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Feasibility and effectiveness of specialised exercise training/rehabilitation programme for patients with pulmonary hypertension and heart failure

DOCTORAL DISSERTATION

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TABLE OF CONTENTS

ABBREVIATIONS

A (m/s) – late mitral inflow velocity

a’ (m/s) – tissue Doppler mitral annular late diastolic velocity

ACEI – angiotensin-converting enzyme inhibitor

AE – adverse event

ARB – angiotensin receptor blocker

A-V O2 difference – oxygen content between arterial and venous blood

BMI – body mass index

BNP – brain natriuretic peptide

BPM – beats per minute

CCB – calcium channel blockers

CI – cardiac index

CO – cardiac output

CpcPH – combined post- and pre-capillary pulmonary hypertension

CTEPH – chronic thromboembolic pulmonary hypertension

DecT – mitral flow E wave deceleration time

DLCO – diffusing capacity for carbon monoxide

dPAP – diastolic pulmonary artery pressure

E – early mitral inflow velocity

E/A – ratio of early mitral inflow velocity and late mitral inflow velocity

E/e’ – ratio of early mitral inflow velocity and tissue Doppler mitral annular early diastolic velocity

e’ – tissue Doppler mitral annular early diastolic velocity

ECG – electrocardiogram

EF – ejection fraction

eGFR – estimated glomerular filtration rate

ERS – European Respiratory Society

ESC – European Society of Cardiology

FEV1 – forced expiratory volume in the first second

FU – follow-up

FVC – forced vital capacity

Hb – haemoglobin

HF – heart failure

HFpEF – heart failure with preserved ejection fraction

HFrEF – heart failure with reduced ejection fraction

HIIT – high intensity interval training

HIV – human immunodeficiency virus

HR – heart rate

IpcPH – isolated post-capillary pulmonary hypertension

IVRT (ms) – isovolumetric relaxation time

LAVI (ml/m2) – left atrium volume index

LV – left ventricle

LVEDP – left ventricular end-diastolic pressure

LV-GLS – left ventricle global longitudinal strain

LV-GSR (s-1) – left ventricle global longitudinal strain rate

LVMI – left ventricle mass index

LVVI – left ventricle volume index

MI-ACT – moderate intensity aerobic continuous training

mPAP – mean pulmonary arterial pressure

mPAWP – mean pulmonary arterial wedge pressure

MRA – mineralocorticoid receptor antagonist

mRAP – mean right atrial pressure

PAC – pulmonary arterial compliance

PAH – pulmonary arterial hypertension

PAP – pulmonary arterial pressure

PAWP – pulmonary arterial wedge pressure

PH – pulmonary hypertension

PH-HFpEF – pulmonary hypertension associated with heart failure with preserved ejection fraction

PH-LHD – pulmonary hypertension associated with left heart disease

PVR – pulmonary vascular resistance

QOL – quality of life

RA – right atrium

RCT – randomised controlled trial

RHC – right heart catheterization

RV – right ventricle

RV-GLS – right ventricle global longitudinal strain

RV-GSR (s-1) – right ventricle global longitudinal strain rate

s' – tissue Doppler mitral annular systolic velocity

SGLT2 – sodium-glucose Cotransporter-2

sPAP – systolic pulmonary artery pressure

SV – stroke volume

SVI – stroke volume index

TAPSE – tricuspid annular plane systolic excursion

TLC – total lung capacity

VD/VT – the ratio of the dead space ventilation to tidal volume

VE/VCO2 slope – ventilatory equivalent for carbon dioxide

VO_2peak – peak oxygen uptake

WHO – World Health Organization

WU – Wood Units

6MWD – 6-minute walk test distance

LIST OF PUBLICATIONS

This doctoral thesis is based on the following publications which shall be referred to in the Roman numerals in this text.

I. Grünig E, MacKenzie A, Peacock AJ, Eichstaedt CA, Benjamin N, Nechwatal R, Ulrich S, Saxer S, Bussotti M, Sommaruga M, Ghio S, Gumbienė L, **Palevičiūtė E**, Jurevičienė E, Cittadini A, Stanziola AA, Marra AM, Kovacs G, Olschewski H, Barberà JA, Blanco I, Spruit MA, Franssen FME, Vonk Noordegraaf A, Reis A, Santos M, Viamonte SG, Demeyer H, Delcroix M, Bossone E, Johnson M. *Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial*. Eur Heart J. 2021 Jun 14;42(23):2284-2295. doi: 10.1093/eurheartj/ehaa696. PMID: 33232470.

