Article:

Tang, Lars Hermann, Zwisler, Ann-Dorthe, Doherty, Patrick Joseph orcid.org/0000-0002-1887-0237 et al. (3 more authors) (2019) Changes in Physical Performance and their Association with Health Related Quality of Life in a Mixed Non-ischemic Cardiac Population. Journal of cardiopulmonary rehabilitation and prevention. ISSN 1932-7501

https://doi.org/10.1097/HCR.0000000000000416

Journal of Cardiopulmonary Rehabilitation and Prevention

Changes in Physical Performance and their Association with Health Related Quality of Life in a Mixed Non-ischemic Cardiac Population

--Manuscript Draft--

Manuscript Number:	JCRP-D-18-00148R2
Full Title:	Changes in Physical Performance and their Association with Health Related Quality of Life in a Mixed Non-ischemic Cardiac Population
Short Title:	Physical Performance and HRQoL in Cardiac Rehabilitation
Article Type:	Original Investigation/Manuscript
Keywords:	Cardiac rehabilitation; Associations; Atrial fibrillation; Heart valve surgery; Infective endocarditis
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Manuscript Region of Origin:	DENMARK
Abstract:	Purpose: Exercise-based cardiac rehabilitation (CR) improves physical performance and health-related quality of life (HRQoL). However, whether improvements in physical performance are associated with changes in both generic and disease-specific HRQoL has not been adequately investigated in a non-ischemic cardiac population. Methods Patients who were ablated for atrial fibrillation, who underwent heart valve surgery or who were treated for infective endocarditis and who participated in one of three randomised control rehabilitation trials were eligible for the current study. Change in physical performance and HRQoL were measured before and after a 12-week exercise intervention. Physical performance was assessed using a cardiopulmonary exercise test, a 6-min walk test and a sit-to-stand test. HRQoL were assessed using the generic Short-Form-36 and the disease-specific HeartQoL questionnaire. Spearman's correlation coefficient (rho) and linear regressions quantified the association between changes in physical outcome measures and changes in HRQoL. Results

	A total of 344 patients were included (mean age 60.8 (11.6) years and 77% males). Associations between changes in physical outcome measures and HRQoL ranged from very weak to weak (Spearman's correlation coefficient = -0.056-0.228). The observed associations were more dominant within physical dimensions of the HRQoL compared to mental or emotional dimensions. Adjusted for sex, age and diagnosis changes in physical performance explained no more than 20% of the variation in the HRQoL. Conclusion Our findings show that the positive improvement in HRQoL from exercise-based CR cannot simply be explained by an improvement in physical performance.
Response to Reviewers:	A detailed point-by-point response to editor and reviewers has been uploaded in a separat word file. We look forward to hearing your decision regarding our revised manuscript.

Monday, November 19, 2018

To the associate Editor-in-Chief

Dear Dr. Leonard A. Kaminsky,

On behalf of myself and my colleagues, I would like to thank you for the opportunity to submit a revised version of the manuscript "*Changes in Physical Performance and their Association with Health Related Quality of Life in a Mixed Non-ischemic Cardiac Population*" to the *Journal of Cardiopulmonary Rehabilitation and Prevention.*

We would also like to thank the reviewers for their valuable comments. Our detailed point-by-point response to these comments is provided below and our edits in the manuscript and the tables are indicated with red font. A 'clean' version of the manuscript and tables has also been submitted.

We look forward to hearing your decision regarding our manuscript.

Yours sincerely,

First author

Ms. Ref. No.: JCRP-D-18-00148 "Changes in Physical Performance and their Association with Health Related Quality of Life in a Mixed Non-ischemic Cardiac Population"

Comment	**Author' reply**	**Action Taken / Manuscript revision**
Editor		
As you will note, I am recommending acceptance but with minor revision. This decision is based on a reviewer's comments that are included and the recommendation of the Associate Editor.	We who like to thank the editor for their decision. We have undertaken all the requested editorial changes and all changes suggested by the reviewer. We hope this meets your expectations.	
Editorial changes		
- Provide a complete postal mailing address for the corresponding author	A complete postal mailing address for the corresponding author has been added to the title page	
- Present references as described in the Instructions for Authors (e.g. doi should not be listed)	The reference list has been corrected.	
- The title page lists number of references as 47, however, the reference list has 52; please reduce this to no more than 50 references	The number of references has been reduced to 50 and number of references in the title page has been updated.	
- List all abbreviations used in tables as a footnote to the table in alphabetical order formatted like this: Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; BMI, body mass index; etc	Has been corrected in all four tables.	
Reviewer #1		
#1. Regard to your comments on my suggestion for table 2, I can not agree with your answer. Clear presentation of study results is important in scientific paper and readers in this journal may be smart enough to understand the main focus of this study. I still recommend you to show both scores at baseline and follow-up and the p-values for the statistical test to see the before and after difference.	Table 2 has been changed and includes absolute follow-up scores and p-values	The following has been added to the text "*Significant changes were explored using a paired t-test*" Page 4, Line 85

#2. in addition, the number of subjects in baseline and follow-up is different for some items (e.g. peak Vo2, power, 6MWT). There should be follow-up losses but I think they have to be excluded from analysis. So the number in 6MWT should be just 314.	We agree with the reviewer. This has already been taken into account in the analysis. All analyses only include the patients with a change score which varies for each variable. However, this was not taken into account in the baseline scores in table 2 but has now been corrected.	
#3. in line with comment 2, what was the sample size used for the correlation analysis (table 3). Was it same in each correlation analysis? What is the value in table 3? Maybe, correlation coefficient but it has to be described clearly in the table (e.g. The values are the correlation coefficients by Spearman correlation analysis). Where is the 95% CI in table 2?	Based on this comment we have added the number of patients in the correlation analysis and changed the title of table 3. To our knowledge a 95% CI is already presented in table 2. We are therefore unsure about what is missing?	The number of patients has been added in table 3 in line with the previously comment. Table 3 has been renamed to: "Associations between change scores in physical outcome measures and health related quality of life calculated using Spearman's correlation coefficient"
#4. Table 1: Please clarify your results presentation. For example, the values of categorical variables in the column of the mean(SD) may be the percent. Medical records may be just the medication.	All categorical variables are already presented in percent. The column "mean (SD)" changes throughout the table. However we have made this clear.	Changes made in table 1: Medical records has been changed to medication and percentage has been added to clarify this.
#5. Table 4: What was the sample size used for the regression analysis? Were the values in table 4 beta coefficient? Please clarify it in the table. Were the values the mean? What is heart diagnosis? Was it the patient type in table 1? Clarify it. Why did you exclude other important confounders which may impact on the QoL and Physical fitness changes such as employment status, depression, NYHA class?	The number of patients has been added to table 4. The mean in table 4 represents the slope of the best fitted line between the dependent and independent variable. We have clarified this in table 4 Confounders were widely discussed before performing the analysis. Many variables are known to influence physical capacity and especially QOL, which has already been highlighted in the discussion section. Adjusting for all these variables will 1)	Changes made in table 4: *Mean, the mean represents the slope of the best fitted line between the Dependent and independent variables* Heart diagnosis has been changed to patient type, as in table 1.

	decrease the external validity of the findings as the population will become highly selective and 2) it will lower the power in the analysis for each included variable. Due to the clinical perspective of this paper we decided only to control for the most common clinical confounders - sex and age. We further controlled for patient type due to the difference in pathologies between the three included patient groups. The overall results showed a weak association between changes in physical capacity and QOL. From a clinical stand-point this tells us that an increase in physical capacity by itself is not the key to increased QOL. From our perspective this is a very important clinical statement.	
Reviewer #2		
The authors have included a rationale and detailed response to my concerns. In my opinion, they have adequately answered my concerns	We appreciated this and think the comments previously provided from the reviewer have strengthened the paper.	

