Exercise-based cardiac rehabilitation improves physical fitness in patients with permanent atrial fibrillation – A randomized controlled study

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Abstract
The aim of this multicenter randomized controlled trial was to compare physiotherapist-led exercise-based cardiac rehabilitation (PT-X) with physical activity on prescription (PAP) with regard to physical fitness, physical activity, health-related quality of life (HR-QoL), and metabolic risk markers in patients with permanent atrial fibrillation. Ninety six patients (28 women), age 74 (5) years, and ejection fraction ≥45% were randomized. An exercise tolerance test (primary outcome measure), muscle endurance tests, HR-QoL, physical activity assessments (questionnaire and accelerometer), and blood sampling were performed. The PT-X consisted of 60-minute group sessions and home-based exercise, both twice a week. The PAP consisted of 40 minutes of active walking, 4 times a week. Eighty seven patients completed the study. Exercise tolerance (maximum exercise capacity) improved significantly after PT-X (n = 40) but not after PAP (n = 47) (16 vs −3 W; P < .0001). Muscle endurance also improved after PT-X: shoulder flexion left arm (7 vs −1 repetition; P < .001), heel-lift right leg (4 vs 1 repetition; P < .05), left leg (4 vs −1 repetition; P < .001), and shoulder abduction (17 vs −4 s; P < .010). PAP significantly increased energy expenditure. Health-related quality of life and lab-tests did not differ. PT-X improved physical fitness in patients with permanent atrial fibrillation.

KEYWORDS
exercise, heart, physical activity
1 | INTRODUCTION

Patients with atrial fibrillation (AF) commonly experience symptom-related limitations in physical fitness and physical activity and reduced health-related quality of life (HR-QoL).\(^1\) Physical inactivity in healthy people leads to reduced physical fitness, with an increased risk of premature morbidity and mortality.\(^2\) For patients with AF there is, however, currently no consensus regarding the recommended amount of physical activity and fitness training. In patients with AF, the mechanism for reduced physical fitness (usually measured as peak oxygen uptake, VO\(_{2}\)peak, or maximum workload, W\(_{\text{max}}\), at exercise testing) is presumably multifactorial. Reduced cardiac output (estimated average ~ 20%) due to the irregular ventricular rhythm with variable stroke volume and afterload, and the loss of atrial systole, which results in reduced ventricular filling especially when ventricular compliance is reduced, contributes to impaired physical fitness.\(^3\) Reduced physical fitness might, however, also be due to skeletal muscle dysfunction like in elderly patients with chronic heart failure (HF)\(^4\) since AF and HF often coexist.\(^1\) A recent Cochrane review concluded that exercise-based cardiac rehabilitation in patients with AF improved VO\(_{2}\)peak, but this conclusion was, according to the authors, based on a small number of studies including few patients.\(^5\) Therefore, further studies are warranted to assess the benefits and risks of such intervention and determine whether it should be offered more generally.\(^5\) In this study, we have defined exercise-based cardiac rehabilitation as physiotherapist-led exercise-based cardiac rehabilitation (PT-X).

Positive effects of physical activity on prescription (PAP) have been reported on metabolic risk factors, HR-QoL, and self-reported physical activity.\(^6\) In the last decade, PAP, together with motivational interviewing, has therefore been used by health professionals to counteract a low physical activity level, and to reduce the risk of cardiovascular morbidity and premature mortality.\(^7\) PAP does, however, not include any supervised exercise and is often prescribed without prior assessment of physical fitness in contrast to PTX. While PT-X has been evaluated in patients with AF (although in relatively few patients),\(^5\) that seems not to be the case for PAP, and these methods have not been compared in AF patients.

Therefore, the aim of this study was to compare PT-X vs PAP by evaluating physical fitness, physical activity level, HR-QoL, metabolic risk markers, and safety in patients with permanent AF in a randomized design. The primary endpoint was maximum exercise capacity and the hypothesis that PT-X was superior to PAP.