II. **Palevičiūtė E**, Gumbienė L, Jurevičienė E, Šimbelytė T, Laucevičienė I, Laucevičius A, Barysienė J, Eichstaedt CA, Benjamin N, Grünig E, Čelutkienė J. *The Experience, Prerequisites, and the Barriers in Organizing a Specialized Rehabilitation Program for Patients with Pulmonary Hypertension.* Respiration. 2021;100(10):949-957. doi: 10.1159/000516331. Epub 2021 May 27. PMID: 34044412.

III. Nagel C, Benjamin N, Egenlauf B, Eichstaedt CA, Fischer C, **Palevičiūtė E**, Čelutkienė J, Harutyunova S, Mayer E, Nasereddin M, Marra AM, Grünig E, Guth S. *Effect of Supervised Training Therapy on Pulmonary Arterial Compliance and Stroke Volume in Severe Pulmonary Arterial Hypertension and Inoperable or Persistent Chronic Thromboembolic Pulmonary Hypertension*. Respiration. 2021;100(5):369-378. doi: 10.1159/000512316. Epub 2021 Mar 25. PMID: 33765679.

IV. **Palevičiūtė E**, Šimbelytė T, Eichstaedt CA, Benjamin N, Egenlauf B, Grünig E, Čelutkienė J. *The effect of exercise training and physiotherapy on left and right heart function in heart failure with preserved ejection fraction: a systematic literature review*. Heart Fail Rev. 2022 Jul 13. doi: 10.1007/s10741-022-10259-1. Epub ahead of print. PMID: 35831689.

Publications not included in the thesis

1. Lycholip E, **Palevičiūtė E**, Aamodt IT, Hellesø R, Lie I, Strömberg A, Jaarsma T, Čelutkienė J. Non-invasive home lung impedance monitoring in early post-acute heart failure discharge: Three case reports. World J Clin Cases. 2019 Apr 26;7(8):951-960. doi: 10.12998/wjcc.v7.i8.951. PMID: 31119140; PMCID: PMC6509267 **(IF 1.337; Q3).**

2. Gumbiene L, Kapleriene L, Jancauskaite D, Laukyte-Sleniene M, Jureviciene E, Rudiene V, **Paleviciute E**, Mataciunas M, Sileikiene V. Insights to correlations and discrepancies between impaired lung function and heart failure in Eisenmenger patients. Pulm Circ. 2020 Feb 28;10(1):1350650120909729. doi: 10.1177/2045894019899239. PMID: 32166016; PMCID: PMC7052468 **(IF 3.017; Q3).**

3. Hoeper MM, Pausch C, Grünig E, Klose H, Staehler G, Huscher D, Pittrow D, Olsson KM, Vizza CD, Gall H, Benjamin N, Distler O, Opitz C, Gibbs JSR, Delcroix M, Ghofrani HA, Rosenkranz S, Ewert R, Kaemmerer H, Lange TJ, Kabitz HJ, Skowasch D, Skride A, Jureviciene E, **Paleviciute E**, Miliauskas S, Claussen M, Behr J, Milger K, Halank M, Wilkens H, Wirtz H, Pfeuffer-Jovic E, Harbaum L, Scholtz W, Dumitrescu D, Bruch L, Coghlan G, Neurohr C, Tsangaris I, Gorenflo M, Scelsi L, Vonk Noordegraaf A, Ulrich S, Held M. Idiopathic pulmonary arterial hypertension phenotypes determined by cluster analysis from the COMPERA registry. J Heart Lung Transplant. 2020 Dec;39(12):1435-1444. doi: 10.1016/j.healun.2020.09.011. Epub 2020 Sep 30. PMID: 33082079 **(IF 13.569; Q1).**

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1. INTRODUCTION

1.1. Background

1.1.1. Epidemiology of PH

Pulmonary hypertension (PH) and chronic heart failure (HF) are severe cardiovascular disorders, both of which are characterised by reduced physical capacity of the patients, low health-related quality of life, and poor survival. Even though pulmonary arterial hypertension (PAH) (*Group 1 PH, according to PH clinical classification*) is considered an orphan disease, PH, as a broader syndrome, is frequent, highly heterogeneous, and may complicate the majority of cardiovascular, respiratory, and systemic diseases [1, 2]. Present estimates suggest a PH prevalence of about 1% of the global population, which increases up to 10% in individuals aged over 65 years of age [1, 3].

