










Protocol

# Preoperative Nutritional Optimization and Physical Exercise for Patients Scheduled for Elective Implantation for a Left-Ventricular Assist Device—The PROPER-LVAD Study

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**Abstract:** Background: Prehabilitation is gaining increasing interest and shows promising effects on short- and long-term outcomes among patients undergoing major surgery. The effect of multi-modal, interdisciplinary prehabilitation has not yet been studied in patients with severe heart failure scheduled for the implantation of a left-ventricular assist device (LVAD). Methods: This randomized controlled multi-center study evaluates the effect of preoperative combined optimization of nutritional and functional status. Patients in the intervention group are prescribed daily in-bed cycling and oral nutrition supplements (ONS) from study inclusion until the day before LVAD-implantation. Patients in the control group receive standard of care treatment. The primary outcomes for the pilot study that involves 48 patients are safety (occurrence of adverse events), efficacy (group separation regarding the intake of macronutrients), feasibility of the trial protocol (compliance (percentage of received interventions) and confirmation of recruitment rates. Secondary outcomes include longitudinal measurements of muscle mass, muscle strength, physical function and quality of life, next to traditional clinical outcomes (30-day mortality, hospital and ICU length of stay, duration of mechanical ventilation and number of complications and infections). If the pilot study is successful, a larger confirmatory, international multicenter study is warranted.

**Keywords:** prehabilitation; medical nutrition therapy; in-bed cycling; left-ventricular assist device; trial protocol; clinical trial; oral nutrition supplements

## 1. Introduction

With more than 23 million diagnosed patients worldwide, heart failure remains a major public health problem [1,2]. With a life-time risk of 20–46% of being diagnosed with heart failure, the prevalence of heart failure ranges from about 1 to 12% worldwide [3] and about 10% in the elderly population [4,5]. Heart failure is a common cause of death and 50% of patients die within 5 years after the diagnosis [3,6].

When the symptoms of chronic heart failure are non-responsive to medical therapy, the implantation of a left-ventricular assist-device (LVAD) is one possible invasive treatment that is increasingly used as a definitive therapy for terminal heart failure or a bridge-to-transplant. Roughly 1000 LVAD systems are implanted in Germany every year [7]. From 2006 until 2016, 19,000 LVAD devices were implanted in the USA, with increasing numbers of new LVAD implants per year, as well as LVAD implants as destination therapy [1]. In-hospital mortality decreased significantly during the last few years and roughly 60–80% of the patients survived the first year after LVAD implantation [8,9] with a median survival time of 48 months [10].

However, all major surgical procedures are associated with systemic inflammatory response syndrome (SIRS). While SIRS is anticipated after cardiac surgery and LVAD implantation, this syndrome can cause multiple acute and persistent organ dysfunctions, perioperative complications, longer hospital stay and delayed rehabilitation [11–15]. Post-operative complications are a major determinant of morbidity, mortality, length of hospital stay, hospital costs and quality of life after heart surgery [16].

With an increasingly comorbid and elderly population with severe chronic heart failure (CHF) and reduced general conditions receiving more complex cardiac surgeries, new strategies are, therefore, urgently needed to improve the long-term outcome and quality of life of these patients [17–19]. The patient's nutritional status and muscle mass, along with other preoperative factors, such as age and comorbidities, influence the patient's post-operative clinical and functional outcome in the ICU and the years after discharge [20,21]. Prehabilitation involves optimizing the patient's health status before elective surgery. Possible strategies include optimization of the patients' nutritional and functional status via optimization of blood glucose and vital parameters to psychological interventions and beyond [15].

In patients with heart disease, preoperative ONS have been administered in the setting of elective cardiac surgery and patients with heart failure (Table 1), showing feasibility and safety, as well as good patient compliance. However, the benefits observed so far cannot be generalized and should lead to an increased interest in these subjects.

**Table 1.** Studies addressing preoperative oral nutrition supplements in cardiac surgery and chronic heart failure. Abbreviations: CHF: chronic heart failure, EF: ejection fraction, LOS: length of stay, NYHA: heart failure classified by New York Heart Association, ONS: oral nutrition supplements, TNF: tumor necrosis factor; QOL: quality of life.

