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Abstract: Background: To date, eccentric cycling (EC) in patients suffering from cardiovascular limitations has proven its efficacy. However, progressively increasing the intensity of EC during training programs has not been tested.
Objective: To evaluate the feasibility and safety of an incremental workload program in coronary heart disease patients.
Methods: Coronary heart disease patients participated in four sessions of EC (25-min). The first and second sessions were interspaced by one week, and the subsequent sessions by three days. During EC, power output and gas exchanges were recorded. Blood CPK concentration was measured 72-h after each session. During the first session, the intensity was fixed at the power output developed at the first ventilatory threshold (measured in a preliminary session during concentric cycling). Then, power output was increased by ~25%/session.
Results: Fifteen coronary heart disease patients were included. Power output increased ($P<0.001$) from 62 ± 5% peak power output (PPO, obtained in a preliminary visit during concentric cardiopulmonary exercise testing) to 118 ± 13 %PPO. While HR remains stable ($P=0.316$) during the four sessions (session 1: 65 ± 6 %HRpeak ; session 4: 67 ± 6 %HRpeak), VO2 increased ($P=0.002$) from 34 ± 4 %VO2peak to 42 ±8 %VO2peak. Blood CPK concentration peaked (157 ± 42 UI/L) after the third session and remained lower than the clinical relevance for all patients. Leg muscle pain in all patients remained low (< 4/10) following each session.
Conclusions: Our results confirm the feasibility of progressively increasing EC intensity during training program in coronary heart disease patients.

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Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
The authors do not have permission to share data

HIGHLIGHTS

1. Increasing eccentric cycling intensity in coronary heart disease patients is feasible.
2. The increased intensity was progressive (+25%) between sessions.
3. The power output reached was above the one obtained during CPET.
4. Blood CPK concentration remained low following each session (+72 h).
5. Leg muscle pain remained low following each session (+72 h).

*Complete Manuscript (Fichier Manuscrit)

Progressively increasing the intensity of eccentric cycling over four training sessions: a feasibility study in coronary heart disease patients

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- *Delphine Besson:* Data collection and analysis, screening and inclusion of participants, approved the final version of the manuscript.
- *Jean-Marie Casillas*: Funding acquisition, data analysis, screening and inclusion of the participants, approved the final version of the manuscript.
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Background: To date, eccentric cycling (EC) in patients suffering from cardiovascular limitations has proven its efficacy. However, progressively increasing the intensity of EC during training programs has not been tested.

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KEYWORDS (3 TO 5)

Oxygen consumption

Eccentric training

Muscle pain

Perception of effort

Eccentric rehabilitation

ABBREVIATION

CPET: CardioPulmonary Exercise Testing

CPK: Creatine PhosphoKinase

HR: Heart Rate

PPO: Peak Power Output

RPE: Rating of Perceived Exertion

VO_{2peak}: peak oxygen consumption

VCO_2: carbon dioxide production

W: Watt

INTRODUCTION

It is now well known that compared to concentric muscle contraction, eccentric muscle contraction presents the advantage of producing a higher level of force for a lower cardiovascular, respiratory and metabolic solicitation [1-5]. For this reason, the integration of eccentric muscle contraction in rehabilitation programs is of great interest for patients limited by cardiorespiratory symptoms [1, 6-9]. The specificity of eccentric muscle contraction led to the development of eccentric cycling ergometers that can be easily integrated in rehabilitation programs in various populations [10-12]. While the feasibility of integrating eccentric cycling at fixed intensity in rehabilitation program has been previously shown [7], it remains unknown whether a progressive increase in eccentric cycling intensity is feasible in patients suffering from cardiovascular limitations. Such knowledge would allow clinicians and therapists to plan the increased intensity of eccentric cycling during rehabilitation program, in order to maximize muscle solicitation and minimize the associated side effects (increased leg muscle pain and associated inflammation processes).

The aim of this study is to test this possibility in coronary heart disease patients. Based on a previous study with patients suffering from respiratory limitations [12], we hypothesized that a progressive increase in eccentric cycling would be feasible in coronary heart disease patients. By measuring blood creatine phosphokinase (CPK) concentration and leg muscle pain 72-h following each session, we also hypothesized that the training program will be well tolerated by the patients.

METHODS

Overview of the study

A detailed report of the inclusion/exclusion criteria and methods is presented in *Supplementary Material 1*. Fifteen coronary heart disease patients were included in this study and written informed consent approved by the local ethics committee was obtained for all participants after they had been informed of all potential risks, discomfort and benefits generated by the study. Briefly, the inclusion criteria were patients : i) referred for a rehabilitation program, ii) with a left ventricular ejection fraction on echocardiography (Simpson method) > 45 %, iii) without oxygen therapy ; and exclusion criteria were patients with : i) severe obstructive cardiopathy, ii) severe aortic valve stenosis, iii) heart rhythm or conduction disorders, iv) intracavitary thrombus, v) severe pulmonary hypertension, vi) impaired executive and physical functions not compatible with rehabilitation procedure.

Patients visited the laboratory on five different occasions (one familiarization with cardiopulmonary exercise testing + four eccentric cycling training sessions).

Visit 1 was a preliminary visit consisting of the familiarization with the eccentric cycling ergometer and the completion of a maximal cardiopulmonary exercise testing (CPET) to determine concentric cycling peak power output (PPO) as well as peak oxygen consumption (VO_{2peak}), peak breathing frequency and the first ventilatory threshold. The power output at the first ventilatory threshold was used to fix the intensity of the first eccentric cycling session (*visit 2*, one week following visit 1). Then, power output was increased by 25% per session (*visit 3 to 5*, interspaced by 72-h). Each experimental session started with a 10 min warm-up consisting of concentric cycling at 50 W, followed by 25-min eccentric cycling. This duration of exercise was chosen to match the duration of training sessions in our rehabilitation center. A 25% increment per session was determined based on a preliminary study performed on a fifteen healthy age-matched population. Overview of the results of the preliminary study is presented in *supplementary material 2*.

Physiological and psychological measurements

Patients performed isokinetic eccentric cycling during 25-min on a prototype (TechMed, TMS, Champs/Yonne, France[a]). Cadence was fixed at 15 revolutions/min, and the patients had to resist against the pedal movement to produce the required torque. During the eccentric cycling sessions, respiratory-gas exchange parameters and heart rate (HR) were monitored using the K4b^2 (Cosmed, Rome, Italy[b]) and a chest belt with a HR sensor. Rating of perceived exertion (RPE) was obtained immediately after cessation of the eccentric cycling exercise. A 5 mL blood sample was collected from the cubital vein and send to the Dijon University Hospital's biological center for blood CPK concentration analysis. Blood sample was collected at the onset of visit 1 (i.e., baseline) and 72-h post each session when the patients returned to the laboratory for the subsequent visits. Leg muscle pain was monitored 72-h after each session when the patients returned to the laboratory for blood sample collection.

