PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (Error! Hyperlink reference not valid.) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Effects of High- and Low-Load Resistance Training in Patients with Coronary Artery Disease: rationale and design of a randomised controlled clinical trial
AUTHORS	Kambic, Tim; Sarabon, Nejc; Hadžić, Vedran; Lainscak, Mitja

VERSION 1 – REVIEW

REVIEWER	Scott, Andrew University of Portsmouth, Department of Sport and Exercise Science
REVIEW RETURNED	29-Mar-2021

GENERAL COMMENTS	This is a useful study. Resistance training is recommended in cardiac rehabilitation but is often implemented only as recovery in between aerobic training intervals. Cardiac rehabilitation is a clinical intervention so it is a little surprising to see performance measures being used as primary outcomes and clinical measures being used as secondary measures. Whilst these are relevant to the interventions being proposed these are not as clinically impactful for informing health services. The abstract and introduction are written slightly differently so reword the primary and secondary outcomes in the introduction. There are a number of secondary outcomes that are not really previewed in the introduction. The rationale for measuring these should be justified. The independent variables (high and low load RT) should be defined in the introduction. The method presumes 100% compliance, ie. 36 sessions from 3 sessions per week for 12 weeks. Is adherence going to be measured over the 36 sessions or do participants carry on exercising until they compete 36 sessions. Make this clear. The data analysis section states that 36 is the maximum number of sessions. Will intensity not be linearly progressed as indicated in table 3 and only progressed at week 8? It is a shame that no patient or public involvement was included

	for this study. This would have been useful for indicating the relative importance of outcome measures, for inclusion of genuine RT into CR or for communicating the study findings in the various centres. Whilst it makes scientific sense by being easy to implement and measure it is a shame that only the leg press RT is implemented. This may have a significant effect on the primary measures, but possibly negligible effect on some of the more clinically important secondary measures. The method of data analysis should be indicated in the abstract. It is not common practice for cardiac rehabilitation services to employ high intensity intervals. Interval-based aerobic training yes, but not necessarily high intensity, as per this study. The measurement of the haemodynamic responses to the exercises and adaptation to training in these is interesting. These are more clinically-relevant outcomes. The roles and responsibilities required by the SPIRIT checklist were not well-defined (5b, 5c, 5d, 21a). 6a is not well justified and requires more thorough literature review. The trial design is good and adequately described. The method is adequately described, however the study is not powered to detect changes between the two resistance training interventions, with no indication of re-powering the study. The blinding methods are unclear; will assessors be blinded as to the cluster the participants are allocated? Reporting of adverse and serious adverse events is not indicated. A data management committee would be useful.

REVIEWER	Gecaite, Julija Lithuanian University of Health Sciences, Neuroscience Institute, Laboratory of Behavioral Medicine
REVIEW RETURNED	10-Apr-2021

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. This protocol could serve as a great foundation for the RCT that may lead to the practical recommendations within the area of resistance training and its importance in cardiac rehabilitation programs. This protocol represents the rationale and the study design for the RCT with the interesting, novel and relevant potential findings. The following comments are intended to help the authors improve the quality and strength of this study. Language. I am of the view that the manuscript may need to undergo the language editing. In the certain places it is not good enough and may need to be improved: E.g. Enroll, Enrollment in many places are written without double “l” (e.g. p.2, line 29; p. 13, line 281 etc.); in some sentences

