CHAPTER 2

Significant improvements in preoperative aerobic fitness following a home-based bimodal prehabilitation program in high-risk patients scheduled for liver or pancreatic resection

Submitted

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ABSTRACT

Objective: To evaluate changes in preoperative aerobic fitness during a 4-week home-based high-intensity interval training program with nutritional support performed by high-risk patients scheduled for elective liver or pancreatic resection.

Summary background data: Exercise prehabilitation can reduce postoperative complications following intra-abdominal surgery. Patients prefer to train in a home-based setting that might improve adherence. The ability of these programs to preoperatively improve aerobic fitness are yet to be evaluated.

Methods: Using a pretest-posttest design, high-risk patients (oxygen uptake [VO_2] at the ventilatory anaerobic threshold (VAT) ≤11 mL/kg/min) participated in a 4-week semi-supervised home-based exercise program (12 sessions in total) in this multicentre study. The program consisted of individualised goal setting followed by titration of high-intensity interval training and moderate-intensity endurance interval training on an advanced cycle ergometer, combined with functional task exercises and protein and vitamin/mineral supplementation. Preoperative changes in aerobic fitness, quality of life, and patient satisfaction with the program were evaluated.

Results: Twenty-six patients participated (recruitment rate 68.4%). After the prehabilitation program, a mean ± SD improvement in VO_2 at the VAT of 1.7 ± 1.1 mL/kg/min was measured, indicating a 17.8% improvement (95% confidence interval −2.23 to −1.15; $P<0.001$). Peak oxygen uptake improved by 2.4 ± 1.4 mL/kg/min, representing a 17.2% increase ($P=0.001$). No statistical difference in quality of life was observed. Overall, patients were satisfied.

Conclusion: Patients with a high-risk profile for postoperative complications were able to substantially improve their aerobic fitness during their preparation for liver and pancreatic surgery via this home-based bimodal prehabilitation program.

Trial registration: Medical Ethics Committee of Twente, Enschede, The Netherlands (NL59702.044.16, April 21, 2017); Netherlands Trial Register (NL6151).

INTRODUCTION

For patients with hepatic, pancreatic, or biliary tumours, surgical resection offers the highest chance for cure. Although postoperative survival rates have improved, morbidity due to postoperative complications remains significant. The Dutch Institute for Clinical Auditing reported the current complication rates after pancreatic surgery as follows: 33.8% no complications, 37.1% mild complications (Clavien-Dindo 1 or 2), and 29.1% severe complications (Clavien-Dindo ≥3).[1] Furthermore, recent studies reported that, after major liver resection (≥3 segments), 43% of the patients had a complicated postoperative course[2] and 30-day mortality was 8.4%.[3]

Low aerobic fitness has been shown to increase the risk of postoperative complications in hepato-pancreato-biliary surgery.[4-7] Preoperative optimization of aerobic fitness (prehabilitation) in such high-risk (low aerobically fit) patients might reduce the incidence and impact of complications following major abdominal surgery[8-10]; however, both attrition and adherence, as well as gaining an adequate response remains a challenge.

Recently, Ormel *et al.* explored predictors of adherence to exercise interventions during and after cancer treatment.[11] The authors reported that one of the most prominent predictors was the location of the rehabilitation centre in relation to the residential area. In addition, in an exploratory survey of patients' acceptance of prehabilitation for major surgery, financial support and home-based programs were found to be essential in maximizing participation and adherence to prehabilitation programs.[12] Moreover, Ferreira *et al.* reported that patients' preferred method of delivery for exercise programs is home-based with at least one supervised exercise session per week.[13] It is therefore important to gain insight into the effects and feasibility of a supervised home-based exercise program. In previous studies that have investigated the feasibility of home-based exercise, the programs were described as feasible and were reported to improve muscle strength.[14-18] Those programs were all self-monitored or minimally supervised by a physical therapist, which probably limited adherence and effectiveness. In addition, most programs consisted of moderate-intensity training. However, to improve aerobic capacity in a short time period, high-intensity interval training seems to be most effective.[19] Furthermore, adequate protein intake is necessary to increase muscle protein synthesis.[20] Insights into the ability to improve a high-risk patient's aerobic fitness and feasibility of a high-intensity supervised bimodal home-based exercise program would be of great interest, as this might be the most preferred and effective method for exercise prehabilitation.

The primary aim of this study was to evaluate the effects of a 4-week home-based high-intensity interval training program with nutritional support on preoperatively improving aerobic fitness of high-risk patients scheduled for elective liver or pancreatic resection. Secondary aims were to evaluate the feasibility of this bimodal prehabilitation program, and its (preliminary) effect on other performance indicators of aerobic fitness and preoperative perceived quality of life.

