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Handgrip exercise in patients scheduled for cardiac surgery to attenuate troponin release: a feasibility study

Handgrip exercise in patients scheduled for cardiac surgery to attenuate troponin release: A feasibility study

Short running head: Handgrip exercise to attenuate cardiac troponin-T release

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Abstract

Background. Cardiac surgery, including surgical aortic valve repair (SAVR) and coronary artery bypass grafting (CABG), are associated with ischaemia-reperfusion (IR)-injury. Single bouts of exercise, including handgrip exercise, may protect against IR-injury. This study explored **(I)** the feasibility of daily handgrip exercise in the week prior to SAVR and/or CABG, and **(II)** its impact on cardiac IR-injury, measured as postoperative cardiac troponin-T (cTnT) release.

*Methods and Results***.** Sixty-five patients undergoing elective SAVR and/or CABG were randomised to handgrip exercise + usual care (intervention, *n*=33) or usual care alone (control, *n*=32). Handgrip exercise consisted of daily 4x5-min handgrip exercise (30% maximal voluntary contraction) for 2-7 days prior to cardiac surgery. Feasibility was assessed using validated questionnaires. Postoperative cTnT release was assessed at 0-6-12-18-24h (primary outcome area-under-the-curve ($cTnT_{AUC}$)). Most patients (93%) adhered to handgrip exercise and 77% was satisfied with this intervention. Handgrip exercise was associated with lower $cTnT_{AUC}$ (402,943±225,206 *versus* 473,300±232,682 ng*min/L), which is suggestive for a medium effect size (Cohen's D 0.31), and lower $cTnT_{peak}$ (313 [190 – 623] *versus* 379 [254 – 699] ng/L) compared to controls.

Conclusions. We found that preoperative handgrip exercise is safe and feasible for patients scheduled for SAVR and/or CABG, and is associated with a medium effect size to reduce postoperative cardiac IR-injury. This warrants future studies to assess the potential clinical impact of exercise protocols prior to cardiac surgery.

Keywords

Handgrip exercise; exercise preconditioning; ischaemia-reperfusion injury; elective cardiac surgery

Word count: 223

Introduction

Surgical aortic valve replacement (SAVR) and/or coronary artery bypass grafting (CABG) procedures are highly common in contemporary medicine. During these surgical procedures, cardiac ischaemia occurs during aortic cross-clamping. Subsequently, upon release of the cross-clamp, the blood flow is restored. Paradoxically, this rapid reintroduction of blood flow can cause additional injury to the myocardium and vascular cells(1). The magnitude of this so-called ischaemia-reperfusion (IR)-injury strongly relates to post-surgical risk of mortality and morbidity(2). Other than ensuring timely reperfusion after cardioplegic arrest, currently no strategy effectively reduces IR-injury.

Previous work revealed that ischaemic preconditioning, *i.e.,* repeated, short-term ischaemia, reduces IR-injury(3, 4). However, these cardioprotective effects seem attenuated with certain types of anaesthesia, in those with cardiovascular disease, and with older age(3, 5, 6). Interestingly, exercise exerts an array of effects, including inducing local ischaemia(7). Studies in animals showed that exercise is associated with less IR-injury in healthy(8, 9), but also in senescent(10, 11) and obese animals(12). In humans, high-intensity exercise protects against IR-injury in healthy volunteers(13) and in older individuals(14), whilst regular cycling exercise attenuates IR-injury in heart failure patients(15). In the context of cardiac surgery, whole-body and/or high-intensity exercise are often contra-indicated preoperatively. We recently explored the effects of local handgrip exercise, which causes minimal cardiac load(16), and observed immediate downregulation of pro-inflammatory proteins in patients with cerebral small vessel disease(17). Moreover, we found handgrip exercise to provide (remote) protection against vascular IR-injury in healthy men(18). Therefore, handgrip exercise may be suitable for patients within the home-based setting prior to undergoing elective SAVR and/or CABG. To assess this hypothesis, the aim of this study is to explore **(I)** the feasibility of handgrip exercise prior to elective cardiac surgery, and **(II)** the release of postoperative markers of cardiac (IR) injury.