Author and Year	Amount and Type of Patients	Nutrition Intervention	Results
Paccagnella 1994 [22]	6 patients with CHF and mitral valve disease	20–30 kcal/kg/d, 2 w before until 3 w after surgery	Proof of safety of nutrition in patients with severe CHF, clinical status improved
Tepaske 2001 [23]	50 patients before cardiac surgery	Immune enhancing ONS, 5–10 L during 5–10 d	No adverse effects Improvements in preoperative host defense, reduced number of postoperative infections, better renal function, reduced requirement of inotropics Trend towards reduced hospital LOS

Table 1. Cont.

Author and Year	Amount and Type of Patients	Nutrition Intervention	Results
Aquilani 2008 [24]	38 stable patients with CHF with sarcopenia and normal weight	Supplementation of essential amino acids for 8 w	Weight gain, increased walking capacity Improved insulin resistance (trend) Decreased lactate and pyruvate levels Improved exercise output and peak oxygen consumption
Rozenryt 2010 [25]	29 CHF patients, NYHA II–IV EF < 30%	ONS: 600 kcal, 20 g protein for 6 w	Increased body weight QOL significantly improved TNF-a levels systemically reduced

While several studies have proven the efficacy and safety of exercise in these patient groups, most studies focused on patients classified as moderate stage CHF and few studies investigated the effects of preoperative aerobic exercise training. To the authors' knowledge, no exercise studies regarding patients with end-stage heart failure or patients planned for ventricular assist devices are currently being carried out or have been published. However, an exercise protocol for patients planned for LVAD implantation should regard the severely reduced functional capacity, as well as the compromised hemodynamics, of this patient group. Therefore, it is necessary to compare preoperative LVAD patients to both patients with CHF, as well as critically ill cardiac surgery patients, and apply similar monitoring and exercise protocols to ensure maximum patient safety.

Exercise programs have been used in patients with CHF and in preoperative cardiac surgery and intensive care unit (ICU) patients, as described in Table 2. In-bed cycling is a physiotherapeutic approach, focusing on the lower limb muscles, which are especially affected by immobilization and are critical to ambulation and functional independence [26,27]. The technique can be used actively or passively and several studies also demonstrated benefits from passive exercise [28,29]. In-bed cycling has proven to be safe, well-tolerated and feasible in patients with heart failure and in critically ill patients. Thus, the treatment has gained popularity within the last few years and several studies are currently being conducted.

**Table 2.** Selected studies of exercise in patients with heart failure, preoperative cardiosurgical patients and ICU patients. Abbreviations: 6MWD: 6-min walk distance, BNP: brain natriuretic peptide, CABG: coronary artery bypass graft, CHF: chronic heart failure, ECMO: extracorporeal membrane oxygenation, EF: ejection fraction, HR: heart rate, ICU: intensive care unit, LOS: length-of stay, NYHA: heart failure classified by New York Heart Association, ONS: oral nutrition supplements, pVO<sub>2</sub>: peak oxygen consumption, SF-36: Short Form 36, TNF: tumor necrosis factor; QOL: quality of life.

Author and Year	Number and Type of Patients	Description of Exercise Intervention	Results
<b>Chronic Heart Failure</b>			
Flynn, O'Connor 2009 [30,31]	2331 stable out-patients NYHA II–IV, EF < 35%	Supervised aerobic exercise 15–35 min, 3 times/w 36 sessions, intensity: 60–70% of HR reserve	Improvement of self-reported health status Significant effect on physical and social limitations, symptoms and QOL Increased pVO <sub>2</sub> , exercise time and 6MWD
Sandri 2012 [32]	60 patients with left ventricular EF < 40%	Supervised bicycle ergometry 4 × 20 min/d, for 4 w, intensity: 70% of pVO <sub>2</sub>	Increased pVO <sub>2</sub> and maximum work output Decreased serum levels pro-BNP

Table 2. Cont.

