ORIGINAL ARTICLE

# Cardiac rehabilitation increases physical capacity but not mental health after heart valve surgery: a randomised clinical trial

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Received 4 February 2016
Revised 28 June 2016
Accepted 29 June 2016
Published Online First 4 August 2016

## ABSTRACT

**Objective** The evidence for cardiac rehabilitation after valve surgery remains sparse. Current recommendations are therefore based on patients with ischaemic heart disease. The aim of this randomised clinical trial was to assess the effects of cardiac rehabilitation versus usual care after heart valve surgery.

**Methods** The trial was an investigator-initiated, randomised superiority trial (The CopenHeart$_{VR}$ trial, VR; valve replacement or repair). We randomised 147 patients after heart valve surgery 1:1 to 12 weeks of cardiac rehabilitation consisting of physical exercise and monthly psycho-educational consultations (intervention) versus usual care without structured physical exercise or psycho-educational consultations (control). Primary outcome was physical capacity measured by $VO_2$ peak and secondary outcome was self-reported mental health measured by Short Form-36.

**Results** 76% were men, mean age 62 years, with aortic (62%), mitral (36%) or tricuspid/pulmonary valve surgery (2%). Cardiac rehabilitation compared with control had a beneficial effect on $VO_2$ peak at 4 months (24.8 mL/kg/min vs 22.5 mL/kg/min, p=0.045) but did not affect Short Form-36 Mental Component Scale at 6 months (53.7 vs 55.2 points, p=0.40) or the exploratory physical and mental outcomes. Cardiac rehabilitation increased the occurrence of self-reported non-serious adverse events (11/72 vs 3/75, p=0.02).

**Conclusions** Cardiac rehabilitation after heart valve surgery significantly improves $VO_2$ peak at 4 months but has no effect on mental health and other measures of exercise capacity and self-reported outcomes. Further research is needed to justify cardiac rehabilitation in this patient group.

**Trial registration number** NCT01558765, Results.

## INTRODUCTION

Almost no evidence exists for cardiac rehabilitation after valve surgery. Thus, clinical recommendations are based on evidence from other cardiac conditions.[1] Heart valve surgery has markedly improved survival and health-related quality of life during the last decades[2] and surgery rates are increasing.[3 4] Postsurgical management has traditionally focused on medical evaluation, echocardiographic assessment and anticoagulation.[5 6] However, despite physical health improvements, deterioration in physical capacity[7] and mental health[8] can occur postsurgery, and the postoperative period may be challenging.[9 10] Therefore, it is important to study whether further postoperative management strategies including cardiac rehabilitation could improve outcomes.

The beneficial effects of cardiac rehabilitation are well documented after myocardial infarction, coronary artery bypass graft surgery and heart failure.[11 12] These include improvements in exercise capacity and health-related quality of life, and reductions in hospital readmissions and costs and are probably transferable to other cardiac populations.[1] While European recommendations include the use of exercise-based cardiac rehabilitation in the management after valvular surgery,[3] the American guidelines currently make no such recommendations.[6]

Observational studies of exercise training found improvement in exercise capacity after heart valve surgery.[13–15] Nevertheless, a recent Cochrane systematic review identified only two randomised clinical trials investigating exercise-based cardiac rehabilitation after valve surgery.[16] While both trials showed improvements in exercise capacity, the evidence was inadequate to judge on the effect on mortality, serious adverse events and health-related quality of life. We, therefore, hypothesised that cardiac rehabilitation increases physical capacity and improves mental health. Thus, the aim of this trial was to investigate the effects of comprehensive cardiac rehabilitation after valve surgery versus usual care on the primary outcome physical capacity and secondary outcome mental health.

## METHODS

### Trial design

The trial protocol is reported elsewhere.[17] The CopenHeart$_{VR}$ trial is a randomised trial comparing comprehensive cardiac rehabilitation versus control. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed. The trial was approved by the local Ethics Committee (protocol no: H-1-2011-157), the Danish Data Protection Agency (j. no: 2007-58-0015), registered at ClinicalTrials.

**To cite:** Sibilitz KL, Berg SK, Rasmussen TB, *et al*. *Heart* 2016;**102**:1995–2003.

gov (NCT01558765) and complied with the Declaration of Helsinki.

### Participants, setting and recruitment

The setting was a large Danish University Hospital, Rigshospitalet. Inclusion criteria were elective right-sided or left-sided heart valve surgery, age ≥18 years, able to speak and understand Danish, and provide informed written consent. Exclusion criteria were known ischaemic heart disease prior to surgery, current recruitment to other rehabilitation trials or participating in trials precluding patients to participate, expected to not cooperate according to the trial instructions, diseases in the musculoskeletal system, comorbidity complicating physical activity, competitive sports, and pregnancy and/or breastfeeding.

Potential participants were approached twice: 3 and 5 days after surgery. Inclusion was allowed within 2 weeks after surgery. Written and oral consent was obtained for all participants.

### Randomisation and blinding

Participants were allocated 1:1 to intervention or control using computer-generated allocation sequence with varying block sizes of 8, 6 and 4, concealed to the investigators by central telephone correspondence with the Copenhagen Trial Unit. Allocation was stratified according to left ventricular ejection fraction (LVEF; <45% vs ≥45%), and planned by the type of valve surgery (open heart surgery or percutaneous valve surgery), but only open heart surgery patients were recruited.[17] LVEF was chosen as stratification variable because of its clinical relevance and possible impact on symptoms and prognosis.