Changes in Physical Performance and their Association with Health Related Quality of Life in a Mixed Non-ischemic Cardiac Population that Participate in Rehabilitation.

Structured Abstract

Purpose:

Exercise-based cardiac rehabilitation (CR) improves physical performance and health-related quality of life (HRQoL). However, whether improvements in physical performance are associated with changes in HRQoL has not been adequately investigated in a non-ischemic cardiac population.

Methods

Patients who were ablated for atrial fibrillation, who underwent heart valve surgery or who were treated for infective endocarditis and who participated in one of three randomised control rehabilitation trials were eligible for the current study. Change in physical performance and HRQoL were measured before and after a 12-week exercise intervention. Physical performance was assessed using a cardiopulmonary exercise test, a 6-min walk test and a sit-to-stand test. HRQoL were assessed using the generic Short-Form-36 and the disease-specific HeartQoL questionnaire. Spearman's correlation coefficient (rho) and linear regressions quantified the association between changes in physical outcome measures and changes in HRQoL.

Results

A total of 344 patients were included (mean age 60.8 (11.6) years and 77% males). Associations between changes in physical outcome measures and HRQoL ranged from very weak to weak (Spearman's correlation coefficient = -0.056-0.228). The observed associations were more dominant within physical dimensions of the HRQoL compared to mental or emotional dimensions. Adjusted for sex, age and diagnosis changes in physical performance explained no more than 20% of the variation in the HRQoL.

Conclusion

Our findings show that the positive improvement in HRQoL from exercise-based CR cannot simply be explained by an improvement in physical performance.

Condensed Abstract

Whether improvements in physical performance are associated with changes HRQoL has not been adequately investigated in a non-ischemic cardiac population. Data obtained from three randomised control cardiac rehabilitation trials showed that changes in physical performance explained no more than 20% of the variation in the HRQoL.

JCRP SUBMISSION CHECKLIST FOR AUTHORS

Please refer to the Information for Authors (edmgr.ovid.com/jcrp/ifauth.htm) for more detailed information. The following is a checklist for authors to help insure that a submission is complete and uses the correct format and JCRP conventions. JCRP requires that the corresponding author complete the checklist and include it with the initial manuscript submission in Editorial Manager. Manuscripts submitted without this checklist will be returned to the authors with a request to complete and submit a completed checklist.

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Manuscript Title: Changes in physical performance and their association with health related quality of life in a mixed non-ischemic cardiac population.

Title page is formatted correctly and includes all elements:

☒ Type of submission

☒ Both a full title and a shortened form (≤50 characters) of the title (running title)

☒ Names and information on all authors

☒ List of 3-5 key words

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☒ Statements regarding both financial support and any conflicts of interest for all authors

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Abstracts:

☒ Structured abstract of ≤250 words (using subheadings appropriate for submission type)

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Text-only:

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☒ Original investigation: ≤3,000 words

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References:

☒ Cited in the text in the order they appear using superscript numbers

☒ Citations formatted following the AMA Manual of Style, 10th edition

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Figures:

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Full Title: Changes in Physical Performance and their Association with Health Related Quality of Life in a Mixed Non-ischemic Cardiac Population that Participate in Rehabilitation.

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Short title: Physical Performance and HRQoL in Cardiac Rehabilitation

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Keyword: Cardiac rehabilitation, Associations, Atrial fibrillation, Heart valve surgery, Infective endocarditis

Conflict of interest: All authors declare no conflicts of interest. All authors have read and approved the manuscript

Sources of support: This work was supported by The Danish Council for Strategic Research (grant number: 10-092790).

Word count (text-only portion): 3000 words

Numbers of tables: 4

Numbers of figures: 0

Numbers of references: 50

Introduction

In recent years, HRQoL has been found to be an important predictor of adverse health outcomes (e.g. risk of readmission and mortality) across cardiac populations.[1–5] Hence, clinical guidelines emphasize the healthcare services like CR need to improve HRQoL for patients.[6]

Exercise training has high priority in cardiac rehabilitation.[7] Exercise-based CR is known to increase physical performance and HRQoL.[8–11] However, whether a positive improvement in physical performance with exercise-based CR can explain changes in HRQoL is uncertain. Previous studies show conflicting results[12–21] where some report a weak to moderate influence of physical performance on HRQoL.[12,15–17,19,21,22] Most studies have utilized cross-sectional designs where physical performance is compared to HRQoL at baseline[17,19–23] or at the end for a CR intervention.[15] To our knowledge, only one study,[12] has investigated the association between changes over time in physical performance and HRQoL with a prospective design demonstrating that changes in peak oxygen uptake (VO_2) after a 8-week exercise-based CR intervention for patients with ischemic heart disease, heart valve disease, and heart failure only explained 4% of the variation in two subscales in the Short Form Health Survey (SF-36) (“physical function” and “vitality”).[12] Since HRQoL has become an important outcome measure in CR a better understanding of the association between increased physical performance and its impact on HRQoL is needed.[6]

Studies on whether increased physical performance has an impact on HRQoL are mainly conducted in patients with coronary heart diseases or heart failure.[12,15–17,19,21–24] In non-ischaemic cardiac populations (e.g. atrial fibrillation, heart valve replacement, infective endocarditis or heart transplant recipients) the topic has barely been investigated. The difference in pathologies between ischaemic and non-ischaemic cardiac diagnoses may impact on the generalisability between the two groups.[25] However, in non-ischaemic cardiac populations reduced HRQoL has also been reported and found to be associated with risk of readmission.[1–3]

Several assessment methods are routinely applied in CR, for example, the cardiac pulmonary exercise test (CPET)[26], cycle ergometer (power in watts), six-minute-walk test (6MWT), and sit-to-stand test which provide additional physical outcome measures for physical performance. As a small number of studies have indicated the relationship between physical performance and HRQoL varies as a consequence of the outcome measurement used to evaluate physical performance.[16,19,22] Hence, different assessment methods may impact HRQoL to varying degrees which is particularly relevant in an intervention where one of the specific aims is to enhance HRQoL.

The objectives of this study was to assess whether changes in physical performance are associated with changes in HRQoL measured with both generic and disease-specific instruments and whether this is related to the physical assessment methods in patients without ischemic heart disease who were ablated for atrial fibrillation, who underwent heart valve surgery or who were treated for infective endocarditis.

Methods

Patients in the current study all participated in one of three randomized controlled trials (RCTs) with a parallel design and conducted simultaneously as a part of the CopenHeart Project.[27–31] A regional Ethical Committee (j.nr: H-1-2011-135, H-1-2011-157 & H-1-2011-129) approved the RCTs. Data handling was approved by the Danish Data Protection Agency (j.nr. 2007-58-0015).

