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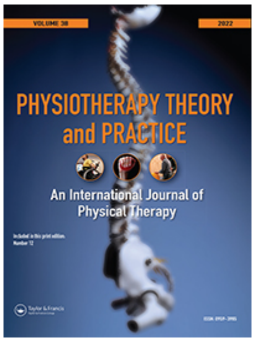

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Submaximal cardiopulmonary exercise testing to assess preoperative aerobic capacity in patients with knee osteoarthritis scheduled for total knee arthroplasty: a feasibility study

Anke Kornuijt PT, MSc[a,b,c], Bart C. Bongers PhD[d,e], Rik G.J. Marcellis PT, PhD[f], and Antoine F. Lenssen PT, PhD[f]

[a]Sports and Orthopedics Research Center, Anna Hospital, Geldrop, the Netherlands; [b]Department of Physical Therapy, Anna Hospital, Geldrop, the Netherlands; [c]Physical Therapy Sciences, Program in Clinical Health Sciences, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; [d]Department of Nutrition and Movement Sciences, School of Nutrition and Translational Research in Metabolism (NUTRIM), Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands; [e]Department of Epidemiology, Care and Public Health Research Institute (CAPHRI), Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands; [f]Department of Physical Therapy, Maastricht University Medical Center+, Maastricht, the Netherlands

ABSTRACT

Objective: To investigate the feasibility of submaximal cardiopulmonary exercise testing (CPET) in patients with knee osteoarthritis (OA) scheduled for primary total knee arthroplasty (TKA) surgery. Secondly, to assess their preoperative aerobic capacity.

Methods: In this observational, single-center study, participants performed a submaximal CPET 3–6 weeks before surgery. To examine their experiences, participants completed a questionnaire and one week later they were contacted by telephone. CPET was deemed feasible when five feasibility criteria were met. Aerobic capacity was evaluated by determining the oxygen uptake (VO_2) at the ventilatory anaerobic threshold (VAT) and oxygen uptake efficiency slope (OUES). OUES values were compared with two sets of normative values.

Results: All feasibility criteria were met as 14 representative participants were recruited (recruitment rate: 60.9%), and all participants were able to perform the test and reached the VAT. No adverse events occurred, and all participants were positive toward submaximal CPET. The median VO_2 at the VAT was 12.8 mL/kg/min (IQR 11.3–13.6). The median OUES/kg was 23.1 (IQR 20.2–28.9), 106.4% and 109.4% of predicted.

Conclusion: Submaximal CPET using cycle ergometry seems feasible in patients with knee OA scheduled for TKA surgery to evaluate preoperative aerobic capacity.

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Osteoarthritis; knee; exercise testing; physical fitness; feasibility

Introduction

There is uncertainty whether it is feasible to perform submaximal cardiopulmonary exercise testing (CPET) using cycle ergometry in patients with knee osteoarthritis (OA) scheduled for total knee arthroplasty (TKA). As part of usual care before undergoing TKA patients are assessed for risk factors for a delayed postoperative recovery of physical functioning by measuring preoperative physical fitness (Maastricht University Medical Center+, 2021; Van der Sluis et al., 2017). Various practical performance-based tests are used for the physical fitness assessment mainly to assess preoperative muscle strength and functional mobility. As such, handgrip strength, timed up-and-go (TUG) test (Podsiadlo and Richardson, 1991) and the de Morton mobility index (DEMMI) (De Morton, Davidson, and Keating, 2008) are frequently used. However, aerobic capacity is normally not part of the preoperative assessment prior to TKA.

In patients undergoing cancer surgery (Cuijpers et al., 2022; Steffens et al., 2021) or intra-abdominal surgery (Moran et al., 2016) it is already demonstrated that a higher preoperative aerobic capacity is associated with better postoperative outcomes (i.e. lower perioperative morbidity and mortality and reduced length of stay). Preoperative aerobic capacity in patients scheduled for TKA may also be associated with postoperative outcomes and could therefore have added value in preoperative risk assessment to guide perioperative care. Before being able to investigate this association it is necessary to have a feasible exercise test that can be used to accurately assess preoperative aerobic capacity.

CPET involves the assessment of the integrative cardiorespiratory responses during progressively increasing exercise up to exhaustion and is considered the gold standard for objectively measuring aerobic capacity by

CONTACT Anke Kornuijt A.Kornuijt@st-anna.nl Sports and Orthopedics Research Center, Anna Hospital, Bogardeind 2, 5664 EH Geldrop, the Netherlands

the achieved oxygen uptake (VO_2) at peak exercise (VO_{2peak}) (Levett et al., 2018). Submaximal CPET is considered more suitable than maximal CPET in patients with end-stage knee OA, as peak exercise is more likely limited in these patients due to musculoskeletal symptoms (e.g. joint and muscle pain) rather than generalized fatigue or dyspnea as a result of maximally stressing the cardiovascular or pulmonary system (Philbin, Ries, and French, 1995). In addition, maximal CPET can provoke and/or aggravate knee pain during moderate-to-high exercise intensities in the already affected knee joint (Roxburgh et al., 2021).

In the few studies which examined maximal aerobic capacity using CPET prior to TKA surgery, the minimum threshold values indicative of a maximal exercise response (in these studies defined as attaining ≥ 80% of the age-predicted maximum heart rate (220 minus age) and/or a respiratory exchange ratio at peak exercise of ≥ 1.00) were not achieved in 11–28% of the patients (Philbin, Groff, Ries, and Miller, 1995; Philbin, Ries, and French, 1995) due to musculoskeletal limitations (Philbin, Ries, and French, 1995). In patients unable to perform a maximal effort during CPET, the attained VO_{2peak} does not accurately reflect their true aerobic capacity. Furthermore, approximately 40% of the patients could not cycle due to a restricted knee flexion range of motion or pain, possibly leading to selection bias (Philbin, Groff, Ries, and Miller, 1995; Philbin, Ries, and French, 1995; Ries, Philbin, and Groff, 1995; Ries et al., 1996). One study reported recruitment difficulties (recruitment rate 37%), of which an important reason was that eligible patients (15%) did not volunteer because of fear of inability to perform CPET (Philbin, Ries, and French, 1995).