2 | MATERIAL AND METHODS

2.1 | Study population

Ninety-seven patients (29 women), aged 65-85 years, were enrolled in a randomized controlled trial conducted in southwestern Sweden between 2014 and 2016. Patients were recruited from two hospitals, from primary care and through advertisements in local newspapers. The investigation conformed to the Declaration of Helsinki, was approved by the Regional Ethics Committee of Gothenburg, and was registered in ClinicalTrials.gov (NCT02493387). All patients received written and verbal information about the study and provided written informed consent. Inclusion criteria were permanent AF [verified by electrocardiography (ECG) and patient records], and a left ventricular (LV) ejection fraction (EF) ≥45% at transthoracic echocardiography. Exclusion criteria were permanent AF [verified by electrocardiography (ECG) and patient records], and a left ventricular (LV) ejection fraction (EF) ≥45% at transthoracic echocardiography. Exclusion criteria were significant valvular lesions, a coronary event within 3 months prior to inclusion, stroke sequel, or a pacemaker.

2.2 | Study protocol

The tests described below were performed at baseline and after 3 months of intervention (PT-X or PAP). As far as possible, all tests for physical fitness were performed at the same time of the day before and after intervention. A physiotherapist blinded to randomization performed the tests at baseline and after 3 months of intervention.

2.2.1 | Physical fitness

Exercise capacity, primary outcome measure, was assessed by a symptom-limited ergometer cycle test
The workload began at 25 W and was increased every 4.5 minutes by 25 W until the patient's rated perceived exertion (RPE) was 17 (Very Heavy) on the Borg scale. Heart rate was assessed using telemetric monitoring or a pulse watch (Polar Electro OY) every 2nd minute, and right brachial blood pressure was measured manually using a sphygmomanometer and a stethoscope every 3rd minute at each workload. If the patient did not sustain the entire final step, the estimation of maximum work load (Wmax) was adjusted according to Strandell's formula.

2.2.2 | Muscular endurance tests

*Unilateral isoinertial shoulder flexion*, secondary outcome measure, was assessed with the patient sitting on a stool with their back touching the wall holding a dumbbell in their hand, 2 kg for women and 3 kg for men. Twenty shoulder flexions per minute were performed at a pace of 40 beats per minute (bpm) kept by a digital metronome (Seiko instruments). The patient was told to do as many shoulder flexions as possible. Both arms were tested.

*Bilateral isometric shoulder abduction*, secondary outcome measure, was assessed with the patient holding a 1 kg dumbbell in each hand using the same body position as above. The patient was asked to elevate both arms to 90° of shoulder abduction and to maintain this position as long as possible (measured in seconds).

*Unilateral isoinertial heel-lift*, secondary outcome measure, was assessed with the patients performing as many unilateral heel-lifts as possible with a straight knee, on a 10° tilted wedge, with shoes on. Thirty heel-lifts per minute were performed at a pace of 60/bpm. Both legs were tested, and the patient was allowed to touch the wall for balance.

2.2.3 | Physical activity level

*Accelerometer and questionnaire*, secondary outcome measure. The accelerometer (Actigraph® GT3x+: Actigraph) was placed on the patient's left hip and worn throughout the whole day for 7 days except when taking a shower or bath. Accelerometer data were calculated according to Choi et al. The time period, considered as the minimum wear time per day, was set at ≥540 minutes per day, and the number of days considered as a valid week was set at ≥4 days. In addition, self-reported physical activity was measured and categorized by the Swedish version of the short form international physical activity questionnaire (IPAQ) as low = 1, medium = 2, and high = 3.

2.2.4 | Health-related quality of life

*General HR-QoL*, secondary outcome measure, was assessed by the Swedish version of the short form 36 Health Survey Questionnaire (SF-36).

2.2.5 | Cardiac function

*Transthoracic echocardiography* was performed to rule out significant systolic cardiac dysfunction and/or valvular disease. Left ventricular (LV) ejection fraction (EF), LV-volumes, and valvular function were evaluated by both visual estimates and using the apical two- and four-chamber views according to the biplane method of disks (Simpson’s rule) to determine the end-diastolic volume and end-systolic volume. Two-dimensional Doppler echocardiography (Vivid 7 and Vivid E9; General Electric Medical systems) was performed using a phased-array transducer (1.5-4.0 MHz). Image acquisition was obtained from the parasternal long axis and apical four- and two-chamber views. Pulsed and continuous Doppler flow velocities across the mitral valve and left ventricular outflow tract were acquired according to the American Society of Echocardiography. Offline analysis was performed using commercially available Echopac PC software (General Electric Ultrasound).

2.2.6 | Metabolic risk factors

Venous blood samples were obtained after an overnight fast and assessed according to the European accreditation system: plasma glucose, glycosylated hemoglobin, total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides. These tests were also part of the secondary outcome measures.