	articles are missing (e.g. the protocol p. 2, line 37; with a stable CAD p. 6, line 113). On the other occasions the structure of the sentence makes it difficult to understand the intended meaning (e.g. the secondary aim should be clarified or paraphrased p. 5, lines 80-81). Furthermore, there are some more specific comments in relation to different parts of the protocol: STRENGTHS AND LIMITATIONS OF THIS STUDY The authors state that their "primary aim is to examine the effects of HL-RT and LL-RT combined with AT in comparison with standard care (AT) on aerobic capacity, maximal muscle strength […] in patients with CAD." They also give the rationale for the calculation of the sample size, assuming that 60 participants should be enough for this study (p. 12, lines 258-259). However, on p. 3, lines 51-52 they state that "This study may lack adequate statistical power to compare the effects of HL-RT and LL-RT on maximal aerobic capacity and muscle strength ". I am lacking the rationale why the number of the participants cannot be increased so that this study limitation could be resolved? Especially, when it is related to the primary outcomes. INTRODUCTION Overall, the introduction has the important components of novelty and relevance of the study. • I assume that some of the parts from the discussion section can be moved to the introduction. • Please review the abbreviations. For example, in some places you use LL-RE and HL-RE. However, no explanations for these abbreviations are given. METHODS AND ANALYSIS This section is overall well-developed, detailed and integrates all the required parts for the protocol. Also, the protocol is pre-registered, it is an ongoing study, which has the ethical approval and meets the criteria listed in the SPIRIT statement. • Please list the preliminary dates when the RCT should be carried out. Currently, I could find only the date for the recruitment (July 2020). • What is the rationale for not including those with left ventricular ejection fraction<40% (p.6, line 115)? Usually, they represent a significant number of CAD patients in cardiac rehabilitation. • On p. 11 you state that you will use SF-12. First, I may suggest to specify that you will measure health related quality of life (since quality of life is a very broad term) or give the description for quality of life in your study. Second, there should be some elaboration about SF-12, its domains, type of administration and information on the psychometric characteristics (e.g. an internal consistency) in similar studies. ETHICS AND DISSEMINATION • On p. 13 line 282 you mentioned about "[the] potential risk during the study". What is the risk (s)? It might be important to mention it/them and shortly describe how you are planning to minimize

	it/them (risk management). DISCUSSION • Since there are no findings yet (thus, they cannot be interpreted or compared with other studies), I am not sure whether the extensive “Discussion” section is needed. Some of the earlier protocols, published in BMJ Open, either omitted or kept the discussion part relatively concise. Most of the parts can be moved to introduction part in order to elaborate on the relevance of this future study within the context of earlier studies or to emphasize the novelty of the results. The expectations of the results might also be moved to introduction and possibly formed as the hypotheses. Nevertheless, this is more of the recommendation to consider. • Also, since this study may have a potential high clinical importance, the emphasis on clinical relevance could be made to even further strengthen this protocol.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Andrew Scott, University of Portsmouth

Comments to the Author:

This is a useful study. Resistance training is recommended in cardiac rehabilitation but is often implemented only as recovery in between aerobic training intervals.

Cardiac rehabilitation is a clinical intervention so it is a little surprising to see performance measures being used as primary outcomes and clinical measures being used as secondary measures. Whilst these are relevant to the interventions being proposed these are not as clinically impactful for informing health services.

Thank you for your comment. We agree that clinical measures are a primary concern in clinical practice. However, since the effects of cardiac rehabilitation with or without resistance training on clinical measures (e.g. blood biomarkers) have been established, we focused our aims to key performance measures directly induced by a combination of resistance training and aerobic training. Similar approach was used in the previous randomised controlled trials in the field of cardiac rehabilitation.

The abstract and introduction are written slightly differently so reword the primary and secondary outcomes in the introduction. There are a number of secondary outcomes that are not really previewed in the introduction. The rationale for measuring these should be justified.

Thank you for your observations. The primary and secondary outcomes are now in line in both sections. Please see rows 95-101.

Copied text from the manuscript:

Rows 95-101:

The primary aim is to examine the effects of HL-RT and LL-RT combined with AT in comparison with standard care (AT) on aerobic capacity and maximal muscle strength in patients with CAD. The secondary aim is to examine the effects of HL-RT and LL-RT combined with AT in comparison with standard care (AT) on blood biomarkers, physical activity and quality of life. In addition, this study will compare the safety and acute haemodynamic responses to LL-RE and HL-RE at baseline and after 36 training sessions.

The independent variables (high and low load RT) should be defined in the introduction.

Thank you for your suggestion. The exact percentage of 1-RM was already defined in the introduction. Please see rows 93-94:

Copied text from the manuscript:

Rows 93-94:

However, no study has investigated the safety and efficacy of HL-RT (>70% of 1-RM) in comparison with LL-RT (<40% 1-RM) in such patients.

