

Study Protocol

Efficacy and Safety of Hybrid Cardiac Telerehabilitation in Patients with Hypertrophic Cardiomyopathy without Left Ventricular Outflow Tract Obstruction and Preserved Ejection Fraction—A Study Design

Krzysztof Sadowski ^{1,*} , Ryszard Piotrowicz ¹, Mariusz Kłopotowski ², Jadwiga Wolszakiewicz ¹, Agnieszka Lech ³, Adam Witkowski ², Edyta Smolis-Bąk ¹, Ilona Kowalik ¹ , Anna Mierzyńska ¹, Dorota Piotrowska ¹, Piotr Dobrowolski ⁴, Maciej Dąbrowski ², Ewa Sadowy ¹ and Ewa Piotrowicz ⁵

- ¹ Department of Coronary Artery Disease and Cardiac Rehabilitation, National Institute of Cardiology, 04-628 Warsaw, Poland; rpiotrowicz@ikard.pl (R.P.); wolszakiewiczjadwiga@gmail.com (J.W.); esmolis@ikard.pl (E.S.-B.); ikowalik@ikard.pl (I.K.); anna.mierzynska1@gmail.com (A.M.); dpotrowska@ikard.pl (D.P.); esadowy@ikard.pl (E.S.)
- ² Department of Interventional Cardiology and Angiology, National Institute of Cardiology, 04-628 Warsaw, Poland; mkopotowski@ikard.pl (M.K.); awitkowski@ikard.pl (A.W.); mdabrowski@ikard.pl (M.D.)
- ³ Department of Congenital Heart Diseases, National Institute of Cardiology, 04-628 Warsaw, Poland; alech@op.pl
- ⁴ Department of Hypertension, National Institute of Cardiology, 04-628 Warsaw, Poland; pdobrowolski@ikard.pl
- ⁵ Telecardiology Center, National Institute of Cardiology, 04-628 Warsaw, Poland; epiotrowicz@ikard.pl
- * Correspondence: ksadowski@ikard.pl; Tel.: +48-223-434-409; Fax: +48-223-434-519



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Abstract: Hypertrophic cardiomyopathy (HCM) is the most common congenital disease increasing the risk of sudden cardiac death. For many years, HCM patients were excluded from exercise training. However, there are data showing that patients with HCM undergoing supervised exercise training could improve physical performance without serious adverse events. A project was designed as a randomized clinical trial to assess the effectiveness and safety of hybrid cardiac rehabilitation (HCR)—a combination of hospital-based cardiac rehabilitation (1 month) with a new form of home-based telemonitored cardiac rehabilitation (2 months) in HCM patients without left ventricular (LV) outflow tract obstruction and preserved systolic function. Sixty patients who fulfil the inclusion criteria have been randomly assigned (1:1) to either HCR plus usual care (training group) or usual care only (control group). The primary endpoint is a functional capacity evaluated by peak oxygen uptake (pVO_2). Secondary endpoints include workload time during the cardiopulmonary exercise testing, a six-minute walk test distance, NT-pro BNP level, echocardiographic parameters of the left ventricular diastolic function (E/A , E/e' , myocardial strain rate), right ventricular systolic pressure, a gradient in the LV outflow tract, and quality of life. The tertiary analysis includes safety, acceptance and adherence to the HCR program. Our research will provide innovative data on the effectiveness and safety of hybrid cardiac rehabilitation in HCM patients without LV outflow tract obstruction and preserved systolic function. Clinical trials registry: ClinicalTrials.gov Identifier NCT03178357.

Keywords: hypertrophic cardiomyopathy; exercise training; rehabilitation; telerehabilitation

1. Background

Hypertrophic cardiomyopathy (HCM) is the most frequent congenital heart disease. Its spread is assessed at 0.2% in the overall population [1]. It features hypertrophy of the left ventricle (LV) and impaired LV diastolic function [2–4].

Numerous papers have shown that HCM is the most common cause of sudden cardiac arrest in young athletes, responsible for approximately 1/3 of deaths [5]. The risk of

sudden cardiac death (SCD) in all HCM patients is reckoned below 1% per year, but in the athletes' group, it is much lower—in the range of 0.03–0.1% per year. For many years, the diagnosis of HCM has been tantamount to a reduction in exercise training. Still, the relationship between HCM and cardiac arrest or exercise-induced sudden cardiac death was hypothesized mainly due to the lack of national registries. The results of the first study of HCM patients undergoing exercise training were published in 2015. Klempfner and colleagues demonstrated that most moderate-risk patients with HCM benefit from supervised exercise training—in some patients seen in the evident improvement in achieved workloads (expressed in metabolic equivalents—METs) and NYHA class [6]. Suggested beneficial training mechanisms in patients with HCM were: improvement in chronotropic response and vascular endothelial function, increase in vagal nerve tension, improvement in LV diastolic function, reduction in neurohormonal activation and cytokine expression [6]. No adverse events were observed, including significant arrhythmias.