2.3 | Interventions

2.3.1 | Training program

The PT-X and PAP programs, Table 1, are designed based on the patient's individual requirements and including the result of the baseline exercise test. PT-X consisted of central circulatory interval exercise and circuit training at two 60-minute hospital-based sessions at a RPE of 13-17 together with two home-based exercise sessions per week, and PAP consisted of active walking for 40 minutes at a RPE of 13-15 at four sessions per week. The patients kept a diary to record home-based exercises and PAP.

*Randomization* in a 1:1 ratio was performed after the baseline tests and stratified for sex and age and achieved...
workload below and over 50 watts at the baseline test. An independent person not working at the clinic performed the randomization tickets with a computer-based randomizer in Excel as high and low plots. The plots were kept in sealed envelopes.

### 2.4 Statistics

The sample size was calculated using a power of 80% and a significance level of 5%. Based on the assumption of a mean (SD) difference in improvement in physical fitness expressed as an improvement in exercise capacity of 10 (15) W in the PT-X group vs the PAP group, ≥41 patients in each group were needed. A drop-out rate of 8% was estimated; thus, we aimed to enroll ≥90 patients. Ratios and interval data are presented as mean (SD), ordinal data are presented as median (range), and nominal data are presented in absolute and relative numbers. The Mann-Whitney U test and the chi-square test were used to evaluate between-group differences. Cohen’s d was used to calculate the effect size using the mean difference between groups and pooled standard deviation of the mean differences. The effect size was considered small for d = 0.2-0.3, medium for d = 0.5, and large for d = 0.8. An intention-to-treat (ITT) analysis was performed including participants with both baseline and follow-up values. Due to 9 drop-outs, we used a baseline observation carried forward (BOCF), that is, no change from baseline imputation for nine participants with missing follow-up data. An ITT sensitivity analysis was performed using this augmented dataset applying baseline values for the drop-outs. A P-value < .05 was considered significant. The Statistical Package for Social Science was used for statistical analyses (SPSS Statistics for Windows, version 22.0, 2013. IBM Corp.).

### 3 Results

One patient was excluded from analysis because she showed an ECG with sinus rhythm during the intervention, indicating she had persistent rather than permanent AF. Altogether, 96 patients were enrolled and randomized. Nine participants dropped out during the intervention and have no follow-up values. All participants stayed in their allocated group. In the ITT BOCF analysis, all 96 patients were analyzed (PT-X n = 46 and PAP n = 50). A flowchart describing the inclusion process is presented in Figure 1. Demographic and clinical characteristics of the participants are shown in Table 2. There were no significant between-group differences at baseline. More than 90% received anticoagulants and 80% were treated with heart rate regulating therapy, similar in both groups. ACE-inhibitors and/or angiotensin receptor antagonists were, however, significantly more common in the PT-X group (29 vs 20; P = .024), Table 3.

| TABLE 1 Exercise program in the PT-X group and active walking in the PAP group |
|---------------------------------|-----------------|-----------------|
| **Interval exercise on ergometer cycle, PT-X** | **Duration, min** | **Reps** | **RPE** |
| Warm-up period | 6 | 1 | 11 |
| Interval I | 2 | 4 | 15-17 |
| Interval II | 2 | 4 | 13 |
| Cool-down period | 2 | 1 | 11 |
| **Resistance exercises, PT-X** | **Duration, s** | **Sets** | **RPE** |
| Straight arm pull down in cable pulley | 45/15/30 | 2 | 13-15 |
| Leg extension | 45/15/30 | 2 | 13-15 |
| Heel lift on wedge | 45/15/30 | 2 | 13-15 |
| Step-up | 45/15/30 | 2 | 13-15 |
| Shoulder flexion with dumbbell | 45/15/30 | 2 | 13-15 |
| Shoulder abduction with dumbbell | 45/15/30 | 2 | 13-15 |
| Bench press | 45/15/30 | 2 | 13-15 |
| Squats with exercise ball against the wall | 45/15/30 | 2 | 13-15 |
| Wide grip push down in cable pulley | 45/15/30 | 2 | 13-15 |
| **Home exercise program, PT-X** | **Duration, s** | **Sets** | **RPE** |
| Warm-up period with step-up | 120 | | 13-15 |
| Step-up, between exercises | 120 | | 13-15 |
| Elbow flexion, M. Biceps | 45/15/30 | 2 | 13-15 |
| Straight arm shoulder flexion | 45/15/30 | 2 | 13-15 |
| Shoulder abduction | 45/15/30 | 2 | 13-15 |
| Standing row | 45/15/30 | 2 | 13-15 |
| Heel lift | 45/15/30 | 2 | 13-15 |
| Sit up | 45/15/30 | 2 | 13-15 |
| **Active walking PAP** | **Duration, min** | **Reps** | **RPE** |
| Warm-up period | 5 | 1 | 11 |
| Active walking | 30 | 1 | 13-15 |
| Cool-down period | 5 | 1 | 11 |