Author and Year	Number and Type of Patients	Description of Exercise Intervention	Results
<b>Chronic Heart Failure</b>			
Lenk 2012 [33]	24 CHF patients, NYHA IIIb	Bicycle ergometry Supervised: 3–6/d, 5–20 min, for 3 w plus, At home: 20–30 min/d for 12 w Intensity: 60% of pVO <sub>2</sub>	Increase pVO <sub>2</sub> Reduction in myostatin mRNA and protein levels of myostatin
Hoellriegel 2013 [34]	37 CHF patients NYHA IIIb	Bicycle ergometry	Increase in skeletal muscle cross sectional area
<b>Preoperative Cardiac Surgery Patients</b>			
Arthur 2000 [35]	49 low-risk CABG	Supervised exercise + education 90 min twice/week for 8 weeks Intensity: 40–70% of functional capacity	Reduced hospital, ICU and postoperative LOS, improved QOL, greater participation in postop physical therapy
Herdy 2008 [36]	56 waiting CABG	Exercise program > 5 d	Shorter time to extubation, fewer postop pulmonary complications, shorter hospital LOS
Rosenfeldt 2011 [37]	17 elective cardiac surgery	Aerobic exercise and mental training 2 × 60 min/w for >2 w at 60% of max HR	No significant changes
Tung 2012 [38]	35 elective cardiac surgery, NYHA I–III	Individualized exercise using a treadmill 40–60 min, 1–2 /w, >3 times at 50–60% pVO <sub>2</sub>	Out of bed earlier, improvement in QOL
<b>Critically Ill Patients</b>			
Burtin 2009 [39]	90 critically Ill	Bedside cycling 20 min/d, 4/w Intensity: <70% of max. HR	Enhanced recovery of functional status and exercise capacity, increased muscle force Increased 6MWD and SF-36
Pires-Neto 2013 [40]	19 critically Ill	In-bed cycling 20 min	Demonstration of safety, minimal changes in vital parameters during passive cycling
Rahimi 2013 [41]	3 case reports on ECMO patients	Individualized in-bed cycling	Increased lower leg strength
Preiser 2014 [29]	27 critically ill	Passive in-bed cycling 2 × 30 min/d vs. 2 × 60 min/d	Less myofibrillar proteolysis No difference between groups
Kho 2015 [42]	688 critically Ill	In-bed cycling Mean: 2 sessions per patient (1–4)	Cycling patients received more physical therapy interventions and were more likely to be ventilated mechanically
Fossat 2018 [43]	312 critically ill adult patients	Early in-bed leg cycling 15 min/d plus electrical stimulation of the quadriceps muscles 50 min/d for 5 d/w	No difference in Medical Research Council score, ICU Mobility Score, ventilator-free days or outcomes assessed at 6 months
Nickels 2020 [44]	72 mechanically ventilated	In-bed cycling 30 min/d	No significant differences in muscle atrophy strength, function or quality of life
Waldauf 2021 [45]	150 mechanically ventilated < 72 h with expected ICU LOS > 7 d	Functional electrical stimulation-assisted Cycle ergometry, 90 min/d	No difference in Physical Component Summary of SF-36 at 6 months, ICU LOS, functional performance, rectus femoris cross-sectional diameter or muscle power

Table 2. Cont.

Author and Year	Number and Type of Patients	Description of Exercise Intervention	Results
<b>Critically Ill Patients</b>			
Berney 2021 [46]	162 mechanically ventilated with expected ICU stay $\geq$ 4 d	Median: 5 (IQR 3–9) functional electrical stimulation-assisted cycle ergometry > 5 d/w, median duration 56 (34–63) min/d	No differences between muscle strength at hospital discharge, cognitive impairment at 6 months, or secondary outcomes measured in-hospital and at 6- and 12-month follow-up

As shown above, a multitude of studies over the last few years have shown that neither the sole adequacy of energy-protein intake nor exercise alone are sufficient to induce anabolism in past trials and to significantly improve the nutritional and functional status of the patients. In addition, neither pure weight gain nor gain of fat mass without the buildup of muscle mass should be the main target of therapy, especially against the background of sarcopenic obesity. In the same vein, the pure gain of muscle mass does not always lead to improved physical function, which should be the overall aim to improve the patient's long-term outcome and quality of life. Therefore, the authors hypothesize that a combination of both exercise and nutrition may have a greater prehabilitation effect than one of the interventions given alone.

To our knowledge, there are no studies regarding the preoperative optimization of nutrition and physical exercise in patients scheduled for elective cardiac surgery or for LVAD implantation. Therefore, the PROPER-LVAD study aims to optimize the nutritional and functional status of patients scheduled for an elective LVAD implantation via a preoperative combined intervention that consists of oral nutritional supplements (ONS) and exercise (in-bed cycling).

## 2. Materials and Methods

### 2.1. Registration and Ethics

The study will be conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committees of all participating centers, including RWTH Aachen University (EK 313-19, initial date of approval 3 December 2019) and Bad Oeynhausen (AZ 2021-859\_1). This study was registered at clinicaltrials.gov (NCT04205760).