Instead of focusing on determining a valid VO_{2peak} that requires a maximal effort submaximal CPET-derived variables like the VO_2 at the ventilatory anaerobic threshold (VAT) and the oxygen uptake efficiency slope (OUES) can alternatively be used as indicators for aerobic capacity (American Thoracic Society and American College of Chest Physicians, 2003). Studies have shown a strong correlation ($r \geq 0.80$) between these two submaximal variables and VO_{2peak} (Baba et al., 1996; Bongers, Berkel, Klaase, and Van Meeteren, 2017) making it of interest to further investigate the value of these submaximal aerobic capacity variables for optimizing preoperative risk assessment and perioperative management in TKA surgery. Therefore, the primary objective of this study was to investigate the feasibility of submaximal preoperative CPET in patients with knee OA scheduled for TKA in three domains as defined by Orsmond and Cohn (2015): 1) recruitment rate of participants who are representative of the target study population; 2) feasibility of submaximal CPET using cycle ergometry; and 3) acceptability of CPET as reported by participants. Secondly, this study will explore preoperative aerobic capacity levels of the study population using submaximal variables and compare these results with normative values.

Methods

Study design and setting

This observational single-center feasibility study was performed in May and June 2021 at the Anna Hospital, Geldrop, the Netherlands. The initial purpose of a multicenter study including also patients at the Maastricht University Medical Center (MUMC+), Maastricht, the Netherlands could not be realized since no TKA procedures were performed at the MUMC+ in this timeframe due to the COVID-19 pandemic. The MUMC+ was responsible for the integrity and conduct of the study. The study protocol was approved by the Medical Ethics Committee of the MUMC+ (METC azM/UM, reference 21–009) and was registered in ClinicalTrials.gov (ID number NCT04773262). The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (Vandenbroucke et al., 2007).

Study participants and procedure

Participating orthopedic surgeons referred all patients scheduled for TKA for a standard preoperative assessment of physical fitness by a physical therapist. Potential participants for this study received verbal and written information about the study by the surgeon and, if interested, contacted the investigator who gave them further verbal information. Written informed consent was given face-to-face by the patient and investigator prior to participating in any study-related activities, after which the investigator assessed the eligibility criteria. Inclusion criteria were: 1) scheduled for primary unilateral TKA surgery at the Anna Hospital; 2) diagnosis of knee OA; 3) CPET planned three to six weeks before TKA surgery following the preoperative assessment; and 4) sufficient mastery of the Dutch language. Exclusion criteria were: 1) contraindications for CPET according to the American Thoracic Society and American College of Chest Physicians statement on CPET (American Thoracic Society and American College of Chest Physicians, 2003) or based on the American Heart Association/American College of Sports Medicine health/fitness facility pre-participation screening questionnaire (Balady et al., 1998); 2) unable to get on and off a cycle ergometer; 3) serious comorbidities (e.g. malignancy and stroke); 4) cognitive impairments; or 5) unable to sign the informed consent form.

Recruited patients were first subjected to the preoperative assessment of physical fitness. Demographic data and participant characteristics including the use of walking aids, smoking status, and degree of comorbidities (American Society of Anesthesiologists (ASA) classification (Mayhew, Mendonca, and Murthy, 2019) and Charnley classification (Dunbar, Robertsson, and Ryd, 2004)) were collected. The Oxford knee score, a 12-item questionnaire regarding pain and function of the knee (scores range from 0 to 48) with higher scores indicating better knee function and less pain was registered as well (Dawson, Fitzpatrick, Murray, and Carr, 1998). Patients were asked to complete this baseline questionnaire as part of usual care when the shared decision for surgery was made.

Subsequently, participants performed a submaximal CPET in an upright position on an electronically braked cycle ergometer (Lode Corival CPET, Lode B.V. Groningen, the Netherlands) supervised by a trained clinical exercise physiologist. Participants were preinstructed to continue their regular medication but avoid caffeine, alcohol, and cigarettes at the test day (Levett et al., 2018). Participants were also advised to abstain from vigorous physical activity the day before the test and at the test day, as well as to not consume a large meal in the two hours before the test (Levett et al., 2018). Seat height of the cycle ergometer was adjusted to the participant's leg length. Before commencement of the test, spirometry was performed to assess the forced expiratory volume in one second (FEV_1) obtained from maximal flow-volume curves (Vyntus CPX, Vyaire Medical, Hoechberg, Germany). The highest value of three technically well-executed maneuvers was recorded. In addition, the use of beta blockers was registered. Submaximal CPET included a resting measurement of 3 min, followed by 3 min of unloaded cycling where after the work rate increased progressively by 7.5, 10, 12.5, or 15 W/min as a continuous ramp protocol, depending on the patient's subjective physical fitness level. Work rate gradually increased throughout the ramp phase of the test with the pre-selected protocol.

During the incremental phase, participants were asked every minute to indicate their level of perceived effort using the 6–20 Borg scale for rating of perceived exertion (RPE) (Borg, 1970), which was carefully explained to them prior to the test. Throughout the test, participants were instructed to continue cycling at a pedaling rate between 60 and 80 revolutions per minute (Bongers, Berkel, Klaase, and Van Meeteren, 2017; Tomlinson et al., 2021) until they felt unable to continue due to cardiovascular and/or musculoskeletal complaints, or when they wanted to stop volitionally. To ensure submaximal CPET, the clinical exercise physiologist ended the test when the participant rated the perceived effort as 'hard,' defined as a score ≥ 15 on the 6–20 Borg scale for RPE, even in case the participant was able to continue cycling without complaints. This was done to prevent the possible provocation and/or aggravation of knee pain and associated complaints to the affected knee joint afterward. In addition, previous research in patients referred to an outpatient cardiovascular screening demonstrated that about 95% of the patients reached the VAT with a 6–20 Borg RPE score < 15 (Scherr et al., 2013). The test ended with unloaded cycling to recover.

During CPET, participants breathed through a facemask (Hans Rudolph, Kansas City, MO, USA) connected to an ergospirometry system (Vyntus CPX, Vyaire Medical, Hoechberg, Germany) that was calibrated for respiratory gas analysis measurements (i.e. ambient air and a gas mixture of 16% oxygen and 5% carbon dioxide) and volume measurements using a high flow of 2 L/s followed by a low flow of 0.2 L/s. Flow meter and gas analyzers were connected to a computer which calculated breath-by-breath minute ventilation, VO_2, and carbon dioxide production. Heart rate was measured by continuous 12-lead electrocardiography.