Since all three RCTs have been described in detail and their effectiveness has been studied elsewhere, the following section briefly outlines the trials in relation to the objectives of the current study.[27–31] Patients without ischemic heart disease who either were ablated for atrial fibrillation, who underwent heart valve surgery or who were treated for infective endocarditis were included if they were over 18 years, able to understand and speak Danish, and had no musculoskeletal or organ disease precluding physical activity.[27–31] Patients were randomized to either a comprehensive CR intervention or usual care.[27,29,31] The intervention consisted of psycho-education and exercise training. The psycho-educational consultations were performed five times over a period of 6 months from hospital discharge either as face-to-face consultations or by telephone. Exercise training was initiated one month after hospital discharge and consisted of 36 exercise sessions performed over 12 weeks. The exercise program was individually tailored and involved both aerobic and strength exercises. The programme could be performed either in supervised centre-based setting or a home-based setting based on patients own preference. The participant's choice of settings did not impact the effect of the intervention.[32]

The outcomes of the three RCTs were physical performance and patient-reported HRQoL. To evaluate physical performance patients underwent three objective assessment methods performed before and after the exercise intervention (e.g. one month and four months after hospital discharge). Detailed information about these tests have been described elsewhere.[27,29,31]

Peak VO_2 and maximum power (watts) were measured during a maximum CPET using a ramp protocol on a cycle ergometer. Physical performance was further assessed using the 6-min walk test (6MWT) and a sit-to-stand test. In the current study, HRQoL was assessed with both generic and disease-specific instruments and collected at baseline and six months after hospital discharge. The generic 36-item Short-Form Health Survey (SF-36)[33] was used to assess patient-reported HRQoL and presented as mental component summary (MCS) and physical component summary (PCS) scores. The disease-specific HeartQoL [34,35] questionnaire was used to assess heart HRQoL with Global, Physical and Emotional scores.

Patient demographics, clinical variables and classification of disease severity were measured at baseline. For classification of disease severity, the New York Heart Association (NYHA) Functional Classification was used for patients who underwent heart valve surgery and for patients with infective endocarditis. The European Heart Rhythm Association (EHRA) score indicating atrial fibrillation-related symptoms was used in patients who underwent an ablation for atrial fibrillation. The Hospital Anxiety and Depression Scale (HADS)[36] was used to screen for symptoms of anxiety and depression at baseline.

Only patients who performed at least one of the exercise tests before and after the exercise intervention and who fulfilled at least one of the HRQoL questionaries at baseline and at six months were included in current study. Both the intervention and the control group from the three RCTs were included. A sub analysis adjusting for allocation to either the intervention or control group was performed.

Statistical analyses

Baseline demographics are presented as mean ± standard deviation (SD) for parametric data and as medians and interquartile ranges (IQR) for non-parametric data.

To assess the strength of association between changes in physical performance and changes in HRQoL, change scores (post CR minus pre CR values) were calculated for all outcome measures. Significant changes were explored using a paired t-test. Spearman's correlation coefficient (rho) was used to calculate the association between change scores in physical outcome measures and HRQoL. The strength of the correlation was interpreted as suggested by Evans et al.[37] with the absolute value for rho: very week (0.00-0.19), weak (0.20-0.39), moderate (0.40-0.59), strong (0.60-0.79), and very strong (0.80-1.00). A univariate linear regression model was used to quantify the strength of association between changes in physical outcome measures and changes in HRQoL. Where univariate linear regression showed a significant relationship, a multivariate linear regression model was conducted controlling for age, sex and patient type. The coefficient of determination (R^2) was calculated for all models. All statistical analyses were performed using the software SAS Enterprise Guide 5.1 (SAS Institute Inc., Cary, NC, USA). Level of statistical significant was expressed as a $p < 0.05$.

Results

In total, 474 patients were enrolled in the three RCTs.[27–31] Of these patients, 344 were included in the current analysis as they performed at least one of the three exercise tests before and after the exercise intervention and had completed at least one of the HRQoL questionnaires at baseline and at six months. Participants and non-participants were similar; age (p=0.159), sex (p=0.151) and BMI (p=0.812). The mean age of the patients included in the study was 60.8 (± 11.6) years with the majority male (77%). Participant characteristics at baseline are presented in Table 1. Baseline and change scores (post intervention score minus pre intervention score) in physical outcome measures and HRQoL scores are reported in Table 2.

Spearman correlations coefficients between change scores in physical outcome measures and HRQoL are presented in Table 3. The majority of the 20 associations were very weak (rho=0.00-0.19) with four categorised as weak (rho=0.20-0.39). The four weak associations were found between the HeartQoL Global score and HeartQoL Physical score changes and maximum power (watts) changes (rho=0.209 and rho=0.204, respectively) and changes in sit-to-stand test (rho=0.228 and rho=0.215, respectively).

Results from univariate and multivariate linear regression analysis are presented in Table 4. The change in peak VO_2 showed statistically significant association with the SF-36 physical component score. However, findings were not significant when adjusted for sex, age and heart diagnosis in the multivariate model (mean change score = 0.128 with 95% CI: -0.077 to 0.334). Changes in maximum power (watts) showed statistically significant associations with the four out of five HRQoL scores. Only the SF-36 mental component and the HeartQoL Emotional scores were not significantly associated with changes in maximum power when adjusted for sex, age and diagnose. In the multivariate model, changes in maximum power (watts) explained from 5% to 17% of the changes in HRQoL (HeartQOL Emotional: R^2 = 0.050, HeartQol physical score: R^2 = 0.169). Changes in 6-MWT were only statistically significantly associated with changes in the SF-36 physical component score - both in univariate (R^2=0.026) and multivariate regression model (R^2=0.164). Changes in the number of repetitions during the sit-to-stand test were statistically significantly associated with changes in SF-36 physical component score and all three dimensions in HeartQoL (Global, Emotional and Physical). When adjusted for sex, age and heart diagnosis, the R^2 ranged from 5% to 20% (HeartQoL Emotional score R^2 = 0.054, HeartQol physical score: R^2 = 0.200). Adjusting for allocation (intervention vs control) did not change the overall interpretation of the results.

Discussion

The objective of this study was to assess whether changes in physical performance are associated with changes in HRQoL in a mixed non-ischaemic cardiac population. Results showed very weak to weak associations between changes in physical performance outcomes measures and HRQoL. The observed associations between change scores in physical performance and HRQoL tended to be more dominant within physical dimensions of HRQoL compared to emotional dimensions. Still, adjusted for sex, age and diagnosis, changes in physical performance never accounted for more than for 20% of the variation in the HRQoL.

