

ABSTRACT

Background

Hybrid comprehensive telerehabilitation (HCTR) is an innovative form of cardiac rehabilitation. A key element of HCTR is telesupervised exercise training. According to current guidelines the recommended method of home-based cardiac telerehabilitation supervising, in moderate and high-risk patients, is electrocardiographic (ECG) monitoring. The optimal form of ECG monitoring (real-time, sequential, on demand) during HCTR is still under discussion and the effect of cardiac rehabilitation on ventricular arrhythmia in heart failure patients is still remains unclear. The problem of ventricular arrhythmia in the context of cardiac rehabilitation in heart failure patients should be considered in several aspects:

- a) the occurrence of arrhythmias triggered by the exercise training, which acutely impacts the rehabilitation safety,
- b) the potentially antiarrhythmic effect of the total rehabilitation process and its influence on prognosis,
- c) the possibility of the occurrence of proarrhythmic effect associated with the rehabilitation process and its prognostic significance.

Objectives

The aim of the doctoral thesis, which consists of three related- papers, is to assess the impact of a 9-week HCTR on arrhythmias in patients with heart failure in terms of:

- a) the safety of HCTR when using the sequential ECG monitoring method (publication no.1),
- b) the effect of HCTR on prognostically significant ventricular arrhythmias (publications no.1,2,3),
- c) the impact of the potential antiarrhythmic and proarrhythmic effect of the 9-week HCTR on long-term cardiovascular mortality (publications no. 2,3).

Methods

The study population included patients from The Telerehabilitation in Heart Failure Patients (TELEREH-HF) trial conducted in 2015-2021 in 5 locations in Poland, with the Telecardiology Center of the National Institute of Cardiology as a coordinating center. The study was a randomized, multicenter, prospective, open-label, parallel-group clinical trial which enrolled 850 patients with heart failure up to 6 months after a cardiovascular hospitalization with New York Heart Association class I, II, or III and left ventricular ejection

fraction of 40% or less. Patients were randomized 1:1 to HCTR plus usual care or usual care (UC) only and followed up for 14 to 26 months after randomization.

Publication no. 1 analyzed ECG recorded during sequentially telemonitored Nordic training in 386 patients who completed a 9-week HCTR. We focused primarily on incidence and type of cardiac arrhythmias, analyzed newly appearing arrhythmias on exercise and assessed the percentage of training sessions with the target training heart rate achieved. In order to assess the antiarrhythmic effect (publication no. 2) and the proarrhythmic effect (publication no. 3) of 9-week HCTR, we performed analysis based on the assessment of 24-h Holter ECG monitoring at baseline and after 9 weeks of HCTR (382 patients - HCTR group) or UC (391 patients - UC group).

In publication no. 2, a prognostically significant ventricular arrhythmia, as a factor linked to an increased risk for cardiac mortality in heart failure patients, were defined as the presence of non-sustained ventricular tachycardia (nsVT) or frequent premature ventricular complexes ≥ 10 per hour (PVCs $\geq 10/h$) on 24-h Holter ECG. The improvement effect (antiarrhythmic effect) on nsVT/PVCs $\geq 10/h$ was defined as presence of nsVT (or PVCs $\geq 10/h$) at baseline Holter ECG and absence in Holter ECG after 9-week of HCTR or UC. We assessed the differences in ventricular arrhythmias incidence before and after the 9-week HCTR or UC (HCTR/UC group) in each group (within-group analysis) and between the groups. The impact of the antiarrhythmic effect of 9-week HCTR on cardiovascular mortality in long-term follow up (from randomization through to the end of follow-up at 14 to 26 months) were also analyzed. In publication no. 3, according to the recommendation, three criteria for the occurrence of proarrhythmia were strictly defined. The proarrhythmic effect existed if there was:

- a) an increase of >3 -fold in the frequency of PVCs when baseline PVCs are >100 PVCs/h,
- b) an increase of >10 -fold in the frequency of PVCs when baseline PVCs are <100 PVCs/h
- or
- c) new onset of arrhythmia (PVCs, nsVT) not presented at the baseline.