Blinding of clinicians and participants is impossible in a rehabilitation trial. However, outcome assessment, data management and all statistical analyses were performed blinded to allocation group.

### Intervention group

#### Physical exercise

The aim of the physical exercise was to improve physical capacity and initiated 1 month after surgery, comprising three weekly exercise sessions for 12 weeks. No rehabilitation was provided before 1 month except all patients were provided early mobilisation immediately following surgery as part of usual care. To monitor adherence, a training diary and heart rate (HR) monitor were used (Polar Watch, Polar HR RS 400 monitors, Polar Electro, Finland). A single exercise protocol was applied to all participants but individualised where necessary and initiated at the hospital with 1–3 sessions using t-shirts with wireless integrated ECG electrodes (Corus-Fit Cardio and Corus Exercise Assistant, CEA, V.2.0.16, Finland). The continuing programme was identical regardless of training location: (1) supervised training (at hospital or at a local study-protocol-certified supervised facility) (69%) or (2) home-based training (31%) with contact to a physiotherapist when indicated. The programme consisted of graduated cardiovascular training and strength exercises. The cardiovascular training was based on the intensity of the Borg scale,[18] altered stepwise during each training session, with progressively increasing intensity during the 12 weeks. The strength exercises were lower body exercises due to the sternal wound, described elsewhere.[17]

#### Psycho-educational intervention

The aim of the intervention was to improve disease coping applying a patient-centred approach, based on the theories of R. R. Parse's *Human Becoming Practice Methodologies*.[19] To assure standardisation of the intervention, a consultation guide was followed,[17] including relevant topics: changed body-image and self-image, recovery from major surgery, dependency on relatives and medical issues.

The intervention comprised one monthly consultation (five in total) initiated within the first month after surgery. Two specially trained nurses conducted all consultations to ensure high internal consistency, and all participants met only one nurse to achieve a confidential relationship and ensure high adherence. Consultations were conducted as either face-to-face meeting or by telephone consultation.

### Control group

Usual care according to current guidelines was provided.[3] However, when giving consents to participate in the trial, participants were not allowed to participate in a physical exercise programme. During the trial period, a physician examined all patients after 1 and 4 months, including physical, biochemical and echocardiographic assessments.

### Outcomes

Outcome assessments were at six time points; baseline (prior to randomisation), and 1, 4, 6, 12 and 24 months postrandomisation. Data from the 12 and 24 months follow-up will be presented elsewhere.

#### Primary outcome: physical capacity ($VO_2$ peak)

Physical capacity at 4 months was measured by peak oxygen uptake ($VO_2$ peak) using cardiopulmonary exercise testing with a cycle ergometer (Ergo-Spiro CS-200, Schiller, Switzerland) following standardised principles.[20] Test duration of 10 min was pursued, excluding 2–4 min before and after, with gas, volume and ambient calibration before each test. A ramp protocol with initial work load of 25 or 50 W was used depending on prior physical activity level, increasing by 12.5 W/min gradually. Criteria for exhaustion were a respiratory exchange ratio ≥1.1, reaching anaerobic threshold or the patient's subjective exhaustion. The $VO_2$ peak was the highest achieved $VO_2$ measured during the test. Due to pitfalls (such as calibration errors, flow errors and mask leakage), 16 tests were estimated, with no overrepresentation in either randomisation group, using the following estimation equation: $VO_2 = 10.8 \times (\text{Watt max/weight}) + 3.5$.[21] The estimation was validated on all measurements, and compared with non-estimated values the equation generally underestimated the $VO_2$ peak value.

#### Secondary outcome: mental health

Mental health was measured by Short Form-36 (SF-36), Mental Component Scale (MCS) at 6 months postrandomisation.[22]

#### Exploratory outcomes

Physical exploratory outcomes included systolic blood pressure (SBP) at rest and maximal, HR at rest, total exercise time, distance walked on a 6-min walk test, number of repetitions at sit-to-stand test and New York Heart Association (NYHA) class. Self-reported exploratory outcomes included the Short Form-36 eight domains, Hospital Anxiety Depression Scale (HADS) and the HeartQoL.[23]

### Safety considerations

Cardiopulmonary exercise testing was undertaken by an experienced nurse, physiotherapist or physician. Criteria for early termination were defined.[17] A physician was on call at all times. Deaths at 6 months were registered. All serious adverse events

associated with the intervention and outcome measurement were registered by a trial physician, and self-reported non-serious adverse events were captured using a patient-reported questionnaire at 6 months.

### Sample size

Our original recruitment target was 210.[17] Due to difficulties in recruitment, we reached a sample size of 147 patients. Not reaching our target, we recalculated the power before data analysis of the accrued sample.[24]

### Statistical analysis

The analysis was based on intention to treat using a mixed model with repeated measures (MMRM) and adjusted for the stratification variable of LVEF, ensuring that missing data will not create bias as long as the values are missing at random.[25] The MMRM was used for continuous outcomes (both primary and secondary outcomes). This model assumes normally (Gaussian) distributed residuals. However, the residuals were not normally distributed for the primary outcome, and therefore transformed. We used log-transformation, and when log-transformation did not result in normally distributed residuals, we used Box–Cox transformation. In the MMRM we assumed correlation within the individual patient, but no correlation between patients. The fixed effects for the primary outcome were randomisation group, time, interaction between random and time and LVEF.