Shortly after the exercise test, acceptability of the CPET procedure was examined by a questionnaire to explore the subjective experiences and perceptions of participants. The questions were drafted by the research team according to the American Thoracic Society and American College of Chest Physicians statement on CPET (2003) and four constructs of the theoretical framework of acceptability, namely, 1) 'affective attitude' (feelings); 2) 'burden' (amount of effort); 3) 'self-efficacy' (confidence); and 4) 'intervention coherence' (understanding of CPET) (Sekhon, Cartwright, and Francis, 2017) (Appendix I). The construct 'perceived effectiveness' was evaluated by the investigators by verifying whether the participants had reached the VAT. Two constructs: 1) 'ethicality' defined as 'the extent to which CPET has good fit with an individual's value system'; and 2) 'opportunity costs' defined as 'the extent to which benefits, profits, or values must be given up to engage in CPET,' could not be evaluated as patients volunteered to participate in this feasibility study. However, both constructs are important to evaluate when considering implementing CPET in routine practice.

Items that were added to the questionnaire included the reason to terminate CPET and the perceived willingness of participants to perform CPET again in the future. The measurement of pain perception in the week before CPET and directly after CPET, motivation, burden, self-efficacy, and the extent of feeling well informed about the aim, performance, and possible side effects of the CPET were recorded, using the numeric rating scale-11 (NRS-11). The pain NRS is a reliable and valid pain measurement with a minimal detectable change of 1.3 in patients with knee pain due to OA (Alghadir, Anwer, Iqbal, and Iqbal, 2018). One week after the exercise test the investigator contacted the participants by phone to: 1) verify whether any CPET-related physical complaints had occurred; 2) measure the pain perception during the week after CPET (NRS-11); 3) evaluate whether they changed their opinion concerning performing CPET again in the future; and 4) whether we could improve anything during the entire process (Appendix II). An overview of the assessments during the study is presented in Figure 1.

During all assessments, strict infection control practices were followed, according to the hospital COVID-19 guidelines. This meant the use of facemasks for participants (except during CPET), caregivers, and investigators, keeping at least 1.5-m distance when possible, adequate hand hygiene, and cleaning and disinfection of equipment.

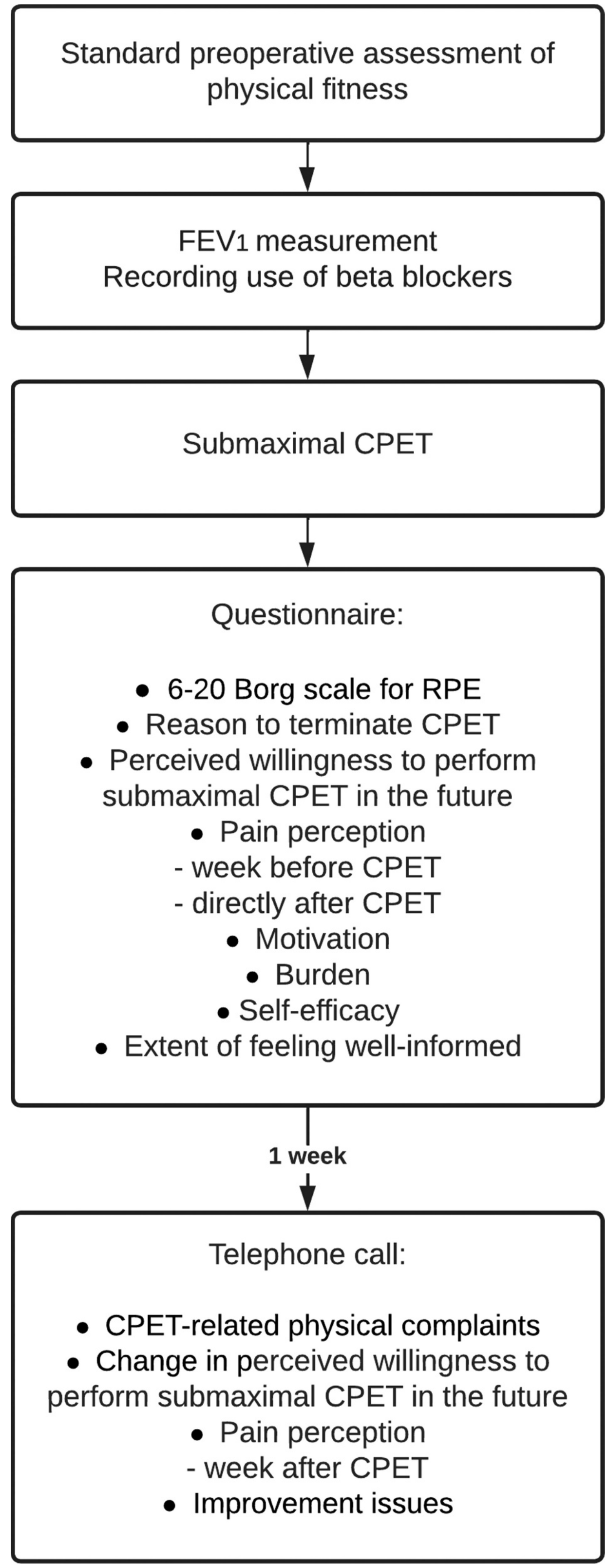

Figure 1. Overview of assessments.

Study outcomes

The primary outcome of the present study was the feasibility of submaximal CPET, as operationalized by five feasibility criteria, specifically: 1) a recruitment rate for study participation ≥ 20%; 2) a CPET performance rate ≥ 90%; 3) a CPET success rate ≥ 90%; 4) no occurrence of adverse events during CPET (0%); and 5) a positive attitude toward performing CPET again in ≥80% of the participants. Recruitment rate was defined as the percentage of eligible patients that participated (signed informed consent). Reasons for nonparticipation in the study were also explored. Previous physical therapy studies within the MUMC+ had shown a recruitment percentage ≤ 20%. Performance rate was calculated as the percentage of recruited participants who performed submaximal CPET. They were able to pedal the cycle ergometer with a pedaling frequency ≥ 60 revolutions per minute and cycling was not hindered by restricted knee flexion. Success rate was defined as the percentage of participants who reached the VO_2 at the VAT during the submaximal CPET procedure. Safety was assessed by recording any adverse events (e.g. faintness and chest pain suggestive of ischemia) that occurred during or after the test. Finally, a positive attitude toward CPET was defined as willingness to perform submaximal CPET again in the future. As recommended by Thabane et al. (2010) the feasibility targets for success were defined a priori by the research team and were consensus-based.

