to -257	**<.001**
V'E [L/min]	30.1 ± 8.3	20.2 ± 8.3	-9.9 (33%)	-12.8 to -6.9	**<.001**
Vt [L]	1.5 ± 0.4	1.1 ± 0.4	-0.4 (27%)	-0.6 to -0.3	**<.001**
Bf [1/min]	22 ± 6	20 ± 6	-2 (9%)	-4 to 1	**.239**
V'E/V'O$_2$	32 ± 6	33 ± 6	1 (3%)	-1 to 3	.295
V'E/V'CO$_2$	35 ± 6	39 ± 6	4 (11%)	2 to 6	**.002**
RER	0.92 ± 0.08	0.86 ± 0.08	-0.06 (7%)	-0.09 to -0.03	**<.001**
SpO$_2$ [%]	95 ± 2	95 ± 2	0.1 (0%)	-1 to 1	.856
Step III — 14:30-15:00 min					
Watts	80-110	80-110	NA	NA	NA
V'O$_2$ [mL/min]	1065 ± 294	643 ± 296	-422 (40%)	-535 to -307	**<.001**
V'CO$_2$ [mL/min]	989 ± 279	550 ± 279	-439 (44%)	-544 to -333	**<.001**
V'E [L/min]	34.4 ± 8.3	21.5 ± 8.3	-12.9 (38%)	-16.4 to -9.4	**<.001**
Vt [L]	1.5 ± 0.4	1.0 ± 0.4	-0.5 (33%)	-0.6 to -0.3	**<.001**
Bf [1/min]	23 ± 6	20 ± 6	-3 (13%)	-6 to 1	**.080**
V'E/V'O$_2$	32 ± 6	33 ± 6	1 (3%)	-2 to 3	.586
V'E/V'CO$_2$	34 ± 6	38 ± 6	4 (12%)	2 to 6	**<.001**
RER	0.94 ± 0.08	0.86 ± 0.08	-0.08 (9%)	-0.12 to -0.04	**<.001**
SpO$_2$ [%]	95 ± 2	95 ± 2	-0.1 (0%)	-1 to 1	.768
BorgCR10$_{leg\ fatigue}$	2.4 ± 1.3	2.6 ± 1.3	0.2	-0.5 to 0.9	.613
BorgCR10$_{dyspnea}$	3.0 ± 1.5	1.6 ± 1.5	-1.4	-2.0 to -0.7	**<.001**

NOTE. Data are presented as means ± standard deviations, mean differences (plus percentage change (%)), and corresponding 95% confidence intervals.
Abbreviations: Bf, breathing frequency; BorgCR10, Borg scale from 1 to 10 for leg fatigue and dyspnea; SpO$_2$, oxygen saturation by pulse oximetry.