Statistical analysis

The sample size was based on a similar study of Rocha Vieira et al. [12] (N = 6 chronic obstructive pulmonary disease patients). We increased the sample size to 15 to increase the chance of observing side effects (leg muscle pain > 4/10 and CPK concentration >1000 UI/L) and performed first this experiment with 15 healthy participants (see Supplementary Material 2) before replicating it with 15 coronary heart disease patients. Results are presented as mean ± 95 %CI and normality as well as sphericity were checked as appropriate. Greenhouse–Geisser correction to the degree of freedom was applied when sphericity was violated. One-way repeated-measures ANOVA (4 sessions) were used to test the effects of increasing the intensity of eccentric cycling on cardiorespiratory parameters and perception of effort. If significant, this test was followed up with LSD Fisher tests. Significance was set at 0.05 (2-tailed) for all analyses. The effect sizes for the repeated measures ANOVAs were calculated as partial eta squared (η_p^2). Stata software v15 (StataCorp, College Station, TX, USA) was used for the analysis.

RESULTS

Fifteen patients were included in this study (13 men and 2 women; age: 58.8 ± 10.6 yr; height: 171 ± 5 cm; weight: 76.9 ± 11.8 kgs; concentric PPO: 125 ± 18 W; concentric CPET VO_{2peak}: 21.6 ± 5.6 mL/kg/min). Two patients withdrawn from the study in relation to an injury non-related to the eccentric cycling protocol. Also, due to technical issues with the prototype software and the gas analyzer, cardiorespiratory data was not available for all patients. Consequently, the data analysis was carried out on eleven patients for power output and ten patients for cardiorespiratory parameters. This information is presented in the study flowchart in Figure 1.

PLEASE INSERT FIGURE 1

Figure 2 presents eccentric cycling power output and all cardiorespiratory data. Power output, VO_2, VCO_2, ventilation, and tidal volume increased from the first to the fourth session (all $P < 0.041$, $\eta_p^2 = 0.902$). All follow-up tests are presented in Figure 2. The increase in VO_2, VCO_2, ventilation and tidal volume was significant only from the third session. and remained below the values reached during concentric CPET (visit 1). Similarly, RPE increased only from the third session ($P = 0.009$, $\eta_p^2 = 0.315$; from 11.9 ± 1.1 to 14 ± 1.8 –i.e., from light effort to ~ somewhat hard effort–). HR ($P = 0.591$, $\eta_p^2 = 0.067$) and breathing frequency ($P = 0.316$, $\eta_p^2 = 0.121$) remained stable during the four sessions. At session 4, despite reaching an eccentric cycling power output corresponding to 118 ± 13 % PPO obtained during concentric CPET, the VO_2, HR and breathing frequency remained respectively at 42 ± 8, 67 ± 6 and 71 ± 11 % of their peak values obtained during concentric CPET.

PLEASE INSERT FIGURE 2

Individual blood CPK concentration values and reports of leg muscle pain 72 h post exercise are presented in Figure 3. Briefly, blood CPK concentration peaked (157 ± 42 UI/L) after the third session and remained low following each session. Leg muscle pain in all patients remained low (< 4/10) following each session.

PLEASE INSERT FIGURE 3

DISCUSSION

The aim of this study was to test the feasibility of progressively increasing eccentric cycling power output in coronary heart disease patients.

Previous articles highlighted the potential for using eccentric cycling in chronic heart disease patients [6-9, 13], and demonstrated the feasibility of tailoring the exercise intensity based on the first ventilatory threshold [6, 7]. In line with these studies, we decided to use the power output at the first ventilatory threshold to determine the intensity of our first training session, and then progressively increased the power output by ~25 % / session. The progressive increase in eccentric cycling power output allowed the patients to reach high level of muscular work by achieving a power output above the peak power output obtained during concentric CPET (~115 % PPO). This high level of muscular work was associated with low cardiorespiratory solicitations as attested by the VO_2, HR and breathing frequency values, confirming per se the feasibility of progressively increasing eccentric cycling intensity in coronary heart disease patients. Furthermore, the low solicitation of the myocardial system during eccentric cycling suggests that including this exercise during rehabilitation program might be of great interest for coronary patients that cannot be revascularized. Further research is needed to confirm this hypothesis.

As leg muscle pain and blood CPK concentration remained at low values following all sessions [14, 15], our results confirm the tolerance to a progressive increase in power output during an eccentric cycling training program. However, the inter-subject variability in leg muscle pain and blood CPK concentration suggests the need of individualizing eccentric training program based on participants' leg muscle pain perception.

Even so coronary heart disease patients do not seem to have a deficit in quadriceps muscle strength, coronary heart disease patients are less resistant to muscle fatigue compared to healthy subjects [16, 17]. Therefore, it seems crucial to include in coronary heart disease patients' rehabilitation program a high muscular solicitation with low inflammation processes. Due to the high muscular solicitation reached and tolerated at session 4, the protocol tested in our study is of great interest for this purpose.

Study Limitations. While our study demonstrates the feasibility of reaching a high-power output (~115 %PPO) in only four sessions, future studies should now investigate the tolerance to a rehabilitation program performed at this workload, as well as changes in functional capacities induced by such rehabilitation program. As improvements in functional capacities are directly relevant to a better patient's quality of life, future studies should include functional tests when performing a progressive increase in eccentric cycling intensity. Furthermore, this study being a pilot study with a small sample size, our observations need to be replicated with a larger sample size and to be extended with other cardiovascular and respiratory pathologies.

CONCLUSION

Our data confirm the feasibility of progressively increasing power output during an eccentric cycling training program in coronary heart disease patients. Our protocol allowing a progressive increase in eccentric cycling power output has a strong potential for helping clinicians and therapists to target a safe, feasible and high-power output during rehabilitation programs. As the adherence to training program could be limited by high perceived effort during physical exercise [18], our low RPE values reported from the first session to the fourth session provide promising results for the use of eccentric cycling in training program. Future studies should now investigate the adherence to the inclusion of this specific exercise in rehabilitation programs with various populations [19, 20].

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FIGURES

Figure 1. Flowchart presenting an overview of the study course.

Figure 2. Changes in cardiorespiratory parameters during the four sessions of eccentric cycling. The first session was performed at the power output corresponding to the first ventilatory threshold measured during concentric cardiopulmonary exercise testing. Then, power output was increased by ~25% per session (absolute values -Panel A- and relative to the concentric cycling peak power output -Panel B-). Mean oxygen consumption (Panel C), carbon dioxide production (VCO2, Panel D), breathing frequency (Panel E), ventilation (Panel F), tidal volume (Panel E) and heart rate (Panel G) during the 25 min of eccentric cycling exercise. Data are presented as mean ± 95 %CI. † 0.05 < P < 0.1, * P < 0.05, ** P < 0.01, ** P < 0.001.

Figure 3. Changes in blood creatine phosphokinase (CPK, Panel A) and leg muscle pain (Panel B) following the four eccentric cycling sessions. The first session was performed at the power output corresponding to the first ventilatory threshold measured during concentric cardiopulmonary exercise testing. Then, power output was increased by ~25% per session. Blood CPK concentration was obtained at baseline (i.e., onset of visit 1 for cardiopulmonary exercise testing) and 72-h following each session. Leg muscle pain was recorded 72-h following each session, just before blood sample was collected.