Note: Borg scale 6-20.

Abbreviations: PAP, Physical activity on prescription; PT-X, Physiotherapist-led exercise-based cardiac rehabilitation; Reps, Repetitions; RPE, Rating of perceived exertion.

*aThe exercises were performed in two sets, each 45 s, with 15 s rest between sets. Time to change exercise was set as 30 s.*
FIGURE 1  Flowchart over the inclusion process
### 3.1 Adherence

The median adherence to PT-X and home-based exercise sessions was 24 (17-24) and 23 (8-24) out of a maximum of 24 for both. The adherence to PAP active walking was similar, 47 (14-48) out of a maximum of 48.

### 3.2 Physical fitness

The primary end-point exercise capacity improved significantly more in PT-X vs PAP participants (16 (18%) vs −3 (−3%) W, \( P < .0001 \)), and according to Cohen's delta, the effect size was large. Other fitness measures also improved significantly more in the PT-X group, shoulder flexion left arm (7 vs −1 repetitions, \( P = .00059 \)), shoulder abduction (17 vs −4 s, \( P = .010 \)), and heel-lift right leg (4 vs 1 repetitions, \( P = .045 \)) and left leg (4 vs −1 repetitions, \( P = .00082 \)). The differences between groups were due to improvements in the PT-X group, while the PAP group did not show any improvement in measures of physical fitness compared with baseline, Table 4, Figure 2A-D.

### 3.3 Physical activity

The PAP group spent significantly more kilocalories (14 vs −422, \( P = .038 \)) than the PT-X group. In contrast, there was no difference between groups regarding intensity of the physical activity nor in total valid steps measured by the accelerometer or in physical activity level according to the IPAQ questionnaire, Table 4.

### 3.4 Health-related quality of life

There were no significant between-group differences in any dimension of the SF-36, Table 5.

### 3.5 Metabolic risk markers

There was no significant difference between groups in the metabolic risk markers, Table 6.
3.6 | Sensitivity analysis

ITT BOCF did not alter the significance level for the between-group comparison and the observed effect size.

3.7 | Safety

No major or minor adverse event occurred during the study period in any group. Nine patients withdrew participation (PT-X = 6 and PAP = 3) for medical reasons and accidents not related to the intervention (dizziness, traffic accident, psychological issues, rheumatic disease, and unknown medical cause) or because of a lack of time and travel inconveniences.

4 | DISCUSSION

This study shows the benefits and safety of PT-X in patients with permanent AF. PT-X improved physical fitness, assessed as the maximum exercise capacity and muscle endurance, while PAP did not. PAP increased physical activity measured as calorie expenditure assessed with an accelerometer. Participation in PAP therefore increased the energy expenditure on physical activity, but was insufficient to increase physical fitness.

In the present study, the average maximum workload at baseline was approximately 88 W, which is less than the value observed for age-matched healthy individuals, but similar to what was reported in other patients with AF. When converted from workload (W), the improvement in physical fitness in the PT-X group corresponded to an average increment in VO2peak of 2 mL/kg/min, an increment similar to what has been found in patients with chronic HF. When converted from workload (W), the improvement in physical fitness in the PT-X group corresponded to an average increment in VO2peak of 2 mL/kg/min, an increment similar to what has been found in patients with chronic HF. When converted from workload (W), the improvement in physical fitness in the PT-X group corresponded to an average increment in VO2peak of 2 mL/kg/min, an increment similar to what has been found in patients with chronic HF.

Furthermore, an increase in VO2peak by 1 mL/kg/min is associated with approximately 15% decrease in the risk of death in patients with CHD. Extrapolated to our study group, we assume there might be an improvement in prognosis after PT-X also in patients with permanent AF, but this remains to be proven. PT-X also improved muscle endurance, which also might be of benefit in patients with AF.