Methods

Participants and design

The study was conducted in accordance with the Declaration of Helsinki and approved by the local Medical Ethics Review Committee (CMO Arnhem-Nijmegen). This explorative pilot study was prospectively registered under NL8583 on the International Clinical Trial Registry Platform and is reported according to the CONSORT reporting guidelines. In this single centre, randomised, controlled study we included patients that were scheduled for elective primary SAVR and/or CABG in the Radboud University Medical Center between August 2020 and March 2022. The inclusion criteria were age ≥18 years, mentally able to give informed consent and good understanding of the Dutch language. The exclusion criteria were previous cardiac surgery, polyneuropathy, and inability to perform handgrip exercise.

After providing informed consent, patients were stratified for sex and surgical procedure (SAVR, CABG or SAVR+CABG) and randomised to handgrip exercise + usual care (intervention) or usual care alone (control) using Castor Electronic Data Capture (Castor EDC, v2023.1.0.1, Amsterdam, the Netherlands). Following surgery, patients were requested to fill in questionnaires to evaluate feasibility and blood was drawn as part of routine clinical practice to evaluate cardiac troponin-T (cTnT).

Intervention

Usual care. Usual care consisted of a standard pre-surgical outpatient clinic visit three months prior to cardiac surgery and included blood tests, electrocardiogram, and visiting the anaesthesiologist and cardiothoracic surgeon.

Handgrip exercise. Patients were educated for handgrip exercise during their pre-surgical visit. Maximal voluntary contraction (MVC) was assessed by three efforts of maximal handgrip force (in kg) with the dominant arm, separated by one minute of rest. The maximum value was used to determine MVC. Handgrip exercise consisted of 4x5-minutes exercise, separated by 5 minutes rest ***(Supplemental figure 1)***, which is in line with previous handgrip exercise protocols(17, 18). Handgrip exercise was performed at 30% MVC, which causes local ischaemia during exercise(16), with a dynamic 1 second contraction: 1 second relaxation cycle (frequency of 0.5 Hz). Handgrip was performed by the dominant or non-dominant arm, based on personal preference of the patient. Patients were allowed to switch between arms on subsequent days. Patients were instructed to start handgrip exercise once surgery was scheduled, with a maximum of 8 days and minimum of 2 days prior to surgery. The last handgrip exercise was planned on the day of surgery. To facilitate training at home, patients received an instruction video to coach handgrip training frequency, using a metronome, and training duration.

Measurements

Patients' characteristics were collected at the first study visit. Physical activity level was assessed using the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH), which is a commonly used questionnaire to assess physical activity with respect to occupation, leisure time, and other daily activities. Habitual activity level is assessed by the metabolic equivalent of task (MET-)score as MET-hours/week(19). Feasibility of home-based handgrip exercise was assessed using an adjusted System Usability Scale (SUS) questionnaire(20), with a maximum of 40 points. Post-surgery, venous blood samples were collected 6-hourly in the first 24 hours and sent to the local laboratory to determine cTnT-levels (in ng/L). CTnT area-under-the-curve (AUC) was calculated according to the trapezoidal method. Linear interpolation was used if values at T12h or T18h were missing. For cTnT analyses, patients who did not perform handgrip exercise ≥2 days(9) were excluded from analysis. Post-surgery major adverse cardiovascular events (MACE) were collected during the initial hospital stay and included cerebrovascular events, myocardial infarction, acute kidney injury and death.

Statistical analysis

Given the explorative nature of the study, descriptive statistics were used. Categorical data are presented as frequencies and percentages. Continuous data are presented as mean ± standard deviation or median [interquartile range]. For our primary analysis, we tested feasibility of handgrip exercise using the SUS questionnaire with "acceptable feasibility" being classified as a score of ≥28. For our secondary research question, we evaluated cardiac IR-injury by measuring cTnT, with postoperative $cTnT_{AUC}$ as our primary parameter. We assessed effect size using Cohen's D, with classification of the effect size being no (d<0.1), small (0.1≤d<0.3), medium (0.3≤d<0.7) and large (≥0.7)(21). Secondary objectives are $cTnT_{peak}$, intensive care and hospitalisation duration, and MACE during hospitalisation. Association between variables was assessed by Pearson's R. All analyses were performed using SPSS statistics (IBM SPSS Statistics version 27).