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- *Benjamin Pageaux*: data and statistical analysis, figure preparation, data interpretation, first draft of the manuscript, edited the manuscript, approved the final version of the manuscript.
- *Delphine Besson:* Data collection and analysis, screening and inclusion of participants, approved the final version of the manuscript.
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Eccentric rehabilitation

ABBREVIATION

CPET: CardioPulmonary Exercise Testing

CPK: Creatine PhosphoKinase

HR: Heart Rate

PPO: Peak Power Output

RPE: Rating of Perceived Exertion

VO_{2peak}: peak oxygen consumption

VCO_2: carbon dioxide production

W: Watt

INTRODUCTION

It is now well known that compared to concentric muscle contraction, eccentric muscle contraction presents the advantage of producing a higher level of force for a lower cardiovascular, respiratory and metabolic solicitation [1-5]. For this reason, the integration of eccentric muscle contraction in rehabilitation programs is of great interest for patients limited by cardiorespiratory symptoms [1, 6-9]. The specificity of eccentric muscle contraction led to the development of eccentric cycling ergometers that can be easily integrated in rehabilitation programs in various populations [10-12]. While the feasibility of integrating eccentric cycling at fixed intensity in rehabilitation program has been previously shown [7], it remains unknown whether a progressive increase in eccentric cycling intensity is feasible in patients suffering from cardiovascular limitations. Such knowledge would allow clinicians and therapists to plan the increased intensity of eccentric cycling during rehabilitation program, in order to maximize muscle solicitation and minimize the associated side effects (increased leg muscle pain and associated inflammation processes).

The aim of this study is to test this possibility in coronary heart disease patients. Based on a previous study with patients suffering from respiratory limitations [12], we hypothesized that a progressive increase in eccentric cycling would be feasible in coronary heart disease patients. By measuring blood creatine phosphokinase (CPK) concentration and leg muscle pain 72-h following each session, we also hypothesized that the training program will be well tolerated by the patients.

METHODS

Overview of the study

A detailed report of the inclusion/exclusion criteria and methods is presented in *Supplementary Material 1*. Fifteen coronary heart disease patients were included in this study and written informed consent approved by the local ethics committee was obtained for all participants after they had been informed of all potential risks, discomfort and benefits generated by the study. Briefly, the inclusion criteria were patients : i) referred for a rehabilitation program, ii) with a left ventricular ejection fraction on echocardiography (Simpson method) > 45 %, iii) without oxygen therapy ; and exclusion criteria were patients with : i) severe obstructive cardiopathy, ii) severe aortic valve stenosis, iii) heart rhythm or conduction disorders, iv) intracavitary thrombus, v) severe pulmonary hypertension, vi) impaired executive and physical functions not compatible with rehabilitation procedure.

Patients visited the laboratory on five different occasions (one familiarization with cardiopulmonary exercise testing + four eccentric cycling training sessions).

Visit 1 was a preliminary visit consisting of the familiarization with the eccentric cycling ergometer and the completion of a maximal cardiopulmonary exercise testing (CPET) to determine concentric cycling peak power output (PPO) as well as peak oxygen consumption (VO_{2peak}), peak breathing frequency and the first ventilatory threshold. The power output at the first ventilatory threshold was used to fix the intensity of the first eccentric cycling session (*visit 2*, one week following visit 1). Then, power output was increased by 25% per session (*visit 3 to 5*, interspaced by 72-h). Each experimental session started with a 10 min warm-up consisting of concentric cycling at 50 W, followed by 25-min eccentric cycling. This duration of exercise was chosen to match the duration of training sessions in our rehabilitation center. A 25% increment per session was determined based on a preliminary study performed on a fifteen healthy age-matched population. Overview of the results of the preliminary study is presented in *supplementary material 2*.

Physiological and psychological measurements

Patients performed isokinetic eccentric cycling during 25-min on a prototype (TechMed, TMS, Champs/Yonne, France[a]). Cadence was fixed at 15 revolutions/min, and the patients had to resist against the pedal movement to produce the required torque. During the eccentric cycling sessions, respiratory-gas exchange parameters and heart rate (HR) were monitored using the K4b^2 (Cosmed, Rome, Italy[b]) and a chest belt with a HR sensor. Rating of perceived exertion (RPE) was obtained immediately after cessation of the eccentric cycling exercise. A 5 mL blood sample was collected from the cubital vein and send to the Dijon University Hospital's biological center for blood CPK concentration analysis. Blood sample was collected at the onset of visit 1 (i.e., baseline) and 72-h post each session when the patients returned to the laboratory for the subsequent visits. Leg muscle pain was monitored 72-h after each session when the patients returned to the laboratory for blood sample collection.

Statistical analysis

The sample size was based on a similar study of Rocha Vieira et al. [12] (N = 6 chronic obstructive pulmonary disease patients). We increased the sample size to 15 to increase the chance of observing side effects (leg muscle pain > 4/10 and CPK concentration >1000 UI/L) and performed first this experiment with 15 healthy participants (see Supplementary Material 2) before replicating it with 15 coronary heart disease patients. Results are presented as mean ± 95 %CI and normality as well as sphericity were checked as appropriate. Greenhouse–Geisser correction to the degree of freedom was applied when sphericity was violated. One-way repeated-measures ANOVA (4 sessions) were used to test the effects of increasing the intensity of eccentric cycling on cardiorespiratory parameters and perception of effort. If significant, this test was followed up with LSD Fisher tests. Significance was set at 0.05 (2-tailed) for all analyses. The effect sizes for the repeated measures ANOVAs were calculated as partial eta squared (η_p^2). Stata software v15 (StataCorp, College Station, TX, USA) was used for the analysis.

RESULTS

Fifteen patients were included in this study (13 men and 2 women; age: 58.8 ± 10.6 yr; height: 171 ± 5 cm; weight: 76.9 ± 11.8 kgs; concentric PPO: 125 ± 18 W; concentric CPET VO_{2peak}: 21.6 ± 5.6 mL/kg/min). Two patients withdrawn from the study in relation to an injury non-related to the eccentric cycling protocol. Also, due to technical issues with the prototype software and the gas analyzer, cardiorespiratory data was not available for all patients. Consequently, the data analysis was carried out on eleven patients for power output and ten patients for cardiorespiratory parameters. This information is presented in the study flowchart in Figure 1.

PLEASE INSERT FIGURE 1

Figure 2 presents eccentric cycling power output and all cardiorespiratory data. Power output, VO_2, VCO_2, ventilation, and tidal volume increased from the first to the fourth session (all $P < 0.041$, $\eta_p^2 = 0.902$). All follow-up tests are presented in Figure 2. The increase in VO_2, VCO_2, ventilation and tidal volume was significant only from the third session. and remained below the values reached during concentric CPET (visit 1). Similarly, RPE increased only from the third session ($P = 0.009$, $\eta_p^2 = 0.315$; from 11.9 ± 1.1 to 14 ± 1.8 –i.e., from light effort to ~ somewhat hard effort–). HR ($P = 0.591$, $\eta_p^2 = 0.067$) and breathing frequency ($P = 0.316$, $\eta_p^2 = 0.121$) remained stable during the four sessions. At session 4, despite reaching an eccentric cycling power output corresponding to 118 ± 13 % PPO obtained during concentric CPET, the VO_2, HR and breathing frequency remained respectively at 42 ± 8, 67 ± 6 and 71 ± 11 % of their peak values obtained during concentric CPET.