METHODS

Study design, participants, and recruitment

This multicenter study ran from October 2017 until April 2020 at the Medical Spectrum Twente (Enschede), Máxima Medical Centre (Veldhoven/Eindhoven), and the University Medical Centre Groningen. The study was approved by the Medical Ethics Committee Twente, The Netherlands (registration number P17-08, NL59702.044.16, April 2017), and was registered in the Netherlands Trial Register (NL6151). Protocol amendments were approved by the Medical Ethics Committee Twente. A complete overview of the study protocol has been published.[21] Eligible patients were informed about the study and invited to participate. Inclusion criteria involved 1) being diagnosed with a liver tumour (benign tumour, primary cancer (liver or biliary), suspicion of a malignancy, or colorectal liver metastasis), premalignant pancreatic tumour, or (the suspicion of) a pancreatic malignancy, 2) scheduled for liver (segmental resection or hemihepatectomy) or pancreatic surgery (pancreaticoduodenectomy, subtotal or total pancreatectomy), 3) having a life expectancy >6 months as estimated by the surgeon, and 4) having an oxygen uptake (VO_2) at the ventilatory anaerobic threshold (VAT) ≤11 mL/kg/min as measured at the baseline cardiopulmonary exercise test (CPET).[22] This (baseline) CPET was performed as part of usual care when patients were suspected of a reduced preoperative aerobic fitness by having a metabolic equivalent of task (MET) score ≤7 on the veterans-specific activity questionnaire (VSAQ).[23] Written informed consent was obtained from all included patients.

Interventions

Supervised home-based exercise prehabilitation

Included patients participated in a personalised 4-week (3 sessions per week, 12 sessions in total) semi-supervised home-based physical exercise training program prior to surgery. The program aimed to improve aerobic fitness and was developed using the CONTENT scale for therapeutic validity.[24] Each patient received an advanced cycle ergometer in upright position (Lode Corival, Lode BV, Groningen, The Netherlands) at home for the training sessions. In the first week of training week, all three sessions were supervised by a community physical therapist specialised in oncology; thereafter, only the first session of each week was supervised. Participants were required to train for at least three sessions per week, and training progress was titrated on the basis of progress in the steep ramp test,[25] which was performed weekly under the supervision of the physical therapist. Community physical therapists specialised in oncology were contacted by the research coordinators (LvW, AB, MR) and instructed about the use of the cycle ergometer and the goals and content of the preoperative physical exercise training program supported by a training manual and video consultation. An

experienced oncologic physical therapist and/or the research coordinator was available to discuss practical challenges of the program. Each training session lasted at least 30 minutes. Two sessions per week consisted of high-intensity interval training and one session per week of moderate-intensity endurance interval training (Table 1). In addition, the training was combined twice a week with context-specific and individually tailored moderate-to-high intensity functional exercises, such as stair climbing, chair-stand exercises, and outdoor cycling, which were determined by the physical therapist in close collaboration with the participant.[26] Detailed information about the home-based prehabilitation program can be found in the published protocol.[21]

Nutritional supplementation

Participants were provided with nutritional supplementation to increase muscle protein synthesis.[20] They were advised to take the protein supplementation daily immediately after exercise or before sleep on the days with no exercise. They were provided with a standard dosage of 30 g of a high-quality (whey and casein) protein that contained at least 10 g of essential amino acids, including 2 g to 3 g of leucine. Participants were also provided with multivitamins/minerals to prevent deficiencies.[27]

Measurements

Cardiopulmonary exercise test to assess aerobic fitness

A baseline CPET was performed to verify participant eligibility (VO_2 at the VAT ≤11 mL/kg/min), to assess baseline aerobic fitness, and to check for potential contraindications for the physical exercise training program. To assess the effects of the prehabilitation program on preoperative aerobic fitness, all participants performed a second CPET after completion of the program. The CPET was performed using an electronically braked cycle ergometer (Ergoline, Ergoselect 100, Bitz, Germany, at Medisch Spectrum Twente; Lode Corival, Lode BV, Groningen, The Netherlands, at Máxima Medical Centre; and Monark LC6, Monark Exercise AB, Vansbro, Sweden, at University Medical Centre Groningen). The CPET consisted of a two-minute resting phase, a three-minute unloaded warm-up phase, an incremental phase with constant work rate increments of 5, 10, or 15 W/min (aimed at reaching a maximal effort within eight to twelve minutes) until voluntary exhaustion despite strong verbal encouragement and, and a five-minute recovery phase.

Throughout the CPET, participants breathed through a facemask connected to a calibrated ergospirometry system (Oxycon Pro, Jaeger, Höchberg, Germany at Medisch Spectrum Twente, Vyntus CPX, CareFusion, Höchberg, Germany at Máxima Medisch Centrum, and Quark CPET, Cosmed, Roma, Italy at University Medical Centre Groningen) for breath-by-breath measurement of VO_2, carbon dioxide production, minute ventilation, and the respiratory exchange ratio (RER) averaged at ten-second

intervals. Heart rate was measured by continuous 12-lead electrocardiography. A test was considered to be at or near the maximal level when participants achieved a heart rate at peak exercise (HR_{peak}) of >95% of predicted (predicted HR_{peak} [beats/min] = 208 - (0.7 × age [years]) and/or an RER at peak exercise >1.10. When a maximal effort was delivered, VO_2 at peak exercise (VO_{2peak}) was calculated as the average value over the last 30 seconds prior to test termination to assess aerobic fitness. The VAT was defined as a submaximal indicator of aerobic fitness by using the V-slope method and the ventilatory equivalents method[28, 29], whereas the oxygen uptake efficiency slope (OUES) was evaluated as an effort-independent indicator of aerobic fitness.[30] Extensive details about the CPET protocol and interpretation can be found in the published protocol.[21]