Exercise-based CR is known to increase physical performance and HRQoL.[8,9] Previous studies investigating the association between physical performance and HRQoL show conflicting results spanning very weak to moderate associations.[12,15–17,19,21,22] The understanding of this association between physical performance and HRQoL has mainly been investigated in patients with ischemic heart disease or heart failure using a cross-sectional design and therefore not investigated from improvement over time.[15,17,19–23] In addition to our study, changes in physical performance and its associations to HRQoL have only been investigated in one other prospective study.[12] Andersen et al. compared changes in SF-36 with changes in peak VO_2 after an 8-week exercise-based CR intervention conducted in patients with ischemic heart disease, heart valve disease, or heart failure. They found that peak VO_2 explained 4% of the changes in SF-36 physical function and vitality subscale scores.[12] In contrast to our study, Andersen et al. did not show a statistically significant associations between changes in peak VO_2 and changes in SF-36 physical component score with a mean change of -0.37 (95% CI −0.12 to 0.86). Although this difference may be due to a lack of power in the Andersen study with 166 patients compared to 341 in our study, the 4% explained variance in SF-36 subscale *physical function* and *vitality* score with change in physical performance reported by Andersen et al. [12] is similar to the 2% (R^2) seen in our crude estimate of SF-36 (R^2 = 0.016 SF-36 physical component score). This indicates similarities in findings between the patient populations between the two studies (Patients with ischemic heart disease, heart valve disease, or heart failure VS patients ablated for atrial fibrillation, undergone heart valve surgery or treated for infective endocarditis) However, when we adjusted for age, sex and heart diagnosis, the changes in peak VO_2 explained about 15% of the changes in SF-36 physical component score (R^2 = 0.153) which indicate a variation between age, sex and each individual heart diagnosis.

As the first study to compare changes in physical performance measures over time to changes in both HRQoL measured with both generic and disease-specific instruments, we observed associations correlating predominantly with the physical dimensions of HRQoL. However, the associations between physical performance and the HeartQoL physical score were weak with only very weak associations with the SF-36 PCS score. This difference in the strength of associations between physical dimensions measured by generic and disease-specific instruments could possibly be explained by the fact that the HeartQoL is a heart disease-specific questionnaire where physical items are more common in cardiac patients across conditions than physical items used in generic questionnaires.

A few cross sectional design studies have investigated how different physical performance outcome measures correlate with HRQoL.[16,19,22] Unfortunately, heterogeneity due to different outcome measures, RCT patient populations and HRQoL measures complicate comparison across studies. Collected in a prospective study, our findings indicate that certain physical outcome measures can, to a greater extent, explain the variation in HRQoL than others. For instance, changes in all four physical outcome measures explained 15% to18% of the variation in SF-36 physical component score but only changes in maximum power and repetitions during sit-to-stand test explained changes in HRQoL (HeartQoL Global and Physical score). Changes in power and repetitions during sit-to-stand test explained from 15% to 18% of the variation on the HeartQoL Global score and 18% to 20% of the variation in the HeartQoL Physical score. One explanation for why maximum power and sit-to-stand test better explain variations in disease-specific related HRQoL than peak VO_2 and 6MWT could be that these are surrogate measures for strength in the lower extremities. In elderly participants, previous research have found an association between lower limb strength and physical function[38,39] and, in patients with diabetes mellitus, lower limb strength is known to correlate with HRQoL.[40]

Evidence shows that exercise-based CR increases both physical performance and HRQoL across cardiac patients groups.[8,9,41] However, changes in physical performance explain little of the changes observed in HRQoL. Other mechanisms and elements than increased physical performance must be explored before the impact of exercise-based CR on HRQoL will be fully understood. For instance depression and anxiety scores are known predictions for HRQoL in cardiac patients and are positively influenced by exercise-based CR.[42,43] Baseline levels in physical performance and sizes of improvement may also affect the association. A low physical performance level at baseline will perhaps to a larger extent affect association with HRQoL in comparison to a performance level that does not prevent a patient from daily routines. According to the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation exercise training alone cannot be categorised as CR. Hence exercise-based CR will normally contains patient-education or psychological counseling likely to affect HRQoL.[44,45]

Strength and limitation

To our knowledge this is the largest study to investigate the relationship between physical performance and HRQoL based on change scores from patients who participated in exercise-based CR. Further, the study is the first to compare intervention changes obtained from different physical outcome measures to changes in HRQoL measured by both generic and disease-specific instruments.

Most of the previous studies on the topic have been conducted in patients with ischemic heart disease or heart failure.[12,15–17,19,21,22] In contrast, we analysed a mixed group of non-ischemic cardiac patients with ablation for atrial fibrillation, or who underwent heart valve surgery or who were treated for infective endocarditis recognizing that the three pathologies are very different. However, this was taken into consideration by adjusting for diagnosis in our analysis. Following this line, the generalisability of our findings is likely to be limited to the three patients groups include in this study. However, compared to the findings of Andersen et al.[46] who included patients with ischemic heart disease, heart valve disease or heart failure, our findings are remarkably similar.

All our regression analyses were based on the underlying assumption of linearity between the independent and dependent variables. Complete linearity is however hypothetical and it is not known how this affects our results.[47] For instance, we cannot verify whether different levels in physical performance or HRQoL would differentially impact the observed associations. Further, the study performs multiple comparisons without correction of the p-values. The rational is that the probability of a type I error cannot be lowered without increasing the probability of a type II error.[48] As this is an explorative study, solid conclusions cannot be drawn but help generate strong hypotheses that must be tested by a future study.[49] Hence, it would be more appropriate to generate a possible significant association then to miss out on a type I error.[48]

Of the 473 patient included in the three RCT's only 344 fulfilled the inclusion criteria in our study - corresponding to an attrition rate of 27%. In clinical trials a drop-out rate of approximately 15-20 % can be expected.[50] Particularly in patients with non-ischemic cardiac conditions readmission rates are high where patients who undergo heart valve surgery or have endocarditis, readmission rates one year after hospital discharge are as high as 56% and 65%, respectively.[1,2] So despite, a drop-out rate of 27%, our data still likely reflect those patients who participate in exercise-based CR.

Conclusion

Both physical performance and HRQoL are improved with exercise-based CR in the current study. Nevertheless, our findings demonstrate that changes in physical performance only have a very weak to weak association with changes in HRQoL. The magnitude of changes in HRQoL explained by changes in physical performance are, not surprisingly, more evident in the physical dimensions of HRQoL. Unlike peak VO_2, physical outcome measures reflecting lower limb strength may explain variation in HRQoL. Overall, our findings show that the positive impact of exercise-based CR on HRQoL cannot simply be explained by an increase in physical performance. Other mechanisms and elements must therefore be investigated before impact of exercise-based CR on HRQoL is fully understood.

Acknowledgement

First of all, we would like to thank all patients who participated in the CopenHeart trials. Furthermore we will acknowledge all CopenHeart staff especially Signe Stelling Risom, Kirstine Lærum Sibilitz, Trine Rasmussen for their effort in the CopenHeart project.