PLEASE INSERT FIGURE 2

Individual blood CPK concentration values and reports of leg muscle pain 72 h post exercise are presented in Figure 3. Briefly, blood CPK concentration peaked (157 ± 42 UI/L) after the third session and remained low following each session. Leg muscle pain in all patients remained low (< 4/10) following each session.

PLEASE INSERT FIGURE 3

DISCUSSION

The aim of this study was to test the feasibility of progressively increasing eccentric cycling power output in coronary heart disease patients.

Previous articles highlighted the potential for using eccentric cycling in chronic heart disease patients [6-9, 13], and demonstrated the feasibility of tailoring the exercise intensity based on the first ventilatory threshold [6, 7]. In line with these studies, we decided to use the power output at the first ventilatory threshold to determine the intensity of our first training session, and then progressively increased the power output by ~25 % / session. The progressive increase in eccentric cycling power output allowed the patients to reach high level of muscular work by achieving a power output above the peak power output obtained during concentric CPET (~115 % PPO). This high level of muscular work was associated with low cardiorespiratory solicitations as attested by the VO_2, HR and breathing frequency values, confirming per se the feasibility of progressively increasing eccentric cycling intensity in coronary heart disease patients. Furthermore, the low solicitation of the myocardial system during eccentric cycling suggests that including this exercise during rehabilitation program might be of great interest for coronary patients that cannot be revascularized. Further research is needed to confirm this hypothesis.

As leg muscle pain and blood CPK concentration remained at low values following all sessions [14, 15], our results confirm the tolerance to a progressive increase in power output during an eccentric cycling training program. However, the inter-subject variability in leg muscle pain and blood CPK concentration suggests the need of individualizing eccentric training program based on participants' leg muscle pain perception.

Even so coronary heart disease patients do not seem to have a deficit in quadriceps muscle strength, coronary heart disease patients are less resistant to muscle fatigue compared to healthy subjects [16, 17]. Therefore, it seems crucial to include in coronary heart disease patients' rehabilitation program a high muscular solicitation with low inflammation processes. Due to the high muscular solicitation reached and tolerated at session 4, the protocol tested in our study is of great interest for this purpose.

Study Limitations. While our study demonstrates the feasibility of reaching a high-power output (~115 %PPO) in only four sessions, future studies should now investigate the tolerance to a rehabilitation program performed at this workload, as well as changes in functional capacities induced by such rehabilitation program. As improvements in functional capacities are directly relevant to a better patient's quality of life, future studies should include functional tests when performing a progressive increase in eccentric cycling intensity. Furthermore, this study being a pilot study with a small sample size, our observations need to be replicated with a larger sample size and to be extended with other cardiovascular and respiratory pathologies.

CONCLUSION

Our data confirm the feasibility of progressively increasing power output during an eccentric cycling training program in coronary heart disease patients. Our protocol allowing a progressive increase in eccentric cycling power output has a strong potential for helping clinicians and therapists to target a safe, feasible and high-power output during rehabilitation programs. As the adherence to training program could be limited by high perceived effort during physical exercise [18], our low RPE values reported from the first session to the fourth session provide promising results for the use of eccentric cycling in training program. Future studies should now investigate the adherence to the inclusion of this specific exercise in rehabilitation programs with various populations [19, 20].

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FIGURES

Figure 1. Flowchart presenting an overview of the study course.

Figure 2. Changes in cardiorespiratory parameters during the four sessions of eccentric cycling. The first session was performed at the power output corresponding to the first ventilatory threshold measured during concentric cardiopulmonary exercise testing. Then, power output was increased by ~25% per session (absolute values -Panel A- and relative to the concentric cycling peak power output -Panel B-). Mean oxygen consumption (Panel C), carbon dioxide production (VCO2, Panel D), breathing frequency (Panel E), ventilation (Panel F), tidal volume (Panel E) and heart rate (Panel G) during the 25 min of eccentric cycling exercise. Data are presented as mean ± 95 %CI. † 0.05 < P < 0.1, * P < 0.05, ** P < 0.01, ** P < 0.001.

Figure 3. Changes in blood creatine phosphokinase (CPK, Panel A) and leg muscle pain (Panel B) following the four eccentric cycling sessions. The first session was performed at the power output corresponding to the first ventilatory threshold measured during concentric cardiopulmonary exercise testing. Then, power output was increased by ~25% per session. Blood CPK concentration was obtained at baseline (i.e., onset of visit 1 for cardiopulmonary exercise testing) and 72-h following each session. Leg muscle pain was recorded 72-h following each session, just before blood sample was collected.

Dear Editor and Reviewers

Thank you very much for your interest in our study and considering our manuscript for re-submission.

Please find below your comments in black and our responses in blue.
To help you in the review process and navigate between documents we have also submitted a redlined version of our manuscript containing the line numbers as well as our amendments in red.

We have integrated in our manuscript most of your recommendation. When we did not integrate your suggestion, we carefully justified our decision in the present document.

Thank you very much for your feedback that helped us to significantly improve the quality of our manuscript. We hope that this new version will answer your questions

Kind regards

The authors

Reviewers' comments:

Reviewer #1: General comments

The present study evaluated the feasibility and safety of eccentric cycling on coronary heart disease patients based on 4 acute sessions (25 min) in which power output was increased 25% per session. In spite of the increased power output from 62% to 118% of peak power output, heart rate did not increase, and oxygen consumption increased slightly from 34% to 42% VO2 peak. Muscle soreness was low, and CK activity was not high after eccentric cycling. The authors concluded that patients with coronary heart disease tolerated well for the progressively increased eccentric cycling protocol.

Since eccentric cycling could be a good exercise modality for patients with coronary heart disease, the study is important and valuable.

This reviewer has some specific comments as shown in below to improve the quality of the manuscript.

→ Thank you very much for your positive comments and your interest in our study.

Specific comments

Title: It may be better to reconsider the title.

→ Thank you for your suggestion. We have now updated the title by providing the number of training sessions (see copy-paste below). We believe that i) this information was important and ii) the new title appropriately recap the experimental protocol and results of our study.

New title:

Progressively increasing the intensity of eccentric cycling ***over four training sessions****: a feasibility study in coronary heart disease patients*

Abstract: Please clarify the sample size. What were the 15 controls for?

→ The inclusion of the 15 controls in the abstract was a mistake. The 15 controls are in fact the 15 healthy participants who performed the preliminary study presented in Supplementary Material 2. We apologise for this mistake. Thank you for noticing it.

→ We have clarified the sample size in the abstract as follow (line 88): *Fifteen coronary heart disease patients were included*.

→ Our updated abstract now contains 250 words and the journal limit is 250 words for short reports. More information on the sample size within the abstract would force us to remove some information that are crucial for the clarity of the abstract. To address your question and ensure clarity in our sample size and analysis, we have now added a Flowchart of the study (see figure 1, lines 192) presenting the process from subject screening to data analysis.