Steep ramp test to personalise the physical exercise training program

Steep ramp tests were performed on the advanced cycle ergometer (Lode Corival, Lode BV, Groningen, The Netherlands) at the participant's home using a modified protocol[31] to increase its feasibility in unfit (elderly) patients. The test consists of a two-minute unloaded warm-up phase, an incremental phase with constant work rate increments of 10 W every 10 seconds (1 W/s) until voluntary exhaustion despite strong verbal encouragement, and a three-minute recovery phase. The achieved work rate at peak exercise (WR_{peak}) was the primary outcome measure, which was used to individually set-up and adjust the training intensity of the high-intensity interval training and moderate-intensity endurance interval training sessions (titration) on a weekly base. Additional information regarding the steep ramp test protocol can be found in the published protocol.[21]

Feasibility of the prehabilitation program

Feasibility of the home-based prehabilitation program was determined by recruitment rate from October 2017 until April 2020, reasons for non-participation, adherence, completion rate, dropout rate, attrition rate, and adverse events. Recruitment rate was defined as the ratio of the recruited patients to those who were eligible, whereas adherence to the program was calculated as the ratio of completed exercise sessions to the number of prescribed sessions. Completion rate was defined as the proportion of participants who completed all the prescribed sessions. Dropout rate was defined as the proportion of participants who withdrew during the study to the total included patients. Attrition rate was calculated as the number of participants who completed the program divided by the total number of eligible patients. The number and severity of adverse events were recorded by the physical therapist. After the program, participants were asked to complete a patient appreciation questionnaire based on a previous study.[32] On eight statements, participants were asked if they fully agree on a 5-point scale, where 5 means the respondent fully agrees with the statement.

Table 1. Characteristics of the 4-week home-based physical exercise training program.

Training type	Phase	Duration
High-intensity interval training *2 sessions/week*	Warm-up	5 min
	Intervals	19.5 min
	Recovery	5.5 min
Moderate-intensity endurance interval training *1 session/week*	Warm-up	7 min
	Intervals	30 min
	Recovery	3 min

Abbreviation: WR_{peak} = peak work rate.
[a]: the steep ramp test was performed on a weekly base to objectively monitor training progress (titration) and to adjust training intensity accordingly.

Perceived health-related quality of life
Before the start of the training program, participants were asked to complete two health-related quality-of-life questionnaires, respectively the short-form 36 (SF-36) questionnaire[33] and the EuroQoL 5-dimensional questionnaire (EQ-5D).[34] After the 4-week training period, participants were asked to complete both questionnaires again to assess whether the prehabilitation program had influenced quality of life.

Other study parameters
Preoperative factors that may be associated with physical fitness were also recorded. These included age, sex, body mass index, smoking, haemoglobin level, (suspected) type of tumour at diagnosis, American Society of Anaesthesiologists score, and age-adjusted Charlson comorbidity index.

Study outcomes
Primary and secondary endpoints
The primary endpoint of this study was the change in VO_2 at the VAT and VO_{2peak} following the 4-week home-based bimodal prehabilitation program. Secondary endpoints were 1) the feasibility of this program, as measured by recruitment rate,

Intensity	Pedaling frequency
20 W	40-80 rpm
Work interval 30 seconds at 60% of steep ramp test WR_{peak} (W) [a] *Recovery interval* 60 seconds at 20 W Alternating work-recovery intervals	60-100 rpm
20 W	40-80 rpm
20% of steep ramp test WR_{peak} (W) [a]	40-80 rpm
Moderate-intensity intervals [b] 40% of steep ramp test WR_{peak} (W) [a] *Low-intensity intervals* [b] 20% of steep ramp test WR_{peak} (W) [a] Alternating moderate- and low-intensity intervals	60-100 rpm
25% of steep ramp test WR_{peak} (W) [a]	40-80 rpm

[b]: duration of the moderate- and low-intensity intervals were 120 and 180 seconds, 140 and 160 seconds, 160 and 140 seconds, and 180 and 120 seconds for week 1, 2, 3, and 4, respectively.

adherence, completion rate, dropout rate, attrition rate, and adverse events; 2) the (preliminary) effect of the program on other CPET values; and 3) the effect of the program on the perceived health-related quality of life.

Data analysis

Sample size calculation

The primary endpoint VO_2 at the VAT was used for sample size calculation. In a previous study in patients with low aerobic fitness scheduled for elective liver resection, preoperative VO_2 at the VAT improved by 1.5 mL/kg/min after a prehabilitation program.[35] Prior data indicate that the difference in the response of matched pairs is normally distributed with a standard deviation of 2.5 mL/kg/min. It was calculated that 24 participants needed to be included to be able to reject the null hypothesis that this response difference is zero with a probability (power) of 0.80 if the true difference in the mean response of matched pairs is 1.5 mL/kg/min. The type I error probability associated with this test of this null hypothesis is 0.05.

Statistical analysis

Continuous variables were presented as the mean and standard deviation or as the median and interquartile range (IQR), as appropriate. Categorical data were summarised by frequency and percentage. Analysis was performed according to the intention-to-treat principle. To evaluate the effects of the home-based program, the difference in the CPET variables before the start of the training and after four weeks of prehabilitation were analysed using a paired samples t-test or Wilcoxon signed rank test, as appropriate. Feasibility and patient appreciation of the prehabilitation program were described by use of descriptive statistics. The differences between quality-of-life measures pre- and post-prehabilitation were analysed with the paired samples t-test or Wilcoxon test, as appropriate. P-values <0.05 were considered statistically significant.