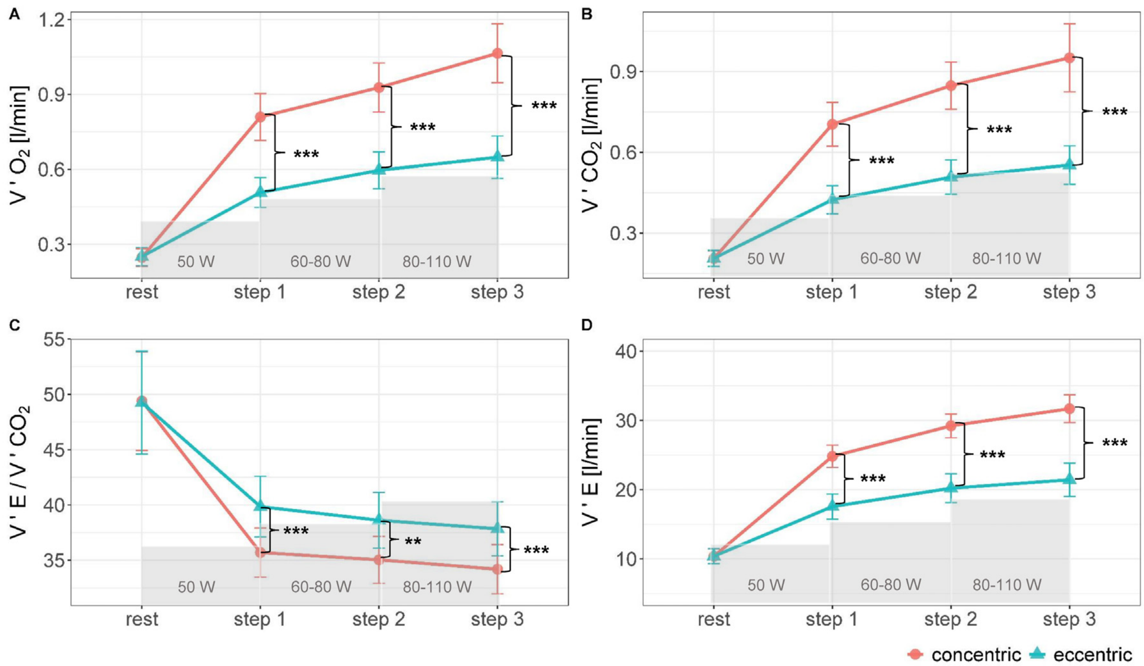

Fig 2 The ventilation and gas exchange during eccentric (blue triangle) compared with traditional concentric (red circles) stepwise incremental cycling exercise in 24 participants, according to a randomized-crossover design with identical protocols each. Data are presented as means with standard deviations and the corresponding *P* values for statistically significant differences between the 2 conditions. Panel A shows the V'O_2, Panel B shows the V'CO_2, Panel D shows the V'E, all were significantly reduced by -40%, -44%, and -38% during eccentric vs concentric cycling exercise at end-step III. Panel C shows the ventilator equivalent for CO_2 (V'E/V'CO_2) which was significantly increased by +12% in eccentric vs concentric exercise. $^{***}P<.001$; $^{**}P<.01$; $^{*}P<.05$.

Discussion

This randomized controlled crossover trial investigated the ventilatory and circulatory differences between 15 minutes of submaximal ECC vs CON in 24 middle-aged untrained healthy participants. The primary outcome, V'O_2, was significantly reduced by 40% during ECC compared with CON.

Nevertheless, we could not observe the up to 80% reduced O_2 demand as previously described.[2] We attribute this to the submaximal exercise intensity in our study, as indicated by the RER, which was <1 during both conditions at end-exercise. Dufour et al (2004) graphically illustrated differences in O_2 kinetics in 8 healthy, young men, where the slopes between ECC and CON consistently diverge at higher intensities.[8] While V'O_2 in healthy subjects consistently increases by ~10 mL/W/min during CON,[21] the slope of increase appears to be much smaller in ECC (fig 2, panel A).

Ventilation and gas exchange

Ventilation was reduced during ECC compared with CON, as reflected in lower V'E, Vt, and V'CO_2. However, V'E/V'CO_2, typically used by clinicians to assess breathing pattern efficiency, was higher by 12% at end-exercise during ECC, despite participants were not hyperventilating (RER 0.86). The economization of breathing patterns during exercise involves a linear increase of both V'E and V'CO_2 until a certain level is reached, at which anaerobic metabolism increases and V'CO_2 becomes steeper. The consecutively stimulation of V'E, is a physiological response resulting from intensified metabolic acidosis and increasing metabolic demand.[22] However, since the metabolic demand is lower during ECC, participants did not reach the point of steep increase in V'CO_2. Consequently, V'E/V'CO_2 is higher, indicating that ventilation appears to be less efficient in ECC. This suggests that there is still a considerable reserve to increase ventilation.

To date, the study by Lipski et al (2018) is the only 1 in which incremental ECC and CON tests were performed until exhaustion. They reported similar differences in breathing patterns, even during high to maximal loads.[23]

Participants reported less dyspnea during ECC compared with CON, while perceived leg fatigue remained unchanged. Although subjective, this outcome is important. The reduction in dyspnea appears to be obviously related to the reduced metabolic costs, while the unchanged perceived leg fatigue suggests that the submaximal load was well tolerated. Similar leg fatigue despite lower metabolic costs in ECC may reflect that the perception of leg fatigue is not only related to metabolic costs but also to the level of musculo-tendinous tensions. That might have changed with a longer prior familiarization process in our study.[14] Since ECC bears the risk of microlesions in muscular fibers, potentially leading to muscle damage and soreness (some cases of exertional rhabdomyolysis during high ECC loads[2] have been reported), determining the appropriate exercise intensities for ECC may be challenging.