The secondary outcome of the current study was the aerobic capacity of the study population, indicated by the VO_2 at the VAT and the OUES, presented both at the individual and group level. VO_2 at the VAT was determined independently by two trained investigators (BB and AK) using both the ventilatory equivalents method (Whipp, Ward, and Wasserman, 1986) and the V-slope method (Beaver, Wasserman, and Whipp, 1986) and expressed in absolute (mL/min) and relative values (mL/kg/min). A consensus discussion was planned between the two investigators to reach agreement in all patients. A previous study showed high agreement in determining the VAT in a large cohort of asymptomatic volunteers with an intraclass correlation coefficient (ICC) of 0.95 (95% confidence interval (CI) 0.95–0.96) and a mean difference of 5 mL/min (95% limits of agreement ± 161 mL/min) (Kaczmarek et al., 2019). Work rate and heart rate were also recorded at the VAT. The OUES was mathematically determined from the linear relationship of VO_2 versus the logarithm of the minute ventilation during exercise using all test data from the start of the work rate increments up to test termination expressed in absolute and relative values (Baba et al., 1996). High intra-test reliability has been found for the OUES in healthy participants with ICCs ranging from 0.89 to 0.99 between submaximal (OUES calculated using the first 70% and 90% of the exercise data) and maximal derived values of OUES, indicating that it is an effort-independent measure that is highly correlated with VO_{2peak} and VO_2 at the VAT (Akkerman et al., 2010; Baba et al., 1996; Bongers, Berkel, Klaase, and Van Meeteren, 2017). The test–retest reliability coefficient of OUES was 0.93 (Van Laethem, De Sutter, Peersman, and Calders, 2009). In addition, OUES values of the participants were compared with normative values of healthy participants from two studies: 1) participants from Germany without structural heart disease, or echocardiographic or lung function pathology (Barron et al., 2015); and 2) participants from the United States of America free of known cardiac disease, cerebrovascular disease, and musculoskeletal impairment (Hollenberg and Tager, 2000). Hence, OUES values of the total group were also expressed as a percentage of predicted value using the predictive equations of these studies.

Sample size justification

Sample size estimation was based on justification (Thabane et al., 2010) that the feasibility study was large enough to provide useful information about participant experiences and attitude toward submaximal CPET. With a sample size of 12 participants, the 90% CI of reaching the VAT in ≥ 90% of the participants will be ± 14%, which is considered acceptable. With at least 12 participants, continuous variables of aerobic capacity will yield an adequate estimate of the mean and variance, resulting in an acceptable width of the confidence interval (Julious, 2005; Moore, Carter, Nietert, and Stewart, 2011).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (version 25.0; IBM, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to evaluate primary (feasibility) and secondary (aerobic capacity) study outcomes and characteristics of the study population. Categorical variables were presented as numbers and proportions. For continuous variables, normality was assessed visually (e.g. histograms and boxplots) and through the Shapiro–Wilk test. Normally distributed data were described as mean ± standard deviation (SD), while median and interquartile range (IQR) were used for non-parametric data (Ghasemi and Zahediasl, 2012). The correlation between the VO_2 at the VAT and OUES was evaluated by Pearson's r for normally distributed data, or Spearman's rho for non-normally distributed data, as appropriate (Schober, Boer, and Schwarte, 2018). A P-value < 0.05 was considered statistically significant. To examine the representativeness of the study population, age, and sex were compared between participants and all patients with knee OA who performed preoperative risk assessment prior to TKA during the study period. To be representative, the percentage of females was allowed to deviate by a maximum of ± 20%, whereas age had to be within 1 SD of the mean, or within the IQR using the median, according to distribution type.

Results

During the study period, a total of 34 patients with knee OA were scheduled for TKA, of which there were 23 eligible patients (67.6%). Of these eligible patients 14 were willing to participate and provided informed consent (recruitment rate of 60.9%). A flow chart, including reasons for nonparticipation of nine eligible patients is presented in Figure 2.

Participant characteristics are summarized in Table 1. The age (median 73.5 years (IQR 65.8–82.3)) and sex (64.3% female) of the participants were similar to the age (median 69.9 years (IQR 63.1–77.7)) and sex (58.8% female) of all patients who participated in preoperative assessment of physical fitness during the study period. All criteria for feasibility were met (Figure 2), as the

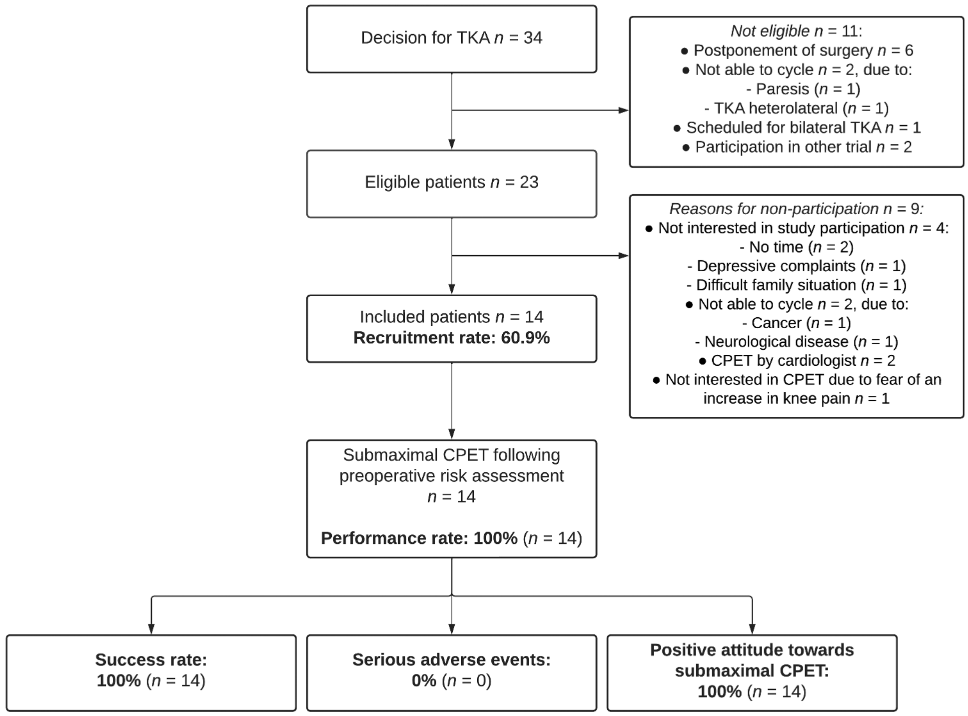

Figure 2. Study population flow chart.

recruitment rate was 60.9%, all participants were able to perform the test, all participants reached the VAT, no adverse events occurred, and all participants were positive toward submaximal CPET. Reasons for participants to be willing to perform submaximal CPET again in the future were that it does not require a maximal effort and that they perceived submaximal CPET as a relevant experience to gain more insight in their health status.