For each outcome, a sensitivity analysis was conducted for statistically significant results. We used the Markov Chain Monte Carlo method for imputing missing values. To evaluate the clinical effect size, Cohen's d was calculated for the primary outcome, as a measure of difference between two means divided by a standard deviation for the data.[26]

We undertook a per-protocol analysis to take account of adherence to the prescribed cardiac rehabilitation intervention. The prespecified per-protocol level of intervention adherence was defined as at least 75% of the exercise session (ie, ≥27 sessions); and at least 80% (4 out of 5) psycho-educational consultations. Adherence to the exercise intervention was measured by the exercise diary and the HR, and to the psycho-educational intervention recordings were made at each visit (duration of the consultation, participation of relatives and transportation). All analyses were two-sided tests with a level of significance set at 5%. Data were analysed using SAS V.9.3 (SAS Institute, Cary, North Carolina, USA) and *R* V.3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).(R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

## RESULTS

### Baseline characteristics

Between 17 February 2012 and 7 May 2014, we identified 901 patients, of whom 355 were excluded and 393 (44%) declined participation (figure 1). One hundred and fifty-three patients gave informed written consent, 6 dropped out before randomisation, leaving 147 participants randomised. Those declining were more often women, with no difference in valve surgery, and often living farther away from the hospital. The included population was 76% men, mean age 62 years, 62% with aortic valve surgery, 36% with mitral valve surgery or 2% with tricuspid/pulmonary valve surgery. NYHA class ranged from I to IV, with evidence of few comorbidities and a low mean EuroSCORE II score (table 1). There was no evidence of baseline imbalances.

### Outcomes

#### Primary outcome: physical capacity ($VO_2$ peak)

There was evidence of a statistically significant interaction between intervention and time between groups after 4 months (24.8 mL/kg/min vs 22.5 mL/kg/min, p=0.045) (table 2, figure 2). We found no difference in the mean value of $VO_2$ peak between groups after 1 month (21.0 vs 21.1, p=0.34). The crude mean difference between the groups at 4 months was 2.3 mL/kg/min (SD 7.6), resulting in a Cohen's d of 0.31, indicating a moderate clinical effect.

#### Secondary outcome: mental health

No interaction between intervention and time was observed for SF-36 MCS (table 3, figure 3) between groups at 6 months (53.7 points vs 55.7 points, p=0.40).

#### Exploratory outcomes

The effect of intervention was not significant for any of the physical exploratory outcomes between months 1 and 4 (table 2). However, in both groups a trend over time in a number of outcomes was observed, that is, $VE/VCO_2$ slope and resting HR decrease, increase in SBP rest and maximal SBP, total exercise cardiopulmonary exercise test time, 6 min walk test duration and number sit-to-stand test repetitions.

No interaction between intervention and time was observed for any of the self-reported outcomes (HADS and HeartQoL). HeartQoL subscores increased from baseline to 6 months in both groups, and the number with HADS-A and HADS-D scores ≥8 decreased from baseline to 6 months in both groups (table 3).

### Sensitivity analyses

The significant interaction between intervention and time remains significant in a best-worst-case scenario, that is, when assuming all patients in the intervention group that did not complete the intervention (the drop outs) would have improved their peak $V0_2$ at follow-up (p=0.01), but becomes statistically insignificant in a worst-best-case scenario, that is, when assuming all patients in the intervention group that did not complete the intervention (the drop outs) would not have improved their $V0_2$ at follow-up (p=0.15) and in multiple imputation (p=0.08).

### Per-protocol analysis

We found no interaction between intervention and time of those training ≥75% and <75% of the training sessions at 1 month (p=0.18) or at 4 months (p=0.56) in a mixed-model analysis.

### Safety

Two serious adverse events were reported in the intervention group versus one in the control group at 6 months (table 4). We evaluated the serious adverse events in the intervention group not to be caused by the intervention (one with postsurgical cardiac tamponade and one with a heart failure related readmission). Eleven of 72 (15.3%) in the intervention group versus 3/75 (4.0%) in the control group had self-reported non-serious adverse events (p=0.02) (table 4). These events were primarily caused by musculoskeletal problems and related to exercise training in general.

At the psycho-educational intervention, a physician was contacted in 5% (15/308) of the consultations (arrhythmias, HR,

