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# Improved preoperative aerobic fitness following a home-based bimodal prehabilitation programme in high-risk patients scheduled for liver or pancreatic resection

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## Introduction

For patients with hepatic, pancreatic or biliary tumours, surgical resection offers the highest chance of cure. Although postoperative survival rates have improved, morbidity owing to postoperative complications remains significant[1]. Low aerobic fitness has been shown to increase the risk of postoperative complications in hepatopancreatobiliary surgery[2–4]. Preoperative optimization of aerobic fitness (prehabilitation) in high-risk (low aerobically fit) patients might reduce the incidence and impact of postoperative complications[5,6]. However, both attrition and adherence, as well as gaining an adequate response, remain a challenge[7].

Ferreira *et al.*[8] reported that patients' preferred method of delivery of preoperative exercise programmes is home-based, with at least one supervised exercise session per week. To improve aerobic fitness in a short time period, high-intensity interval training seems to be most effective[9]. Furthermore, adequate protein intake is necessary to increase muscle protein synthesis[10]. Insights into the ability to improve a high-risk patient's aerobic fitness and feasibility of a high-intensity supervised bimodal home-based exercise programme 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 programme with nutritional support on preoperative improvement of aerobic fitness of high-risk patients scheduled for elective liver or pancreatic resection. Secondary aims were to evaluate the feasibility of this bimodal prehabilitation programme, and its (preliminary) effect on other performance indicators of aerobic fitness and preoperative perceived quality of life.

## Methods

Medical ethical approval was granted by the Medical Ethics Committee Twente, Enschede, the Netherlands (P17-08, NL59702.044.16, April 2017) and the study was registered in the Netherlands Trial Registry (NL6151). Written informed consent was received from all patients before enrolment.

A complete description of the methodology for this multicentre study is available in *Appendix S1* and in the previously published study protocol[11]. In brief, using a pretest–post-test design, high-risk patients (preoperative oxygen uptake ($V_{O_2}$) at the ventilatory anaerobic threshold (VAT) 11 ml per kg per min or less) scheduled for elective liver or pancreatic resection, and who provided informed consent, participated in a 4-week semisupervised home-based exercise programme (12 sessions in total). The programme consisted of individualized goal setting followed by titration of high-intensity interval training and moderate-intensity endurance interval training on an advanced cycle ergometer (Lode Corival; Lode, Groningen, the Netherlands), combined with functional task exercises and protein and vitamin/mineral supplementation. The primary endpoint of this study was the change in $V_{O_2}$ at the VAT and oxygen uptake at peak exercise ($V_{O_{2peak}}$) after the 4-week prehabilitation programme. Secondary endpoints were: programme feasibility (recruitment rate, adherence, completion rate, drop-out rate, attrition rate, and adverse events); the

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(preliminary) effect of the programme on other cardiopulmonary exercise testing (CPET) values; and the effect of the programme on perceived health-related quality of life.

## Results

In total, 112 patients were assessed for eligibility. Of the 52 initially eligible patients ($Vo_2$ at the VAT 11 ml per kg per min or less), 8 were eventually not scheduled for surgery, whereas surgeons preferred short-term surgery because of borderline resectability in 6 patients. Of the 38 eligible patients, 26 were included, corresponding to a recruitment rate of 68 per cent (*Fig. S1*). The other 12 eligible patients were not included in the study for various reasons (*Appendix S2*). Baseline characteristics of the study participants are summarized in *Table 1*.

**Table 1 Preoperative characteristics of patients in the study cohort**

| | Study cohort ($n = 26$) |
|---|---|
| **Age (years)** | |
| 18–64 | 6 |
| 65–74 | 9 |
| ≥ 75 | 11 |
| Mean (s.d.) | 71.6 (8.7) |
| **Sex** | |
| M | 18 |
| F | 8 |
| **BMI (kg/m$^2$)** | |
| < 18.5 | 0 |
| 18.5–25.0 | 6 |
| 25.1–29.9 | 4 |
| ≥ 30.0 | 16 |
| Median (i.q.r.) | 31.3 (27.0-34.9) |
| **Smoker** | 8 |
| **Charlson Co-morbidity Index score** | |
| < 5 | 3 |
| 5–9 | 17 |
| ≥ 10 | 6 |
| Mean (s.d.) | 7.6 (2.4) |
| **ASA fitness grade** | |
| I–II | 10 |
| ≥ III | 16 |
| **Aerobic fitness** | |
| $Vo_2$ at VAT (ml per kg per min), mean (s.d.)* | 9.5 (0.9) |
| $Vo_{2peak}$ (ml per kg per min), mean (s.d.)† | 14.5 (2.2) |
| **Haemoglobin (mmol/l), median (i.q.r.)** | 8.3 (7.2-9.2) |
| **Indication for referral** | |
| Colorectal liver metastases | 3 |
| Liver tumour | 6 |
| Gallbladder and biliary tract tumour | 5 |
| Pancreatic head tumour | 8 |
| Pancreatic body/tail tumour | 3 |
| Other‡ | 1 |
| **Eventually underwent surgery** | |
| Yes | 20 |
| No, (partly) owing to patient's condition | 1 |
| No, other reason§ | 5 |
| **Interval between baseline CPET and surgery (days), median (i.q.r.)¶** | 53 (50-72) |
| **Interval between second CPET and surgery (days), median (i.q.r.)#** | 12 (3-18) |