I do not think that CPK concentration was measured in the study - CPK activity.

→ We considered the reviewer comment and we contacted the laboratory that performed the analysis for clarification. The laboratory confirmed us that the measurement is a concentration and not an activity, as confirmed by the unit of this variable (UI/L). In line with the confirmation of our laboratory, we decided to keep the wording "concentration" in our manuscript. Thank you for your understanding.

Introduction: It is better to explain a more why a protocol to increase intensity of eccentric cycling progressively is important for coronary heart disease patients.

→ We agree with the reviewer and we have added the following information lines 125-128:

Such knowledge would allow clinicians and therapists to plan the increased intensity of eccentric cycling during rehabilitation program, in order to maximize muscle solicitation and minimize the associated side effects (increased leg muscle pain and associated inflammation processes).

I am not sure whether CPK activity in the blood is "psychophysiological" marker.

→ We understand that the formulation in the first submission could be ambiguous. In line with the reviewer comment, we have updated the information as follow (lines 131-133):

By measuring blood creatine phosphokinase (CPK) concentration and leg muscle pain 72-h following each session, we also hypothesized that the training program will be well tolerated by the patients.

Methods

Please justify the sample size.

→ Thank you for this comment. We have now justified our sample size as shown below (lines 172-176). Thank you for this comment that helped us to strength the rationale and methodology of our study:

The sample size was based on a similar study of Rocha Vieira et al. [12] (N = 6 chronic obstructive pulmonary disease patients). We increased the sample size to 15 to increase the chance of observing side effects (leg muscle pain > 4/10 and CPK concentration >1000 UI/L) and performed first this experiment with 15 healthy participants (see Supplementary Material 2) before replicating it with 15 coronary heart disease patients.

Please explain why the main exercise time was set for 25 minutes.

→ The duration of exercise was 25 minutes to match the duration of training sessions in our rehabilitation center. The aim was to integrate easily this procedure in clinical setting. We have added this information in the updated manuscript, lines 155-156, as follow:

[…] followed by 25-min eccentric cycling. This duration of exercise was chosen to match the duration of training sessions in our rehabilitation center.

How did you measure CPK "concentration"? Did you actually measure "concentration"?

→ As presented in an aforementioned response, we confirm that we measured blood CPK concentration. This information is presented lines 165-168 in our manuscript, and full details are presented in Supplementary Material 1. As our submission is a short report and we are constrained by the specific words limit of a short report (limit = 1,800 words ; our manuscript = 1,797 words), we believe that i) the information in the manuscript is sufficient to allow the reader to understand our protocol, and ii) the reader interested in more details can access these details in our Supplementary Material. Thank you for your understanding.

"Controls" described in the abstract are not mentioned. ,

→ The inclusion of the 15 controls in the abstract was a mistake. The 15 controls are in fact the 15 healthy participants who performed the preliminary study presented in Supplementary Material 2. We apologise for this mistake. Thank you for noticing it.

Results

Please clarify the number of patients included in the results (n=13?).

→ To clarify this point we have now added a Flowchart of the study (see figure 1, lines 192) presenting the process from subject screening to data analysis. Thank you for this suggestion that helps us to increase the clarity of our manuscript.

Figure 1: Are all figures necessary? For example, I am not sure whether D. F and G are necessary.

→ This study being mainly descriptive, it is important to present these figures. These figures will provide information for other research groups willing to replicate or re-use our data for other purposes. With these figures, future studies will be able to test the reproducibility of our results with a different sample size or with a different population.

Figure 2: How important is it to show individuals?

→ The answer of this comment is closely related to the previous answer. Also, showing individual data allows the reader to appraise the true variability of our results. We believe that presenting individual data provide complementary information to the readers than the classical mean +/-SD or CI. Furthermore, these "dots data" can be extracted into "numerical data" via various platform and software (e.g., WebPlotDigitizer), and therefore being re-used by other research groups for meta-analysis or estimation of required sample size. For these reasons, we would like to keep individual data within our figures. Thank you for your understanding.

Discussion

It is very superficial. Can you make extend the discussion more and what should be considered for the use of eccentric cycling for chronic heart disease patients?

→ We agree with the reviewer that our discussion was not sufficient. We have now expanded the discussion in line with the words limit and the suggestions provided by both reviewers. We have added:

- Lines 214-218 the rationale for using the power output at the first ventilatory threshold for the intensity of session 1.
- Lines 223-226: as requested by reviewer 2 a brief mention of the interest of eccentric cycling for patients who cannot be revascularized.
- Lines 232-236: information on the potential of our protocol for coronary heart disease patients who have been shown to be less resistant to muscle fatigue than healthy subjects.
- Lines 242-244: acknowledgment that our study is a pilot study with small sample size and the need to replicate this study with a larger sample size.
- Lines 247-249: perspectives for clinicians and therapist in using our protocol to target a safe, feasible and high-eccentric cycling power output during rehabilitation programs.

We hope that the reviewer will find our amendments satisfactory.

References

Some recent articles on eccentric cycling may be better to be included.

→ In line with the reviewer comment and various amendments made in the manuscript, we have added additional references. The number of references included is now 20 and is in line with the limit imposed by the journal (i.e., 20). Thank you for directing us to some important references.

Reviewer #2: This is an interesting study. However, several issues should be clarified.

→ Thank you very much for your positive comment. We hope that our answers provided below as well as the amendments made in the manuscript will clarify these issues.

* Fifteen patients were recruited into study, whereas the results were reported for 11 and 10 patients for po wer output and cardiovascular parameters, respectively. Therefore, the correct number of analyzed patients should be mentioned in the Abstract (not 15, but 10 or 11).

→ We considered the reviewer comment, and when trying to integrate this suggestion in our abstract we realised that our previous abstract was above the words limit for short report abstract (250 words). Our updated abstract now contains 250 words. More information on the analysis sample size within the abstract would force us to remove some information that are crucial for the clarity of the abstract. As we agree with the reviewer comment that the number of analyzed patients for each variable should be clear for the reader, we have now added a Flowchart of the study (see figure 1, lines 192) presenting the process from subject screening to data analysis. We believe that the addition of figure 1 clarifies the issue raised by the reviewer. Thank you for your understanding.

* The inclusion/exclusion criteria for coronary heart patients (stable, revascularized, completing rehabilitation, functional class, etc…?) should be included in the original manuscript, since this is very important and relevant information.

→ Thank you very much for this suggestion that helps to clearly present our study. We have added in the manuscript the main inclusion/exclusion criteria. To be in line with the words limit for short reports (1,800 words), the complete list of inclusion/exclusion criteria is presented in Supplementary Material 1.

* Authors reported low RPE (from the first session to the fourth session) during eccentric cycling and stressed that this is an advantage of incremental eccentric cycling, although no comparison of RPE during eccentric and concentric cycling had been done in this study.

→ As the aim of our study was **not** to compare perception of effort during eccentric vs concentric cycling, we are unsure about the reviewer comment.