Although PAP has been associated with positive effects on metabolic risk factors, HR-QoL, and self-reported physical activity.
FIGURE 2  Physical fitness at baseline (black bars) and after intervention (gray bars). P-values for between-group comparisons of differences between baseline and after intervention; mean (SD) and Cohen's d (C's d). A, Bicycle ergometer test (16 vs −3 W, PT-X vs PAP, P < .0001), C's d 1.7. B, Shoulder flexion left arm (7 vs −1 repetitions, PT-X vs PAP, P = .00059), C's d 0.73, and right arm (6 vs 1 repetitions, PT-X vs PAP, P = .14), C's d 0.39. C, Shoulder abduction (17 vs −4 s, PT-X vs PAP, P = .010), C's d 0.55. D, Heel-lift left leg (4 vs −1 repetitions, PT-X vs PAP, P = .00082), C's d 0.81, and right leg (4 vs 1 repetitions, PT-X vs PAP, P = .045), C's d 0.53.

TABLE 5  Data at baseline and after intervention, health-related quality of life

| SF-36     | Baseline | PAP | P-value | After intervention | PAP | P-value | C's d |
|-----------|----------|-----|---------|--------------------|-----|---------|-------|
| PF        | 71 (19)  | 71 (18) | .92 | 74 (18) | 73 (18) | .13 | 0.28 |
| RP        | 59 (42)  | 68 (35) | .34 | 73 (37) | 68 (39) | .24 | 0.37 |
| BP        | 70 (25)  | 72 (24) | .73 | 74 (23) | 76 (23) | .79 | 0.015 |
| GH        | 62 (19)  | 67 (16) | .24 | 65 (18) | 70 (17) | .50 | 0.13 |
| VT        | 59 (20)  | 67 (19) | .05 | 64 (21) | 69 (19) | .42 | 0.16 |
| SF        | 90 (17)  | 89 (17) | .92 | 89 (19) | 89 (21) | .98 | 0.088 |
| RE        | 70 (37)  | 76 (34) | .34 | 83 (33) | 79 (31) | .19 | 0.20 |
| MH        | 78 (17)  | 81 (17) | .18 | 81 (19) | 87 (15) | .62 | 0.083 |
| PCS       | 42 (10)  | 43 (8)  | .69 | 44 (9)  | 44 (9)  | .19 | 0.32 |
| MCS       | 49 (11)  | 51 (10) | .10 | 51 (11) | 54 (9)  | .83 | 0.063 |

Note: P-values are for between-group comparisons at baseline and for differences between baseline and after intervention; the mean, (SD) and Cohen's d (C’s d) are given. Not all patients completed the post-test.

Abbreviations: BP, Bodily pain; GH, General health; MCS, Mental Component Score; MH, Mental health; PAP, Physical activity on prescription; PCS, Physical Component Score; PF, Physical function; PT-X, Physiotherapist-led exercise-based cardiac rehabilitation; RE, Role emotional; RP, Role physical; SF, Social functioning; SF-36, Short Form-36; VT, Vitality.
activity, older patients might have difficulties achieving the recommended levels of physical activity. Orrow et al found that physical activity counseling in primary care did not increase physical fitness (assessed as VO2max), which is in line with our results. In contrast to previous studies on PT-X and PAP, we did not find any improvement in metabolic risk factors in our patients with permanent AF. Our patients were, however, well medicated at baseline, which may explain the difference.

Our patients received an individual PAP according to the guidelines for physical activity, that is, 150 minutes of moderate physical activity or 75 minutes of vigorous physical activity per week, performed separately or in combination. The PAP in this study included active walking, which is the most common prescription, and a 6-week follow-up visit with a physiotherapist, as recommended in guidelines.

Although PAP improved physical activity, it was not enough to improve physical fitness. The physical activity guidelines are, however, not evaluated for patients with cardiac disease, and it is not established if such patients will benefit from an increase in physical activity. It has, however, been discussed whether a higher volume (larger amount) of exercise than recommended in guidelines is needed in patients with non-permanent AF to reduce the AF burden and long-time recurrence of AF. On the other hand, Lee et al observed that the intensity was the most important factor for physical fitness and not the amount of physical activity (energy consumption) per second.