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Introduction

In recent years, HRQoL has been found to be an important predictor of adverse health outcomes (e.g. risk of readmission and mortality) across cardiac populations.[1–5] Hence, clinical guidelines emphasize the healthcare services like CR need to improve HRQoL for patients.[6]

Exercise training has high priority in cardiac rehabilitation.[7] Exercise-based CR is known to increase physical performance and HRQoL.[8–11] However, whether a positive improvement in physical performance with exercise-based CR can explain changes in HRQoL is uncertain. Previous studies show conflicting results[12–21] where some report a weak to moderate influence of physical performance on HRQoL.[12,15–17,19,21,22] Most studies have utilized cross-sectional designs where physical performance is compared to HRQoL at baseline[17,19–23] or at the end for a CR intervention.[15] To our knowledge, only one study,[12] has investigated the association between changes over time in physical performance and HRQoL with a prospective design demonstrating that changes in peak oxygen uptake (VO_2) after a 8-week exercise-based CR intervention for patients with ischemic heart disease, heart valve disease, and heart failure only explained 4% of the variation in two subscales in the Short Form Health Survey (SF-36) ("physical function" and "vitality").[12] Since HRQoL has become an important outcome measure in CR a better understanding of the association between increased physical performance and its impact on HRQoL is needed.[6]

Studies on whether increased physical performance has an impact on HRQoL are mainly conducted in patients with coronary heart diseases or heart failure.[12,15–17,19,21–24] In non-ischaemic cardiac populations (e.g. atrial fibrillation, heart valve replacement, infective endocarditis or heart transplant recipients) the topic has barely been investigated. The difference in pathologies between ischaemic and non-ischaemic cardiac diagnoses may impact on the generalisability between the two groups.[25] However, in non-ischaemic cardiac populations reduced HRQoL has also been reported and found to be associated with risk of readmission.[1–3]

Several assessment methods are routinely applied in CR, for example, the cardiac pulmonary exercise test (CPET)[26], cycle ergometer (power in watts), six-minute-walk test (6MWT), and sit-to-stand test which provide additional physical outcome measures for physical performance. As a small number of studies have indicated the relationship between physical performance and HRQoL varies as a consequence of the outcome measurement used to evaluate physical performance.[16,19,22] Hence, different assessment methods may impact HRQoL to varying degrees which is particularly relevant in an intervention where one of the specific aims is to enhance HRQoL.

The objectives of this study was to assess whether changes in physical performance are associated with changes in HRQoL measured with both generic and disease-specific instruments and whether this is related to the physical assessment methods in patients without ischemic heart disease who were ablated for atrial fibrillation, who underwent heart valve surgery or who were treated for infective endocarditis.

Methods

Patients in the current study all participated in one of three randomized controlled trials (RCTs) with a parallel design and conducted simultaneously as a part of the CopenHeart Project.[27–31] A regional Ethical Committee (j.nr: H-1-2011-135, H-1-2011-157 & H-1-2011-129) approved the RCTs. Data handling was approved by the Danish Data Protection Agency (j.nr. 2007-58-0015).

Since all three RCTs have been described in detail and their effectiveness has been studied elsewhere, the following section briefly outlines the trials in relation to the objectives of the current study.[27–31] Patients without ischemic heart disease who either were ablated for atrial fibrillation, who underwent heart valve surgery or who were treated for infective endocarditis were included if they were over 18 years, able to understand and speak Danish, and had no musculoskeletal or organ disease precluding physical activity.[27–31] Patients were randomized to either a comprehensive CR intervention or usual care.[27,29,31] The intervention consisted of psycho-education and exercise training. The psycho-educational consultations were performed five times over a period of 6 months from hospital discharge either as face-to-face consultations or by telephone. Exercise training was initiated one month after hospital discharge and consisted of 36 exercise sessions performed over 12 weeks. The exercise program was individually tailored and involved both aerobic and strength exercises. The programme could be performed either in supervised centre-based setting or a home-based setting based on patients own preference. The participant's choice of settings did not impact the effect of the intervention.[32]

The outcomes of the three RCTs were physical performance and patient-reported HRQoL. To evaluate physical performance patients underwent three objective assessment methods performed before and after the exercise intervention (e.g. one month and four months after hospital discharge). Detailed information about these tests have been described elsewhere.[27,29,31]

Peak VO_2 and maximum power (watts) were measured during a maximum CPET using a ramp protocol on a cycle ergometer. Physical performance was further assessed using the 6-min walk test (6MWT) and a sit-to-stand test. In the current study, HRQoL was assessed with both generic and disease-specific instruments and collected at baseline and six months after hospital discharge. The generic 36-item Short-Form Health Survey (SF-36)[33] was used to assess patient-reported HRQoL and presented as mental component summary (MCS) and physical component summary (PCS) scores. The disease-specific HeartQoL [34,35] questionnaire was used to assess heart HRQoL with Global, Physical and Emotional scores.

Patient demographics, clinical variables and classification of disease severity were measured at baseline. For classification of disease severity, the New York Heart Association (NYHA) Functional Classification was used for patients who underwent heart valve surgery and for patients with infective endocarditis. The European Heart Rhythm Association (EHRA) score indicating atrial fibrillation-related symptoms was used in patients who underwent an ablation for atrial fibrillation. The Hospital Anxiety and Depression Scale (HADS)[36] was used to screen for symptoms of anxiety and depression at baseline.

Only patients who performed at least one of the exercise tests before and after the exercise intervention and who fulfilled at least one of the HRQoL questionaries at baseline and at six months were included in current study. Both the intervention and the control group from the three RCTs were included. A sub analysis adjusting for allocation to either the intervention or control group was performed.

Statistical analyses

Baseline demographics are presented as mean ± standard deviation (SD) for parametric data and as medians and interquartile ranges (IQR) for non-parametric data.

To assess the strength of association between changes in physical performance and changes in HRQoL, change scores (post CR minus pre CR values) were calculated for all outcome measures. Significant changes were explored using a paired t-test. Spearman's correlation coefficient (rho) was used to calculate the association between change scores in physical outcome measures and HRQoL. The strength of the correlation was interpreted as suggested by Evans et al.[37] with the absolute value for rho: very week (0.00-0.19), weak (0.20-0.39), moderate (0.40-0.59), strong (0.60-0.79), and very strong (0.80-1.00). A univariate linear regression model was used to quantify the strength of association between changes in physical outcome measures and changes in HRQoL. Where univariate linear regression showed a significant relationship, a multivariate linear regression model was conducted controlling for age, sex and patient type. The coefficient of determination (R^2) was calculated for all models. All statistical analyses were performed using the software SAS Enterprise Guide 5.1 (SAS Institute Inc., Cary, NC, USA). Level of statistical significant was expressed as a $p < 0.05$.

Results

In total, 474 patients were enrolled in the three RCTs.[27–31] Of these patients, 344 were included in the current analysis as they performed at least one of the three exercise tests before and after the exercise intervention and had completed at least one of the HRQoL questionnaires at baseline and at six months. Participants and non-participants were similar; age (p=0.159), sex (p=0.151) and BMI (p=0.812). The mean age of the patients included in the study was 60.8 (± 11.6) years with the majority male (77%). Participant characteristics at baseline are presented in Table 1. Baseline and change scores (post intervention score minus pre intervention score) in physical outcome measures and HRQoL scores are reported in Table 2.

Spearman correlations coefficients between change scores in physical outcome measures and HRQoL are presented in Table 3. The majority of the 20 associations were very weak (rho=0.00-0.19) with four categorised as weak (rho=0.20-0.39). The four weak associations were found between the HeartQoL Global score and HeartQoL Physical score changes and maximum power (watts) changes (rho=0.209 and rho=0.204, respectively) and changes in sit-to-stand test (rho=0.228 and rho=0.215, respectively).