Results regarding acceptability of CPET are summarized in Table 2. Participants perceived the effort during exercise testing as 'hard' (median Borg RPE score of 15, ranging from 13 to 17). The clinical exercise physiologist terminated CPET in 10 participants (71.4%), all due to achieving a 6–20 Borg scale for RPE score ≥ 15. Four participants (28.6%) stopped CPET themselves because of knee pain (n = 1), dyspnea (n = 1), both pain and dyspnea (n = 1), or to prevent the occurrence of knee pain (n = 1).

They rated their pain at three time points with a median NRS score of: 1) 5.0 (IQR 4.8–6.0) in the week before CPET; 2) 4.5 (IQR 2.0–5.3) directly after CPET; and 3) 6.0 (IQR 5.0–7.0) during the week after CPET. At an individual level, four participants (28.6%) experienced more pain in the knee during the week after submaximal CPET. Participants were well informed about and motivated to perform submaximal CPET (both median NRS 10.0, IQR 9.0–10.0). Most patients were confident in performing submaximal CPET with their OA knee (median NRS 8.0, IQR 6.5–8.3). Only the facemask during CPET was experienced somewhat burdensome (median NRS 4.5, IQR 2.0–7.3).

Table 3 displays the aerobic capacity of the study population. The median VO_2 at the VAT was 990 mL/min (IQR 877–1169) and 12.8 mL/kg/min (IQR 11.3–13.6). The median OUES was 1923 (IQR 1586–2558) and 23.1 when normalized for body mass (IQR 20.2–28.9). The median OUES was higher than predicted OUES values, regardless of used reference values, respectively, 106.4% (Barron et al., 2015) and 109.4% of predicted (Hollenberg and Tager, 2000). Individual values of VO_2 at the VAT and OUES of the patients are presented in Figure 3. Four patients (28.6%) had an OUES value that was lower than predicted. A strong positive correlation (Schober, Boer, and Schwarte, 2018) was found between the absolute VO_2 at the VAT and the absolute OUES, indicated by a Spearman's rho of 0.84 ($P < .001$).

Discussion

This study aimed to investigate the feasibility of submaximal CPET in patients with knee OA scheduled for TKA surgery. Main results show that a majority of the target population volunteered to participate in this study, of which all could perform the test procedure and reached the VAT, indicating that this submaximal

Table 1. Characteristics of study participants (n = 14).

Participant characteristics	Outcome
Age (years), median (IQR)	73.5 (65.8–82.3)[#]
Female, *n* (%)	9 (64.3)[#]
Oxford knee score (0–48)[a], mean ± SD	26.9 ± 5.7
Body mass (kg), median (IQR)	
Male	100.1 (87.7–108.4)
Female	76.0 (68.7–83.8)
Body height (cm), median (IQR)	
Male	174.1 (169.7–177.2)
Female	159.8 (152.2–167.9)
Body mass index (kg/m^2), median (IQR)	
Male	33.0 (27.9–37.7)
Female	30.3 (27.6–32.0)
Surgery side right knee, *n* (%)	9 (64.3)
Use of beta blockers, *n* (%)	3 (21.4)
Smoking status, *n* (%)	
Current smoker	0 (0.0)
Previous smoker	6 (42.9)
Never smoked	8 (57.1)
Comorbidities	
ASA classification[b], *n* (%)	
I	1 (7.1)
II	10 (71.4)
III	3 (21.4)
IV	0 (0.0)
Charnley classification[c], *n* (%)	
A	2 (14.3)
B	10 (71.4)
C	2 (14.3)
Use of a walking aid, *n* (%)	
In-house	0 (0.0)
Outside	2 (14.3)[d]

ASA, American Society of Anesthesiologists; IQR, interquartile range; *n*, number; SD, standard deviation; [a]Total score ranging from the worst functional outcome of 0 to a best functional score of 48 (Dawson, Fitzpatrick, Murray, and Carr, 1998): data from 1 patient was missing; [b]Higher score indicates less fit for surgery (Mayhew, Mendonca, and Murthy, 2019); [c]Indication of the function of the knee with regard to the ability to walk, with C less favorable (Dunbar, Robertsson, and Ryd, 2004); [d]One patient used crutches, one patient used a walker outside. [#]Representative characteristic; all patients who performed preoperative risk assessment in the study period (n = 34) had a median age of 69.9 years (IQR 63.1–77.7) and 58.8% (n = 20) was female.

CPET procedure seems feasible. Additionally, the acceptability was affirmed as no adverse events occurred and all participants indicated they would be willing to perform submaximal CPET again. Therefore, submaximal CPET seems suitable to evaluate aerobic capacity in this population by using the VO_2 at the VAT and OUES.

Half of the participants experienced some CPET-related complaints in the week after the CPET like muscle strain experienced for 1 – 3 days (n = 2, 14.3%), fatigue experienced the same day or the day after the CPET (n = 2, 14.3%), or more pain in the knee scheduled for surgery during the week after the CPET (n = 4, 28.6%). Although a difference of only one point in median pain NRS is not considered clinically relevant (Alghadir, Anwer, Iqbal, and Iqbal, 2018) at the group level (pre-CPET score of 5.0 versus a score of 6.0 during the week after submaximal CPET) an increase in knee pain can be unpleasant for an individual. Therefore, this should be stated clearly prior to CPET performance. Despite these complaints experienced by our study population all participants had a positive attitude toward CPET. This may be due to the fact that extensive information about submaximal CPET was provided prior to the test, in which possible physical symptoms and complaints following CPET were indicated. In addition, most patients with knee OA have experience with weekly fluctuations in the level of pain (Hutchings et al., 2007). Nonetheless, fear of an increase in knee pain may be a reason for patients to withdraw from performing CPET. However, one patient was not willing to participate for this reason in our study only.