Table 4 Circulation and right heart function

Step I – 4:30-5:00 min	Concentric	Eccentric	Mean Difference	95% CI	*P* Value
Watts	50	50	NA	NA	NA
TRV [cm/s]	239 ± 38	227 ± 39	-12 (5%)	-32 to 5	.198
TRPG [mmHg]	23 ± 8	21 ± 8	-2 (9%)	-6 to 1	.216
TAPSE [mm]	22.2 ± 3.4	22.2 ± 3.5	-0.01 (0%)	-0.2 to 0.2	.937
CO [L/min]	7.1 ± 2.1	6.0 ± 2.1	-1.1 (16%)	-1.7 to -0.4	**.003**
SV [mL]	74.6 ± 21.7	68.5 ± 21.7	-6.1 (8%)	-10.7 to -1.4	**.017**
HR [bpm]	97 ± 16	87 ± 17	-10 (10%)	-14 to -6	**<.001**
TRPG/CO [WU]	3.9 ± 1.5	4.3 ± 1.4	0.4 (10%)	-0.7 to 1.0	.477
SBP [mmHg]	141 ± 27	141 ± 27	+0.2 (0%)	-11 to 13	.978
DBP [mmHg]	77 ± 18	86 ± 18	+9 (16%)	1 to 18	**.046**
Step II – 9:30-10:00 min					
Watts	60-80	60-80	NA	NA	NA
TRV [cm/s]	276 ± 38	229 ± 38	-47 (17%)	-79 to -14	**.020**
TRPG [mmHg]	31 ± 8	21 ± 8	-10 (32%)	-17 to -3	**.021**
TAPSE [mm]	24.1 ± 3.5	23.9 ± 3.5	-0.2 (1%)	-0.19 to 0.15	.792
CO [L/min]	8.2 ± 2.1	6.9 ± 2.1	-1.3 (16%)	-2.2 to -0.4	**.009**
SV [mL]	75.1 ± 21.8	71.1 ± 21.7	-4.0 (5%)	-10.5 to 2.9	.241
HR [bpm]	105 ± 16	95 ± 17	-10 (10%)	-16 to -5	**<.001**
TRPG/CO [WU]	4.4 ± 1.5	3.9 ± 1.5	-0.5 (11%)	-1.7 to 1.0	.604
SBP [mmHg]	152 ± 27	155 ± 27	3 (2%)	-14 to 20	.739
DBP [mmHg]	80 ± 18	88 ± 18	8 (10%)	-2 to 17	.115
Step III – 14:30-15:00 min					
Watts	80-110	80-110	NA	NA	NA
TRV [cm/s]	289 ± 39	248 ± 39	-41 (14%)	-64 to -17	**.007**
TRPG [mmHg]	34 ± 8	25 ± 8	-9 (26%)	-14 to -3	**.009**
TAPSE [mm]	24.5 ± 3.5	24.1 ± 3.5	-0.4 (2%)	-0.2 to 0.2	.695
CO [L/min]	8.8 ± 2.1	7.0 ± 2.1	-1.8 (21%)	-2.6 to -1.0	**<.001**
SV [mL]	81.8 ± 21.6	69.6 ± 21.7	-12.2 (15%)	-21.2 to -3.0	**.014**
HR [bpm]	114 ± 16	98 ± 16	-16 (14%)	-21 to -11	**<.001**
TRPG/CO [WU]	4.2 ± 1.5	4.3 ± 1.4	0.1 (2%)	-0.6 to 0.9	.717
SBP [mmHg]	161 ± 27	159 ± 27	-2 (3%)	-16 to 12	.820
DBP [mmHg]	80 ± 18	97 ± 18	17 (21%)	11 to 22	**<.001**

NOTE. Data are presented as means ± standard deviations, mean differences (plus percentage change (%)), and corresponding 95% confidence intervals.
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; TRPG/CO, pressure-flow relation.

Circulation and right heart function

We observed significantly lower HR, SV, and CO during ECC at end-exercise compared with CON. These findings are consistent with existing studies in the literature.[8] It is interesting to note that participants not only reduced CO through lower HR but also through lower SV. Both of these may indicate that not only skeletal muscles but also the heart itself has a lower O_2 demand.

The pressure-flow relation in the pulmonary circulation reflects the resistance. Pressure and flow follow the same direction; for example, an increase in CO during exercise is associated with an increase in pulmonary arterial pressure and vice versa.[24] In healthy individuals, this relation should slightly decrease during exercise due to the recruitment and distension of the pulmonary vessels, which accommodate the increased CO.[24] The TRPG, an approximation of systolic pulmonary artery pressure, was lower by 26% during ECC, along with a reduced CO, resulting in an unchanged pulmonary resistance (TRPG/CO). The primary motivation for investigating TRPG and right heart function was to assess right ventricular load, a paramount factor for exercise that is often impaired in the presence of cardiopulmonary diseases. The right ventricular afterload, which cannot be compensated by Starling mechanism, can lead to progressive dilatation, posing potential dangers for these patients during exercise.[25] The presently observed lower TRPG during ECC compared with CON is a crucial finding indicating a reduced right ventricular load at identical exercise intensity.