RESULTS

Between October 2017 and April 2020, 112 patients were assessed for eligibility. Of the 52 initially eligible patients, eight were eventually not scheduled for surgery, whereas surgeons preferred short-term surgery because of borderline resectability in six patients. Of the 38 eligible patients, 26 were included, corresponding to a recruitment rate of 68.4% (Figure 1). The other 12 eligible patients (31.6%) were not included in the study for various reasons: in five cases, no community physical therapist specialised in oncology was available; in another two cases, all three available cycle ergometers in this study were occupied; one patient had no interest in an exercise program; two patients experienced severe knee problems during the CPET and were not able to train on a cycle ergometer; and two patients had intermittent hospital admissions due to cholangitis. The 26 included patients (18 males, 8 females; mean age 71 years [SD 9], range 56 to 87 years), participated in the home-based prehabilitation program. Baseline characteristics of the study participants are presented in Table 2.

Aerobic fitness

Median time between baseline CPET and surgery was 52 days (IQR 21.5). Median time between the second CPET and surgery was 12 days (IQR 15.0). Changes in preoperative aerobic fitness following prehabilitation are presented in Table 3. The progress during the 4-week prehabilitation program on preoperative aerobic fitness are presented in Table 3 and Figure 2. Prehabilitation led to a mean ± SD improvement in VO_2 at the VAT (n = 19) of 1.7 ± 1.1 mL/kg/min (range −0.6 to 4.1), indicating a 17.8% improvement (95% confidence interval [CI] −2.23 to −1.15; P < 0.001). VO_{2peak} (n = 13) improved by 2.4 ± 1.4 mL/kg/min (range 0.1 to 4.9), representing a 17.2% increase (P = 0.001; no 95% CI due to non-parametric data distribution). Moreover, the O_2-$pulse_{peak}$ and peak work rate improved significantly, whereas the oxygen uptake efficiency slope demonstrated no change. Eight patients (42.1%) had a preoperative VO_2 at the VAT >11 mL/kg/min after the prehabilitation program. Five (26.3%) improved less than 1 mL/kg/min in VO_2 at the VAT in the post-prehabilitation CPET and two had an increase in VO_{2peak} of less than 1 mL/kg/min.

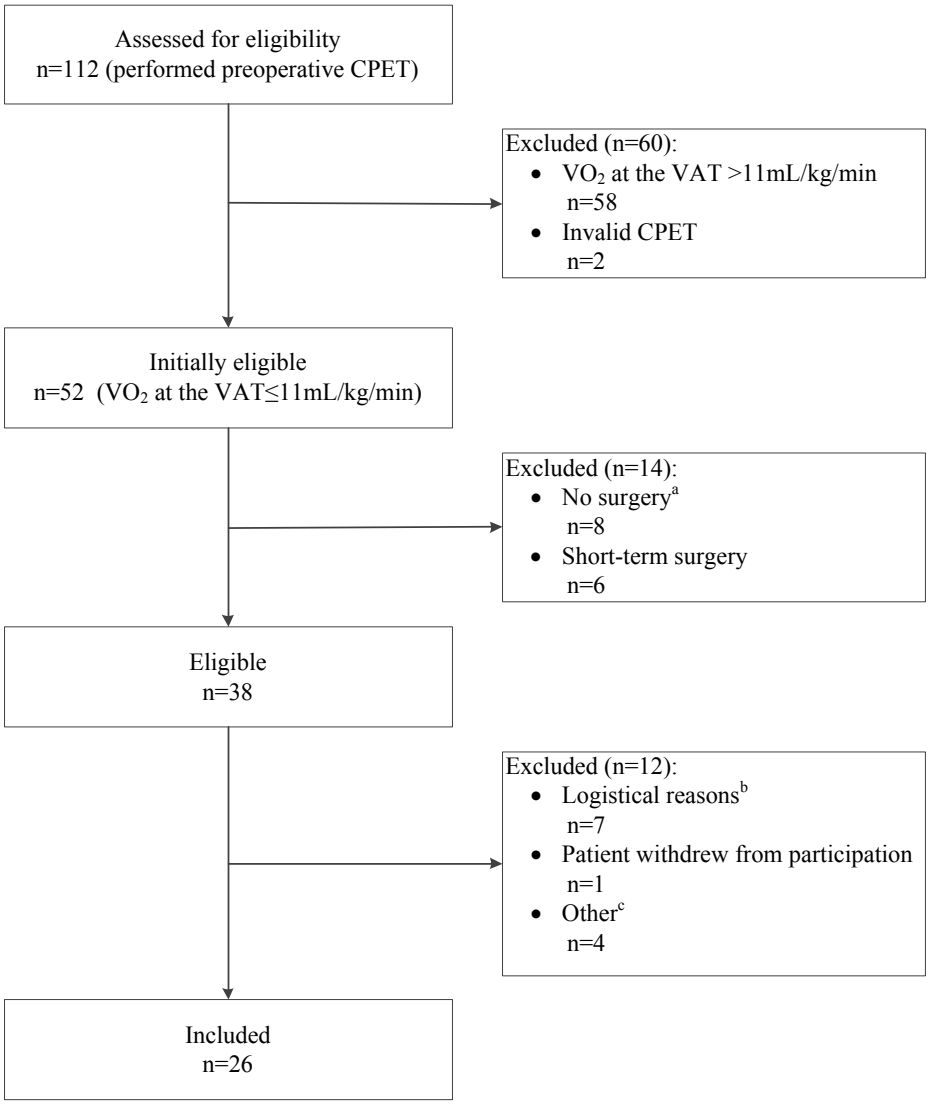

Figure 1. Flowchart of participant inclusion in the study.