To our knowledge, this is the first study that explicitly investigated the feasibility of a submaximal clinical exercise test that evaluated aerobic capacity with submaximal parameters in a population of merely patients with knee OA prior to the TKA procedure. In accordance with results from previous studies in which patients were subjected to maximal exercise testing, no adverse events occurred and all patients reached the VAT (Philbin, Groff, Ries, and Miller, 1995; Ries, Philbin, and Groff, 1995; Ries et al., 1996; Roxburgh et al., 2021). The positive attitude toward CPET in our study was also seen in the study of Roxburgh et al. (2021). It is remarkable that all included patients could perform submaximal CPET and were not hindered by restricted knee range of motion or pain, which was previously observed in approximately 40% of the patients during maximal CPET (Philbin, Groff, Ries, and Miller, 1995; Philbin, Ries, and French, 1995; Ries, Philbin, and Groff, 1995; Ries et al., 1996). This may be partly explained by the inclusion criterion being able to get on and off a cycle ergometer. Nevertheless, no patients were excluded for this reason. Besides cycling is a very familiar mode of exercise in Dutch patients (Ministry of Infrastructure and Water Management, 2018). Two eligible patients (8.7%) were excluded because they were not able to cycle; however, this was unrelated to their knee symptoms. Possibly, this could partly be attributed to our less severely disabled cohort since the preoperative Oxford knee score (mean 26.9 ± 5.7) was slightly higher than in previous recent studies reporting a lower baseline mean score of 23.9 ± 7.3 (Van Egmond et al., 2021) and 22.5 ± 5.2 (Vissers, Van Hove, and Van der Zwaard, 2020).

In terms of aerobic capacity, most studies focused on maximal exercise responses (Casazza, Lum, Giordani, and Meehan, 2020; Philbin, Groff, Ries, and Miller, 1995; Philbin, Ries, and French, 1995; Ries, Philbin, and Groff, 1995; Ries et al., 1996) and often only described that the VAT was reached (Philbin, Groff, Ries, and Miller, 1995; Ries, Philbin, and Groff, 1995; Ries et al., 1996). Two studies reported on submaximal parameters of aerobic capacity in patients with hip and

Table 2. Results from questionnaire and telephone call regarding acceptability of submaximal CPET.

Participant experiences (*n* = 14)	Outcome
6–20 Borg RPE score after submaximal CPET, median (IQR)	15 (15–15)
Knee pain NRS-11, median (IQR)	
Before submaximal CPET (past week)	5.0 (4.8–6.0)
Directly after submaximal CPET	4.5 (2.0–5.3)
The week after submaximal CPET	6.0 (5.0–7.0)
Occurrence of complaints, *n* (%)	
Directly after submaximal CPET	3 (21.4)
Dizziness	1 (7.1)
Pain heterolateral knee joint	2 (14.3)
The week after submaximal CPET[a]	7 (50.0)
More pain in the knee scheduled for surgery	4 (28.6)
Muscle strain (1 – 3 days)	2 (14.3)
Fatigue after submaximal CPET on exercise day or day after	2 (14.3)
Motivation NRS-11, median (IQR)	10.0 (9.0–10.0)
Burden NRS-11, median (IQR)	
Use of facemask	4.5 (2.0–7.3)
Use of electrocardiogram electrodes	0.0 (0.0–2.3)
CPET performance following the preoperative risk assessment	0.0 (0.0–1.0)
Other, *n* (%)	0 (0.0)
Self-efficacy NRS-11, median (IQR)	8.0 (6.5–8.3)
Well-informed about CPET NRS-11, median (IQR)	10.0 (9.0–10.0)
Positive attitude: willingness to perform CPET again, yes, *n* (%)	
Directly after submaximal CPET	14 (100)
The week after submaximal CPET	14 (100)

CPET, cardiopulmonary exercise testing; IQR, interquartile range; *n*, number; NRS-11, numeric rating scale (for knee pain and burden: 0 indicates the best score and 10 indicates the worst score; in contrast, for motivation, self-efficacy, and being well-informed about CPET: 0 indicates the worst score and 10 indicates the best score); RPE, rating of perceived exertion.[a]One participant experienced two complaints.

Table 3. Results of exercise testing of the study population (*n* = 14).

Measure	Outcome
Resting heart rate (beats/min), mean ± SD	79 ± 12.5
FEV_1 (% of predicted)[a], median (IQR)	96.0 (80.5–106.3)
Participants performing CPET, *n* (%)	14 (100)
Participants achieving VAT, *n* (%)	14 (100)
VO_2 achieved at VAT, median (IQR)	
Absolute, mL/min	990 (877–1169)
Relative, mL/kg/min	12.8 (11.3–13.6)
Work rate at VAT (watts), mean ± SD	55 ± 17.1
Heart rate at VAT (beats/min), mean ± SD	108 ± 12.0
OUES, median (IQR)	
Absolute, OUES	1923 (1586–2558)
Relative, OUES/kg	23.1 (20.2–28.9)
OUES (% of predicted)[b]	106.4
OUES (% of predicted)[c]	109.4
Exercise duration with increasing load (s), median (IQR)	549 (429–677)
Stop reason[d], *n* (%)	
6–20 Borg RPE ≥15	10 (71.4)
Dyspnea	6 (42.9)
Knee pain	3 (21.4)
Aiming to prevent knee pain	1 (7.1)

CPET, cardiopulmonary exercise testing; FEV_1, forced expiratory volume in one second; IQR, interquartile range; *n*, number; OUES, oxygen uptake efficiency slope; RPE, rating of perceived exertion; s, seconds; SD, standard deviation; VAT, ventilatory anaerobic threshold; VO_2, oxygen uptake; [a]Reference values calculated according to Quanjer et al. (2012); [b]Reference values calculated according to Barron et al. (2015) using the variables sex, age, body height, body mass, use of beta blocker, smoking status, and FEV_1; [c]Reference values calculated according to Hollenberg and Tager (2000) using the variables sex, age, body surface area, FEV_1, and smoking status; [d]Some participants had multiple stop reasons.

knee OA before surgery (Philbin, Ries, and French, 1995; Roxburgh et al., 2021). One study (*n* = 37) showed a median VO_2 at the VAT of 10.6 mL/kg/min (IQR 8.5–12.3) (Philbin, Ries, and French, 1995) and a recent study (*n* = 15) reported a mean ± SD VO_2 at the VAT of 10.7 ± 2.9 mL/kg/min and a mean ± SD OUES/kg of 21.5 ± 5.9 (Roxburgh et al., 2021). Our study population seems physically more fit as reflected by higher values for both the OUES (106.4% (Barron et al., 2015) and 109.4% (Hollenberg and Tager, 2000) of predicted) and