This comparison (RPE during eccentric vs concentric exercise) has been previously done in numerous studies in the literature, with both healthy subjects and patients, and to the best of our knowledge all studies demonstrated that at same power output, RPE is lower during eccentric cycling vs concentric cycling. This result is now evident and well accepted in the literature (see references presented at the end of this response).

Also please note that we do not compare our RPE values with any other exercise modes, and the RPE values during eccentric cycling could also be compared with other exercise mode used in rehabilitation program (e.g., resistance exercise). Our purpose was solely to provide some perspectives with recent research and publications demonstrating and suggesting that the intensity of perceived effort during an exercise is likely to condition the adherence to this exercise and per se associated rehabilitation program.

We believe that this consideration is crucial, because as stated in one of our previous publication (Pageaux et al., J Appl Physiol, 2017), the success of any rehabilitation program is conditioned by the adherence to this program:

[…] the efficiency of a rehabilitation program should not only be evaluated by physiological responses to the exercise but also in terms of adherence to the exercise. Indeed, if a patient does not adhere to a novel rehabilitation program and is not willing to regularly exercise, the beneficial physiological adaptations induced by the novel rehabilitation program cannot be observed. As the adherence to exercise is thought to be influenced and conditioned by perceptual responses to the exercise performed (REF A and B below), we urge the need of integrative studies merging the fields of exercise physiology and psychology to better understand the acute and chronic perceptual responses to eccentric cycling. Of particular importance are the perception of pain, the perception of effort, and affective responses.

Consequently, and after careful consideration of the reviewer comment, we believe that our statement is appropriate and also important for future research. Therefore, we would like to keep our statement as it is. Thank you in advance for your understanding.

See references below that are included in our submitted manuscript and in Pageaux et al (2017 J Appl Physiol) for more information:

Clos P, Laroche D, Stapley PJ, and Lepers R. Neuromuscular and Perceptual Responses to Sub-Maximal Eccentric Cycling. Front Physiol 10: 354, 2019. 10.3389/fphys.2019.00354

Isner-Horobeti ME, Dufour SP, Vautravers P, Geny B, Coudeyre E, and Richard R. Eccentric exercise training: modalities, applications and perspectives. *Sports Med* 43: 483-512, 2013. 10.1007/s40279-013-0052-y

Pageaux B, Lepers R, Casillas JM, and Laroche D. It is time to investigate acute and chronic perceptual responses to eccentric cycling. *J Appl Physiol (1985)* 123: 1416-1417, 2017. 10.1152/japplphysiol.00507.2017

Penailillo L, Blazevich AJ, and Nosaka K. Factors contributing to lower metabolic demand of eccentric compared with concentric cycling. *J Appl Physiol (1985)* 123: 884-893, 2017. 10.1152/japplphysiol.00536.2016

REF **A** – Ekkekakis P, Parfitt G, Petruzzello SJ. The pleasure and displeasure people feel when they exercise at different intensities: decennial update and progress towards a tripartite rationale for exercise intensity pre- scription. Sports Med 41: 641–671, 2011. doi:10.2165/11590680- 000000000-00000.

REF **B** – Marcora S. Can doping be a good thing? Using psychoactive drugs to facilitate physical activity behaviour. Sports Med 46: 1–5, 2016.

* Authors stated: »Our data confirm the feasibility of progressively increasing power output during an eccentric cycling training program in patients limited by cardiovascular symptom«. It is not clear what the phrase »patients limited by cardiovascular symptom« mean? Is this limitation angina, dyspnea, both, other..?
→ Thank you for your comment that helps to clarify this sentence. We agree that it was not clear, and have now updated lines 246-247 as follow:

Our data confirm the feasibility of progressively increasing power output during an eccentric cycling training program in coronary heart disease patients.

* The authors found that by incremental eccentric cycling the PPO above that (obtained during cardiopulmonary exercise testing) is reached at the similar levels of cardiovascular parameters. Whether this could be translated into beneficial effects for patients is unknown. Since this is a crucial question authors should provide possible explanations/speculations for such beneficial effect in the Discussion.
→ Thank you for your comment highlighting a lack of clarity in our messages. In line with this comment and the next comment, as well as some comments provided by the first reviewer, we have made the following amendments in our results and discussion:

- We would like to emphasize that the cardiovascular responses were **not** similar to the one observed during concentric CPET but lower. Lines 200-203 we have clarified that the high peak power output reached (> 100 % PPO obtained during concentric CPET) was associated with **lower** cardiovascular responses than the one observed during concentric CPET (visit 1).

- Lines 214-218 the rationale for using the power output at the first ventilatory threshold for the intensity of session 1.
- Lines 223-226: as requested by reviewer 2 a brief mention of the interest of eccentric cycling for patients who cannot be revascularized.
- Lines 232-236: information on the potential of our protocol for coronary heart disease patients who have been shown to be less resistant to muscle fatigue than healthy subjects.
- Lines 242-244: acknowledgment that our study is a pilot study with small sample size and the need to replicate this study with a larger sample size.
- Lines 247-249: perspectives for clinicians and therapist in using our protocol to target a safe, feasible and high-eccentric cycling power output during rehabilitation programs.

With the addition of these amendments, our manuscript contains now 1,797 words and is in line with the words limit associated with short reports (1,800 words). We hope that the reviewer will find our amendments satisfactory.

* Eccentric cycling is undoubtedly useful approach for increasing muscular strength (particularly in a sport medicine), however, from a cardiologist point of view it is difficult to find any possible clinically relevant advantage of eccentric over usual concentric cycling based rehabilitation program for patients with coronary heart disease or other heart disease. Please, comment…

→ Thank you for your suggestion that strengths the rationale for using eccentric cycling with coronary heart disease patients. Indeed, the consideration of your comment directed us towards studies demonstrating a greater muscle fatigability in coronary heart disease patients compared to healthy subjects. In line with your comments we have added lines 232-236 the following information:

Even so coronary heart disease patients do not seem to have a deficit in quadriceps muscle strength, coronary heart disease patients are less resistant to muscle fatigue compared to healthy subjects [16, 17]. Therefore, it seems crucial to include in coronary heart disease patients' rehabilitation program a high muscular solicitation. Due to the high muscular solicitation reached and tolerated at session 4, the protocol tested in our study is of great interest for this purpose.

→ Also, for more information on why eccentric cycling is useful for coronary heart disease patients, as well as chronic heart failure patients, we direct the reviewer to the following studies that are cited in our submitted manuscript.

Besson D, Joussain C, Gremeaux V, Morisset C, Laurent Y, Casillas JM, and Laroche D. Eccentric training in chronic heart failure: feasibility and functional effects. Results of a comparative study. Ann Phys Rehabil Med 56: 30-40, 2013. 10.1016/j.rehab.2013.01.003

Casillas JM, Besson D, Hannequin A, Gremeaux V, Morisset C, Tordi N, Laurent Y, and Laroche D. Effects of an eccentric training personalized by a low rate of perceived exertion on the maximal capacities in chronic heart failure: a randomized controlled trial. Eur J Phys Rehabil Med 52: 159-168, 2016.