PH associated with the left heart disease (PH-LHD) is a growing health problem with high morbidity and mortality [1, 4, 5]. Among the various PH groups, PH-LHD represents the most prevalent form and accounts for 65–80% of all PH cases [1, 3, 6–9]. The estimated prevalence of PH-LHD varies depending on the methodology of diagnostic testing (echocardiography or invasive haemodynamics), the definition of PH, the populations studied, and the type of LHD. In heart failure with reduced ejection fraction (HFrEF), the occurrence of PH ranges from 40 to 75%, as assessed by right heart catheterisation (RHC) [10–13]. Most data on the prevalence of PH in heart failure with preserved ejection fraction (HFpEF) are based on echocardiographic signs, where the incidence of PH varies between 36–83% [14, 15]. In an invasive haemodynamic assessment study, among 618 HFpEF patients, 355 (57.4%) were diagnosed with PH, and 75 (21.1%) of them had combined post- and pre-capillary PH (CpcPH) [13].

Across the spectrum of LHD, the increased pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) are related to a higher disease burden and worse outcomes [16–19]. PAP is a marker of the severity and chronicity of pulmonary venous congestion/hypertension in HF [14, 20].

1.1.2. Haemodynamic changes in PAH and PH-LHD

Regardless of the origin, a definite diagnosis of PH can be made only by right heart catheterisation [1, 6]. Based on the most recent data and new ESC/ERS guidelines, invasively measured mPAP >20 mmHg is considered to be abnormal, and the upper limit of normal PVR is 2 Wood units (WU) [1, 21–23]. The distinction of the two main haemodynamic types of PH is based on the invasive measurement of the pulmonary arterial wedge pressure (PAWP). Pre-capillary PH is diagnosed when rest PAWP is ≤15 mmHg, which is typical for PAH and chronic thromboembolic pulmonary hypertension (CTEPH), while an increase in PAWP >15 mmHg is characteristic for post-capillary PH, thereby indicating PH-LHD [1].

In the absence of mitral stenosis, PAWP approximates left ventricular end-diastolic pressure (LVEDP) [24, 25]. The hallmark of left HF is an elevation in left-sided filling pressures, which causes symptoms of dyspnoea [26], impairs exercise capacity [27], and may lead to pulmonary venous congestion and secondary post-capillary PH (*Group 2 PH, according to PH clinical classification*) [14]. Post-capillary PH is subdivided into isolated post-capillary PH (IpcPH), when PVR is ≤2 WU, and combined pre- and post-capillary PH (CpcPH), when PVR is >2 WU [1]. CpcPH is associated with the major degree of reduced exercise capacity and a phenotype similar to PAH [28, 29].

1.1.3. Medical treatment of PAH and PH-LHD

The targeted medication therapy for PAH and CTEPH, including drugs interfering with the endothelin, nitric oxide and prostacyclin pathways, has progressively evolved in the last decades, with an increasing evidence for its efficacy [30, 31]. However, these drugs are not recommended for patients with PH-LHD, as multicentre randomised trials using PAH medications failed to demonstrate any substantial benefit in PH-LHD, but raised safety concerns instead [1, 5, 6, 32–35]. Conventional HF treatments (medical/devices) currently remain the only established therapies for patients with PH-LHD [1, 6, 36].

HFrEF and HFpEF disorders have some differences in pathophysiology, clinical characteristics, haemodynamics, cardiopulmonary interaction, and response to therapy [37–39]. While pharmacological treatments are well-established in HFrEF, not all of them could be convincingly proven to be effective in HFpEF [36], with the recent exception of Sodium-glucose Cotransporter-2 (SGLT2) inhibitors [40, 41].

In patients with HFpEF, medication therapy options remain limited – SGLT2 inhibitors, diuretics, and treatment of comorbidities (e.g. arterial hypertension, obesity, atrial fibrillation) are recommended [36, 40]. At the same time, most PAH and CTEPH patients, despite modern treatment options, still suffer from symptoms, reduced exercise capacity, poor health-related quality of life and disease progression [42]. Therefore, there is a high need for additional therapeutic strategies in PAH, CTEPH and PH-HFpEF.

Currently, ESC/ERS guidelines suggest complex treatment of PH, consisting of disease-targeted and supportive medical therapy together with non-pharmacological general measures [1, 6].