The method presumes 100% compliance, ie. 36 sessions from 3 sessions per week for 12 weeks. Is adherence going to be measured over the 36 sessions or do participants carry on exercising until they compete 36 sessions. Make this clear. The data analysis section states that 36 is the maximum number of sessions.

Thank you for your suggestion. This is now added in the description of training protocol. Please see rows 147-148.

Copied text from the manuscript:

Rows 147-148:

Patients will complete a total of 36 training sessions (three training sessions per week for 12 weeks or until completion, with at least 48 h rest between sessions).

Will intensity not be linearly progressed as indicated in table 3 and only progressed at week 8?

Thank you for your suggestion. Are presented in table 3 and described in rows 160-169. The volume will be linearly progressed in both group from first week until the end of seventh week. On the first exercise session of eighth week the load will be again progressed from 70%-80% of 1-RM and 35%-40% of 1-RM in HL-RT and LL-RT, respectively.

It is a shame that no patient or public involvement was included for this study. This would have been useful for indicating the relative importance of outcome measures, for inclusion of genuine RT into CR or for communicating the study findings in the various centres.

Thank you for your suggestion. We agree that patient involvement can be beneficial in establishing suitable exercise training programmes within CR. Therefore, we added some plans to disseminate our findings within patient community. Please see rows 339-345 and 664-670.

Copied text from the manuscript:

Rows 339-345:

Patients will have the possibility of obtaining their own results. The results of the study will be disseminated in forms of presentations and practical workshops among national cardiac rehabilitation centres in Slovenia and within Slovenian association of coronary clubs. Patients will be invited to share their experience on RT during such events. The combination of patients` experiences along with the results of the study will be used to prepared future feasible exercise training programmes in CR. Data will be shared upon reasonable request.

Rows 666-670:

Patients and/or the public were not involved in the design and/or conduct, and/or reporting of this study. Patients will be invited to share their experience on RT and will be asked to encourage other patients with CAD to enrol into CR programmes within hospital and/or coronary clubs and associations. The authors will gather patients` experience on RT to structure feasible exercise training programmes with emphasis on RT.

Whilst it makes scientific sense by being easy to implement and measure it is a shame that only the leg press RT is implemented. This may have a significant effect on the primary measures, but possibly negligible effect on some of the more clinically important secondary measures.

Thank you for your comment. We agree that this may present a drawback, however, our cardiac rehabilitation capacity (e.g. personnel, time and space) limits the implementation of RT for others muscle group (e.g. upper body), which may elicit greater response in some biomarkers. Nevertheless, we believe that the leg press exercise will provide adequate stimulus for favourable changes in some biomarkers, as this exercise activates the largest muscle groups of the body.

The method of data analysis should be indicated in the abstract.

Thank you for your suggestion. The short description of the method was added in the abstract ("intention to threat principle"). Please see rows 35-36. We believe that the description of others statistical test should be mentioned only in the methods, as these information were not included in the abstract of previous protocols published within the Journal.

Copied text from the manuscript:

Rows 36-37:

The intention-to-treat principle will be used to analyse the data.

It is not common practice for cardiac rehabilitation services to employ high intensity intervals. Interval-based aerobic training yes, but not necessarily high intensity, as per this study.

Thank you for your comment. We believe that the high intensity interval training is still underused within CR programmes, however, we believe that this aerobic training modality has gained adequate body of evidence to be effective and safe in patients with CAD. Several meta-analysis have shown the beneficial effects of high intensity interval aerobic training compared to continuous aerobic training.

The measurement of the haemodynamic responses to the exercises and adaptation to training in these is interesting. These are more clinically-relevant outcomes.

Thank you for your comment. We agree that it is important to establish the safety of high and load resistance exercise prior enrolling patients to training intervention, especially in the early phases of cardiac rehabilitation.

The roles and responsibilities required by the SPIRIT checklist were not well-defined (5b, 5c, 5d, 21a).

Thank you for your comment. We upgraded the item 5b-d and 21a. Please see rows 656-657 (item 5c), rows 334-335 (item 5d) and rows 176-181 (item 21a)

<u>Copied text from the manuscript:</u>

Rows 656-657:

The funding agency has no impact on data collection, analysis or interpretation of the study.