The first randomized study for HCM patients undergoing exercise training was conducted by the Universities of Michigan and Stanford during the period April 2010–October 2015 [7]. In total 136 patients with HCM were randomized into two groups (subjected to aerobic training of moderate intensity for 16 weeks or subjected to ordinary activity). Saberi et al. have assessed that patients in the group subjected to exercise training had a considerable extension in pVO₂. None of the patients had a serious adverse event [7].

Comprehensive cardiac rehabilitation improves the quality of life and its extension, and the omission of rehabilitation in cardiological patients should be considered malpractice.

A few years ago, home-based telemonitored cardiac rehabilitation was introduced to clinical practice as a new, promising cardiac rehabilitation model. It consists of telecare with psychological telesupport, telesupervised exercise training, and remote monitoring of cardiovascular implantable electronic devices [8–15]. Admittedly, some studies compare hospital-based rehabilitation with this type of home-based telemonitored rehabilitation [8,9]. However, there are missing data that evaluate the combination of these two methods in patients with HCM. A typical period of a hospital-based cardiac rehabilitation is one month. The key problem is the patients' motivation to continue the exercise training after the inpatient cardiac rehabilitation program. The way to help the patients continue the rehabilitation is exactly the home-based telemonitored rehabilitation—it is an effective and safe alternative to outpatient rehabilitation and hospital-based rehabilitation for patients with different cardiovascular diseases. Moreover, previous studies have shown that shortly after telerehabilitation, patients present an increase in pVO₂, and then this positive effect of telerehabilitation decreases.

LV outflow tract obstruction and a reduced LV ejection fraction have been affiliated with an elevated risk of SCD. Therefore, the trial authors arbitrarily decided to evaluate the group of HCM patients with a lower probability of SCD—HCM patients without the LV outflow tract obstruction and preserved LV ejection fraction.

The hypothesis of the research is that HCR is effective and safe in HCM patients without the LV outflow tract obstruction and preserved LV ejection fraction.

There are premises that the HCR program contributes to the improvement in physical performance (expressed by an increase in pVO₂) and the improvement in the quality of life.

Data from published studies, including the largest TELEREH-HF randomized clinical trial, demonstrated that telerehabilitation is a safe medical procedure, not leading to any significant adverse events. Only minor events occurred, such as slight skin reactions caused by the electrodes and paroxysmal atrial fibrillation. There were no interventions from CIEDs during the remotely supervised telemonitored exercise training [8–15].

2. Methods

2.1. Study Design

The trial is planned as a single-center, prospective, parallel-group, unmasked, randomized (1:1), controlled trial of HCR—training group (TG) versus usual care—control group

(CG) in HCM patients (ClinicalTrials.gov. NCT03178357) and it was approved by the local Ethics Committee. All patients are obliged to provide written informed consent [16].

2.2. Participants

Patients were recruited from July 2017 to January 2020 in the Department of Cardiac Rehabilitation and Noninvasive Electrocardiology and in the Department of Coronary Artery Disease and Cardiac Rehabilitation, National Institute of Cardiology, Warsaw, Poland. The study has a target enrollment of 60 patients (30 patients in each group). The inclusion/exclusion criteria are demonstrated in Table 1.

Table 1. Inclusion/exclusion criteria.