Results

In total, 77 patients were included and randomised ***(Figure 1).*** A total of 12 patients dropped out due to change in procedure (*e.g.,* CABG to percutaneous coronary intervention, *n*=9), acute hospitalisation (*n*=2), or conservative management (*i.e.,* no surgery, *n*=1). This resulted in 65 patients; 33 were allocated to intervention and 32 to control. Mean age was 67 years and 85% was male ***(Table 1).***

Handgrip exercise. Due to rescheduled surgery, 3 patients were unable to perform handgrip exercise, resulting in 30 patients who performed handgrip exercise. Variation in training duration was primarily related to rescheduled or postponed surgery (*e.g.,* availability intensive care units due to COVID-19), both being unrelated to the patient or intervention.

Feasibility. Two patients (7%) prematurely terminated handgrip exercise because they experienced the training too demanding. Patients performed a median of 5 [2-7] days of handgrip exercise prior to surgery. Most patients (82%) performed the last handgrip exercise bout within 24 hours prior to surgery, with 9 (32%) patients performing handgrip exercise <12 hours prior to surgery. In total, 26 patients (87%) filled in feasibility questionnaire ***(Table 2)***. Reasons for not filling in the questionnaire were post-surgery cerebrovascular event (*n*=1), withdrawal of participation (*n*=1), and lost to follow-up due to hospital transfer (*n*=2). The average satisfaction score was 30±5, with 77% of patients demonstrating a score of ≥28. A total of 69% would recommend handgrip exercise to someone else. Satisfaction score was not associated with baseline physical activity level (Pearson's R=0.07) or MVC (Pearson's R=0.11).

Cardiac troponin-T. Six patients randomised to the intervention group (18%) were excluded for cTnT analyses because of inability to perform handgrip exercise (n=3) or training duration <2 days (n=3). Due to missing cTnT-values at T24h, we excluded 14 patients (24%) for $cTnT_{AUC}$ analysis. $CTnT_{AUC}$ was 402,943±225,206 ng*min/L in the intervention group (n=22) and 473,300±232,682 ng*min/L in the control group (n=23) (AUC $ratio_{handgrip/control}$ 0.851), resulting in a standardised difference of 0.31 (Cohen's D 0.31, 95% confidence interval -0.28-0.89) ***(Figure 2A)***. $cTnT_{peak}$ was 313 [190-623] ng/L in the intervention group (n=27) and 379 [254-699] ng/L in the control group (n=32) ***(Figure 2B)***. We found comparable effects between shorter (≤5 days) *versus* longer (>5 days) handgrip exercise for $cTnT_{AUC}$ (398,750±198,682 *versus* 407,135±258,832 ng*min/L) and $cTnT_{peak}$ (373 [182-656] *versus* 304 [233-591] ng*min/L).

Hospitalisation and MACE. We found no differences between intervention and control group for intensive care (1.2±0.9 *versus* 1.2±0.5 days) or hospital stay (7.6±2.8 *versus* 7.9±2.7 days). Furthermore, MACE was observed in two patients who performed handgrip exercise and in one patient in the control group (n=2 *versus* n=1).

Discussion

Our aim was to explore the feasibility of daily handgrip exercise prior to elective SAVR and/or CABG and to evaluate its impact on postoperative cTnT-release. First, we found that 28 out of 30 patients were able to successfully perform daily, home-based handgrip exercise training. Moreover, the handgrip exercise training was classified as feasible, and patients were satisfied with the intervention. Second, we observed a medium effect size of handgrip exercise training prior to elective cardiac surgery, leading to a smaller postoperative $cTnT_{AUC}$ compared to usual care. These results support future studies to explore the potential effects of (handgrip) exercise prior to cardiac surgery to reduce cardiac IR-injury.

We found that most of our patients were able to adhere to the handgrip exercise protocol prior to elective cardiac surgery, with only two patients (7%) who dropped out because they classified handgrip exercise being too demanding. The high adherence is in agreement with previous studies that performed handgrip exercise in comparable populations(22, 23). We also found that satisfaction with handgrip exercise was not associated with a priori physical activity level or maximal handgrip strength. This suggests that handgrip exercise is also feasible for physically inactive participants and/or those with low handgrip strength (*e.g.,* frail patients). Moreover, previous studies revealed that handgrip exercise is low risk for injuries or complications and cardiac load is limited(16). Indeed, we also did not observe any adverse events related to handgrip exercise. These findings suggest that handgrip exercise prior to cardiac surgery is both safe and feasible.