Rows 334-335:

Only TK and ML will have access to the data and will ensure its integrity. The study will be coordinated by TK and ML.

Rows 176-181:

All major adverse event will be evaluated by the Data management board within the Division of Cardiology at General Hospital Murska Sobota to evaluate potential safety indications. The data management board will consist of experienced consultant cardiologists and medical nurses. During the screening of the potential major event, the patient will not participate in any activity within the CR programme and will resume the training upon medical clearance.

6a is not well justified and requires more thorough literature review.

Thank you for your suggestion. We believe that we included all available data on this topic. All crossover trial on haemodynamic response to resistance exercise in patients with CAD were included. Moreover, we included two latest meta-analysis comparing the effects of high- and low-loads resistance training in healthy older adults, as well as two latest meta-analysis on the effects of resistance training in patients with CAD.

The trial design is good and adequately described. The method is adequately described, however the study is not powered to detect changes between the two resistance training interventions, with no indication of re-powering the study.

Thank you for your suggestion. This limitation is now included, please see rows and 300-305. Since we are limited with time and with the ongoing COVID-19 epidemic, we currently will not re-power our ongoing study.

Rows 300-305:

The sample size calculation for the comparison between LL-RT and HL-RT was not conducted, as no previous studies were available in patients with CAD. Therefore, in that sense, this study will

establish only pilot results on the comparison of HL-RT and LL-RT in combination with AT on co-primary outcomes. Furthermore, no calculation of statistical power was performed for secondary outcomes, thus, all outcomes should be interpreted as hypothesis-generating.

The blinding methods are unclear; will assessors be blinded as to the cluster the participants are allocated?

Thank you for your suggestion. The assessor will not be blinded, although, the patients will be. Each cluster will train separately to ensure the same motivation levels from all three intervention arms. The assessor will be blinded until the patients will be randomised to each intervention arm. Please see added description in rows 111-113.

Copied text from the manuscript:

Rows 111-113:

The patients would not be blinded during the study, however, each cluster of randomised patients will train separately to avoid additional comparison with other interventional arms.

Reporting of adverse and serious adverse events is not indicated. A data management committee would be useful.

Thank you for your suggestion. This section is now added with description of each step of reporting and response. Please see rows 197-205.

Copied text from the manuscript:

Rows 197-205:

The medical staff will document any potential cardiovascular (blood pressure >220/110 mmHg, orthostatic intolerance, atrial fibrillation, arrhythmias, shortness of breath, dizziness, chest pain, etc.) and musculoskeletal (muscle and joint pain, muscle fatigue) adverse symptoms and signs during and after each training session. All major adverse event will be evaluated by the Data management board within the Division of Cardiology at General Hospital Murska Sobota to evaluate potential safety indications. The data management board will consist of experienced consultant cardiologists and medical nurses. During the screening of the potential major event, the patient will not participate in any activity within the CR programme and will resume the training upon medical clearance.

Reviewer: 2

Dr. Julija Gecaite, Lithuanian University of Health Sciences

Comments to the Author:

Thank you for the opportunity to review this manuscript. This protocol could serve as a great foundation for the RCT that may lead to the practical recommendations within the area of resistance training and its importance in cardiac rehabilitation programs. This protocol represents the rationale and the study design for the RCT with the interesting, novel and relevant potential findings. The following comments are intended to help the authors improve the quality and strength of this study.

Language.

I am of the view that the manuscript may need to undergo the language editing. In the certain places it is not good enough and may need to be improved: E.g. Enroll, Enrollment in many places are

written without double "l" (e.g. p.2, line 29; p. 13, line 281 etc.); in some sentences articles are missing (e.g. the protocol p. 2, line 37; with a stable CAD p. 6, line 113).

On the other occasions the structure of the sentence makes it difficult to understand the intended meaning (e.g. the secondary aim should be clarified or paraphrased p. 5, lines 80-81).

Thank you for your suggestion. The language editing was performed by Janet N. Robertson. PhD (Advanced Member, Society for Editors and Proofreaders, and Member, European Association of Science Editors) prior to submission. All language is edited to British English. The sentence including the secondary aim of our study is also now rephrased, please see rows 97-101.