1.1.4. Gaps in knowledge about rehabilitation in PH

In 2015, the ESC/ERS recommendations advised to consider supervised exercise training as an add-on to the optimal medical therapy in stable PH patients (*Class IIa level B recommendation*) [6]. These recommendations were based on previous observational and single-centre randomised controlled trials (RCT) which mainly focused on PAH and CTEPH patients, used different models of exercise training regimens, and demonstrated physical therapy to be safe and effective on the patient's functional capacity and health-related quality of life (QOL) [43–55]. However, a larger sample size, as well as multicentre RCT, was lacking to show stronger evidence regarding the safety and efficacy of this non-pharmacological treatment method.

This doctoral thesis presents part of data obtained in the first multicentre RCT dedicated to PAH and CTEPH exercise training, published in 2021 [56]. By showing the benefit of the exercise capacity and quality of life, this recent trial has changed the class of recommendation for supervised exercise training in patients with PAH to *Class I level A* in the 2022 ESC/ERS guidelines [1].

The ESC guidelines for the diagnosis and treatment of acute and chronic HF recommend exercise rehabilitation for all patients who are able to exercise in order to improve the exercise capacity and QOL, and also to reduce HF hospitalizations, regardless of the LV ejection fraction (*Class I level A recommendation*) [36]. In HF patients with more severe disease, frailty, multiple comorbidities – which is a typical profile of PH-LHD patients – a supervised, exercise-based, cardiac rehabilitation programme should also be considered (*Class IIa level C recommendation*) [36]. These recommendations are based on the data of properly designed exercise interventions alone or as a component of comprehensive cardiac

rehabilitation programs for HF, where an improvement in exercise capacity, symptoms, health-related QOL, and risk reduction of all-cause and HF hospitalizations have been consistently demonstrated [57–64]. Although HFrEF patients were predominant in the largest HF exercise training trials, several systematic reviews and meta-analyses focused specifically on HFpEF, and confirmed the positive impact of exercising on functional capacity in HFpEF, as indicated by the improved peak oxygen uptake (VO_2peak) [58, 65–69] and the 6-minute walk test distance (6MWD) [48, 49]. Moreover, training in HFpEF seemed to be safe [58, 65–68, 70, 71] and beneficial for health-related QOL [58, 65–69].

There are no evidence-based recommendations for exercise therapy of PH-LHD. Importantly, an invasive haemodynamic study revealed that PH-HFpEF patients demonstrate unique haemodynamic limitations during exercise which constrain aerobic capacity – impaired recruitment of LV preload due to excessive right heart congestion and blunted right ventricular (RV) systolic reserve were noticed [72]. These mechanisms are leading to RV and PA uncoupling with further limitations of exercise capacity and poor outcome [73]. It is of note that the number of PH-HFpEF patients in previous HFpEF exercise training trials remains unclear, and none of the previous studies focused specifically on PH-HFpEF.

Taking into consideration the positive impact of exercise training both in PAH and HFpEF, a question arises whether exercising could be beneficial in a particular population of severely ill PH-HFpEF patients. This hypothesis requires dedicated research since most of the PH training studies excluded patients with post-capillary PH, while HFpEF trials usually did not report the presence or absence of PH.

1.1.5. Limited availability of PH rehabilitation programs

Although treatment recommendations advise to incorporate exercise therapy in the comprehensive care of PH and HF patients, this recommendation is limited by some gaps in knowledge (the optimal methodology of rehabilitation, the best intensity and duration of the training) and practical barriers (lack of experience, reimbursement issues, etc.). Finding the right balance between the benefit and the risk of PH exercise therapy is crucially important, as the intensity of the training should be sufficient to be effective, but there is a concern that the wall shear stress in the pulmonary vessels, evoked by higher blood flow due to exercise training, may trigger further pulmonary vascular remodelling and worsen the disease;

thus, excessive physical activity that leads to distressing symptoms is not recommended for these patients [36, 74, 75].

A low-intensity exercise training programme for patients with PAH and CTEPH has been developed and applied in Heidelberg (Germany); in single centre studies it demonstrated safety and ability to increase health-related QOL, exercise capacity, lower limb muscle strength and haemodynamics [43, 47, 53, 54, 76]. However, multicentre interventional studies to assess the effect of this programme in different countries with different health care systems have been lacking up to date; and its impact on patients with PH-HFpEF has never been assessed previously.

Limited availability and underutilisation of exercise training remains a drawback in many PH, HF, and general cardiology centres. Before this study, no specialised rehabilitation programme was available for Lithuanian PH patients, either. The feasibility and the barriers of the development of this rehabilitation programme at the *Pulmonary Hypertension Competence Centre of Vilnius University Hospital Santaros Klinikos* was one of the research questions of this doctoral thesis.