### 2.2. Study Design and Sites

This is a randomized controlled multi-center clinical pilot trial. A total of 40 patients will be recruited in the Heart and Diabetes Center NRW, Bad Oeynhausen and at the University Hospital RWTH Aachen in Germany. The coordination and project management will be performed by the leading site RWTH Aachen University.

This pilot study consists of the following 2 phases:

- Phase 1 is a non-randomized run-in phase, where only ONS are administered to 8 patients. This phase evaluates the safety of the ONS therapy alone in this group of hemodynamically compromised patients.
- Phase 2 is a randomized controlled clinical trial, where the full study protocol is administered to 40 patients. In Phase 2, patients are either randomized to the full study protocol, consisting of ONS + in-bed cycling, or to the control group (regular hospital diet and physiotherapy as per standard protocol only).

### 2.3. Patients

A total of 48 adult patients who are scheduled for the elective implantation of an LVAD are screened and enrolled consecutively. Written informed consent is obtained from all patients, after receiving written information and having the study procedures explained

and questions answered in a face-to face visit with a medical doctor with sufficient time to consider. Eligibility criteria are listed in Table 3.

**Table 3.** In- and exclusion criteria of the PROPER-LVAD study. Abbreviations: ECMO: extracorporeal membrane oxygenation, GFR: glomerular filtration rate, INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support classification; LVAD: left ventricular assist device.

Inclusion Criteria	Exclusion Criteria	Rationale for Exclusion
1. Adult patients ( $\geq 18$ years) 2. Patients suffering from end-stage heart failure and planned for elective LVAD implantation with the use of cardiopulmonary bypass (INTERMACS $> 1$ ) 3. Given informed consent  Additional cardiac surgery, such as bypass grafting, or valve repair is permitted	Hospital admission $< 5$ days prior to planned LVAD implantation	Not enough time for the patient to benefit from the intervention
	Patients on ECMO or INTERMACS score $\leq 1$	Unable to receive proposed intervention
	Patients already receiving intense nutritional support, in addition to normal nutrition upon hospital admission	Confounding of results
	Enteral nutrition is contraindicated	Unable to receive proposed intervention
	Pregnant or lactating patients	Unknown effects in fetus/child
	Patients with clinical fulminant hepatic failure (cirrhosis Child's class C)	Protein supplementation may be harmful in patients with severe liver disease
	Patients with severe clinical kidney failure (GFR $< 30$ mL/min) or requiring hemodialysis	Different nutritional and fluid requirements
	Known allergy or intolerance to study nutrients	Unable to receive proposed intervention
	Intracranial or spinal process affecting motor function	May not benefit from proposed intervention (i.e., different mechanism of muscle weakness)
	Lower extremity impairments that prevent cycling (e.g., amputation, knee/hip injury)	Unable to receive proposed cycling intervention
	Disabling neuropsychiatric disorders or language barriers	Unable to follow instruction or perform outcome assessments
	Weight $> 150$ kg	Exceeds maximum weight of cycle device
	Enrolment in an industry sponsored randomized trial within the last 30 days (co-enrolment in academic randomized trials will be considered on a case-by-case basis)	To avoid conflict of interests

## 2.4. Study Intervention

### 2.4.1. Nutrition Intervention and Monitoring

All patients receive a regular hospital diet according to hospital standard targeting of 2000 kcal and 48–98 g protein per day. All patients are screened for nutritional risk using the NRS 2002.

In the intervention group only, the ONS are started as soon as feasible after study inclusion for Phase 1 and after randomization for Phase 2, but no more than 24 h afterwards. The ONS are administered to the patient until the day before surgery, with the goal to administer the ONS for at least 5 consecutive days.

The ONS used in this study is the Fresubin<sup>®</sup> PRO kcal DRINK (Fresenius Kabi<sup>®</sup> Deutschland GmbH, Bad Homburg/Germany), which is a food for special medical purposes for use under medical supervision. Fresubin<sup>®</sup> PRO kcal DRINK is a nutritionally complete, high energy (2.4 kcal/mL), high protein (0.144 g/mL) milk shake-style nutritional supplement, enriched with vitamins, minerals and trace elements.

The ONS are provided in accordance with the patient's nutritional status. Since actual food intake is expected to be reduced up to 50% in this patient group, patients with high nutritional risk defined as NRS 2002  $\geq 3$  receive 3 ONS/day (equaling 1440 kcal and 86.4 g

protein), in addition to the regular hospital diet. Patients with low nutritional risk defined as NRS < 3 are provided 2 ONS/day (equaling 960 kcal and 57.6 g protein), in addition to the regular hospital diet. The nutritional intake of all patients is assessed during the entire study intervention period using the quarter-plate-method ([www.fightmalnutrition.eu](http://www.fightmalnutrition.eu) (accessed on 1 December 2017)).