Copied text from the manuscript:

Rows 97-101:

The secondary aim is to examine the effects of HL-RT and LL-RT combined with AT in comparison with standard care (AT) on blood biomarkers, physical activity and quality of life. In addition, this study will compare the safety and acute haemodynamic responses to LL-RE and HL-RE at baseline and after 36 training sessions.

Furthermore, there are some more specific comments in relation to different parts of the protocol:

STRENGTHS AND LIMITATIONS OF THIS STUDY

The authors state that their "primary aim is to examine the effects of HL-RT and LL-RT combined with AT in comparison with standard care (AT) on aerobic capacity, maximal muscle strength […] in patients with CAD." They also give the rationale for the calculation of the sample size, assuming that 60 participants should be enough for this study (p. 12, lines 258-259). However, on p. 3, lines 51-52 they state that "This study may lack adequate statistical power to compare the effects of HL-RT and LL-RT on maximal aerobic capacity and muscle strength ". I am lacking the rationale why the number of the participants cannot be increased so that this study limitation could be resolved? Especially, when it is related to the primary outcomes.

Thank you for your suggestion. These two sections are now updated, please see rows 54-64. and 300-305.

Rows 54-64:

- **This will be randomised, controlled, clinical trial comparing the efficacy of HL- versus LL-RT combined with AT in patients with CAD.**
- **The study will evaluate the safety and haemodynamic response to HL-RE (80 % of 1-RM) and to LL-RE (40 % of 1-RM) in a crossover, randomised and load balanced manner at the inclusion to cardiac rehabilitation programme.**
- **The study will implement progressive RT programmes, with balanced training volume by the number of repetitions in LL-RT and HL-RT.**
- **We will investigate the potential dose-dependent relationship between RT load and changes in glucose metabolism, growth hormones and selected biomarkers of inflammation.**
- **A potential limitation of the study is that the training load in both RT groups cannot be blinded within the randomly allocated cluster of patients.**

Rows 300-305:

The sample size calculation for the comparison between LL-RT and HL-RT was not conducted, as no previous studies were available in patients with CAD. Therefore, in that sense, this study will establish only pilot results on the comparison of HL-RT and LL-RT in combination with AT on co-primary outcomes. Furthermore, no calculation of statistical power was performed for secondary outcomes, thus, all outcomes should be interpreted as hypothesis-generating.

INTRODUCTION

Overall, the introduction has the important components of novelty and relevance of the study.

- **I assume that some of the parts from the discussion section can be moved to the introduction.**

Thank you for your suggestion. The discussion is now updated, while we did not include any part of it to the introduction section. We believe that every important objective is well covered in the introduction.

- **Please review the abbreviations. For example, in some places you use LL-RE and HL-RE. However, no explanations for these abbreviations are given.**

Thank you for your suggestions. The abbreviation LL-, HL- and RE are explained in the introduction, please see rows 77-78, 83-89.

Copied text from the manuscript:

Rows 77-78:

Resistance training (RT) is underused in clinical practice (5), despite being recommended for over 20 years for patients with coronary artery disease (CAD) (1,6–8).

Rows 83-89:

Training stimuli in low-load (LL) RT may often be suboptimal for increase in muscle strength when compared with high-load (HL) RT (>70% of 1-RM), as is recommended for both healthy young and older adults (10).10 Thus, in young athletes and the elderly, HL-RT induced greater increase in muscle strength than LL-RT (11,12).11 12 In patients with CAD already experienced in CR training, HL resistance exercise (RE) (70%–90% 1-RM) was proven to be safe, with lower haemodynamic responses (e.g. heart rate, blood pressure, cardiac output) and lower perceived exertion (e.g. Borg scale) than observed in LL-RE (30-40 % 1-RM) (13,14).

METHODS AND ANALYSIS

This section is overall well-developed, detailed and integrates all the required parts for the protocol. Also, the protocol is pre-registered, it is an ongoing study, which has the ethical approval and meets the criteria listed in the SPIRIT statement.