Abbreviations: CPET = cardiopulmonary exercise test; VAT = ventilatory anaerobic threshold; VO2 = oxygen uptake.

[a]: 8 patients were eventually not scheduled for surgery.

[b]: 5 patients could not participate as no physical therapist specialised in oncology was available and 2 patients could not participate as none of the three cycle ergometers was available.

[c]: 2 patients experienced severe knee pain during the CPET and were not able to participate, and 2 patients had intermittent hospital admissions due to cholangitis restricting them from participation.

Table 2. Preoperative characteristics of patients in the study cohort (n=26).

	Study cohort ***n*** **= 26 (100%)**
Age (years)	
18–64	6 (23%)
65–74	9 (35%)
≥75	11 (42%)
Mean ± SD	71.6 ± 8.7
Sex ratio	
Male	18 (69%)
Female	8 (31%)
Body mass index (kg/m^2)	
<18.5	0
18.5–25	6 (23%)
25.1–29.9	4 (15%)
≥30	16 (62%)
Median (IQR)	31.3 (8.6)
Smoking	8 (31%)
Charlson Comorbidity Index	
<5	3 (12%)
5-9	17 (65%)
≥10	6 (23%)
Mean ± SD	7.6 ± 2.4
ASA score	
I–II	10 (38%)
≥III	16 (62%)
Aerobic fitness	
VO_2 at the VAT (mL/kg/min),[a] mean ± SD	9.5 ± 0.9
VO_{2peak} (mL/kg/min),[b] median ± IQR	14.5 ± 2.2
Haemoglobin level (mmol/L), median (IQR)	8.2 (1.9)
Indication for referral	
Colorectal liver metastases	3 (11.5%)
Liver tumour	6 (23.1%)
Gallbladder and biliary tract tumour	5 (19.2%)
Pancreatic head tumour	8 (30.8%)

Table 2. Continued.

	Study cohort *n* = 26 (100%)
Pancreatic corpus/tail tumour	3 (11.5%)
Other[c]	1 (3.9%)
Eventually underwent surgery	
Yes	20 (76.9%)
No, (partly) due to the patient's condition	1 (3.8%)
No, other reason [d]	5 (19.3%)
Time between baseline CPET and surgery (days), median (IQR) [e]	52 (22)
Time between second CPET and surgery (days), median (IQR) [f]	12 (15)

[a]: VO_2 at the VAT during the pre-prehabilitation CPET was indeterminable in 1 patient, so in this case $n = 25$ (the patient was nonetheless included in the study, as the VO_{2peak} at the pre-prehabilitation CPET was <11 mL/kg/min).

[b]: 7 patients did not meet the criteria for a valid maximal effort during the pre-prehabilitation CPET, so in this case $n = 19$.

[c]: Colon tumour with invasion into the pancreas.

[d]: In 5 patients, the tumour was found to be unresectable while the patient was already listed for surgery.

[e]: 6 patients did not undergo surgery, so in this case $n = 20$.

[f]: 7 patients did not perform a second CPET and 4 patients did not undergo surgery, so in this case $n = 15$.

Feasibility

Next to a recruitment rate of 68.4%, patients attended a mean ± SD of 9.9 ± 3.2 of the 12 training sessions, resulting in an adherence rate of 82.5%. Fifteen of the 26 patients attended 100% of the training sessions, giving a completion rate of 57.6%. The drop-out rate was 3 out of 26 (11.5%), which led to an attrition rate of 60.5%. One patient stopped just before the start of the first training session, as concurrent radiotherapy for a lung tumour made the exercise program too stressful. One patient stopped after four training sessions also because of concurrent radiotherapy and because the bicycle saddle hurt too much. One patient stopped after five training sessions because she also needed to give informal care. Three patients missed a total of 13 of the 36 training sessions (36.1%) due to sickness. Three patients missed a total of 7 of the 36 training sessions (19.4%), because their surgery was brought forward. One patient missed 3 of the 12 training sessions because of knee problems (25%). One patient missed 1 of the 12 training sessions (8.3%) because of a busy schedule that day. No serious adverse events were registered. Patients were satisfied with the training program. Patients scored a median value of 4 (range median values 4–5) on eight statements. The median scores of each statement separately are presented in Figure 3.