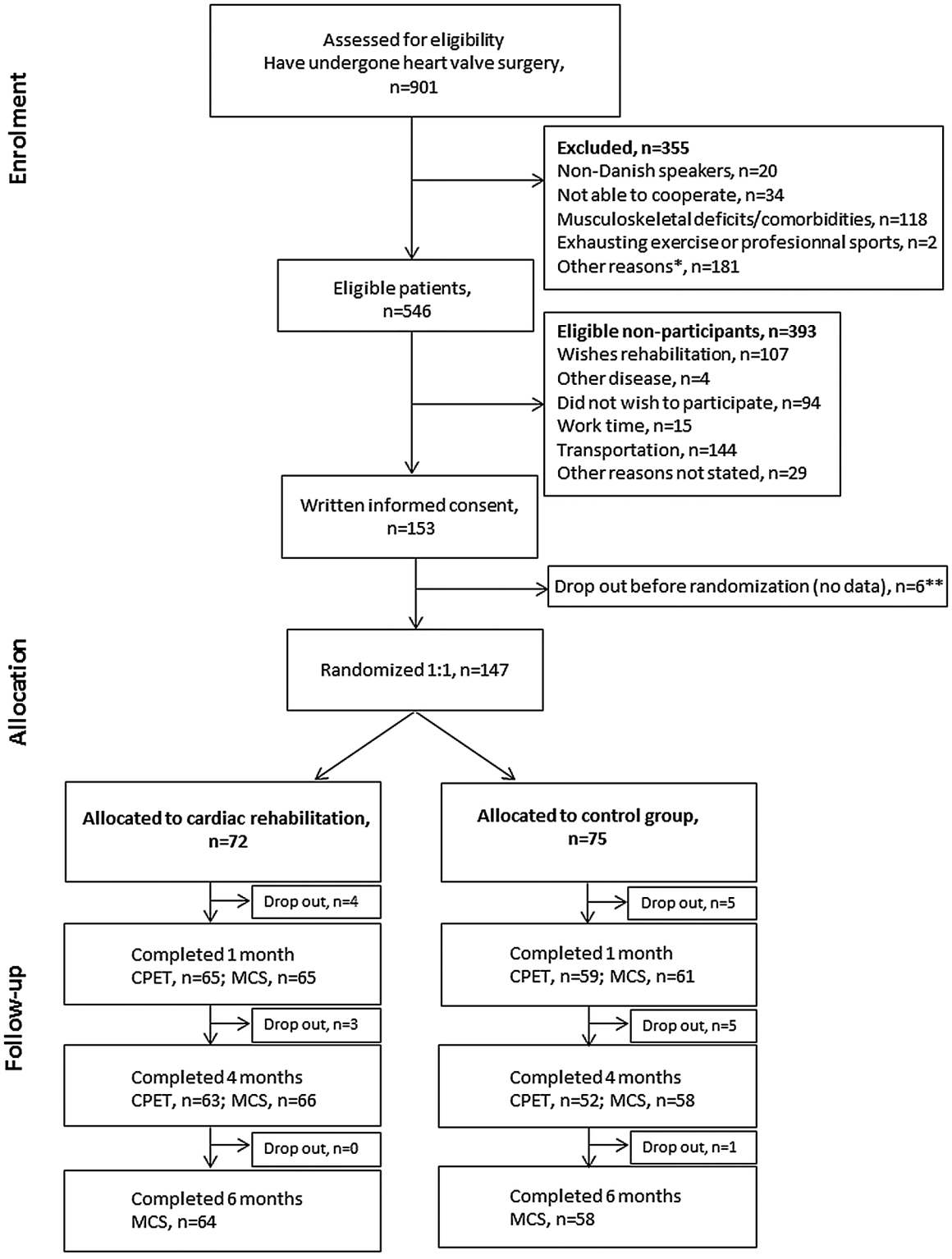


**Figure 1** Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Flow of patients in the CopenHeart$_{VR}$ trial. *Other reasons: ischaemic heart disease, other surgical circumstances, mortality after surgery, participation in trials inhibiting participation. **Reasons: two died, three withdrew their consent and one wished another rehabilitation.

dizziness, sleeplessness, referral to psychologist, pain in the sternal wound, presyncope, anticoagulation treatment).

### Adherence

A total of 61/72 (85%) in the intervention group participated in the exercise training programme. Of the participants, 41 (67%) conducted ≥75% (ie, ≥27 training sessions), 10 (16%) conducted 50–74% (18–26 sessions) and 10 (16%) conducted<50% (≤17 sessions). The 11 drop outs in the control group and 7 drop outs in the intervention group were due to complications after surgery, and withdrawal of consent. Overall, the patients participated in a mean of 28 (median 31) (IQR 23–36) training sessions, defined by completing the training diary and/or turning on the pulse watch. The exercise training was

**Table 1** Baseline characteristics

| | Cardiac rehabilitation group (n=72) | Control group (n=75) |
|---|---|---|
| Male sex, n (%) | 59 (82) | 53 (71) |
| Age, years (±SD) | 62.0 (11.5) | 61.0 (9.9) |
| Aortic valve surgery, n (%) | 46 (64) | 45 (60) |
| Mitral valve surgery, n (%) | 27 (38) | 26 (35) |
| Pulmonal and tricuspid valve surgery, n (%) | 1 (1.4) | 2 (3) |
| Symptoms prior to surgery*, n (%) | 66 (92) | 69 (92) |
| NYHA class I–II, n (%) | 53 (74) | 52 (69) |
| NYHA class III–IV, n (%) | 19 (26) | 23 (31) |
| LVEF, mean (±SD) | 55 (9.6) | 54 (10.2) |
| Preoperative LVEF ≥45%, n (%) | 64 (89) | 64 (85) |
| EuroSCORE II | 1.13 (0.78) | 0.96 (0.58) |
| Body mass index, mean (±SD) | 26.2 (4.2) | 26.1 (3.9) |
| Atrial fibrillation, n (%) | 15 (21) | 64 (85) |
| Hypertension, n (%) | 28 (39) | 34 (45) |
| Diabetes mellitus, n (%) | 2 (3) | 7 (9) |
| Dyslipidaemia, n (%) | 1 (1.4) | 1 (1.3) |
| Current smoking, n (%) | 7 (10) | 5 (7) |
| Beta-blocker, n (%)‡ | 27 (38) | 28 (37) |
| Angiotensin converting enzyme inhibitor, n (%)‡ | 24 (33) | 19 (25) |
| Amiodarone, n (%)‡ | 21 (29) | 21 (28) |
| Antiarrhythmics, n (%)† | 17 (24) | 9 (12) |
| Vitamin K antagonists, n (%)‡ | 54 (75) | 57 (76) |
| Acetylsalicylic acid, n (%) | 21 (29) | 22 (29) |
| Statin, n (%) | 26 (36) | 27 (36) |

*Symptoms prior to surgery are self-reported and include dyspnoea, angina pectoris, palpitations and decreased physical activity level.
†$Ca^{2+}$ antagonist or digoxin.
‡Medication status is at discharge and drawn from the electronic medical records.
EuroSCOREII, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

medically supervised in 69% and not medically supervised in 31%.