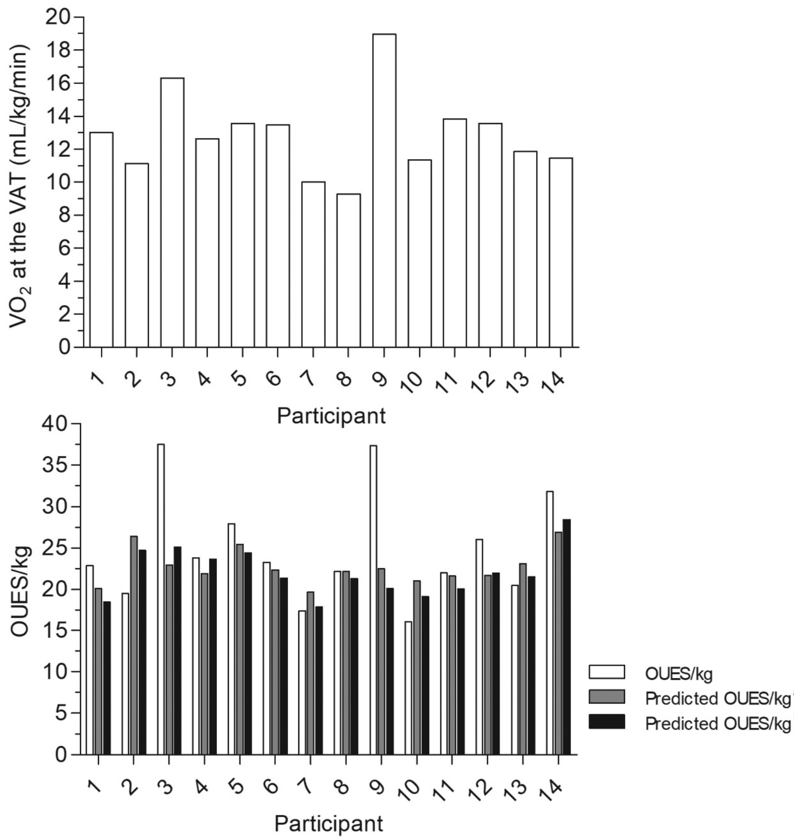

Figure 3. Oxygen uptake at the ventilatory anaerobic threshold and oxygen uptake efficiency slope, including predicted values, for each participant. OUES, oxygen uptake efficiency slope in OUES/kg; VAT, ventilatory anaerobic threshold; VO_2, oxygen uptake in mL/kg/min; [a]Predicted OUES values according to Barron et al. (2015); [b]Predicted OUES values according to Hollenberg and Tager (2000).

VO_2 at the VAT. Although age and sex of the current study population corresponded well with these previous studies (Philbin, Ries, and French, 1995; Roxburgh et al., 2021) none of the participants in our study smoked or used any in-house walking aids and only two participants (14.3%) made use of a walking aid outside. The higher aerobic capacity can also be explained by the fact that all patients were advised by the orthopedic surgeon to stay as physically active as possible before surgery to accelerate recovery after surgery. The general recommendation was aerobic exercise training of moderate intensity for at least 30 minutes per day for at least 5 days a week, according to Dutch and international physical activity guidelines (Garber et al., 2011; Health Council of the Netherlands, 2017).

In addition to the median aerobic capacity at the group level individual values of aerobic capacity can be important to identify patients with a reduced preoperative aerobic capacity possibly at risk for a delayed postoperative recovery. The VO_2 at the VAT was lowest for participant 7 and 8, while participant 2, 7, 10, and 13 showed OUES values that were lower than predicted. Using both measures is probably the best method to distinguish patients with an adequate preoperative aerobic capacity from patients with an insufficient preoperative aerobic capacity. If we apply cutoff values reported earlier in the literature for patients scheduled for major colorectal surgery (OUES/kg < 20.6 and VO_2 at the VAT ≤ 11.1 mL/kg/min) (Bongers, Berkel, Klaase, and Van Meeteren, 2017), the same participants with a reduced aerobic capacity would have been identified.

Future research should investigate whether a higher preoperative aerobic fitness is associated with improved postoperative recovery in patients undergoing total joint arthroplasty. Risk thresholds may be defined based on preoperative aerobic capacity, as seen in other populations undergoing a surgical procedure (Bongers, Berkel, Klaase, and Van Meeteren, 2017; Moran et al., 2016; Smith, Stonell, Purkayastha, and Paraskevas, 2009) which may be used in surgical decision-making in unfit patients and/or in patients undergoing more complex or high-risk surgical procedures. For example, the relevance for preoperative preventive interventions to improve preoperative aerobic capacity in these patients (prehabilitation) can be explored. Most prehabilitation programs in patients undergoing TKA focus primarily on improving muscle strength and flexibility, instead of improving aerobic capacity (Vasileiadis et al., 2022). D'Lima et al. (1996) assigned patients to aerobic training which was tolerated well, but the effectiveness of the training was not assessed preoperatively. However, it is reported that in an earlier conservative treatment phase improvements of aerobic capacity can be achieved in patients with knee OA (Escalante, García-Hermoso, and Saavedra, 2011; Schulz et al., 2020) with a modest increase in VO_{2peak} of 0.84 mL/kg/min (95% CI 0.37–1.31) (Schulz et al., 2020).