We focused on the potential proarrhythmic effect after 9 weeks of HCTR or UC, compared the groups (HCTR and UC) with each other and assessed the impact of the proarrhythmic effect on long-term (from randomization through the end of follow-up at 14 to 26 months) cardiovascular mortality.

Results

The most common arrhythmias recorded during the training sessions were PVC and premature atrial complexes, in 76.4% and 27.7% of patients, respectively. Episodes of nsVT consisting of 3-5 beats were found in 21 (0.03%) ECGs. Three episodes of arrhythmia were recorded at rest. None of the patients experienced them as symptomatic. Among 126 patients (32.7%) without arrhythmias recorded at rest (ECGs were recorded before beginning training session as a part of the preliminary examination – the consent procedure), there were 57 (45.2%) without arrhythmia on exercise, while the remaining 69 (54.8%) were with newly appearing arrhythmias on exercise. In univariable analysis, none of the considered demographic and clinical characteristics were an independent statistically significant risk factor for newly appearing arrhythmias on exercise.

The achievement of target training heart rate in more than 80% of training sessions compared with remaining groups did not reduce the incidence of outcomes (e.g., all-cause mortality, cardiovascular mortality, all-cause hospitalization, cardiovascular hospitalization) in long-term follow-up (14-26 months from randomization). Among 143 patients with nsVT at baseline Holter ECG, arrhythmia subsided in 44 (30.8%) after HCTR. Similarly, among 165 patients randomized to UC who had nsVT at baseline, 57 (34.5%) did not show it after 9 weeks of observation ($p=0.481$). There was no significant difference in the decrease in PVC $\geq 10/h$ over 9 weeks between randomization arms (14.9% vs. 17.8%, respectively $p=0.410$). A significant functional response for 9-week HCTR (assessed by changes – delta (Δ) – in peak oxygen consumption (pVO_2) in a cardiopulmonary exercise test as a result of comparing ΔpVO_2 from the beginning and the end of the program) >2.0 ml/kg/min., did not affect occurrence of arrhythmias. Multivariable analysis did not identify HCTR as an independent factor determining antiarrhythmic effect. However, only in the HCTR group, the achievement of the antiarrhythmic effect on nsVT significantly reduced the cardiovascular mortality in long-term follow-up ($p<0.001$).

The proarrhythmic effect was found in 78 (20.4%) and in 61 (15.6%) patients in the HCTR and UC group respectively, and the difference between groups was not statistically significant ($p=0.081$). However, univariate analysis identified several statistically significant predictors of proarrhythmia in HCTR group (vs. UC). In multivariate analysis ischaemic aetiology of heart failure (OR=2.27, 95%CI: 1.24-4.17, $p=0.008$), pVO_2 at baseline <14 ml/kg/min (OR=2.03, 95%CI: 1.17-3.52, $p=0.012$) and level of N-terminal-pro B-type natriuretic peptide in the first and the second tercile (OR=1.85, 95%CI: 1.02-3.37, $p=0.043$) were identified to be independent predictors of proarrhythmic effect in HCTR group only.

In the same analysis of the UC group only, no independent predictors of proarrhythmia were found. After a mean follow-up of 14-26 months, there was no significant difference in cardiovascular mortality including sudden cardiac death, between the HCTR and UC regardless of the presence or of the absence of proarrhythmic effect ($p=0.474$).

Conclusions

Sequential monitoring of ECG should be sufficient to ensure the safety of hybrid comprehensive telerehabilitation in heart failure patients.

There was no significant difference between the groups (HCTR and UC) in the effect of the 9-week hybrid comprehensive telerehabilitation or usual care on the occurrence of prognostically significant ventricular arrhythmias (nsVT and PVCs $\geq 10/h$) in 24-h Holter ECG.

The achievement of the antiarrhythmic effect in terms of incidence of nsVT after 9 weeks of HCTR significantly reduced cardiovascular mortality in long-term follow-up. This effect was not observed in UC group.

The occurrence of the proarrhythmic effect after the 9-week hybrid comprehensive telerehabilitation did not cause a significant risk of cardiovascular mortality, including sudden cardiac death, in long-term follow-up.

A handwritten signature in blue ink, appearing to read "Peter Medeiros". The signature is fluid and cursive, with a large initial "P" and "M".