It is well known that regular physical activity has cardioprotective effects (24, 25). An active lifestyle improves outcomes of patients with an acute myocardial infarction(26). However, besides the benefits of regular exercise, previous pre-clinical observations propose cardioprotection after short-term exercise. More specifically, short-term exercise is associated with a significantly lower infarct size in various animal models (9, 27). In humans, short-term exercise attenuated IR-injury induced peripheral vascular dysfunction. Importantly, these exercise protocols are mainly based on whole-body and/or moderate-to-high intensity cycling(9), which is not always feasible or safe in patients scheduled for cardiac surgery. Alternatively, local handgrip exercise has already shown favourable effects on inflammatory biomarkers(17) and shows protective effects against vascular IR-injury in healthy men(18). The cardioprotective effects of handgrip exercise have so far not been explored. As our home-based handgrip exercise has shown to be feasible, handgrip exercise may be a suitable alternative for patients undergoing elective SAVR and/or CABG.

To better understand the clinical potential of handgrip exercise, we explored the impact of handgrip exercise on postoperative cTnT-levels. Based on the explorative nature of this study, we refrained from performing parametric statistical analyses, but evaluated the effect size using Cohen's D. For our primary outcome parameter $cTnT_{AUC}$, we found a standardised difference of 0.31, which is suggestive for a medium effect size(21). Evaluating effect sizes are a useful tool for explorative studies to better understand the potential effect (and associated variation) one can expect, and to correctly power future, randomised, controlled trials. A medium effect size corresponds to future trials with a sample size of 34-176 patients per study arm(21), with our effect size of 0.31 being related to the upper end of this spectrum of sample sizes. Previous randomised, controlled trials examining ischaemic preconditioning prior to cardiac surgery reported comparable $cTnT_{AUC}$ ratios (0.629-0.898 *versus* 0.851 for our study) and included 45-811 participants per study arm(28-30). Those studies showed that ischaemic preconditioning reduced the risk of peri-operative myocardial infarction ($cTnT_{AUC}$ ratio 0.629)(28), reduced the incidence of postoperative atrial fibrillation and acute kidney injury, and reduced the intensive care unit stay ($cTnT_{AUC}$ ratio 0.744)(29), whilst these difference were not observed with $cTnT_{AUC}$ ratio 0.898(30). Our $cTnT_{AUC}$ ratio, induced by exercise preconditioning, falls within this range and therefore could support the potential for clinically relevant outcomes in sufficiently powered studies.

Timing of the last exercise bout may be of importance, as exercise seems to induce immediate effects, which disappear within 1-2 hours, but re-emerge 18-24 hours following exercise(31). For logistic reasons, we have not focused on the acute effects of exercise in the present study. Therefore, potential effects pertaining to handgrip exercise on $cTnT_{AUC}$ should be ascribed to the later effects, or to the summative effects of repeated handgrip exercise leading to early adaptations. Whether handgrip exercise performed within 1-2 hours prior to surgery leads to additional benefits, is currently unknown.

This could be considered for future studies, especially since we observed no potentially detrimental acute effect of handgrip exercise in this population.

Our study population consisted of older individuals with cardiovascular risk and/or comorbidities. Since cardiovascular risk factors interfere with the efficacy of ischaemic preconditioning(3, 5, 6), these factors may potentially interfere with the efficacy of exercise. In contrast to ischaemic preconditioning, exercise-induced cardioprotective effects were observed in animals with increased age and obesity(10-12). The stimulus of exercise may be distinct from ischaemic preconditioning, whilst various factors may affect the exercise stimulus (*e.g.,* mode, intensity and/or frequency). Previous studies on exercise reported a higher effect of high-intensity exercise compared to moderate-intensity, which may relate to presence and magnitude of local ischaemia(9). Within the context and associated limitations of exercise prior to cardiac surgery, increasing the intensity(18) and/or volume(17) of handgrip exercise may potentiate its effects to attenuate IR-injury. In an attempt to increase muscle volume, previous work found that 4x5-minutes 'squats' (repeated sitting-standing in a chair) also successfully prevented IR-injury in middle-aged participants with increased cardiovascular risk(32). These data support exploring alternative exercise strategies, involving higher (muscle) volume and/or intensity, to evaluate the potential benefit of exercise.