Inclusion Criteria
• Patients with hypertrophic cardiomyopathy (defined in accordance with European Society of Cardiology guidelines for the diagnosis and management of cardiomyopathy and hypertrophy in 2014): thickness ≥ 15 mm of one or more segments of the left ventricular wall measured using an imaging technique, which cannot be explained entirely by left ventricular loading conditions, without left ventricular outflow tract obstruction (at rest gradient <30 mmHg). • Stable general condition (1 month period). • Heart failure—New York Heart Association Classes II and III. • Preserved left ventricle systolic function (ejection fraction $\geq 50\%$). • Implanted cardioverter-defibrillator. • Written informed consent. • Adult patient (≥ 18 years old).
Exclusion Criteria
• Life-threatening ventricular arrhythmias not amenable to treatment. • Poorly controlled hypertension or diabetes. • Advanced atrioventricular block. • Aortic stenosis with symptoms. • Pericarditis or myocarditis (up to 6 months). • Thrombus in the heart cavities. • Relevant ischemia caused by low-intensity exercise test (2 metabolic equivalents, 50 Watts). • Pulmonary embolism (up to six months). • Thrombophlebitis. • A new incident of atrial fibrillation or atrial flutter. • Drop in systolic blood pressure during exercise. • Acute systemic illness. • Coexisting diseases limiting exercise tolerance and physical activity.

2.3. Intervention in a Training Group

The training group patients undergo the HCR program, consisting of 1 month of hospital-based rehabilitation and 2 months of home-based telemonitored rehabilitation. Every patient is followed for one year after the HCR program. Hybrid cardiac rehabilitation contains all key elements of comprehensive cardiac rehabilitation: education, exercise training, psychological support, tobacco cessation and, if needed, blood pressure, lipid and diabetes management. Exercise training is planned according to the published guidelines [17–23]. The HCR program consists of endurance, resistance, strength, and respiratory training. The details are presented in Table 2. Patients train five times a week.

The methodology of telemonitoring during home-based cardiac rehabilitation has been presented in the past [24–27]. In summary, every TG patient receives the device (the telerehabilitation set) for telemonitoring and guided exercise training (Pro Plus Company, Poland), composed of an EHO mini device that records and transmits the ECG and blood pressure measurements, a body scale, and a mobile phone.

Table 2. Exercise training model of hybrid cardiac rehabilitation.

Hospital-based rehabilitation Training session. Group gymnastics (not ECG monitored): breathing exercises, dynamic exercises of all muscle groups, isometric exercises of smaller muscle groups. Twice a day up to 15 min. Resistance and strength training session (not ECG monitored) using a yellow Thera-Band, consists of: • Warm-up (strength exercise): dynamic exercises of all muscle groups and breathing exercises; duration 5 min. • Resistance exercises 8–10 muscle groups (including forearm flexors, shoulder extensors, shoulder flexors, extensors and thigh flexors, thigh abductor) for about 10 min daily, 10 repetitions, after a series of repetitions 30–60 s rest. • Cool down: breathing and relaxation exercise; duration 3–5 min. Endurance training: interval training on a cycloergometer, five days a week, lasting 31 minutes each; training load and breaks selected individual (depending on heart rate training limit and patient symptoms)—monitored. • Intensity: 60–80% of heart rate reserve *. • Frequency: 1 session/day.
Home-based telemonitored rehabilitation Endurance training session (telemonitored) comprises: • Warm-up: breathing exercise duration 5 min. • Nordic walking training ○ Intensity: 60–80% of heart rate reserve *. ○ Duration: start at 10–15 min/per session/per day and gradually boosted to 30–45 min/per session/per day. • Cool down: breathing and relaxation exercise; period 3–5 min. • Frequency: 1 session/per day. Resistance and strength training session (not monitored) using a yellow Thera-Band, consists of: • Warm-up: (strength exercise: dynamic exercises of all muscle groups and breathing exercises); duration 5 min. • Resistance exercises: 8–10 muscle groups (including forearm flexors, shoulder extensors, shoulder flexors, extensors and thigh flexors, thigh abductor) for about 10 min/daily, 10 repetitions, after a series of repetitions 30–60 s rest. • Cool down: breathing and relaxation exercise; duration 3–5 min.

* Target heart rate during endurance training was calculated according to Karvonen formula (heart rate at rest plus a result of a subtraction of a maximum heart rate and heart rate at rest multiplied by 60–80%).

An EHO device is designed to register 16 s–5 min pieces of ECG recording from three precordial leads and transmit the data via a mobile phone network to the monitoring center. This device has training sessions programmed personally for every patient (established exercise duration, intervals or coordination of ECG registration). The moments of automatic ECG recording are preset and harmonized with the exercise training [24].

Before every training session, participants answer questions concerning their current health status and medicaments taken by mobile phone. Then patient transmits ECG at rest, blood pressure and weight data to the monitoring center. If no contraindications to training are recognized, participants receive approval to begin a training session. If no adverse events occur, a patient sends out an ECG recording to the monitoring center immediately after each training session. The data are stored and analyzed in the Telecardiology Center.