Results from univariate and multivariate linear regression analysis are presented in Table 4. The change in peak VO_2 showed statistically significant association with the SF-36 physical component score. However, findings were not significant when adjusted for sex, age and heart diagnosis in the multivariate model (mean change score = 0.128 with 95% CI: -0.077 to 0.334). Changes in maximum power (watts) showed statistically significant associations with the four out of five HRQoL scores. Only the SF-36 mental component and the HeartQoL Emotional scores were not significantly associated with changes in maximum power when adjusted for sex, age and diagnose. In the multivariate model, changes in maximum power (watts) explained from 5% to 17% of the changes in HRQoL (HeartQOL Emotional: R^2 = 0.050, HeartQol physical score: R^2 = 0.169). Changes in 6-MWT were only statistically significantly associated with changes in the SF-36 physical component score - both in univariate (R^2=0.026) and multivariate regression model (R^2=0.164). Changes in the number of repetitions during the sit-to-stand test were statistically significantly associated with changes in SF-36 physical component score and all three dimensions in HeartQoL (Global, Emotional and Physical). When adjusted for sex, age and heart diagnosis, the R^2 ranged from 5% to 20% (HeartQoL Emotional score R^2 = 0.054, HeartQol physical score: R^2 = 0.200). Adjusting for allocation (intervention vs control) did not change the overall interpretation of the results.

Discussion

The objective of this study was to assess whether changes in physical performance are associated with changes in HRQoL in a mixed non-ischaemic cardiac population. Results showed very weak to weak associations between changes in physical performance outcomes measures and HRQoL. The observed associations between change scores in physical performance and HRQoL tended to be more dominant within physical dimensions of HRQoL compared to emotional dimensions. Still, adjusted for sex, age and diagnosis, changes in physical performance never accounted for more than for 20% of the variation in the HRQoL.

Exercise-based CR is known to increase physical performance and HRQoL.[8,9] Previous studies investigating the association between physical performance and HRQoL show conflicting results spanning very weak to moderate associations.[12,15–17,19,21,22] The understanding of this association between physical performance and HRQoL has mainly been investigated in patients with ischemic heart disease or heart failure using a cross-sectional design and therefore not investigated from improvement over time.[15,17,19–23] In addition to our study, changes in physical performance and its associations to HRQoL have only been investigated in one other prospective study.[12] Andersen et al. compared changes in SF-36 with changes in peak VO_2 after an 8-week exercise-based CR intervention conducted in patients with ischemic heart disease, heart valve disease, or heart failure. They found that peak VO_2 explained 4% of the changes in SF-36 physical function and vitality subscale scores.[12] In contrast to our study, Andersen et al. did not show a statistically significant associations between changes in peak VO_2 and changes in SF-36 physical component score with a mean change of -0.37 (95% CI −0.12 to 0.86). Although this difference may be due to a lack of power in the Andersen study with 166 patients compared to 341 in our study, the 4% explained variance in SF-36 subscale *physical function* and *vitality* score with change in physical performance reported by Andersen et al. [12] is similar to the 2% (R^2) seen in our crude estimate of SF-36 (R^2 = 0.016 SF-36 physical component score). This indicates similarities in findings between the patient populations between the two studies (Patients with ischemic heart disease, heart valve disease, or heart failure VS patients ablated for atrial fibrillation, undergone heart valve surgery or treated for infective endocarditis) However, when we adjusted for age, sex and heart diagnosis, the changes in peak VO_2 explained about 15% of the changes in SF-36 physical component score (R^2 = 0.153) which indicate a variation between age, sex and each individual heart diagnosis.

As the first study to compare changes in physical performance measures over time to changes in both HRQoL measured with both generic and disease-specific instruments, we observed associations correlating predominantly with the physical dimensions of HRQoL. However, the associations between physical performance and the HeartQoL physical score were weak with only very weak associations with the SF-36 PCS score. This difference in the strength of associations between physical dimensions measured by generic and disease-specific instruments could possibly be explained by the fact that the HeartQoL is a heart disease-specific questionnaire where physical items are more common in cardiac patients across conditions than physical items used in generic questionnaires.

A few cross sectional design studies have investigated how different physical performance outcome measures correlate with HRQoL.[16,19,22] Unfortunately, heterogeneity due to different outcome measures, RCT patient populations and HRQoL measures complicate comparison across studies. Collected in a prospective study, our findings indicate that certain physical outcome measures can, to a greater extent, explain the variation in HRQoL than others. For instance, changes in all four physical outcome measures explained 15% to18% of the variation in SF-36 physical component score but only changes in maximum power and repetitions during sit-to-stand test explained changes in HRQoL (HeartQoL Global and Physical score). Changes in power and repetitions during sit-to-stand test explained from 15% to 18% of the variation on the HeartQoL Global score and 18% to 20% of the variation in the HeartQoL Physical score. One explanation for why maximum power and sit-to-stand test better explain variations in disease-specific related HRQoL than peak VO_2 and 6MWT could be that these are surrogate measures for strength in the lower extremities. In elderly participants, previous research have found an association between lower limb strength and physical function[38,39] and, in patients with diabetes mellitus, lower limb strength is known to correlate with HRQoL.[40]

Evidence shows that exercise-based CR increases both physical performance and HRQoL across cardiac patients groups.[8,9,41] However, changes in physical performance explain little of the changes observed in HRQoL. Other mechanisms and elements than increased physical performance must be explored before the impact of exercise-based CR on HRQoL will be fully understood. For instance depression and anxiety scores are known predictions for HRQoL in cardiac patients and are positively influenced by exercise-based CR.[42,43] Baseline levels in physical performance and sizes of improvement may also affect the association. A low physical performance level at baseline will perhaps to a larger extent affect association with HRQoL in comparison to a performance level that does not prevent a patient from daily routines. According to the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation exercise training alone cannot be categorised as CR. Hence exercise-based CR will normally contains patient-education or psychological counseling likely to affect HRQoL.[44,45]

Strength and limitation

To our knowledge this is the largest study to investigate the relationship between physical performance and HRQoL based on change scores from patients who participated in exercise-based CR. Further, the study is the first to compare intervention changes obtained from different physical outcome measures to changes in HRQoL measured by both generic and disease-specific instruments.

Most of the previous studies on the topic have been conducted in patients with ischemic heart disease or heart failure.[12,15–17,19,21,22] In contrast, we analysed a mixed group of non-ischemic cardiac patients with ablation for atrial fibrillation, or who underwent heart valve surgery or who were treated for infective endocarditis recognizing that the three pathologies are very different. However, this was taken into consideration by adjusting for diagnosis in our analysis. Following this line, the generalisability of our findings is likely to be limited to the three patients groups include in this study. However, compared to the findings of Andersen et al.[46] who included patients with ischemic heart disease, heart valve disease or heart failure, our findings are remarkably similar.