Regular monitoring of blood sugars, electrolytes, phosphate, and triglycerides occur as per standard clinical protocol, but at least twice weekly. Possible adverse effects of ONS, such as nausea, vomiting, diarrhea and obstipation, are monitored daily, and the amount of nutrition and medication will be adjusted.

Special cases include the following:

- In the unlikely event that the patient is discharged from the hospital prior to LVAD implantation, the study ONS will be stopped at the day of discharge and further nutrition therapy will be left to the discretion of the following facility.
- If a single dose of ONS was failed to be administered to the patient, it can be made up for the next day, since it is the average protein and energy intake that will allow the patient to improve physical function and adverse effects, due to the fact that increasing the amount of ONS by a single unit on a day is not likely.
- If more than a single dose of ONS was failed to be administered to the patient, it shall not be made up for on the next day to avoid adverse effects for the patient.
- In case of gastrointestinal or metabolic intolerance, patients with fluid restriction and patients experiencing discomfort during the nutrition intervention, the dosage of ONS will be adjusted according to the clinical symptoms and blood work. This will allow the patients to consume one drink less per day than initially planned (e.g., 1 ONS/d in patients without nutritional risk or 2 ONS/d in patients with nutritional risk).

#### 2.4.2. Exercise Intervention and Monitoring

In Phase 2 only, in-bed cycling is started as soon as possible after randomization, but no more than 24 h thereafter. The in-bed cycling is delivered once daily for 50 min for at least 5 days a week, with vigorous verbal encouragement from the trained research staff who are delivering the intervention to promote active cycling. The cycling is continued until evening before LVAD implantation.

Standard safety criteria will be assessed prior to initiating cycling treatments. The cycling is supervised by medically trained research staff. The patients are placed in a semi-recumbent position. The patient's heart rate and transcutaneous oxygen saturation of blood (SpO<sub>2</sub>) is monitored continuously; the systolic and diastolic blood pressure is measured non-invasively in 2.5-min intervals. The in-bed cycling is performed actively with graded increasing resistance or passively, according to our protocol (Figure 1). There are 3 cycling periods for 12 min each with a 2-min assisted interval in-between the cycling periods, allowing the patient to rest. Before and after the in-bed cycling, there is a 5-min warm-up, as well as a 5-min cool-down. In between the cycling periods, the resistance of the ergometer will be adjusted according to the physiologic response of the patient, as shown in Figure 1.