A total of 66 (92%) of the intervention group participated in the psycho-educational intervention, of whom 92% attended at least four consultations with 72% consultations face to face and mean time per consultation 39 min. Of the participants, 41 (62%) met the per-protocol definition of both the exercise and psycho-education.

At 6 months, among 26% of the control group participants the self-reported participation rate in rehabilitation was: at a general practitioner or cardiologist (2%), at Rigshospitalet (4%), at a local hospital (12%), or at municipal setting and other places (8%).

## DISCUSSION

This is the largest randomised trial including a heterogeneous group of patients after heart valve surgery to date to examine the impact of a comprehensive cardiac rehabilitation intervention. Our hypothesis was accepted in terms of the primary outcome and rejected regarding the secondary outcome: cardiac rehabilitation improved physical capacity at 4 months but did not affect the secondary outcome mental health or the exploratory outcomes. The intervention appeared reasonably safe although associated with a number of adverse events, and with relatively high adherence.

Our findings are in keeping with previous studies of physical exercise training being beneficial on $V0_2$ peak after heart valve surgery.[7 13 14 27 28] However, the optimal exercise programme remains unclear. It appears 12 weeks with exercise training combining aerobic and resistance training, three times weekly is appropriate to improve oxygen uptake but we cannot judge on the prognostic value of this effect.

When comparing the peak $VO_2$ data with reference values for a healthy population,[29] the baseline values of the trial population is not critically reduced. Even though the participants received a high dose of intervention of both interventions, we could not measure an improvement in any of the self-reported outcomes, health-related quality of life, anxiety and depression. We believe that there are several possible explanations for this finding.

First, we observed a spontaneous recovery following heart valve surgery in both physical capacity and all parameters of the self-reported outcomes including mental health for both the intervention and control group. The intervention did not seem to add further improvement, probably explained by the fact that most patients were asymptomatic before surgery. Second, it is possible that the intensity of the psycho-educational intervention was insufficient to positively impact on mental health or that the outcome measures did not capture a possible effect. Additionally, more detailed questionnaires, such as depression questionnaires, may have been needed.

To our knowledge, no previous trials have investigated the effect of psycho-education after heart valve surgery. We chose that nurses with specific clinical knowledge within patients after heart valve surgery, and not psychologists, should perform the intervention, in order to reflect real life, and allow for possible implementation of the intervention. Additionally, a nurse would be able to answer possible healthcare questions and refer to physician where needed, while there would be a risk that a psychologist might overlook clinical important issues. In studies with patients undergoing coronary artery bypass surgery, psycho-education interventions have exerted a positive effect on patients' level of depression, perception of fear and physical activity.[30] Based on our data, we cannot assess the effect and optimal dose of psycho-education after valve surgery. Therefore, more randomised clinical trials are needed to provide general recommendations.

Currently, the favourable effect of exercise-based cardiac rehabilitation on physical capacity in patients after valve surgery is now, including this trial, ascertained in three randomised controlled trials.[16] Taken together, the evidence points towards that cardiac rehabilitation including exercise training could be applied for the physical capacity benefit after valve surgery, but due to limited high-quality trials the evidence is yet inadequate to imply general clinical implications. Moreover, we observed a significant increase in the number of self-reported non-serious adverse events. Accordingly, the European guideline needs to be modified.

Participating in a cardiac rehabilitation programme is resource consuming with extensive involvement of professionals. In a healthcare system with limited funds for even life-threatening conditions, only interventions with good evidence backing should be applied. Therefore, before implementation of cardiac rehabilitation, proof of more beneficial effects on patient-relevant outcomes with the absence of evidence for major harms are needed. It is pivotal to identify those who profit from cardiac rehabilitation from those not because participating in exercise after heart valve surgery is not without risks of non-serious adverse events.[15] Further randomised clinical trials are needed to determine optimal screening strategies, and to demonstrate the long-term effects of cardiac rehabilitation on mortality and serious adverse events.

**Table 2** Physical tests results: means reported

| | Cardiac rehabilitation | | Control group | | | |
|---|---|---|---|---|---|---|
| | 1 month n=65 | 4 months n=63 | 1 month N=59 | 4 months n=52 | p Value* | p Value† |
| Cardiopulmonary exercise test | | | | | | |
| Log($VO_2$ peak) (mL/kg/min)‡ | 3.045 (21.0)§ | 3.212 (24.8) | 3.047 (21.1) | 3.114 (22.5) | 0.34 | 0.045 |
| Log(anaerobic threshold $VCO_2$) (L/min) | 0.236 (1.27) | 0.490 (1.63) | 0.256 (1.29) | 0.441 (1.55) | 0.76 | 0.23 |
| VE/$VCO_2$ slope | 27.3 | 26.6 | 27.3 | 25.2 | 0.94 | 0.15 |
| Log(Watt max) | 4.873 (131) | 5.072 (159) | 4.857 (129) | 4.990 (147) | 0.80 | 0.07 |
| SBP rest (mm Hg) | 140.6 | 141.7 | 135.2 | 138.7 | 0.10 | 0.51 |
| SBP max (mm Hg) | 191.4 | 201.8 | 188.5 | 195.2 | 0.56 | 0.39 |
| Heart rate rest | 78.4 | 69.7 | 77.0 | 70.4 | 0.57 | 0.47 |
| Heart rate max | 142.7 | 154.3 | 145.6 | 152.0 | 0.51 | 0.33 |
| Total exercise time (min) | 7.62 | 9.56 | 7.57 | 8.82 | 0.94 | 0.13 |
| 6-min walk test | | | | | | |
| Length (m) | 546.8 | 595.2 | 542.9 | 594.5 | 0.81 | 0.82 |
| Sit-to-stand test | | | | | | |
| Repetitions | 2.67 (14.4) | 2.82 (16.8) | 2.70 (14.9) | 2.83 (16.9) | 0.57 | 0.74 |
| NYHA class¶,** | | | | | | |
| I, n (%) | 48 (72) | 46 (78) | 53 (84) | 46 (89) | 0.69 | 0.59 |
| II, n (%) | 18 (27) | 12 (20) | 9 (14) | 6 (12) | | |
| III, n (%) | 1 (1) | 1 (2) | 1 (2) | 0 (0) | | |
| IV, n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | |

Results of mixed model analyses of exercise data. Test of main effect of intervention and of interaction between intervention and time. Mean estimates from the mixed model at 1 and 4 months are calculated.
AR(1), autoregressive; CS, compound symmetry; SP(pow), spatial power; UN, unstructured.
*Test for effect of intervention at time 1 (main effect of intervention in regression model) in mixed model and adjusted for LVEF.
†Interaction between intervention and time in mixed model and adjusted for LVEF.
‡The AIC was 82.2 (UN), 80.3 (CS), 80.3 (SP(pow)) and 80.3 (AR(1)). CS is chosen because of its simplicity.
§Some variables are skewed and therefore log-transformed to normalise the distribution. In these instances, the estimated means are back-transformed to the original scale using exp(x). These numbers are presented in the parentheses.
¶$\chi^2$-test whether NYHA class is different between group A and B at 1 month.
**$\chi^2$-test whether NYHA class is different between group A and B at 4 months.
LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; $VCO_2$, flow of carbon dioxide.

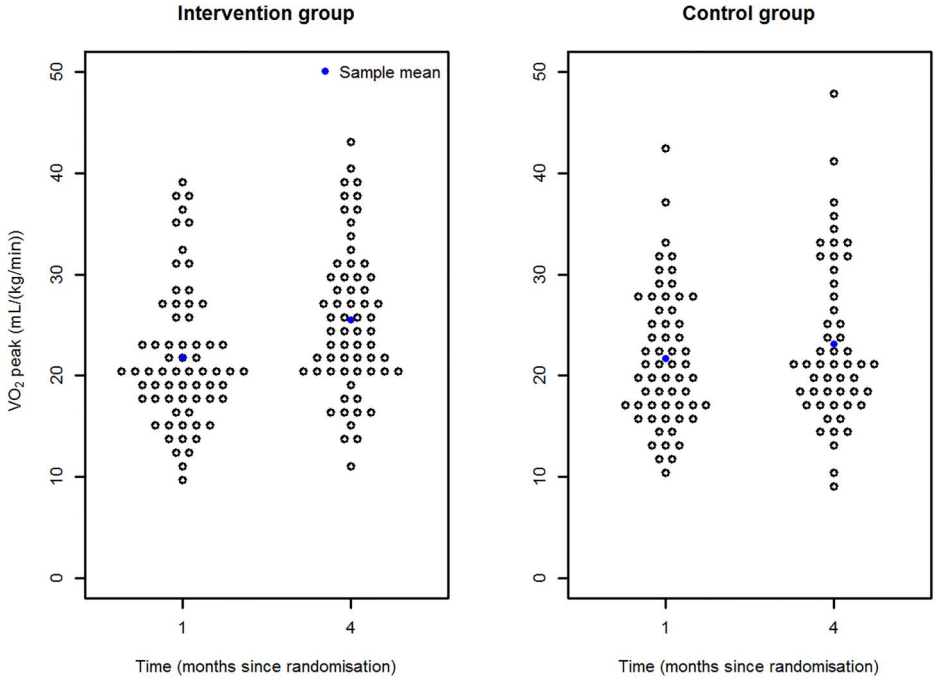


**Figure 2** $VO_2$ for groups by allocation group. Summary primary outcome ($VO_2$ peak) mean score of groups by allocation group by time in months.

## Strengths and limitations

We included consecutive patients in an unselected heart valve surgery population with a reasonable number of inclusion and exclusion criteria securing external validity. The trial applied central, stratified randomisation securing against selection bias, and blinded outcome assessment and blinded statistical analyses, reducing detection and interpretation bias. Only 147 of 546 eligible entered the trial, but all were analysed according to intention to treat.