- **Please list the preliminary dates when the RCT should be carried out. Currently, I could find only the date for the recruitment (July 2020).**

Thank you for your suggestion. We added the exact date of study recruitment, however, we can not anticipate the date of completion due to COVID-19 pandemic. Please see rows 143-144.

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Rows 143-144:

Recruitment of patients began in July 2020 and is expected to be completed in July 2021.

- **What is the rationale for not including those with left ventricular ejection fraction<40% (p.6, line 115)? Usually, they represent a significant number of CAD patients in cardiac rehabilitation.**

Thank you for your suggestion. Patients with left ventricular ejection fraction <40% are classified as heart failure patients, and for whose patients the high loads resistance training is not advised, especially in the early phase of cardiac rehabilitation. In addition, we based our inclusion criteria on the recent recommendations published in European Journal of Preventive Cardiology by the European Association of Preventive Cardiology. Finally, we believe that majority of cardiac rehabilitation programmes consist of patients with stable CAD with left ventricular ejection fraction above 45 %.

- **On p. 11 you state that you will use SF-12. First, I may suggest to specify that you will measure health related quality of life (since quality of life is a very broad term) or give the description for quality of life in your study. Second, there should be some elaboration about SF-12, its domains, type of administration and information on the psychometric characteristics (e.g. an internal consistency) in similar studies.**

Thank you for your suggestion. We changed the title as proposed, please see row 284 (Health related- quality of life). We also added data on the validity and reliability of both questionnaire, and additionally illustrated which domains will be assessed within each questionnaire. Please see rows 282-290.

<u>Copied text from the manuscript:</u>

Rows 282-290:

Health related-quality of life

Health related-quality of life will be assessed with the short form 12-item quality of life questionnaire (SF-12) (28) and psychological well-being (e.g. depression) will be assessed with the patient health 9-item questionnaire (PHQ-9) (29) at baseline and post-CR. We will calculate the total score of the SF-12, the Physical component summary and the Mental Component Summary score (30). The SF-12 questionnaire has good internal consistency and good construct validity (31), and was shown to be an excellent alternative to longer version (36-item quality of life questionnaire) (28) in patients with CAD. Similarly, the PHQ-9 has shown excellent internal consistency and good construct validity in patients with CAD (32).

<u>ETHICS AND DISSEMINATION</u>

- **On p. 13 line 282 you mentioned about "[the] potential risk during the study". What is the risk (s)? It might be important to mention it/them and shortly describe how you are planning to minimize it/them (risk management).**

Thank you for your suggestion. The list of adverse event with plan of procedures in case of occurrence in now added. Please see rows 173-181.

<u>Copied text from the manuscript:</u>

Rows 173-181:

The medical staff will document any potential cardiovascular (blood pressure >220/110 mmHg, orthostatic intolerance, atrial fibrillation, arrhythmias, shortness of breath, dizziness, chest pain, etc.) and musculoskeletal (muscle and joint pain, muscle fatigue) adverse symptoms and signs during and after each training session. All major adverse event will be evaluated by the Data management board within the Division of Cardiology at General Hospital Murska Sobota to evaluate potential safety indications. The data management board will consist of experienced consultant cardiologists and medical nurses. During the screening of the potential major event, the patient will not participate in any activity within the CR programme and will resume the training upon medical clearance.

DISCUSSION

- **Since there are no findings yet (thus, they cannot be interpreted or compared with other studies), I am not sure whether the extensive "Discussion" section is needed. Some of the earlier protocols, published in BMJ Open, either omitted or kept the discussion part relatively concise. Most of the parts can be moved to introduction part in order to elaborate on the relevance of this future study within the context of earlier studies or to emphasize the novelty of the results. The expectations of the results might also be moved to introduction and possibly formed as the hypotheses. Nevertheless, this is more of the recommendation to consider.**

- **Also, since this study may have a potential high clinical importance, the emphasis on clinical relevance could be made to even further strengthen this protocol.**

Thank you for your suggestion. The discussion section is now rewritten, please see rows 346-376.