All our regression analyses were based on the underlying assumption of linearity between the independent and dependent variables. Complete linearity is however hypothetical and it is not known how this affects our results.[47] For instance, we cannot verify whether different levels in physical performance or HRQoL would differentially impact the observed associations. Further, the study performs multiple comparisons without correction of the p-values. The rational is that the probability of a type I error cannot be lowered without increasing the probability of a type II error.[48] As this is an explorative study, solid conclusions cannot be drawn but help generate strong hypotheses that must be tested by a future study.[49] Hence, it would be more appropriate to generate a possible significant association then to miss out on a type I error.[48]

Of the 473 patient included in the three RCT’s only 344 fulfilled the inclusion criteria in our study - corresponding to an attrition rate of 27%. In clinical trials a drop-out rate of approximately 15-20 % can be expected.[50] Particularly in patients with non-ischemic cardiac conditions readmission rates are high where patients who undergo heart valve surgery or have endocarditis, readmission rates one year after hospital discharge are as high as 56% and 65%, respectively.[1,2] So despite, a drop-out rate of 27%, our data still likely reflect those patients who participate in exercise-based CR.

Conclusion

Both physical performance and HRQoL are improved with exercise-based CR in the current study. Nevertheless, our findings demonstrate that changes in physical performance only have a very weak to weak association with changes in HRQoL. The magnitude of changes in HRQoL explained by changes in physical performance are, not surprisingly, more evident in the physical dimensions of HRQoL. Unlike peak VO_2, physical outcome measures reflecting lower limb strength may explain variation in HRQoL. Overall, our findings show that the positive impact of exercise-based CR on HRQoL cannot simply be explained by an increase in physical performance. Other mechanisms and elements must therefore be investigated before impact of exercise-based CR on HRQoL is fully understood.

Acknowledgement

First of all, we would like to thank all patients who participated in the CopenHeart trials. Furthermore we will acknowledge all CopenHeart staff especially Signe Stelling Risom, Kirstine Lærum Sibilitz, Trine Rasmussen for their effort in the CopenHeart project.

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Table 1: Patient characteristics

	N	Mean (SD)
Age (years)	344	60.8 (11.6)
BMI (kg/m^2)	332	26.0 (4.4)
Sex		**%**
Male	266	77
Female	78	23
Employment status		**%**
Employed	173	50.3
Unemployed	171	49.7
Marital status		**%**
Living alone	68	19.8
Living with partner	276	80.2
Patient type		**%**
Radiofrequency ablation	151	43.9
Valve replacement	107	31.1
Infective endocarditis	86	25.0
NYHA/EHRA class		**%**
I	80	23.7
II	161	47.6
III	92	27.2
IV	5	1.5
Medication		**%**
Warfarin	237	69.5
Beta-blockers	141	41.4
Statin	114	33.4
Calcium antagonists	58	17.0
HADS		**Median (IQR)**
Depression	343	2.0 (1.0-4.0)
Anxiety	344	4.0 (2.0-7.0)

Abbreviations: **EHRA**, European Heart Rhythm Association (EHRA) score of atrial fibrillation related symptoms; **HADS**, Hospital Anxiety and Depression Scale; **IQR**, Interquartile range **N,** Number of patients; **NYHA class;** the New York Heart Association (NYHA) Functional Classification.

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Table 2_with_editions

Table 2: Baseline scores and the changes scores for both physical outcome measurements and health related quality of life

	N	Score at baseline Mean (95% CI)	Score at follow-up Mean (95% CI)	Change score†* Mean (95% CI)
Physical performance				
Peak Vo_2 (ml/min/kg)	341	22.6 (21.7-23.4)	24.7 (23.9-25.6)	2.2 (1.7-2.7)
Maximum power (watts)	341	149.1 (143.2-155.1)	166.5 (159.7-173.3)	17.4 (14.3-20.4)
6 min walk test (meter)	314	558.0 (546.6-569.4)	592.6 (581.3-603.3)	34.6 (26.8-42.3)
Stand-to-sit test (repetitions)	315	14.8 (14.3-15.3)	17.1 (16.4-17.7)	2.3 (1.9-2.6)
SF-36				
Mental component score	337	47.3 (46.2-48.4)	53.3 (52.3-54.3)	6.0 (4.8-7.1)
Physical component score	337	43.1 (42.1-44.1)	50.2 (49.3-51.2)	7.0 (6.1-8.3)
HeartQol				
Global	342	1.7 (1.6-1.8)	2.5 (2.4-2.5)	0.8 (0.7-0.8)
Emotional	342	2.0 (1.9-2.1)	2.5 (2.4-2.6)	0.5 (0.4-0.6)
Physical	342	1.6 (1.5-1.7)	2.5 (2.4-2.5)	0.9 (0.8-1.0)

Abbreviations: N, Number of patients; **Peak Vo_2**, Peak oxygen uptake; **SF-36**, 36-items Short Form Health Survey; **95% CI**, 95 % confidence interval.

†Post intervention score minus pre intervention score

*P ≤ .001 for all changes from baseline to follow-up.

Table 2_without_editations

Table 2: Baseline scores and the changes scores for both physical outcome measurements and health related quality of life

	N	**Score at baseline** Mean (95% CI)	**Score at follow-up** Mean (95% CI)	**Change score†*** Mean (95% CI)
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Physical	342	1.6 (1.5-1.7)	2.5 (2.4-2.5)	0.9 (0.8-1.0)

Abbreviations: N, Number of patients; **Peak Vo_2**, Peak oxygen uptake; **SF-36**, 36-items Short Form Health Survey; **95% CI**, 95 % confidence interval.

†Post intervention score minus pre intervention score

***P** $\leq$ .001 for all changes from baseline to follow-up.

Table 3_with_editions

Table 3: Associations between change scores in physical outcome measures and health related quality of life calculated using Spearman's correlation coefficient

	SF36 MCS	SF36 PCS	HeartQol global	HeartQoL Emotionel	HeartQoL Physical
Peak VO_2 (ml/kg/min)	-0.045 (n=334)	0.154 (n=334)	0.110 (n=339)	0.064 (n=339)	0.115 (n=339)
Maximum power (W)	0.005 (n=334)	0.187 (n=334)	0.209 (n=339)	0.128 (n=339)	0.204 (n=339)
6-MWT	-0.056 (n=307)	0.143 (n=307)	0.071 (n=313)	0.026 (n=313)	0.080 (n=313)
Sit-to-stand test	0.019 (n=308)	0.162 (n=308)	0.228 (n=314)	0.169 (n=314)	0.215 (n=314)

Abbreviations: **SF-36 MCS**, SF-36 mental component scale; **SF-36 PCS**, SF-36 physical component scale; **6-MWT**, 6 minutes walk test; **n,** Number of patients; **95% CI**, 95 % confidence interval.

Table 3_without_editations

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Abbreviations: **SF-36 MCS**, SF-36 mental component scale; **SF-36 PCS**, SF-36 physical component scale; **6-MWT**, 6 minutes walk test; **n,** Number of patients; **95% CI**, 95 % confidence interval.