*Based on 25 patients, as oxygen uptake ($Vo_2$) at the ventilatory anaerobic threshold (VAT) during pre-prehabilitation cardiopulmonary exercise testing (CPET) could not be determined for 1 patient; the patient was nonetheless included in the study, as the oxygen uptake at peak exercise ($Vo_{2peak}$) at pre-prehabilitation CPET was below 11 ml per kg per min. †Based on 19 patients as 7 patients did not meet the criteria for a valid maximal effort during pre-prehabilitation CPET. ‡Colonic tumour with invasion of pancreas.§Tumour found to be unresectable when the patient was already listed for surgery. ¶Based on 20 patients as 6 did not have surgery. #Based on 15 patients as 7 did not undergo second CPET and 4 did not have surgery.

### Aerobic fitness

Progress on preoperative aerobic fitness during the 4-week prehabilitation programme is shown in *Fig. 1* and *Table S1*. Prehabilitation led to a mean(s.d.) improvement in $Vo_2$ at the VAT of 1.7(1.1) (range −0.6 to 4.1) ml per kg per min (19 patients) indicating a 17.8 (95 per cent c.i. −2.23 to −1.15) per cent improvement ($P < 0.001$). $Vo_{2peak}$ improved by 2.4(1.4) (range 0.1–4.9) ml per kg per min, representing a 17.2 per cent increase ($P = 0.001$; no 95 per cent c.i. as data were not distributed normally). The oxygen pulse and work rate at peak exercise improved significantly, whereas the oxygen uptake efficiency slope demonstrated no change. Eight patients had a preoperative $Vo_2$ at the VAT higher than 11 ml per kg per min after the prehabilitation programme. Five showed an improvement of less than 1 ml per kg per min in $Vo_2$ at the VAT in the post-prehabilitation CPET, and 2 had an increase in $Vo_{2peak}$ of less than 1 ml per kg per min.

### Feasibility

Next to a recruitment rate of 68 per cent, patients attended a mean (s.d.) of 9.9 (3.2) of the 12 training sessions, resulting in an adherence rate of 83 per cent. Fifteen of the 26 patients attended all of the training sessions, giving a completion rate of