Limitations. This explorative pilot study has some limitations. The study sample included more male than female participants. However, this relates to the clinical population as more CABG and SAVR procedures are performed in male compared to female patients(33, 34). Due to the COVID-19 pandemic, several elective cardiac surgeries were rescheduled according to intensive care availability, often resulting in <7 training days. However, analysis revealed no differences in $cTnT_{AUC}$ between ≤5 and >5 training days, suggesting that benefits may be present within 5 days of handgrip exercise. A third limitation is that we relied on self-reported adherence. Another limitation is that cTnT-measurements (at 18h or 24h) were missing in some patients. Nonetheless, we found comparable effect sizes for $cTnT_{AUC}$ and $cTnT_{peak}$, suggesting that missing data have not importantly affected our main observations.

In conclusion, our findings suggest that 2-7 day handgrip exercise prior to elective cardiac surgery is safe and feasible. Moreover, we found that handgrip exercise is associated with a medium effect size for the presence of smaller $cTnT_{AUC}$-levels compared to controls. These results warrant further exploration of the potential clinical effects of handgrip exercise prior to elective cardiac surgery in a larger sized study. Importantly, even when only a "small effect size" will be found, one should consider the feasibility, simplicity, low patient burden, and low-cost nature of handgrip exercise for (vulnerable) patients. In addition, variation in the intensity and/or frequency of exercise may further assist in exploring the potential benefits.

Statements & Declarations

Funding

Not applicable.

Conflicts of Interest

None declared.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Hartman, Konijnenberg, and Dinnissen. The first draft of the manuscript was written by Konijnenberg and Hartman, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local Medical Ethics Review Committee (CMO Arnhem-Nijmegen).

Informed consent

Written informed consent was obtained from all individual participants included in the study.

Data availability

The data underlying this article are available in the article.

Figure legends

Fig 1 CONSORT diagram. AUC, area under the curve; cTnT, cardiac troponin T

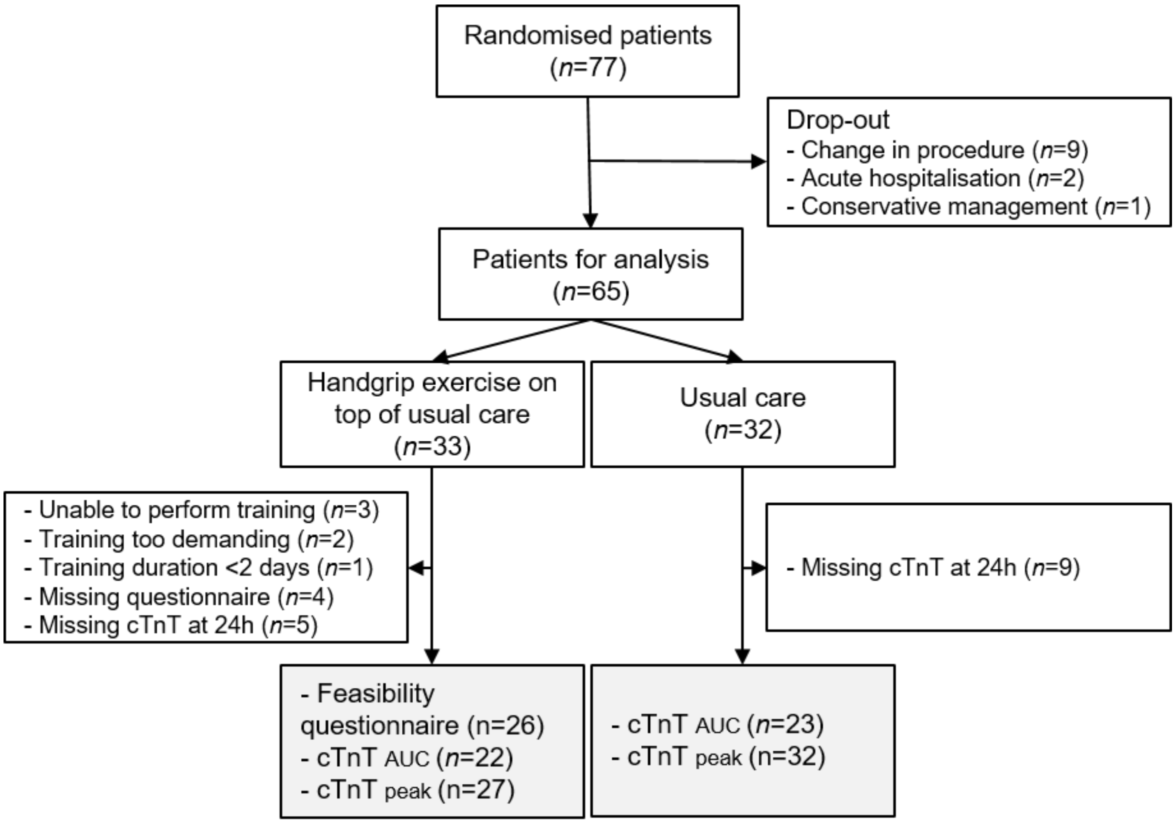
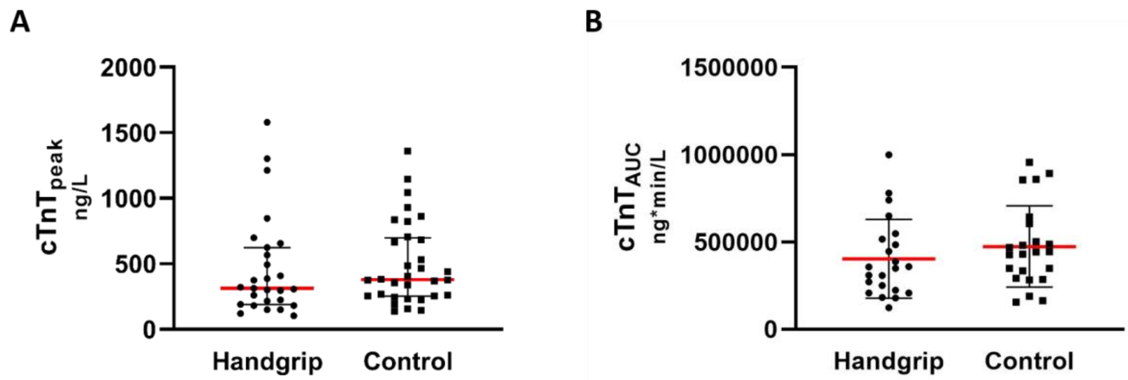