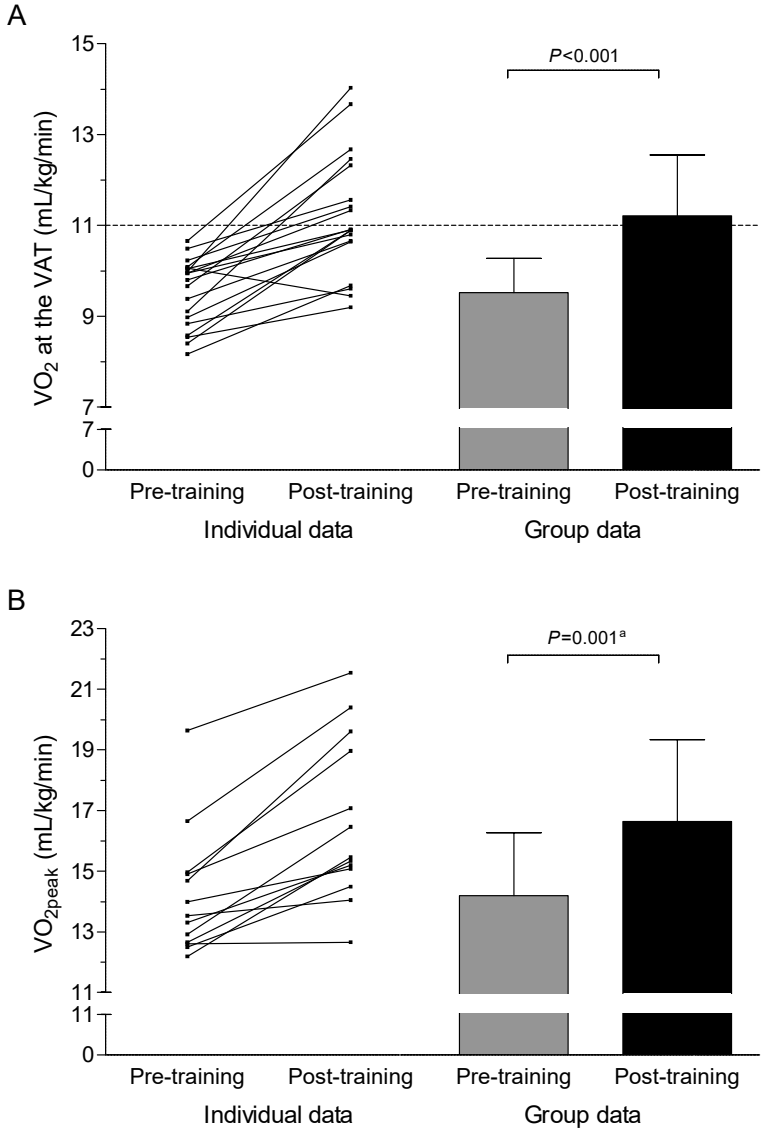

Figure 2. Changes in pre- and post-prehabilitation aerobic fitness, VO_2 at VAT (graph A) and VO_{2peak} (graph B)

Group data are presented as mean ± SD.

The dashed line represents the cut-off for high-risk based on VO2 at the VAT (patients who score below this cut-off have an increased risk for postoperative complications, which was an inclusion criterion of the current study).

Abbreviations: VAT = ventilatory anaerobic threshold; VO2 = oxygen uptake; VO2peak = oxygen uptake at peak exercise; WRpeak = work rate at peak exercise.

[a]: Non-parametric distribution, Wilcoxon signed-ranks test.

Table 3. Changes in pre- and post-prehabilitation aerobic fitness in patients who completed the program (n=23).

	Pre-prehabilitation	Post-prehabilitation	Change (%)
VO_2 at the VAT (mL/kg/min)	9.5 ± 0.8[b]	11.2 ± 0.8[b]	+17.8
VO_{2peak} (mL/kg/min)[a]	14.2 ± 2.1[a, c]	16.6 ± 2.7[a, c]	+17.2
OUES/kg	18.2 ± 3.3[b]	18.8 ± 4.2[b]	+3.6
O_2-pulse$_{peak}$ (mL/kg/beat × 100)	11.8 ± 1.7[c]	13.5 ± 2.5[c]	+14.7
WR_{peak} (W/kg)	1.0 ± 0.2[a, c]	1.3 ± 0.3[a, c]	+19.6

Data are presented as mean ± SD.

Abbreviations: CPET = cardiopulmonary exercise test; O_2-pulse$_{peak}$ = oxygen pulse at peak exercise (values are multiplied by 100 to increase readability); OUES = oxygen uptake efficiency slope (normalised for body mass); VAT = ventilatory anaerobic threshold; VO_2 = oxygen uptake; VO_{2peak} = oxygen uptake at peak exercise; WR_{peak} = work rate at peak exercise.

[a]: Non-parametric distribution, Wilcoxon signed-ranks test.

[b]: n = 19, as the VAT at the pre-prehabilitation CPET was indeterminable in 1 patient (the patient was nonetheless included in the study, as the VO_{2peak} at the pre-prehabilitation CPET was <11 mL/kg/min), 1 patient was unable to perform the post-prehabilitation CPET due to an ankle injury, 1 patient was unable to perform the post-prehabilitation CPET due to a nasogastric feeding tube, and 1 patient did not want to perform the post-prehabilitation CPET due to illness (fever) in the last training week.

Perceived health-related quality of life

There was no significant difference in health-related quality of life pre- and post-prehabilitation, as measured with the SF-36 questionnaire. Scores for each item in the SF-36 are presented in Figure 4. The mean ± SD scores were 7.2 ± 1.8 pre-training and 7.7 ± 1.3 post-prehabilitation (P = 0.106). Furthermore, an improving trend was observed in the EQ-5D questionnaire pre- and post-prehabilitation; however, this improvement was not statistically significant (P = 0.262).