Neither PT-X nor PAP improved HR-QoL in this study, in concordance with the result of the Cochrane review. With regard to HR-QoL, our patients were, however, already before the intervention comparable to the normative Swedish population at the same age. This can explain the absence of change in HR-QoL after intervention. It also suggests that patients with permanent AF might have fewer symptoms or have adjusted to their situation compared with patients with paroxysmal or persistent AF, since the degree of symptoms is important for HR-QoL. Symptoms were, however, not evaluated in our study.

The 2016 European Guidelines for the management of AF patients emphasize the need for multidisciplinary management and the importance of lifestyle changes but PT-X is not mentioned. Our results, however, suggest that PT-X is an important means to improve physical fitness (and potentially longevity) in patients with AF, as it is in other cardiac diseases. PT-X was well tolerated and no adverse events occurred in this study, in line with previous observations in patients with CHD and chronic HF.

### Conclusion and Perspective

It is established that exercise-based cardiac rehabilitation should be offered to patients with CHD and HF, but the situation for AF patients is less clear. This study adds knowledge to this issue and corroborates the benefit and safety of PT-X also in AF patients of relatively advanced age with several co-morbidities. These results imply that PT should be part of the multidisciplinary team management of patients with permanent AF. While safe, PAP as applied in this study did not improve physical fitness despite increasing the energy expenditure.

### Methodological Aspects and Limitations

Our patients had several concomitant diseases as expected from their age. We assume that around 20% of them might have had heart failure with preserved LV-EF, but no attempts were made to pursue this diagnosis. Diastolic function is difficult to assess with transthoracic echocardiography especially in AF patients. Furthermore, the NT-pro-BNP level is usually elevated during AF also in

### Table 6: Metabolic risk makers in blood samples. Data at baseline and after intervention

|                      | Baseline |         | After intervention |         | P-value | P-value | C’s d   |
|----------------------|----------|---------|--------------------|---------|---------|---------|---------|
|                      | PT-X     | PAP     | PT-X               | PAP     |         |         |         |
| Plasma glucose       | 5.9 (0.9) | 6.0 (1.2) | 5.9 (0.8)          | 6.2 (1.1) | .98     | .37     | 0.27    |
| Cholesterol          | 4.8 (1.1) | 5.0 (1.3) | 4.7 (1.0)          | 4.9 (1.2) | .54     | .51     | 0.064   |
| HDL                  | 1.4 (0.4) | 1.4 (0.4) | 1.4 (0.4)          | 1.4 (0.4) | .97     | .63     | 0.083   |
| LDL                  | 3.0 (1.0) | 3.2 (1.2) | 3.0 (0.9)          | 3.0 (1.1) | .6      | .43     | 0.12    |
| Triglycerides        | 1.4 (0.8) | 1.4 (0.7) | 1.4 (0.6)          | 1.5 (1.0) | .59     | .55     | 0.00098 |
| HbA1c                | 40 (4.6)  | 40 (5.5)  | 41 (5.9)           | 40 (5.6)  | .95     | .76     | 0.10    |

Note: P-values are for between-group comparisons at baseline and for differences between baseline and after intervention; the mean (SD) are presented and the effect size is expressed as Cohen’s d (C’s d) which is small when d < 0.3; all measures are in mmol/L except for HbA1c (mmol/mol).

Abbreviations: HbA1c, Glycosylated hemoglobin A1c; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; PAP, Physical activity on prescription; PT-X, Physiotherapist-led exercise-based cardiac rehabilitation.
patients with paroxysmal and persistent AF without symptoms or signs of HF when sinus rhythm is resumed. For ethical reasons, we compared two interventions, which a priori were expected to have positive effects, instead of using a control group with no intervention as suggested in the Cochrane review. This may have affected the result but there was no change in physical fitness after PAP. We also chose active walking as the PAP intervention, although PAP can include regular physical activity in other forms. The reason was that we wanted to stay as close to clinical reality as possible and compare two methods available in the clinical setting. For the same reason, we used a symptom-limited ergometer cycle test instead of a maximal ergo spirometry test to assess aerobic physical fitness. The former clinically based test is the standard test used at the physiotherapy clinic and provides similar results as a maximal test. We used a non-generic instrument to measure HR-QoL (SF-36), instead of a disease-specific instrument. The reason was that we wanted to be able to compare the patients across diseases and with the normative population. Finally, a detailed analysis of the accelerometer data might provide additional information.

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CONFLICT OF INTEREST

None.

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