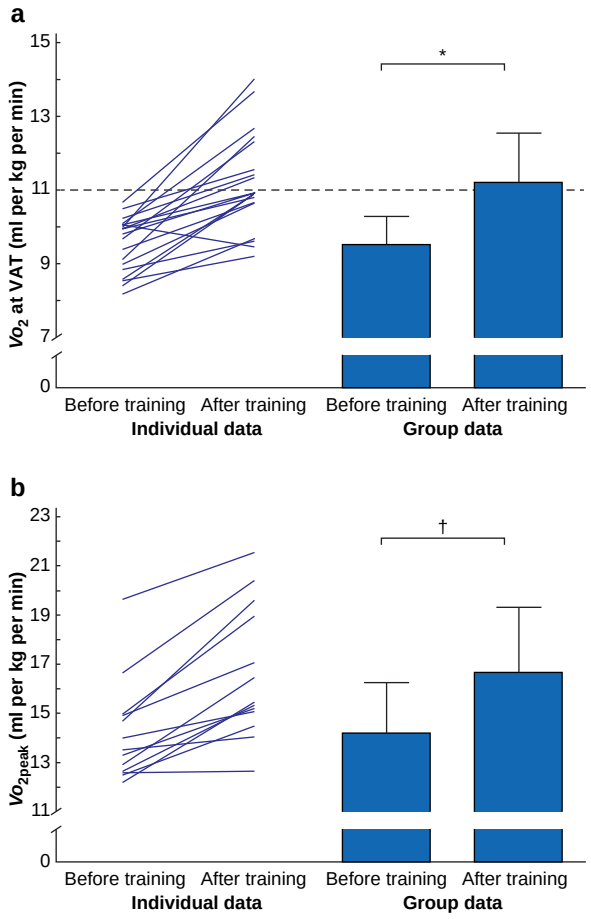


**Fig. 1 Pre- and post-prehabilitation aerobic fitness measurements**

**a** Oxygen uptake ($Vo_2$) at the ventilatory anaerobic threshold (VAT) and **b** oxygen uptake at peak exercise ($Vo_{2peak}$). Group data are presented as mean (s.d.). The dashed line represents the cut-off for high risk based on $Vo_2$ at the VAT; patients who score below this cut-off have an increased risk of postoperative complications, which was an inclusion criterion for the present study. *$P < 0.001$ (paired samples t-test), †$P = 0.001$ (Wilcoxon signed-rank test).

58 per cent. The drop-out rate was 3 of 26 (12 per cent), which led to an attrition rate of 61 per cent. Reasons for drop-out or missing training sessions are listed in *Appendix* S3. No serious adverse events were registered. Patients were satisfied with the training programme. Patients scored a median value of 4 (range of median values 4–5) on 8 statements. The median scores for each statement separately are presented in *Fig. S2*.

### 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 Short Form 36 (SF-36) questionnaire. Scores for each item in the SF-36 are presented in *Fig. S3*. Mean(s.d.) scores were 7.2(1.8) before training and 7.7(1.3) after prehabilitation ($P = 0.106$). Furthermore, an improving trend was observed in the EQ-5D™ (EuroQol Group, Rotterdam, the Netherlands) questionnaire scores after prehabilitation; however, this improvement was not statistically significant ($P = 0.262$).

## Discussion

The results of the present study showed that this prehabilitation programme led to a mean improvement in $V_{O_2}$ at the VAT of 17.8 per cent, whereas $V_{O_{2peak}}$ improved by 17.2 per cent. In addition, patients completed 83 per cent of the training sessions, and on average they were satisfied with the programme. These results indicate that semisupervised home-based training is a highly efficient in improving preoperative aerobic fitness in these high-risk patients.

Following a 3-week supervised community-based exercise prehabilitation programme in high-risk patients with colorectal cancer ($V_{O_2}$ at the VAT 11 ml per kg per min or less), $V_{O_2}$ at the VAT increased by 10.1 per cent ($P = 0.006$) and $V_{O_{2peak}}$ by 8.8 per cent ($P = 0.05$)[6]. Patients attended a mean(s.d.) of 8.1(2.4) of the 9 supervised exercise sessions (90 per cent)[6]. The present study showed an improvement of 17.8 per cent in $V_{O_2}$ at the VAT and 17.2 per cent in $V_{O_{2peak}}$, with an adherence rate of 83 per cent. A similar improvement was observed in a 4-week prehabilitation programme before liver resection[12]. As reported adherence rates to training sessions in prehabilitation programmes vary from 70 per cent on average in unsupervised programmes to 98 per cent on average in supervised programmes[13], an adherence rate of 83 per cent seems acceptable for the present semisupervised programme.

The moderate recruitment rate (68 per cent) might have led to selection bias, as the results of the programme are unknown for the patients who were not recruited. However, the main reason for non-participation was lack of a physiotherapist specialized 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 a tertiary referral centre with a large catchment area, which made it difficult to use the same physiotherapist for multiple patients. As well as compromising the recruitment rate, this logistical challenge resulted in each physiotherapist training only one or two patients, which limited the ability of physiotherapists to gain experience with the training protocol. Community-based perioperative care networks should be established, in which trained and competent physiotherapists, along with the patient and their informal support system, aim to make a patient fit for surgery, either in a home- or community-based context[14].

Strengths of this study were that the training sessions were personalized based on the steep ramp test, partly supervised by a specialised physiotherapist, supplemented with nutritional support, and that the effect of the programme was evaluated with CPET. An important limitation is the fact that adherence to the nutritional intervention was not monitored. Furthermore, not only does a patient's aerobic fitness need to be optimized before treatment, but their nutritional status, presence of anaemia, frailty, use/abuse of intoxicants, and low psychological resilience should also be addressed in a multimodal prehabilitation programme[15].

In the context of all recent evidence in favour of prehabilitation, the authors urge profound but swift dialogue on 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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*Disclosure.* The authors declare no conflict of interest.

## Supplementary material

Supplementary material is available at *BJS* online.

## Data availability

Data, analytical methods, and study materials will be available from the corresponding author (l.van.wijk@umcg.nl) upon reasonable request.

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