A strength of this study was the assignment of a central role to the patients, exploring their experiences and perceptions of performing submaximal CPET directly after CPET performance and one week later. Also, representative patients with knee OA were included and, except for one missing Oxford knee score, no data was missing. Some limitations must be considered. First, although this study focused on submaximal performance and the clinical exercise physiologist would stop the test if the participant rated the effort with a 6–20 Borg RPE score ≥ 15 two participants may have delivered a (near) maximal effort. Both participants had a heart rate at the end of exercise > 95% of their predicted peak heart rate (208 – (0.7 × age in years)). A respiratory exchange ratio at peak exercise ≥ 1.10 also indicative of a (near) maximal effort (Bongers, Berkel, Klaase, and Van Meeteren, 2017) was not achieved by any participant. Secondly, patients from the MUMC+ could not be included due to COVID-19 measures, making this study a single-center study that might affect the generalizability of the study results. Thirdly, we have to acknowledge the time burden and associated costs of completing CPET, which can be a challenge in clinical practice, particularly when expanding the feasibility study. However, to properly investigate the association of preoperative aerobic capacity and postoperative outcomes in patients undergoing TKA surgery, patients need to be able to validly perform an exercise test that objectively quantifies aerobic capacity. When preoperative aerobic capacity seems to be associated with postoperative outcomes in this population future studies are necessary to discuss the usefulness of preoperative CPET in patients with knee OA in routine practice. For example, using a screening questionnaire to select potentially unfit patients for CPET or by utilizing a practical alternative exercise test to estimate aerobic capacity when CPET is not possible. The incremental shuttle walk test (iSWT) could be used as such a practical alternative exercise test. The iSWT is a 12-level test (1 min in each level) imposing an incremental acceleration as the person walks up and down a 10-m course and tries to complete as many 'shuttles' as possible (Singh et al., 1992). A second alternative could be a (modified) steep ramp test (SRT), in which patients are required to cycle against a rapidly increasing work rate until exhaustion. The SRT consists of 3 min of unloaded or low-intensity (25 Watts) cycling as warm-up, followed by a rapid increase in work rate of 25 Watts every 10 seconds, until volitional exhaustion despite strong verbal encouragement (Meyer et al., 1996). Although CPET VO_{2peak} has been found to be highly correlated with the attained work rate at peak exercise during the SRT in several (patient) populations (Bongers, De Vries, Helders, and Takken, 2013; Rozenberg et al., 2015; Weemaes et al., 2021) and the distance covered during the iSWT (Parreira et al., 2014) these tests still need validation in patients with knee OA. In addition, both tests require a (cardiorespiratory) maximal effort to validly estimate aerobic fitness, which may not be possible in these patients due to their knee pain. Finally, the acceptability of CPET was studied quantitatively. By using qualitative methods, subjective experiences of the participants could have been explored in more detail.

This study demonstrated the feasibility of submaximal CPET using cycle ergometry in patients with knee OA scheduled for TKA surgery to evaluate preoperative aerobic capacity using the VO_2 at the VAT and OUES. All participants were able to perform the test, reached the VAT and were willing to perform the CPET again in the future. The study population demonstrated a median VO_2 at the VAT of 12.8 mL/kg/min (IQR 11.3–13.6). The median OUES/kg was 23.1 (IQR 20.2–28.9), and 106.4% and 109.4% of predicted. The exercise test can be used preoperatively to assess a patient's aerobic capacity. Future studies can safely investigate the effect of preoperative aerobic capacity on postoperative recovery using submaximal CPET-derived variables of aerobic capacity.

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ORCID

Anke Kornuijt PT, MSc http://orcid.org/0000-0003-3957-4979
Bart C. Bongers PhD http://orcid.org/0000-0002-1948-9788
Rik G.J. Marcellis PT, PhD http://orcid.org/0000-0003-4819-4863
Antoine F. Lenssen PT, PhD http://orcid.org/0000-0003-3627-4452

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Appendix I. Questionnaire directly after submaximal CPET

Dear sir/madam,

You have just performed an exercise test. We are curious about your experiences. The questionnaire will discuss various topics, such as the perception of the effort delivered by you during the test, possibly occurring knee complaints, and your motivation.

6–20 Borg scale for RPE

The Borg scale for rating of perceived exertion (RPE) is a scale for the subjective perception of the delivered effort during physical exercise. Please, rate your perceived exertion during the exercise test (submaximal cardiopulmonary exercise testing on a cycle ergometer). Perception of effort depends mainly on the level of exertion, muscle fatigue, and the feeling of shortness of breath. Take a close look at the scores on the scale. Indicate (by circling) your score in a range from 6 to 20. A rating of 6 means that you perceived 'no exertion at all' and a rating of 20 means that you perceived a 'maximal exertion' of effort.

Scale	Perceived exertion
6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	

Reason to stop cycling

Can you indicate why you stopped cycling?

Pain Numeric Rating Scale

Pain in the knee scheduled for surgery prior to the exercise test

Select the number that best describes the severity of your pain.

How severe was your pain (on average) in the past week (7 days) before performing the exercise test?

0 1 2 3 4 5 6 7 8 9 10

no pain *most imaginable pain*

Pain in the knee scheduled for surgery after the exercise test

Select the number that best describes the severity of your pain.

How severe was your pain after performing the exercise test?

0 1 2 3 4 5 6 7 8 9 10

no pain *most imaginable pain*

Other complaints

Do you experience other bodily complaints after the exercise test?

○ Yes, specifically:

○ No

Motivation

On a scale of 0 to 10, to what extent were you motivated to perform the exercise test?

0 1 2 3 4 5 6 7 8 9 10

not motivated *somewhat motivated* *very motivated*

Equipment

On a scale of 0 to 10, to what extend was the facemask burdensome?

0 1 2 3 4 5 6 7 8 9 10

not burdensome somewhat burdensome very burdensome

On a scale of 0 to 10, to what extend were the electrodes on your chest burdensome?

0 1 2 3 4 5 6 7 8 9 10

not burdensome *somewhat burdensome* *very burdensome*

Were other things related to the exercise test burdensome?

○ Yes, specifically:

○ No

If applicable, on a scale of 0 to 10, to what extend was the above item burdensome?

0 1 2 3 4 5 6 7 8 9 10

not burdensome *somewhat burdensome* *very burdensome*

Exercise test on the bike

On a scale of 0 to 10, to what extend did you experience the exercise test together with the other tests of the physical therapist as too much?

0 1 2 3 4 5 6 7 8 9 10

not too much *somewhat much* *very much*

Self-efficacy

On a scale of 0 to 10, how confident were you that you could perform the exercise test with your affected knee?

0 1 2 3 4 5 6 7 8 9 10

not confident *somewhat confident* *very confident*

Information

On a scale of 0 to 10, to what extent were you well-informed about the exercise test?

0 1 2 3 4 5 6 7 8 9 10

not informed *somewhat informed* *very well informed*

Exercise test on the bike in the future

Are you willing to perform the exercise test on the bike again at a later moment?

○ Yes

○ No, because:

- End of the questionnaire – Thank you for completing

Appendix II – Telephone call one week after submaximal CPET

Complaints

Have you experienced past week any complaints due to the exercise test on the bike?

○ Yes, specifically:

○ No

Pain Numeric Rating Scale

Pain in the knee scheduled for surgery

How severe was your pain (on average) in the past week (7 days)?

0 1 2 3 4 5 6 7 8 9 10

no pain *most imaginable pain*

Exercise test on the bike in the future

Directly after the exercise test on the bike, you indicated that you would not/would like to perform the test again. Do you still have this opinion?

○ No, because:

○ Yes, because:

Process

Is there anything we can improve?

○ Yes, item for improvement:

○ I have no item(s) for improvement

○ I do not know

Additional information/comments