Fig 2 Postoperative peak and area under the curve for cardiac troponin-T for handgrip exercise and control. A) cardiac troponin-T peak (in ng/L) for both groups (handgrip exercise, n=27; control, n=32), with median (red) and interquartile range. **B)** cardiac troponin-T area under the curve (in ng*min/L) for both groups (handgrip exercise, n=22; control, n=23), with mean (red) and standard deviation. AUC, area under the curve; cTnT, cardiac troponin T



Supplemental Fig 1 Overview of study design. After written informed consent, handgrip strength was measured and physical activity was assessed using the SQUASH questionnaire. The handgrip training consisted of daily 4x5-min handgrip exercise separated by 5-min rest. After cardiac surgery, handgrip exercise satisfaction, cardiac troponin-T and cardiovascular events during initial hospitalisation were assessed.

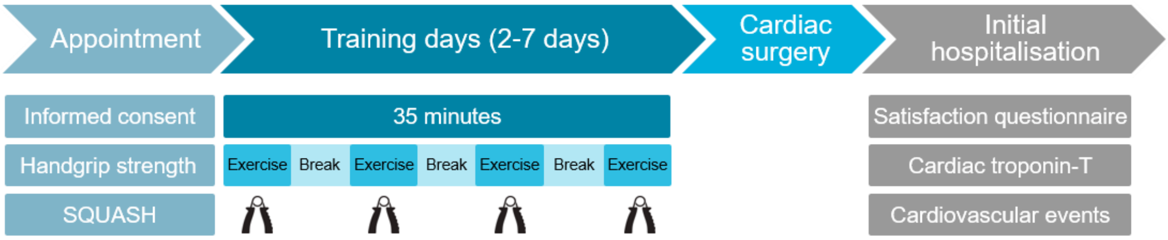

Appointment
Training days (2-7 days)
Cardiac surgery
Initial hospitalisation
Informed consent
Handgrip strength
SQUASH
35 minutes
Exercise
Break
Exercise
Break
Exercise
Break
Exercise
Satisfaction questionnaire
Cardiac troponin-T
Cardiovascular events