In a study by Meyer et al (2003), patients with coronary disease were exposed to either ECC or CON training periods for 6 weeks. During a training session in the fifth week, right heart catheters were conducted. Among the reported outcomes was the pulmonary capillary wedge pressure, a marker of left ventricular preload. In these patients with coronary disease, the pulmonary capillary wedge pressure increased significantly during the first 5 minutes of ECC to the upper limits of normal but decreased during further exercise, returning to normal physiological ranges.[11] These findings indicate that, in addition to our results showing the lower TRPG, left heart load might also be within normal ranges during ECC.

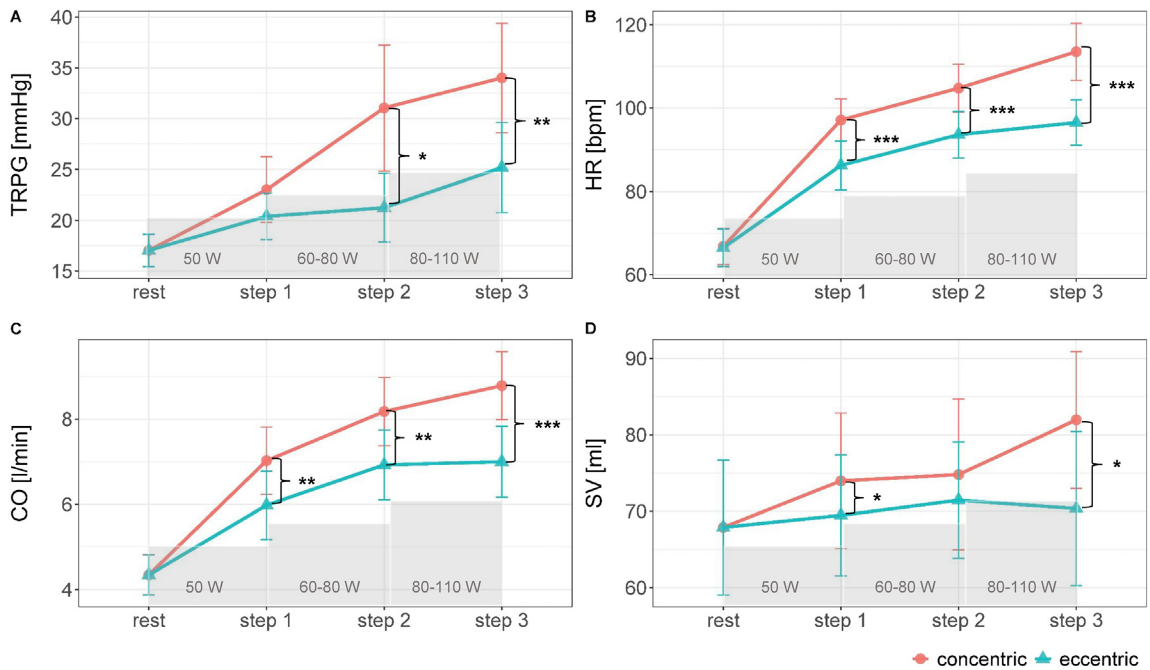

Fig 3 The circulation and right heart function during eccentric (blue triangle) vs concentric (red circles) stepwise incremental cycling exercise in 24 participants, according to a randomized-crossover design with identical protocols each. Data are presented as means with standard deviations and the corresponding *P* values for statistically significant differences between the 2 conditions. Panel A shows the TRPG as surrogate for pulmonary artery pressure, Panel B shows HR, Panel C shows CO, and Panel D shows SV. All were significantly reduced by -26%, -16%, -21%, and -15% during eccentric vs concentric cycling exercise at end-step III. $^{***}P<.001$; $^{**}P<.01$; $^{*}P<.05$.

When comparing end-exercise ECC with end-step-I CON, HR seems to be similar. This could allow for a comparison of ECC and CON at similar HR levels. Hypothetically, in our study $V'O_2$ would still be reduced by -21% (review by Barreto et al (2020) -23%[1]), while TRPG and CO would be in similar ranges. The only difference would be higher blood pressure during ECC compared with CON at the same HR level.