	Intention-to-treat			
P-value	Pre-prehabilitation	Post-prehabilitation	Change (%)	*P*-value
<0.001	9.7 ± 0.8[d]	11.1 ± 1.3[d]	+14.5	<0.001
0.001	14.4 ± 2.2[a, e]	16.0 ± 2.8[a, e]	+11.0	0.001
0.347	18.0 ± 3.3[d]	18.6 ± 4.1[d]	+3.3	0.297
0.002	11.9 ± 1.9[f]	13.1 ± 2.5[f]	+10.6	0.004
0.001	1.0 ± 0.3[e]	1.2 ± 0.3[e]	+12.8	<0.001

[c]: *n* = 13, as the criteria for a valid maximal effort were not met during the pre-prehabilitation CPETs of 3 patients, post-prehabilitation CPETs of 2 patients, and both CPETs of 2 patients; and 3 patients were unable to perform the post-prehabilitation CPET (see reasons specified under note *b*).

[d]: *n* = 23.

[e]: *n* = 20, as 2 patients did not meet the criteria for a valid maximal effort at both the pre- and post-prehabilitation CPETs, and 1 patient did not meet the criteria for a valid maximal effort at the pre-prehabilitation CPET and was unable to perform the post-prehabilitation CPET due to a nasogastric feeding tube.

[f]: *n* = 18, as, in addition to the reasons for an invalid maximal effort specified under note *e*, heart rate was invalid during both the pre- and post-prehabilitation CPETs of 1 patient and during the pre-prehabilitation CPET of 1 patient; the latter was unable to perform the post-prehabilitation CPET due to an ankle injury.

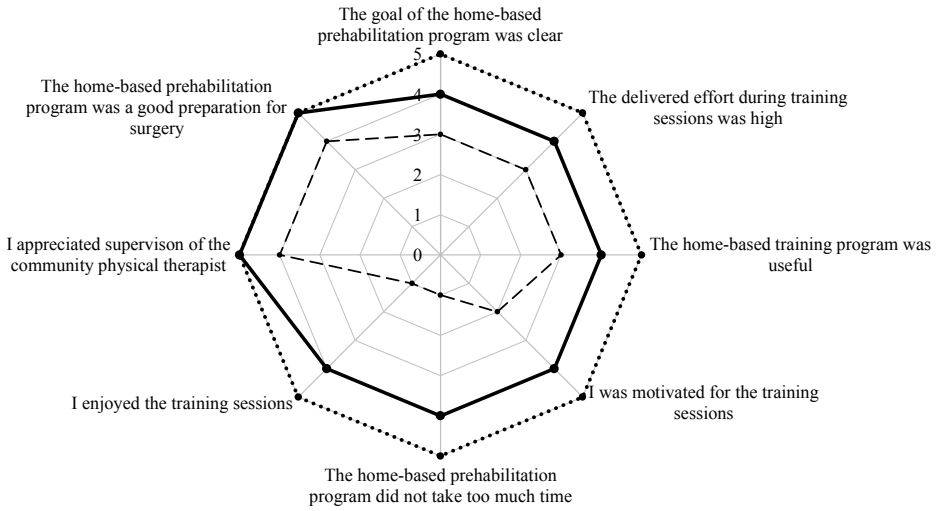

Figure 3. Overall satisfaction with the exercise prehabilitation program.

Scores range from 1 = disagree to 5 = completely agree
Thick solid line represents the median score, dotted line the maximum score, and dashed line the minimum score
Data of 11 patients (42%) were missing, so in this case n = 15.

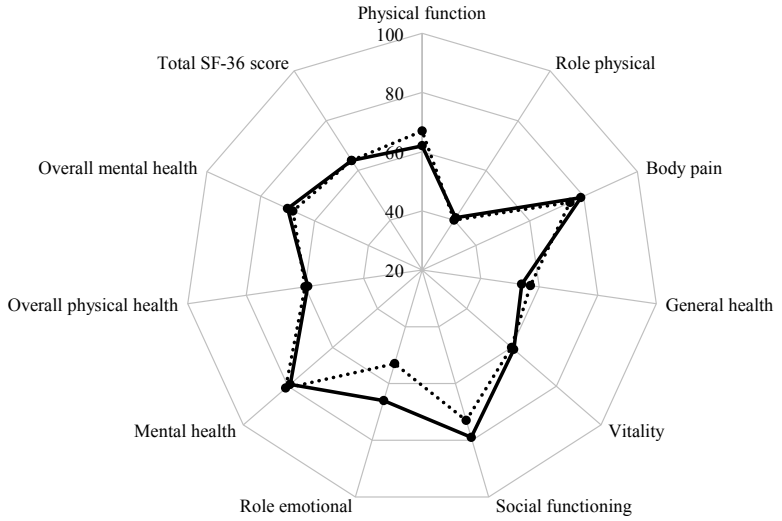

Figure 4. Radar graph demonstrating changes in SF-36 quality-of-life scores per item pre- and post-prehabilitation.