Table 1. Baseline characteristics

	Handgrip exercise (*n*=33)	**Control (*n*=32)**
Patient characteristics		
Age, years	67.1±7.0	66.0±7.8
Men, n (%)	27 (82)	28 (88)
BMI, kg/m^2	27.7±3.8	27.4±3.9
Previous arterial disease, n (%)		
TIA	4 (12.1)	2 (6.3)
CVA	2 (6.1)	1 (3.1)
PCI	5 (15.2)	5 (15.6)
Myocardial infarction	5 (15.2)	6 (18.8)
Peripheral artery disease	8 (24.2)	1 (3.1)
Diabetes Mellitus, n (%)	4 (12.1)	5 (15.6)
Hypercholesterolaemia, n (%)	17 (51.5)	15 (46.9)
Hypertension, n (%)	22 (66.7)	18 (56.3)
Smoking, n (%)		
No	5 (15.2)	10 (31.3)
Active	5 (15.2)	1 (3.1)
Former	23 (69.7)	21 (65.6)
Chronic Kidney Disease, n (%)	2 (6.1)	3 (9.4)
Atrial Fibrillation, n (%)	4 (12.1)	3 (9.4)
Systolic blood pressure, mmHg	148±18	142±20
Diastolic blood pressure, mmHg	80±9	77±11
Heart rate, beats/min	72±15	66±11
Left ventricular ejection fraction, n (%)		
Normal	25 (75.8)	25 (78.1)
Mildly abnormal	4 (12.1)	2 (6.3)
Moderately abnormal	4 (12.1)	4 (12.5)
Severely abnormal	0 (0)	1 (3.1)
Maximal voluntary contraction, kg	32±11	36±11
Relevant medication		
Beta-blocker	18 (54.5)	17 (53.1)
ACE-inhibitor or ARB	18 (54.5)	20 (62.5)
Physical activity		
SQUASH, MET-hours/week	77 [47-113]	96 [36-131]

Handgrip exercise duration, days	5 [2-7]	Not applicable
Cardiac surgery		
Surgery procedure, n (%)		
SAVR	13 (39.4)	10 (31.3)
CABG	15 (45.5)	16 (50.0)
Number of anastomoses	3.5±1.0	3.3±1.1
SAVR + CABG	5 (15.2)	6 (18.8)
Number of anastomoses	2.2±1.6	1.8±1.0
Duration of surgery, h:m	3:22±0:53	3:39±1:06
Extracorporeal circulation time, h:m	1:45±0:35	1:50±0:45
Aortic cross-clamp time, h:m	1:07±0:28	1:14±0:33
Type of cardioplegia		
Cold custodiol	15 (45.5)	17 (53.1)
Warm blood	18 (54.5)	15 (46.9)
Type of anaesthesia, n (%)		
Midazolam	7 (21.2)	12 (37.5)
Midazolam + propofol	5 (15.2)	4 (12.5)
Midazolam + sevoflurane	18 (54.5)	11 (34.4)
Midazolam + propofol + sevoflurane	3 (9.1)	5 (15.6)

Values are presented as mean ± standard deviation, median [interquartile range], or absolute number (%). ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; MET, metabolic equivalent of task; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve repair; SQUASH, Short Questionnaire to Assess Health-enhancing physical activity; TIA, transient ischaemic attack

Table 2: Experiences with handgrip exercise					
	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I enjoyed performing the handgrip training regularly	3.8%	0%	42.3%	34.6%	19.2%
I found the handgrip training easy to use	3.8%	3.8%	3.8%	46.2%	42.3%
I think I need a coach to perform the handgrip training properly	46.2%	26.9%	11.5%	7.7%	7.7%
I can imagine that most people quickly learn how to use the training	0%	0%	3.8%	53.8%	42.3%
I felt comfortable with the training	0%	3.8%	11.5%	50.0%	34.6%
I had to learn a lot before I could start training	46.2%	30.8%	0%	19.2%	3.8%
I found the instruction letter clear	0%	0%	7.7%	61.5%	30.8%
I found the coaching useful	3.8%	0%	53.8%	38.5%	3.8%
In general, I am satisfied with the training	3.8%	0%	3.8%	73.1%	19.2%
I would recommend the training to someone else.	0%	0%	30.8%	50.0%	19.2%

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