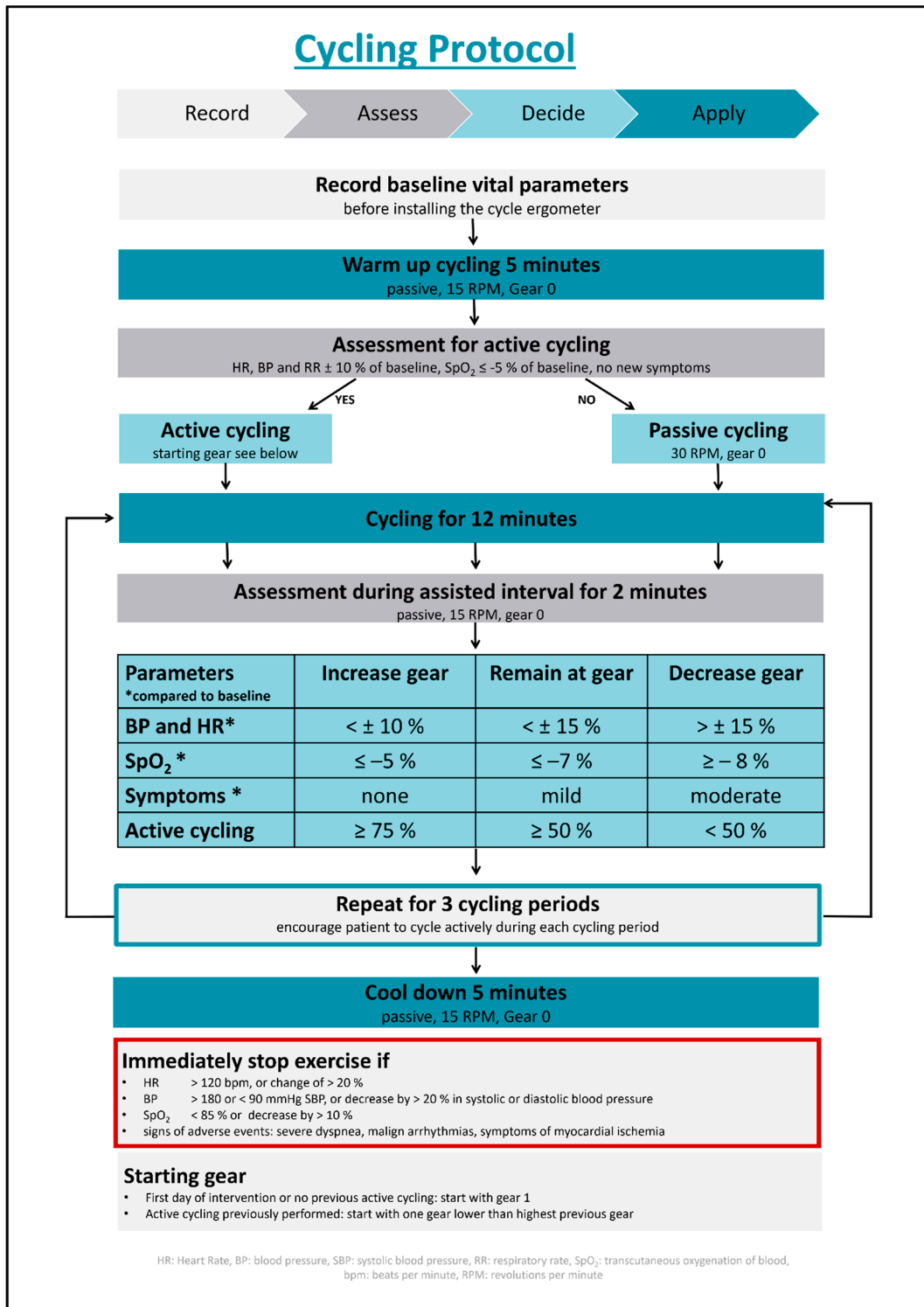
The ergometer used in this study is the MotoMed Letto II cycle ergometer (RECK-Technik GmbH & Co. KG Medizintechnik, Betzenweiler/Germany). It is a bed cycling device approved for intensive care and rehabilitation. This device has one passive gear, a motor assisted gear and several active gears, ranging from a very light to very heavy resistance.

**Monitoring of adverse effects** related to bedside cycling will occur continuously during all exercise sessions. The exercise will immediately be terminated if one of the following adverse effects occurs:

- Severe dyspnea, dizziness, or syncope;
- New malign arrhythmias, new signs of myocardial ischemia;
- Non-physiological reactions of vital parameters, including the following:
  - Heart rate > 120 bpm, or change of >20%;

- Blood pressure (BP) > 180 mmHg systolic BP or decrease by 20% in systolic or diastolic BP;
- Transcutaneous oxygen saturation < 85% or decrease by >10%.

Terminated cycling sessions will be attempted to be completed on the same day, after allowing the patient to rest for a while.



**Figure 1.** Cycling protocol. Abbreviations: BP: blood pressure, HR: heart rate, RPM: rotations per minute, RR: blood pressure; SPO<sub>2</sub>: transcutaneous oxygen saturation.



### Special cases include the following:

- In the unlikely event that the patient is discharged from the hospital prior to LVAD implantation, the exercise will be stopped at day of discharge.
- If an exercise session was missed by the patient, it should not be made up for the next day.
- If an exercise intervention needs to be terminated early due to interruptions, it will be attempted to be completed during the same day, adding warm-up and cool-down phases to the remaining minutes of exercise.

### 2.5. Control Group

Patients randomized to the control group will receive a standard hospital diet. Patients in the control group will not be offered ONS as standard of care. If the treating medical team decides that ONS are detected in a patient and there is no clinical equipoise regarding the administration of ONS, the patient should not be included in this study.

Patients randomized to the control group will receive standard physiotherapy, not involving cycle-ergometry.

### 2.6. Study Duration

The total study duration will be 48 months (including set-up, final evaluation and statistics). The recruitment phase started in January 2022 and will end in June 2023 (15 months). The planned duration of study inclusion per patient will be ~2 weeks for Phase 1 and 7 months for Phase 2, the latter including the perioperative hospital stay (~1 month) and a follow-up period of 6 months.