Thick solid line represents pre-prehabilitation scores, dotted line post-prehabilitation scores
Data of 11 patients (42%) were missing, so in this case n = 15.

DISCUSSION

In this study, we evaluated the preliminary effects of a 4-week home-based bimodal prehabilitation program on an advanced cycle ergometer performed by high-risk patients scheduled for elective oncologic liver or pancreatic resection. Results showed that this prehabilitation program led to a mean improvement in VO_2 at the VAT of 17.8%, whereas VO_{2peak} (n = 13) improved by 17.2%. In addition, patients completed 82.5% of the training sessions, and on average they were satisfied with the program. These results indicate that semi-supervised home-based training is a highly efficient in these high-risk patients to improve their preoperative functional health status.

In a recent randomised controlled trial, Berkel *et al.* described the effects of a 3-week community-based exercise prehabilitation program on a cycle ergometer supervised by a physical therapist in high-risk (VO_2 at the VAT ≤11 mL/kg/min) colorectal cancer patients.[8] After the prehabilitation program, VO_2 at the VAT increased by 0.97 mL/kg/min (10.1%; P = 0.006) and VO_{2peak} increased by 1.3 mL/kg/min (8.8%; P = 0.05). Patients attended a mean of 8.1 (SD 2.4) of the nine supervised exercise sessions (90%). In the present study, we found an improvement of 17.8% in VO_2 at the VAT and an adherence rate of 82.5%. The difference in improvement between our study and that of Berkel *et al.* may be partly attributed to the week of additional training in our study and a higher training intensity.

In the study by Dunne *et al.*, the subgroup of high-risk patients (VO_2 at the VAT ≤11 mL/kg/min) scheduled for liver resection for colorectal liver metastases who trained for four weeks on a cycle ergometer in the hospital under supervision of a physical therapist increased their VO_2 at the VAT by 1.9 mL/kg/min (19%; P = 0.037) and their VO_{2peak} increased by 2.8 mL/kg/min (17%; P = 0.075).[35] This is a similar improvement in VO_2 at the VAT as in our study. To date, there is no standardised way to assess adherence to exercise. Reported rates of adherence to training sessions in prehabilitation exercise programs vary from 98% on average in supervised trials to 70% on average in unsupervised training.[36] In our study, patients attended a mean of 9.9 (SD 3.2) of the 12 training sessions (82.5%), which seems an acceptable rate for the semi-supervised training program.

With respect to the improvement in aerobic fitness, patient adherence, and overall satisfaction with the study, this prehabilitation program seems feasible and led to a clinically highly relevant improvement in preoperative aerobic fitness. However, the low recruitment rate (68%) might have caused a selection bias, as the results of the program are unknown for the non-recruited patients. This potential selection bias

might be a threat to the external validity and generalizability of the results. In a previous study to elucidate the factors influencing older adults' participation in physical activity trials, it was found that tailored trial information and providing evidence that physical exercise is beneficial might increase recruitment.[37] However, in our study, the main cause for non-participation was logistical. One of the surmountable causes that resulted in the exclusion of five patients was that there was no physical therapist specialised in oncology available in the living context of the patient for the supervised home-based training sessions. Most patients were included in the study from the University Medical Centre Groningen, a tertiary referral centre with a large adherence area, which made it difficult to use the same physical therapist for multiple patients. As well as compromising recruitment rate, this logistical challenge resulted in the fact that each physical therapist only trained one or two patients, which limited physical therapist to gain experience with the training protocol, which might have limited the effect of the training. Community-based perioperative care networks should be established, in which trained and competent physical therapists, along with the patient and the patient's informal support system, aim to make a patient fit for surgery, either in a home- or community-based context.[5]

An important strength of our study was that the exercise prehabilitation program was organised at a high-risk patient's home and that most training sessions were supervised by a physical therapist specialised in oncology. Another strength of our study that might have maximised the effect of the training was that the training sessions were personalised based on the weekly steep ramp tests and that nutritional support was provided to increase muscle protein synthesis. Lastly, we used the CPET, the gold standard for assessing a patient's aerobic fitness pre- and post-prehabilitation to objectively evaluate effectiveness of the program.

Home-based semi-supervised physical exercise training seems to lead to large improvements in aerobic fitness in high-risk patients before treatment initiation. Especially in oncologic care, there is often a small window before the start of treatment (e.g., chemotherapy, surgery), meaning that there is a need for short and highly effective exercise programs. Furthermore, as previously described, not only does a patient's aerobic fitness need to be optimised pre-treatment, but their nutritional status, presence of anemia, frailty, use/abuse of intoxicants, and low psychological resilience should also be addressed in a multimodal prehabilitation program. Recently, we demonstrated that it is feasible to screen and assess patients on these six risk factors; however, it was challenging to ensure the patients complied with all the necessary interventions.[38]

This study demonstrated that the home-based bimodal prehabilitation program by high-risk patients scheduled for elective liver or pancreatic resection resulted in a significantly improved preoperative aerobic fitness. In the context of all recent evidence in favour of prehabilitation and the latest recommendations from data sciences and epidemiology, we urge for a profound but swift dialogue on what would be the next experimental step(s) in the context of remedies like multimodal prehabilitation to further improve the recruitment rate, adherence, attrition, and effectiveness. This might translate into improved postoperative outcomes and a reduced demand on hospital resources.

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