Another study investigated the cardiovascular responses to 45-minute constant load protocols with workloads set to achieve similar HR in ECC compared with CON. The authors reported higher cardiovascular strain and altered baroreflex activity during ECC compared with CON, suggesting that ECC may trigger greater sympathetic activity.[26] However, workloads during similar HR might be much higher during ECC compared with CON, and therefore, do not contradict our results but demonstrate that ECC should be handled with caution.

DBP was 21% higher in ECC, but overall, both SBP and DBP remained within normal ranges during exercise and did not exceed any safety thresholds.

The incorporation of echocardiography for non-invasive assessment of right heart function during exercise introduces a novel aspect in studies on the effect of ECC. It may also be used during the evaluation of rehabilitation in patients with cardiopulmonary disease, owing to its safety, prognostic, and diagnostic capabilities.[17]

Submaximal ECC was generally well tolerated. One participant discontinued the ECC test prematurely due to increasing knee pain. Several studies have reported up to a 50% reduction in electromyogram activity during eccentric contractions. This reduction results in decrease in intra and inter muscular fine control, making eccentric control of movements more challenging.[14] When muscular control is reduced during exertion with constant torque, it could potentially increase strain on the knee joint. Although this strain is lower during submaximal ECC compared with higher intensities, clinicians should remain vigilant, especially in multimorbid patients.

Where to go?

Exploring not just the immediate physiological changes and right heart responses but particularly delving into the enduring effects of ECC after several weeks of training is of significant interest. According to systematic reviews, which included numerous small studies with varying outcomes and exercise modes, it is reported that eccentric exercise (not only cycling) during longer exercise periods allow participants to achieve significantly higher exercise intensities. This results in greater exercise gains while reducing metabolic costs and cardiopulmonary stress.[1,2,14,16] A recently published systematic review, which focused exclusively on ECC (only cycling), concluded that ECC was more effective than CON in increasing knee extensor strength, fiber cross-sectional area, 6-minute walking distance in all investigated subjects, and furthermore, in improving $\dot{V}O_{2max}$ in patients with cardiopulmonary diseases.[7]

Improved exercise capacity has been demonstrated to directly affect the quality of life and survival in patients with severely limited cardiopulmonary disease, including those with pulmonary hypertension.[27,28] ECC appears to be a promising exercise modality, even at low intensities. More robust evidence is needed for both acute and chronic aspects of ECC in severe cardiopulmonary conditions. The long-term goal is to incorporate these concepts into specific rehabilitation programs.

Limitation

A limitation of the study is that the participants' maximum exercise capacity was not measured. Therefore, the selected submaximal intensity was estimated on self-reported daily activity and fitness level. Furthermore, due to the intentionally low exercise intensities, gas exchange thresholds were not reached, limiting the interpretability of ventilatory equivalents. The distinct body positions in ECC and CON may have influenced muscle response and hemodynamics; CON was executed upright, while ECC was performed in Fowlers position. Nevertheless, we posit that the hemodynamic difference between upright and Fowlers positions, given the nearly upright upper body in the latter, can be deemed marginal.

Conclusions

ECC was well tolerated, and significant reductions were observed in $V'O_2$, ventilation, and right ventricular load compared with CON, even at low intensity levels. This study, conducted on healthy middle-aged participants, did not raise concerns that would hinder further investigation of the effects of ECC in patients with severely limited cardiopulmonary disease, and it calls for further research on this topic.

Suppliers

a. Ergoselect-200; Ergoline GmbH.
b. Cyclus-2-Recumbent; RBM elektronik-automation GmbH.
c. Ergostick; Geratherm Medical.
d. CX50, Philips; Philips Respironics.
e. R-Studio software Version 4.1.0; R Foundation.

Corresponding author

Silvia Ulrich, Department of Pulmonology, University ?Hospital Zurich, Raemistrasse 100, 8091 Zürich, Switzerland. *E-mail address:* Silvia.ulrich@usz.ch.

Acknowledgments

We acknowledge the infrastructure of the Department of Pulmonology of the University Hospital Zurich including all technicians and the completely nursing team that was supportive for this study.