### 2.7. Outcomes

The primary goal of this pilot study will be to prove the safety and feasibility of the study intervention. The data collected will provide a basic concept for a following larger-scale clinical trial that aims to evaluate the clinical significance of oral nutrition support and exercise in the population of high-risk cardiac surgery patients with LVAD implantation. For Phase one, only safety and compliance will be determined. In Phase 2, the safety and feasibility will be determined, as summarized in Table 4.

**Table 4.** Primary outcome parameters. Abbreviations: ONS: oral nutrition supplements.

Outcome Parameter	Description	Target
Safety	Occurrence of adverse effects	
Feasibility	Aborted cycling interventions	
Compliance	Percentage of patients receiving the prescribed interventions within 24 h	>80%
	Percentage of interventions administered to the patient	>80%
Efficacy	Effective separation of control and intervention group regarding caloric and protein supplementation	>10%
Recruitment	Successful recruitment aspired number of patients/month	>2 patients/month
Contamination	Avoidance of administration of ONS and cycling intervention in the control group	<5%

The secondary outcomes include longitudinal measurements of the following parameters at study inclusion, day before surgery, ICU and hospital discharge and scheduled at routine follow ups at 3 and 6 months after surgery:

- Muscle mass (quadriceps muscle layer thickness);
- Muscle strength (handgrip strength, quadriceps strength);

- Function (6-min walk distance, Short Physical Performance Battery, Functional Status Score for the ICU, Manual Muscle Testing, Clinical Frailty Scale, Barthel Index, Lawton Instrumental and Katz Activities of Daily Living, and Mini Mental State Exam);
- Quality of life (Short Form 36).

In addition, classical clinical outcomes (30-day mortality, hospital and ICU-length of stay, duration of mechanical ventilation, number of complications and infections) will be evaluated.

### 3. Discussion and Outlook

To the best of authors knowledge, this is the first study to evaluate the functional and morphological efficacy of a combined nutrition and exercise intervention as prehabilitation for patients scheduled for LVAD implantation. If this intervention protocol proves to be feasible in the pilot study, it could be considered and used as a preparation program for patients scheduled for LVAD implantation in clinical practice. If this intervention is proven to be effective in a following confirmatory clinical trial in LVAD patients, the combined intervention has the potential to dramatically change the current clinical practice and also benefit other elective (high-risk) cardiac surgeries that involve patients with high nutritional risk and reduced functional status, respectively. These new and additional therapeutic targets may help us to improve perioperative and long-term outcomes of these patients.

**Author Contributions:** Conceptualization and methodology: A.H. (Aileen Hill), C.S. and D.K.H., together with R.R., P.M., G.E., V.v.D. A.B., B.N., H.F., M.M., B.P., A.H. (Assad Haneya), R.Z. and A.M. Validation: A.H. (Aileen Hill) and C.S. Investigation: A.H. (Aileen Hill), C.S., A.H. (Aileen Hill), C.S. and D.K.H., together with R.R., P.M., G.E., V.v.D. A.B., B.N., H.F., M.M., B.P., A.H. (Assad Haneya), R.Z. and A.M. Resources: A.H. (Aileen Hill), C.S. and D.K.H. Data curation: A.H. (Aileen Hill), C.S. and V.v.D. Writing—original draft preparation: A.H. (Aileen Hill). Writing—review and editing: A.H. (Aileen Hill), C.S. and D.K.H., together with R.R., P.M., G.E., V.v.D. A.B., B.N., H.F., M.M., B.P., A.H. (Assad Haneya), R.Z. and A.M. Visualization: A.H. (Aileen Hill). Supervision: C.S., R.R., V.v.D., P.M., A.B. and B.N. Project administration: A.H. (Aileen Hill), C.S. and V.v.D. Funding acquisition: A.H. (Aileen Hill) and C.S. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** The study is conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committees of all participating centers, including RWTH Aachen University (EK 313-19, initial date of approval 3 December 2019) and Bad Oeynhausen (AZ 2021-859\_1).

**Informed Consent Statement:** Written informed consent was and will be obtained from all subjects involved in the study.

**Data Availability Statement:** The data of this study will be published in a peer-reviewed journal and on [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT04205760) (<https://clinicaltrials.gov/ct2/show/NCT04205760> (accessed on 25 September 2022)).

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