**Table 3** Self-reported outcomes: means reported

| | Cardiac rehabilitation | | | | Control group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 1 month n=65 | 4 months n=66 | 6 months n=64 | Baseline | 1 month N=61 | 4 months n=58 | 6 months n=58 | p Value* | p Value† |
| Short Form-36 | | | | | | | | | | |
| Mental Component Scale | 49.4 | 50.4 | 54.9 | 53.7 | 49.8 | 50.2 | 54.0 | 55.2 | 0.89 | 0.40 |
| Physical Component Scale | 41.0 | 40.0 | 50.1 | 50.9 | 40.2 | 39.5 | 50.6 | 51.8 | 0.95 | 0.71 |
| Bodily Pain Index | 65.5 | 61.5 | 86.2 | 88.0 | 64.3 | 62.0 | 85.0 | 88.0 | 0.87 | 0.98 |
| General Health Perception | 69.8 | 70.1 | 73.6 | 74.6 | 71.0 | 71.7 | 77.4 | 76.9 | 0.39 | 0.82 |
| Mental Health Index | 71.7 | 78.5 | 83.5 | 83.6 | 71.7 | 77.3 | 84.9 | 85.3 | 0.82 | 0.81 |
| Physical Functioning Index | 68.3 | 71.1 | 86.9 | 89.2 | 63.5 | 68.1 | 87.8 | 89.7 | 0.51 | 0.31 |
| Role Emotional Index | 71.1 | 57.1 | 85.9 | 83.0 | 67.6 | 56.7 | 78.4 | 88.1 | 0.71 | 0.46 |
| Role Physical Index | 30.0 | 20.9 | 73.8 | 73.1 | 29.6 | 17.1 | 72.4 | 82.7 | 0.83 | 0.34 |
| Social Functioning Index | 75.2 | 78.1 | 92.2 | 92.4 | 73.8 | 74.4 | 89.6 | 93.8 | 0.54 | 0.75 |
| Vitality Index | 49.1 | 53.8 | 72.1 | 69.3 | 50.7 | 54.5 | 74.1 | 74.6 | 0.41 | 0.68 |
| HeartQoL | | | | | | | | | | |
| HeartQoL physical | 1.36 | – | – | 2.57 | 1.27 | – | – | 2.63 | 0.84 | 0.33 |
| HeartQoL emotional | 1.98 | – | – | 2.59 | 1.91 | – | – | 2.70 | 0.84 | 0.24 |
| HeartQoL global | 1.54 | – | – | 2.58 | 1.45 | – | – | 2.65 | 0.92 | 0.24 |
| HADS | | | | | | | | | | |
| HADS-A≥8, n (%) | 18 (25) | 9 (14) | 11 (17) | 8 (12) | 13 (20) | 6 (10) | 5 (8) | 6 (10) | 0.23 | 0.85 |
| HADS-D≥8, n (%) | 2 (3) | 4 (6) | 3 (5) | 4 (6) | 5 (8) | 4 (7) | 2 (3) | 2 (4) | 0.92 | 0.57 |

Results of mixed-model analyses of patient-reported outcomes. Test of main effect of intervention and of interaction between intervention and time. Mean estimates from the mixed model at 0, 1, 4 and 6 months are calculated.
*Test for effect of intervention at time 0 (main effect of intervention in regression model) in mixed model adjusted for left ventricular ejection fraction (LVEF).
†Interaction between intervention and time in mixed model adjusted for LVEF at 4 months.

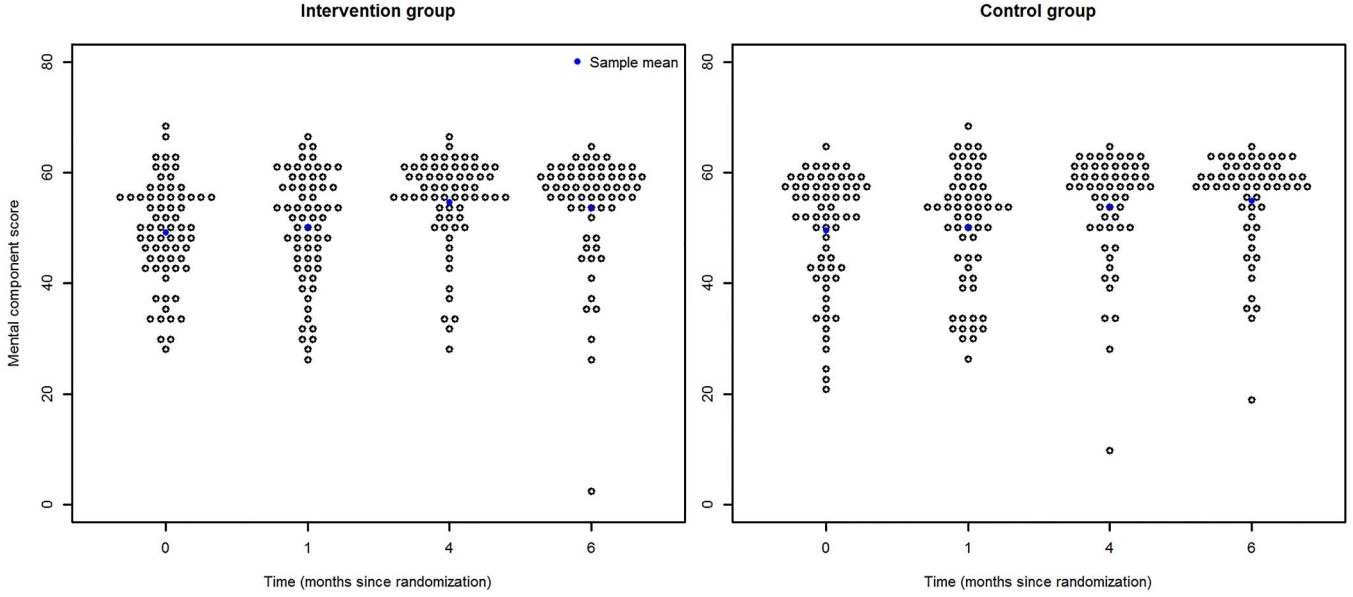


**Figure 3** Mental health scores for groups by allocation group. Summary secondary outcome (mental health scores) for groups by allocation group by time in months.