References

1. Barreto RV, de Lima LCR, Denadai BS. Moving forward with backward pedaling: a review on eccentric cycling. Eur J Appl Physiol 2021;121:381-407.
2. Isner-Horobeti ME, Dufour SP, Vautravers P, Geny B, Coudeyre E, Richard R. Eccentric exercise training: modalities, applications and perspectives. Sports Med 2013;43:483-512.
3. Lindstedt SL, LaStayo PC, Reich TE. When active muscles lengthen: properties and consequences of eccentric contractions. News Physiol Sci 2001;16:256-61.
4. Perrey S, Betik A, Candau R, Rouillon JD, Hughson RL. Comparison of oxygen uptake kinetics during concentric and eccentric cycle exercise. J Appl Physiol (1985) 2001;91:2135-42.
5. LaStayo PC, Pierotti DJ, Pifer J, Hoppeler H, Lindstedt SL. Eccentric ergometry: increases in locomotor muscle size and strength at low training intensities. Am J Physiol Regul Integr Comp Physiol 2000;278:R1282-8.
6. Roig M, O'Brien K, Kirk G, et al. The effects of eccentric versus concentric resistance training on muscle strength and mass in healthy adults: a systematic review with meta-analysis. Br J Sports Med 2009;43:556-68.
7. Barreto RV, de Lima LCR, Borszcz FK, de Lucas RD, Denadai BS. Chronic adaptations to eccentric cycling training: a systematic review and meta-analysis. Int J Environ Res Public Health 2023;20:2861.
8. Dufour SP, Lampert E, Doutreleau S, et al. Eccentric cycle exercise: training application of specific circulatory adjustments. Med Sci Sports Exerc 2004;36:1900-6.
9. Grunig E, MacKenzie A, Peacock AJ, et al. Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial. Eur Heart J 2021;42:2284-95.
10. Spruit MA, Augustin IM, Vanfleteren LE, et al. Differential response to pulmonary rehabilitation in COPD: multidimensional profiling. Eur Respir J 2015;46:1625-35.
11. Meyer K, Steiner R, Lastayo P, et al. Eccentric exercise in coronary patients: central hemodynamic and metabolic responses. Med Sci Sports Exerc 2003;35:1076-82.
12. Besson D, Joussain C, Gremeaux V, et al. Eccentric training in chronic heart failure: feasibility and functional effects. Results of a comparative study. Ann Phys Rehabil Med 2013;56:30-40.
13. Rocha Vieira DS, Baril J, Richard R, Perrault H, Bourbeau J, Taivassalo T. Eccentric cycle exercise in severe COPD: feasibility of application. COPD 2011;8:270-4.
14. Hoppeler H. Moderate load eccentric exercise; a distinct novel training modality. Front Physiol 2016;7:483.
15. LaStayo P, Marcus R, Dibble L, Frajacomo F, Lindstedt S. Eccentric exercise in rehabilitation: safety, feasibility, and application. J Appl Physiol (1985) 2014;116:1426-34.
16. Ellis R, Shields N, Lim K, Dodd KJ. Eccentric exercise in adults with cardiorespiratory disease: a systematic review. Clin Rehabil 2015;29:1178-97.
17. Peteiro J, Bouzas-Mosquera A. Exercise echocardiography. World J Cardiol 2010;2:223-32.
18. Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;172:19-38.
19. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713. quiz 786-8.
20. Bennett DA. How can I deal with missing data in my study? Aust N Z J Public Health 2001;25:464-9.
21. Meyer K, Hajric R, Samek L, et al. Cardiopulmonary exercise capacity in healthy normals of different age. Cardiology 1994;85:341-51.
22. Wasserman K. Breathing during exercise. N Engl J Med 1978;298:780-5.

23. Lipski M, Abbiss CR, Nosaka K. Cardio-pulmonary responses to incremental eccentric and concentric cycling tests to task failure. Eur J Appl Physiol 2018;118:947–57.
24. Naeije R, Chesler N. Pulmonary circulation at exercise. Compr Physiol 2012;2:711–41.
25. Tello K, Seeger W, Naeije R, et al. Right heart failure in pulmonary hypertension: diagnosis and new perspectives on vascular and direct right ventricular treatment. Br J Pharmacol 2021;178:90–107.
26. Ritter O, Isacco L, Rakobowchuk M, et al. Cardiorespiratory and autonomic nervous system responses to prolonged eccentric cycling. Int J Sports Med 2019;40:453–61.
27. Halank M, Einsle F, Lehman S, et al. Exercise capacity affects quality of life in patients with pulmonary hypertension. Lung 2013;191:337–43.
28. Grunig E, Eichstaedt C, Barbera JA, et al. ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. Eur Respir J 2019;53:1800332.