Table 4_with_editions

Table 4: Univariate and multivariate linear regression of changes score in physical performance measurements and health related quality of life

	SF36 MCS	SF36 PCS	HeartQol Global	HeartQOL Emotional	HeartQOL Physical
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Peak VO_2	(n=334)	(n=334)	(n=339)	(n=339)	(n=339)
Crude estimate	-0.075 (-0.317 - 0.166)	0.252 (0.036 - 0.468)*	0.011 (-0.004- 0.027)	0.012 (-0.006 - 0.031)	0.011 (-0.006 - 0.029)
	R^2 = 0.001	R^2 = 0.016	R^2 = 0.006	R^2 = 0.005	R^2 = 0.005
Adjusted estimate	-	0.128 (-0.077 - 0.334)	-	-	-
		R^2 = 0.153			
Maximum power (watts)	(n=334)	(n=334)	(n=339)	(n=339)	(n=339)
Crude estimate	-0.009 (-0.031 - 0.050)	0.072 (0.036 - 0.107)***	0.005 (0.002 - 0.007)***	0.004 (-0.001 - 0.007)*	0.005 (0.002 - 0.008)***
	R^2 = 0.001	R^2 = 0.045	R^2 = 0.038	R^2 = 0.017	R^2 = 0.036
Adjusted estimate	-	0.048 (0.012 - 0.086)***	0.003 (-0.001 - 0.006)***	0.004 (-0.001 - 0.007)	0.003 (0.001 - 0.006)***
		R^2 = 0.167	R^2 = 0.149	R^2 = 0.050	R^2 = 0.169
6-MWT	(n=307)	(n=307)	(n=313)	(n=313)	(n=313)
Crude estimate	-0.001 (-0.018 - 0.017)	0.023 (0.007 - 0.039)**	0.000 (-0.001 - 0.002)	0.001 (-0.001 - 0.002)	0.001 (-0.001 - 0.002)
	R^2 = 0.000	R^2 = 0.026	R^2 = 0.008	R^2 = 0.002	R^2 = 0.007
Adjusted estimate	-	0.018 (0.008 - 0.032)**	-	-	-
		R^2 = 0.164			
Sit-to-stand test	(n=308)	(n=308)	(n=314)	(n=314)	(n=314)
Crude estimate	0.201 (-0.154 - 0.557)	0.431 (0.111 - 0.750)**	0.045 (0.022 - 0.068)***	0.041 (0.015 - 0.068)**	0.047 (0.021 - 0.073)***
	R^2 = 0.004	R^2 = 0.022	R^2 = 0.046	R^2 = 0.029	R^2 = 0.038
Adjusted estimate	-	0.406 (0.105 - 0.706)**	0.042 (0.020 - 0.064)***	0.039 (0.013 - 0.067)**	0.043 (0.018 - 0.067)***
		R^2 = 0.184	R^2 = 0.183	R^2 = 0.054	R^2 = 0.200

Abbreviations: **Mean,** the mean represents the slope of the best fitted line between the dependent and independent variable; **R^2,** Coefficient of determination**;** **SF-36 MCS**, SF-36 mental component scale; **SF-36 PCS**, SF-36 physical component scale; **n,** Number of patients; **6-MWT**, 6 minutes walk test; **95% CI**, 95 % confidence interval.
Adjusted estimate; Adjusted for age, sex and patient type
* p<0.05, **p<0.01,*** p<0.001,

Table 4_without_editations

Table 4: Univariate and multivariate linear regression of changes score in physical performance measurements and health related quality of life

	SF36 MCS	**SF36 PCS**	**HeartQol Global**	**HeartQOL Emotional**	**HeartQOL Physical**
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
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	R^2 = 0.001	R^2 = 0.016	R^2 = 0.006	R^2 = 0.005	R^2 = 0.005
Adjusted estimate	-	0.128 (-0.077 - 0.334)	-	-	-
		R^2 = 0.153			
Maximum power (watts)	(n=334)	(n=334)	(n=339)	(n=339)	(n=339)
Crude estimate	-0.009 (-0.031 - 0.050)	0.072 (0.036 - 0.107)***	0.005 (0.002 - 0.007)***	0.004 (-0.001 - 0.007)*	0.005 (0.002 - 0.008)***
	R^2 = 0.001	R^2 = 0.045	R^2 = 0.038	R^2 = 0.017	R^2 = 0.036
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Adjusted estimate	-	0.406 (0.105 - 0.706)**	0.042 (0.020 - 0.064)***	0.039 (0.013 - 0.067)**	0.043 (0.018 - 0.067)***
		R^2 = 0.184	R^2 = 0.183	R^2 = 0.054	R^2 = 0.200

Abbreviations: **Mean,** the mean represents the slope of the best fitted line between the dependent and independent variable; **R^2,** Coefficient of determination**; SF-36 MCS**, SF-36 mental component scale; **SF-36 PCS**, SF-36 physical component scale; **n,** Number of patients; **6-MWT**, 6 minutes walk test; **95% CI**, 95 % confidence interval.

Adjusted estimate; Adjusted for age, sex and patient type

* p<0.05, **p<0.01,*** p<0.001,

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2018-07-31

To: Larry F. Hamm, Editor-in-Chief of the Journal of Cardiopulmonary Rehabilitation and Prevention.

Dear Editor-in-Chief,

On behalf of myself and my colleagues, I would like to submit this manuscript to the Journal of Cardiopulmonary Rehabilitation and Prevention entitled: *Changes in physical performance and their association with health related quality of life in a mixed non-ischemic cardiac population.*

The present study investigates whether improvements in physical performance are associated with changes in both generic and disease-specific Health-related quality of life (HRQoL).

Exercise-based CR is known to increase physical performance and HRQoL. However, whether a positive improvement in physical performance from exercise-based CR can explain changes in HRQoL is still questioned. Previous studies are showing conflicting results and have been mainly conducted using a cross sectional design where real changes from the intervention not are taken into consideration.

The current study is based on data from three randomized controlled trails (the CopenHeart trials). A total of 344 non-ischemic heart patients who either were ablated for atrial fibrillation, who underwent heart valve surgery or who were treated for infective endocarditis are included. Overall, our findings show that changes in physical performance at their highest, only account for 20% of the variation in the HRQoL. Therefore, the positive impact that exercise-based CR has on HRQoL cannot simply be explained by an increase in physical performance.

The paper is especially interesting as it is the first to compare real intervention changes obtained from different physical outcome measures, to changes in both generic and disease-specific HRQoL. Also, it is the largest study to investigate the relationship between physical performance and HRQoL in a mixed patient group with non-ischemic cardiac conditions.

This study is part of the CopenHeart project and is based on three parallel randomized controlled trials that meet all national and international regulatory guidelines for clinical trial research. All three trials have been approved by the regional Research Ethics Committee (j.nr. H-1-2011-135, j.nr. H-1-2011-129 and j.nr. H-1-2011-157) and the National Agency for Data Security (j.nr. 2007-58-0015).

This study is supported by The Danish Council for Strategic Research (number: 10-092790). There are no conflicts of interest. All grants were “non-restricted research grants” and the funders have no influence on the trial design, the execution of the trial or the interpretation of the data.

All authors have read and approved submission of the manuscript and the manuscript has not been published and is not being considered for publication elsewhere in whole, or part, in any language. It will not be submitted elsewhere, until a decision has been made as to its acceptability by the Journal of Cardiopulmonary Rehabilitation and Prevention has been made.

Thank you for taking the time to review this submission. We look forward to hearing from you in due course. Should you have any questions regarding this submission, please contact the Principal Author Lars Hermann Tang.

Yours sincerely,

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