This doctoral thesis is divided into two parts according to the study populations. The first part of the research concerns the specialised rehabilitation programme for pre-capillary PH patients (PAH, CTEPH), while the second part is dedicated to post-capillary PH patients (PH-HFpEF).

1.2. Hypothesis of the study

A specialised rehabilitation programme as an add-on to medical therapy is feasible, safe, and effective in stable patients with pre- and post-capillary pulmonary hypertension.

1.3. Objectives of the study

1) To investigate the safety and efficacy of a specialised rehabilitation programme for pre-capillary PH patients in a randomised controlled study (*Publications I, II*);
2) To identify the main prerequisites and barriers of the establishment of a specialised rehabilitation programme for PH patients (*Publication II*);
3) To assess the effect of a specialised rehabilitation programme on pulmonary arterial compliance and cardiac output in patients with pre-capillary PH (*Publication III*);

4) To perform a systematic review of the effects of exercise training and physiotherapy on cardiac parameters and pulmonary circulation in HFpEF patients (*Publication IV*);
5) To create a protocol for a multicentre trial of specialised rehabilitation for post-capillary PH – PH-HFpEF patients.

1.4. Scientific novelty of the study

The data of this doctoral thesis on pre-capillary PH rehabilitation, generated at Vilnius University, were pooled with the data from ten other PH centres across ten European countries in the first multicentre and the largest randomised controlled study. Our results have become the rationale to upgrade physical activity recommendations for PAH and CTEPH patients in the most recent 2022 ESC/ERS guidelines. Moreover, this study has demonstrated for the first time that an exercise training programme can be standardised and implemented in different countries with different healthcare systems.

The prerequisites and the barriers of specialised PH rehabilitation programme have never been assessed previously. We collected the data about the organisational aspects, which fills the knowledge gap and encourages the utilisation of specialised PH rehabilitation in dedicated PH centres.

The *post hoc* analysis of prospective randomised controlled trial for the first time assessed the effect of exercise training on the pulmonary arterial compliance and the stroke volume in patients with PAH and persistent/inoperable CTEPH.

To the best of our knowledge, none of the previous PH or HF exercise training studies have focused specifically on post-capillary PH and namely on PH-HFpEF patients. In this doctoral study, we were the first to conduct a systematic literature review of the existing data, thereby assessing the impact of exercise and physiotherapy in HFpEF trials on the left- and right-sided cardiac morphological, functional, and pulmonary circulation parameters.

1.5. Statements to be defended in the doctoral thesis

1) As an add-on to medical therapy, a specialised PH rehabilitation programme in precapillary PH (PAH, CTEPH) patients improves:
   a) physical capacity,
   b) health-related quality of life,
   c) pulmonary arterial compliance and stroke volume.

2) As an add-on to medical therapy, a specialised PH rehabilitation programme in precapillary PH (PAH, CTEPH) patients is safe and feasible.
3) Exercise training and/or physiotherapy improves the cardiac morphological, functional, and pulmonary circulation parameters in patients diagnosed with HFpEF.
4) The new study is justified to be designed for assessing the efficacy of a specialised PH rehabilitation programme in the particular population of PH-HFpEF patients.

2. LITERATURE REVIEW

2.1. Physiology of physical exercise

To cope with the increased metabolic needs during physical exertion, the human body mobilises the heart, lungs, vessels, endothelium, skeletal muscle, and autonomic nervous system in complex interactions [77, 78]. Exercise capacity is usually quantified by the peak oxygen consumption (peak VO_2), achieved during maximal effort exercise. According to the Fick principle, VO_2 is defined by the product of cardiac output (CO), which represents O_2 delivery, and the difference in the oxygen content between the arterial and venous blood (A-V O_2 difference), which indicates the amount of O_2 that was actually used by the muscle (VO_2 = CO x A-V O_2 difference) [79]. CO depends on the stroke volume (SV) and the heart rate (HR), whereas A-V O_2 difference is defined by the ability to oxygenate blood in the lungs, transport O_2 to the tissues bound to haemoglobin, and then distribute, extract and utilise O_2 in exercising muscle [80].

Enhanced peripheral O_2 distribution, utilisation and extraction during exercise plays an important role as a CO reserve [77, 81]. Although the heart increases the output, this enhanced flow needs to be matched to the tissues where perfusion is most needed, which is achieved by regional vasodilation in the skeletal and cardiac muscle and vasoconstriction in such other regions as the skin, splanchnic beds, and kidneys [77].