The trial has limitations and we were not able to reach our sample size target. Based on the accrued sample, the trial statistical power for the primary and secondary outcome remained above 80%. However, that 26% of control patients participated in cardiac rehabilitation which may have reduced the between group difference such that we were able to demonstrate a statistically significance. Further, this was a single-centre trial in Danish patients and due to the low rate of study participation, our results may not generalisable to general population of heart valve surgery patients. The trial lacks preoperative physical and mental health data. Another constraint was the imperfect adherence to the intervention and the risk, however small, of training heterogeneity due to the different options for training locations. Trials investigating a rehabilitation programme as such imply certain limitations. Importantly, the trial was unblinded for patients and staff. Applying physical exercise and physical testing has limitations such as time-of-day and day-to-day variation. However, during evaluation of physical tests, all researchers were blinded to the allocation group. Further, there might be selection bias as only highly selected individuals accept

**Table 4** Adverse events from patient-reported questionnaire

| Adverse events | Intervention group (11 patients) | Control group (3 patients) | Total events (16 events) |
|---|---|---|---|
| Repetitive pericardial effusion | 1 | | 1 |
| Palpitations/heavy heart beat several days after training | 1 | | 1 |
| Dyspnoea after training | 1 | | 1 |
| Symptoms of thromboembolism | 1 | 1 | 2 |
| Chest pain | 2 | 1 | 3 |
| Musculoskeletal injuries | 7 | 1 | 8 |

participation. We find this a general bias in rehabilitation research which also emphasises new research focusing on socially differed rehabilitation according to psychosocial problems (not one size fits all).

Participating in a clinical trial with a comprehensive programme might exert an effect on the physical and mental health due to extensive contact with health professionals. A major concern is that the control group might have received different interventions at the local hospitals, which might diminish the impact of our experimental intervention.

Self-reported outcomes are by nature subjective and therefore likely biased with a risk of recall bias. Nonetheless, the patients answered questionnaires independently of the researchers and all questionnaires were distributed electronically. All data management was handled independently of the researchers who interpreted data.

## Key messages

**What is already known on this subject?**
Cardiac rehabilitation (CR) is recommended as treatment modality for patients with cardiac disease. However, data from randomised controlled trials regarding the effect of CR in patients with heart valve surgery are almost non-existent and comprise only two trials to date. The effect of CR in these patients therefore remains uncertain.

**What might this study add?**
This is the largest randomised clinical trial to date investigating the effect of a comprehensive CR programme after heart valve surgery. We found evidence of superiority in favour of CR compared with control in terms of physical capacity at 4-months follow-up but no effect on mental health. Further, this is the first randomised trial to systematically evaluate self-reported non-serious adverse events and serious adverse events of a CR invervention after heart valve surgery.

**How might this impact on clinical practice?**
These data demonstrate that CR with physical exercise should be offered after valve surgery but planned individually in order to the patients' individual needs with close medical follow-up. Further well-conducted randomised clinical trials assessing both short-term and long-term benefits and harms of CR are needed.

## CONCLUSIONS

The CopenHeart$_{VR}$ trial demonstrated that compared with control, cardiac rehabilitation after heart valve surgery slightly improved physical capacity in the short term but did not seem to improve mental health. The intervention was associated with a relatively high level of adherence. However, further randomised clinical trials assessing both short-term and long-term benefits and harms are needed.

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**Acknowledgements** First of all, we thank the 147 participants. We thank physiotherapists Helena Tjalk-Bøggild, Lars Tang, Signe Gils, Graziella Zangger and Katrine Thingholm Erhardsen for training the patients and Camilla Larsen and Bettina Højbjerg Kirk for conducting the psycho-educational intervention. Thanks to Karina Gregersen Jensen for assisting with exercise testing, to Kim Mechta Nielsen and Albert Navne for contribution to trial enrolment and administration, and to Trine Madsen for assistance with data management.

**Contributors** A-DZ, SKB, KLS, LK, CH, CG, JL and JPS designed the trial and developed the protocol. KLS in collaboration with A-DZ and SKB drafted the manuscript. SSR and TBR contributed significantly during this process. LCT, RST and KLS designed and drafted the statistical analysis plan, LCT performed the statistical analyses for the primary and secondary outcomes, KLS performed all other statistical analyses. LT in collaboration wih A-DZ, SKB and KLS designed the physical exercise intervention. TBH and PPJ contributed significantly during data collection. KLS, SKB, TBH, TBR, SSR, LT, PPJ, CH, LK, CG, LCT, JL, JPS, RST and A-DZ all revised the manuscript critically. All authors have given their final approval of the version to be published.

**Funding** The Danish Strategic Research Foundation (10-092790); The Heart Centre Research Council, Rigshospitalet; Familien Hede Nielsen Foundation (2013-1226); The National Institute of Public Health, University of Southern Denmark; and Region Zealand Health Research Foundation, Denmark (12-000095/jun2014). The funders had no influence on the trial design, the execution of the trial or the interpretation of data.

**Competing interests** None declared.

**Patient consent** Obtained.

**Ethics approval** The Danish Ethics Committee (protocol no: H-1-2011-157) and The Danish Data Protection Agency (j. no 2007-58-0015).

**Provenance and peer review** Not commissioned; externally peer reviewed.

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Heart

# Cardiac rehabilitation increases physical capacity but not mental health after heart valve surgery: a randomised clinical trial

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*Heart* 2016 102: 1995-2003 originally published online August 4, 2016
doi: 10.1136/heartjnl-2016-309414