Chasland LC, Green DJ, Maiorana AJ, Nosaka K, Haynes A, Dembo LG, and Naylor LH. Eccentric Cycling: A Promising Modality for Patients with Chronic Heart Failure. Med Sci Sports Exerc 49: 646-651, 2017. 10.1249/MSS.0000000000001151

Gremeaux V, Duclay J, Deley G, Philipp JL, Laroche D, Pousson M, and Casillas JM. Does eccentric endurance training improve walking capacity in patients with coronary artery disease? A randomized controlled pilot study. Clin Rehabil 24: 590-599, 2010. 10.1177/0269215510362322

Haynes A, Linden MD, Chasland LC, Nosaka K, Maiorana AJ, Dawson EA, Dembo L, Naylor LH, and Green DJ. Acute impact of conventional and eccentric cycling on platelet and vascular function in patients with chronic heart failure. J Appl Physiol (1985) jap 01057 02016, 2017. 10.1152/japplphysiol.01057.2016

* Accordingly, do authors mean that incremental eccentric cycling would be useful for coronary patients that could not be vascularized and are therefore really limited by the angina? Revascularized patients usually do not have important limitations inside the range of expected efforts... Please, comment...
→ Eccentric exercise might be of interest in patients that could not be revascularized due to its low solicitation of the myocardial energetic system. However, to the best of our knowledge, no study tested this hypothesis. We therefore added the following statement lines 223-226:

Furthermore, the low solicitation of the myocardial energetic system during eccentric cycling suggests that including this exercise during rehabilitation program might be of great interest for coronary patients that cannot be revascularized. Further research is needed to confirm this hypothesis.

We believe that the addition of this statement strengthens our discussion by providing interesting perspectives for new research. We thank the reviewer for raising this point.

* Is obtained increased PPO of 115% clinically relevant?
→ Yes, we believe that this result is clinically relevant. The report of this result provides information to clinicians and therapists on the intensity of eccentric cycling that can be safely reached in coronary heart disease patients. In line with this comment, and to emphasize the clinical application/perspectives of our study, we have added the following statement lines 247-249 in the conclusion section:

Our protocol allowing a progressive increase in eccentric cycling power output has a strong potential for helping clinicians and therapist to target a safe, feasible and high-power output during rehabilitation programs.

* Small number of patients should be mentioned as the limitation of the study.
→ We agree with the reviewer and have added lines 242-244 the following statement:

Furthermore, this study being a pilot study with a small sample size, our observations need to be replicated with a larger sample size and to be extended with other cardiovascular and respiratory pathologies.

Figure1

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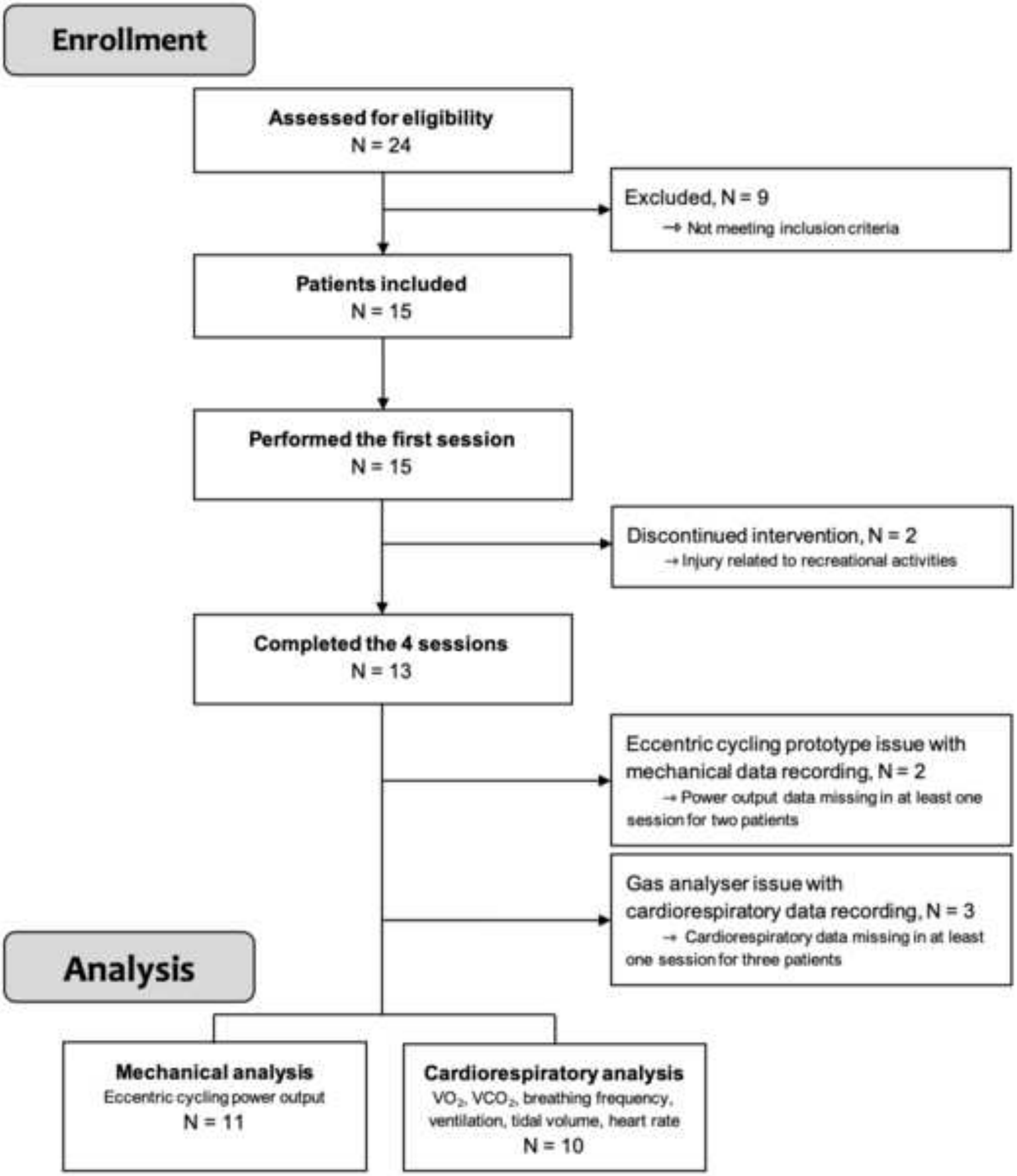