2.4. Control Group

In our study, each patient is encouraged to undertake exercise activity. All patients are given pro-health lifestyle recommendations: physical activity prescription, healthy diet recommendation, encouragement of alcohol limitation, and smoking cessation [14].

The only difference between the groups is that the training group undergo a supervised HCR program (with telesupervised exercise training) while the control group does not. Some patients in the control group can participate in cardiac rehabilitation at their place of residence. Moreover, the control group receives standard medical care under current cardiological guidelines [23].

2.5. Clinical Examination

All 60 patients undergo the following assessments: medical checkup (with NYHA class assessment), blood testing (morphology, concentration of potassium, sodium, magnesium, creatinine, NT-pro-BNP, and CRP), ECG, resting and exercise two-dimensional echocardiography, a six-minute walk test (6-MWT), a cardiopulmonary exercise testing (CPET), 24 h Holter-ECG monitoring, psychological assessment: General Health Questionnaire (GHQ-28) used to assess adult mental health [28], Brief Illness Perception Questionnaire (B-IPQ), used to estimate the intensity of the components of cognitive representation [29,30], Perceived Stress Scale (PSS-10) used to evaluate the intensity of stress associated with one's own life over the last month [31,32] and also International Physical Activity Questionnaire (IPAQ) [33,34]. All tests are done at entry, after completing the 3-month program, and during follow-up. The components are shown in Table 3.

Table 3. Clinical examination and diagnostic tests.

Time Examination	At Entry (Month0)	After Completing HCR (Month3)	Follow-Up (Month6)	Follow-Up (Month9)	Follow-Up (Month15)
Clinical Examination	X	X	X	X	X
International Physical Activity Questionnaire (IPAQ)	X	X	X	X	X
Blood tests (morphology, potassium, sodium, magnesium, creatinine, NT-pro-BNP, CRP)	X	X	X		
Electrocardiogram	X	X	X		
24-h Holter-electrocardiography monitoring	X	X	X		
Transthoracic two-dimensional echocardiography	X	X			
Exercise two-dimensional echocardiography	X	X			
6 min walk test	X	X	X		
Cardiopulmonary exercise test (CPET)	X	X	X	X	
Psychological assessment: General Health Questionnaire (GHQ-28), Brief Illness Perception Questionnaire (B-IPQ), Perceived Stress Scale (PSS-10)	X	X	X	X	X

2.6. Outcomes

The primary endpoint is a functional capacity evaluated by peak oxygen uptake (pVO_2). Secondary endpoints include workload time during CPET, 6-MWT distance, NT-pro BNP level, echocardiographic parameters of LV diastolic function (E/A , E/e' , myocardial strain rate), right ventricular systolic pressure, a gradient in the LV outflow tract, and quality of life (QoL).

The tertiary analysis includes safety, acceptance, and adherence to the HCR program.

The effectiveness of HCR is estimated by changes—delta (Δ) in pVO_2 , workload duration in CPET, and 6-MWT distance—as a result of comparing those parameters at the beginning and the end of the HCR program.

2.7. Randomization

Following baseline measurements, patients are randomly allocated (in a 1:1 proportion), according to simple randomization procedures (a block-based model using sealed opaque envelopes), to TG or CG. Sixty envelopes are divided into six blocks of 10 envelopes. Each block contains five envelopes TG and five envelopes CG. The last patient (number 60) will not draw the envelope but will receive the remaining one.

3. Statistical Analysis

The Shapiro–Wilk test will be used to check for the normal distribution of continuous data. Normally distributed variables will be presented in mean $\pm$ standard deviation (SD), and skewed distribution will be reported as a median and inter-quartile range. Levene's test will be used for the comparison of homogeneity of variance.

The principal analysis compares the primary outcome between the two trial groups at months 3, 6, and 9. First, the difference between the groups in the mean change from baseline to month 3 in the peak VO_2 will be analyzed using Student's test. Second, the peak VO_2 at 3 months will be assessed using an analysis of the covariance model, taking into account baseline VO_2 .

The principal secondary analysis is a comparison of the comprehensive assessment of the efficiency of HCR rated by workload duration during the CPET, 6-MWT distance, psychological parameters evaluating the quality of life, NT-pro BNP, parameters of the LV diastolic function (E/A , E/e' , myocardial strain rate—strain rate), right ventricular systolic pressure, the gradient in the left ventricle, and laboratory parameters (e.g., creatinine, morphology) between months 0 and 3. A random-effects pattern will be used to account for repeated measures within participants. Progress of heart failure will be gauged based on changes in mean values. There is no plan for the correction of multiple comparisons of secondary outcomes. These results will be presented as point estimates with unadjusted 95% confidence intervals without p values.