Copied text from the manuscript:

Rows 346-376:

Despite recent progressions of exercise prescription and modalities in cardiac rehabilitation (1,34,35), the implementation of RT into clinical practice remains limited by its heterogeneous prescription, lack of reported progression of training loads and poor reporting of adverse events in the randomised controlled clinical trials (2,9). This study is designed with the aim to establish whether the HL-RT is efficacious and safe compared to currently advised AT with and without the addition of LL-RT.

The study is the first to implement the progressive LL-RT (35 %-40% of 1-RM) and HL-RT (70 %-80% of 1-RM) programme with balanced training volume in patients with CAD. Currently, no study supports the dose-dependent relationship between RT load and improvement in aerobic capacity and muscle strength in patients with CAD. In healthy young and older adults such a relationship is well established, as meta-analysis has shown the superior effects of HL-RT on improvement of muscle strength and hypertrophy when compared with LL-RT (11,12). With the increasing prevalence of frail elderly patients with CAD enrolled in CR (36), we expect that the implementation of HL-RT will have immediate clinical impact especially in such patients groups.

Despite the well reported safety of RT in patients with cardiovascular disease (2,9),2 9 HL-RT was rarely implemented until recent guidelines were published (1),1 probably due to potential cardiovascular complications with excessive increase in blood pressure (7,38).7 34 In contrast to this common belief, haemodynamic studies have demonstrated that HL-RE (70%–90% 1-RM) elicits lower heart rate, blood pressure and perceived exertion compared with low-to-moderate RE (35%–60% 1-RM) in CAD patients with previous training experience in CR (13,14).13 14 To date, no studies have examined haemodynamic responses to RE before its inclusion in CR; thus, our crossover study will be the first to establish the safety of both types of RE. In contrast to previous studies in patients with CAD (13,14), the exercise load in LL-RE and HL-RE will be balanced to eliminate

potential effects of training intensity, and will measure rating of perceived exertion during the exercise.

The authors acknowledge that the study could be limited by its lack of adequate statistical power to compare the effects of LL-RT and HL-RT on maximal aerobic capacity and muscle strength. In addition, the patients could not be blinded due to scheme of CR programme, however, each cluster of randomised patients will train separately to avoid additional comparison with other interventional arms.

In conclusion, we postulate that implementation of HL-RT as an adjunct exercise therapy to AT will help to optimise improvements in aerobic capacity and muscle strength during routine CR programmes.

VERSION 2 – REVIEW

REVIEWER	Scott, Andrew University of Portsmouth, Department of Sport and Exercise Science
REVIEW RETURNED	03-Jun-2021

GENERAL COMMENTS	This is a satisfactory response to our suggestions.

REVIEWER	Gecaite, Julija Lithuanian University of Health Sciences, Neuroscience Institute, Laboratory of Behavioral Medicine
REVIEW RETURNED	25-May-2021

GENERAL COMMENTS	The manuscript has been improved greatly and I may recommend the acceptance after the very minor change, described below: Health related quality of life (or quality of life) and depressive symptoms though related, are two different constructs. Thus, I may suggest to make two (instead of one) subheadings: one for Health related Quality of Life (as measured by SF-12) and one for depressive symptoms (as measured by PHQ-9) (lines 281-289) or name them both in the subheading "Health related Quality of Life and Depressive Symptoms"

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Andrew Scott, University of Portsmouth

Comments to the Author:

This is a satisfactory response to our suggestions.

Thank you very much again for your time and all valuable suggestions.

Reviewer: 2

Dr. Julija Gecaite, Lithuanian University of Health Sciences

Comments to the Author:

The manuscript has been improved greatly and I may recommend the acceptance after the very minor change, described below:

Health related quality of life (or quality of life) and depressive symptoms though related, are two different constructs. Thus, I may suggest to make two (instead of one) subheadings: one for Health related Quality of Life (as measured by SF-12) and one for depressive symptoms (as measured by PHQ-9) (lines 281-289) or name them both in the subheading "Health related Quality of Life and Depressive Symptoms"

Thank you for taking your time to assess our revised manuscript. Thank you for your suggestion. We changed the subheading as suggested, please see row 287.

Copied text from the row 287:

Health related-Quality of life and Depressive Symptoms