Figure2

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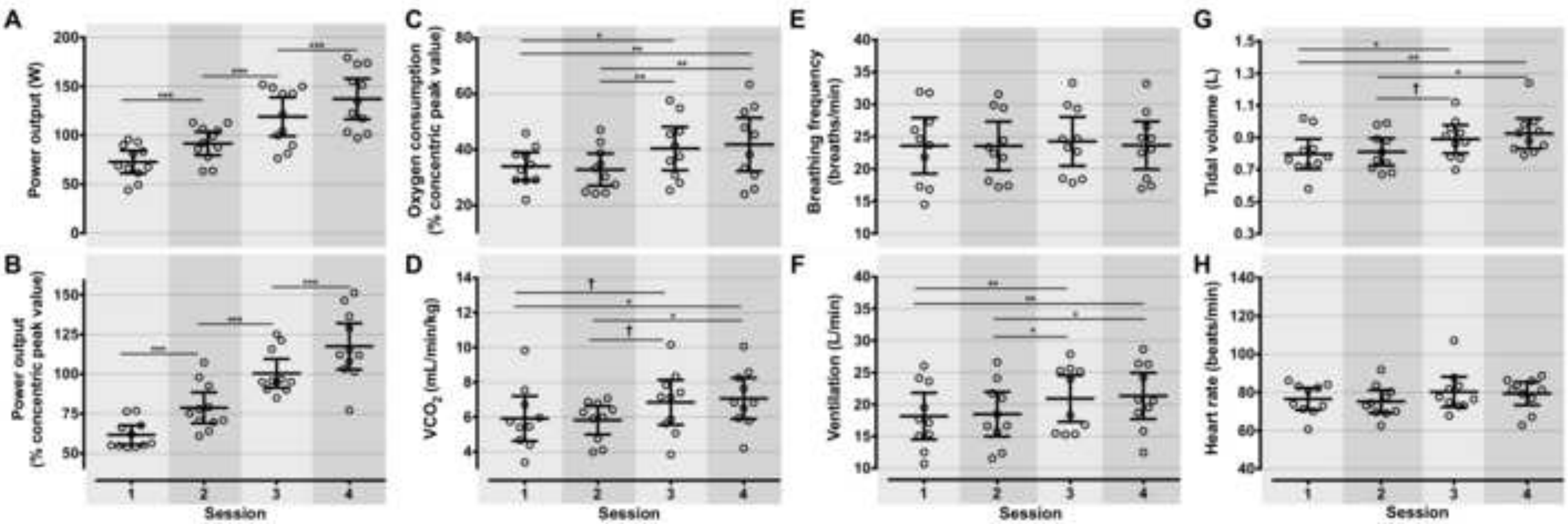

Figure2
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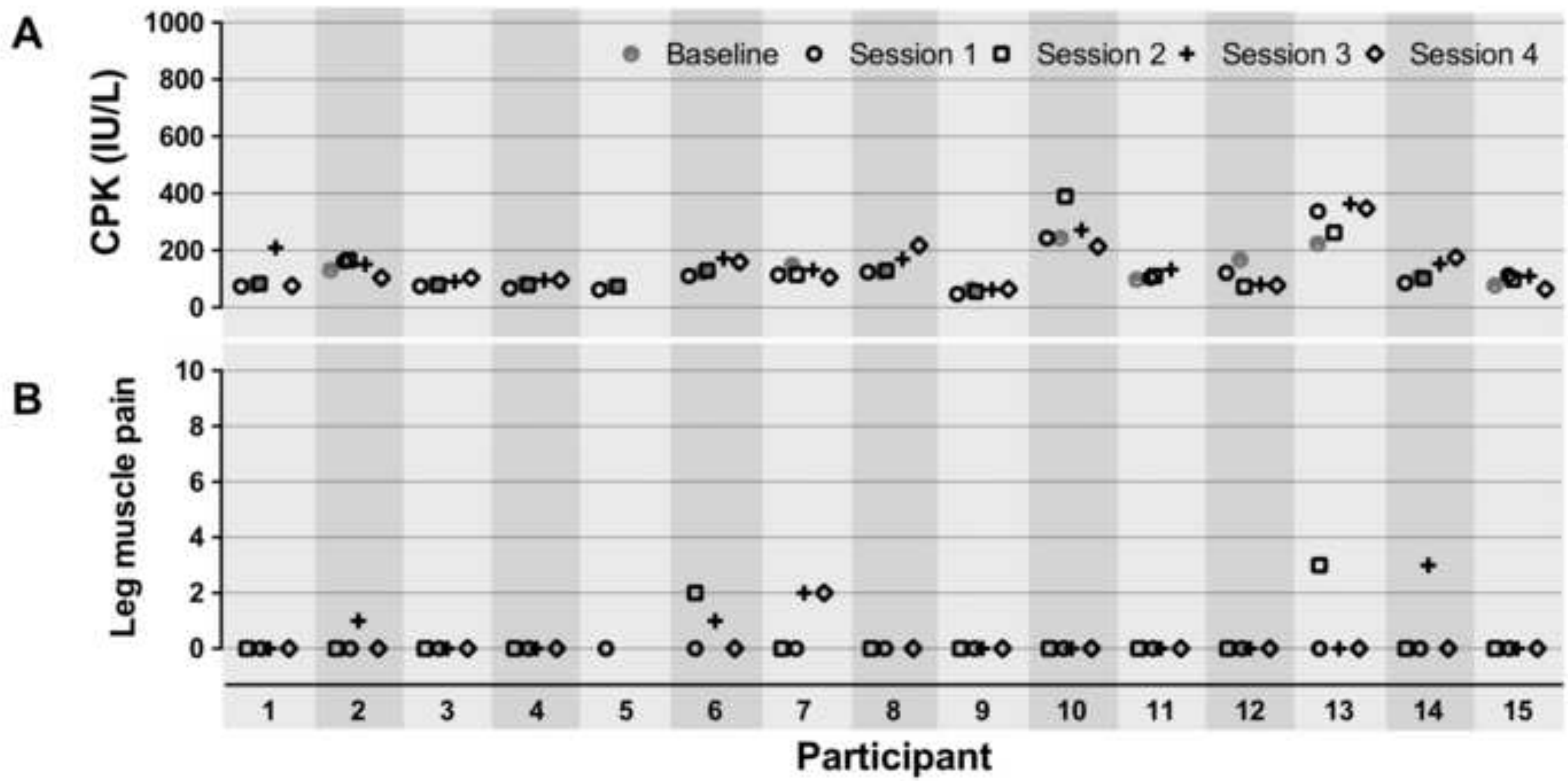

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Covering Letter

Editor-in-Chief
Annals of Physical and Rehabilitation Medicine

April 12, 2019

Dear Professor Editor,

Please find enclosed our manuscript entitled "Progressively increasing the intensity of eccentric cycling: a feasibility study in coronary heart disease patients" that we would like you to consider for publication in the *Annals of Physical and Rehabilitation Medicine.*

This study investigates the modalities and effects of eccentric cycling exercises in patients with cardiovascular disease. In this study, we have assessed in 15 healthy subjects, 15 coronary patients the safety and acute cardiorespiratory effects of an incremental procedure aiming to prevent muscular damages after eccentric contractions. Our results demonstrated that this procedure is safe, well-tolerated, with limited muscular use of oxygen with high mechanical power during exercise. It appears to be a feasible procedure for pre-conditioning before eccentric training and should lead to further applications with cardiac patients.

We hereby confirm that the article has not been published and is not under consideration for publication elsewhere; There were no financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interests that any of the authors may have, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

The manuscript has been read and approved by all of the authors, written permission has been obtained from all persons named in the Acknowledgments and patient consent forms have been collected

We believe our work is relevant and would be appreciated by the audience the *Annals of Physical and Rehabilitation Medicine*. We hope you will agree, and look forward reading your comments.

Yours sincerely,

Davy Laroche, PhD