The sample size calculation was performed with the assumption of a significance level of $p = 0.05$, two-sided testing, and the expected mean increases in peak VO_2 (over 3 months) in the intervention group by 10% ($1.9 \text{ mL} \pm 2.6 \text{ mL/kg/min}$) and in the control group by 0.5% ($0.10 \pm 1.9 \text{ mL/kg/min}$). Two-sample Satterthwaite t -test for mean differences with the above assumptions and a sample of 54 people in total (27 patients in the intervention and control groups) gives the power of 81.2% to achieve a statistically significant result. Considering the possibility of a 10% loss of participants during the trial, the total number of participants was increased to 60 people.

We will also be analyzing the between-groups differences in the other variables. We will use appropriate parametric and nonparametric statistics to compare the other outcomes. Categorical variables will be summed up as absolute frequencies and percentages. Relation between them will be carried out by Pearson's χ^2 test with continuity correction or Fisher's exact test if the expected cell count is less than 5.

Multivariate analysis: multiple binomial or ordinal logistic regression analyses will be applied to examine associations between individual factors (e.g., sex, age, etc.) and secondary endpoints (e.g., hospitalizations due to heart failure aggravation, NYHA class, etc.). Adjusted for confounders, odds ratios (OR) with an adequate 95% confidence interval (CI) will be counted. Patterns will be assessed by calculating the area under the receiver-operating characteristic curve (ROC, C-statistic).

The probability of free events survival by randomized arm will be graphically displayed by the method of Kaplan–Meier, with a comparison of cumulative events by the log-rank test. Multivariate analysis will be performed using Cox proportional hazards regression modeling.

All statistical assumptions will be two-tailed, and the type I error rate will be 5%. Statistical analyses will be carried out using SAS software release 9.4. (SAS Institute Inc., Cary, NC, USA).

3.1. Trial Status

Completed patient recruitment. The follow-up is in progress. Results will be available in 2022/2023.

3.2. Discussion

HCM is the most frequent cause of sudden cardiac death due to cardiovascular diseases in athletes. Altered dynamics of LV filling and reduced LV muscle compliance are related to a decreased ejection volume and increased LV filling pressure. These factors primarily reduce HCM patients' exercise capacity [35–37].

For many years, the management of HCM was restricted to limiting exercise stress activity [38,39]. According to European Society of Cardiology (ESC) guidelines from 2014 concerning the diagnosis and management of HCM, it is advised that HCM patients avoid sport, defined as any involvement in regular training, and avoid participation in official competitions [40]. However, the results of Edelmann's research suggest that exercise leads to a considerable improvement in patients with diastolic dysfunction and can, therefore, be beneficial in patients with HCM [41].

All stable heart failure patients should undergo exercise training (also patients with preserved ejection fraction)—this is the I Class of recommendation, level of evidence A, according to current ESC guidelines [42].

The results of previous studies of patients with HCM subjected to supervised exercise training showed numerous benefits without significant adverse events.

The studies describing telerehabilitation have shown that it is a method that increases the patients' participation in exercise training. TELEREH-HF—the most extensive study in telemedicine—has shown that adherence to the telemonitored exercise training was very high (88.4%). Therefore, we expect that adherence in HCM patients would also be high [8–15].

In our work, we will evaluate HCR: the combination of hospital-based cardiac rehabilitation with a new form of home-based telemonitored cardiac rehabilitation (using telemedicine) in this group of patients. This model of cardiac rehabilitation in HCM patients will be pioneering research. Its results, especially during the SARS-CoV 2 pandemic, will contribute to the greater participation of patients in cardiac rehabilitation. Telerehabilitation provides better epidemic conditions: patients remain at their place of residence, with minimal travel or transportation barriers, protected from virus infection [43–45].

4. Conclusions

Our research will provide innovative data on the effectiveness and safety of hybrid cardiac rehabilitation in HCM patients without LV outflow tract obstruction and preserved systolic function.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of National Institute of Cardiology (statutory work number 2.1/I/17 and date of approval 03.04.2017) for studies involving humans.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data is available in the National Institute of Cardiology.

Conflicts of Interest: The authors declare no conflict of interest.

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