2.1.1. Pathophysiology of Exercise Intolerance in PAH

Exercise intolerance in PAH is multifactorial, determined by a combination of RV dysfunction, chronotropic incompetence, ventilation disorders, and skeletal muscle dysfunction. The mechanisms of exercise intolerance in PAH probably also include respiratory muscle weakness, dynamic hyperinflation and mechanical constraints [82], poor skeletal muscle and cerebral oxygenation, hyperventilation, and enhanced sympathetic drive [83–85].

The main consequence of PAH is RV failure. As both ventricles work together, dilatation and dysfunction of RV affects the geometry, structure, and function of LV [86], thus contributing to a decreased CO, especially during exercise [72, 87]. In addition to the increased afterload, impaired chronotropic response to exercise [88], ventricular–pulmonary arterial decoupling amplified with exercise [89], desynchrony of RV [90], and depressed contractile reserve [91, 92] were demonstrated to result in a

blunted increase of CO during exercise in PAH [93–95]. Moreover, RV failure causes a complex clinical syndrome affecting multiple organ systems, including brain, kidneys, liver, the gastrointestinal tract, the skeletal muscle, as well as the endocrine, immune, and autonomic systems [96].

Impaired ventilation in patients with PAH has multiple origins. A higher ventilatory response to exercise (VE/VCO_2 slope) is characteristic to these patients, and it may be attributed to pulmonary vascular remodelling leading to an increased physiological dead space (VD/VT) ratio on the alveolar level [97–99]. Moreover, in addition to frequent hypoxemia (which increases during exercise [97, 100]) these patients also suffer from hypocapnia [101, 102].

The maximal voluntary and involuntary strength of the quadriceps and inspiratory muscles are reduced in PAH patients and closely correlate to their exercise capacity [103–105]. The underlying cause of the peripheral muscle weakness is not completely clear, but it may involve atrophy, sarcomeric dysfunction, fibre type switch, or capillary rarefaction [106]. Endothelial dysfunction that is characteristic of PAH markedly influences the peripheral endothelium-dependent vascular tone and might adversely affect O_2 transportation, which would result in skeletal muscle microcirculation abnormalities [107, 108].

2.1.2. Pathophysiology of Exercise Intolerance in HFpEF

The mechanisms of the decreased exercise capacity in HFpEF are not completely understood yet. Healthy adults are capable to increase their VO_2 more than 6-fold during exercise by increasing SV, HR, and the extraction of oxygen from peripheral blood, but patients with HFpEF are unable to achieve such adaptations [109]. The currently available data suggests that exercise intolerance in HFpEF is predominantly related to the failure of the Frank-Starling mechanism (the ability to translate an enhanced preload to a stronger cardiac ejection) [110–112]. Greater diastolic stiffness prevents the increase in LV end-diastolic volume which normally accompanies exercise, and thus the Frank-Starling mechanism is blunted in patients with HFpEF despite the greater filling pressures [113]. The limited ability to adjust CO relative to the metabolic needs is thought to be the major contributor to exercise intolerance in HFpEF patients [109, 111, 114]. Normally, LV relaxation is augmented during exercise to compensate for the reduction in the filling time in healthy individuals [115]. However, during exercise in HFpEF patients, augmentation of relaxation velocity fails to occur: despite the increase of HR and diastolic pressure during exercise, SV

fails to increase, and, as a result, patients experience dyspnoea and fatigue [109]. Furthermore, a functional consequence of marked increases in PAWP and PAP amplifies dyspnoea and contributes to a lower VO_2peak [26, 116, 117].

Other cardiovascular limitations, such as the vascular stiffening and dysfunction, the heart rate and rhythm disorders, the right heart failure, or the changes of pulmonary circulation and pericardial restraint, also play a role in the pathophysiology of exercise intolerance in HFpEF [117].

Even though major reasons for exercise intolerance in many patients with HFpEF seem to be cardiac, non-cardiac factors are also important. Reduced peripheral oxygen extraction during exercise was observed in HFpEF patients [81, 118, 119]. Adverse changes in the leg muscle mass and volume may directly limit the increase of peripheral oxygen extraction during exercise [120]. It is also likely that common comorbidities associated with HFpEF, such as pulmonary disease, obesity, and diabetes, may contribute to exercise intolerance [109].

PH-HFpEF patients differ in haemodynamics and exercise intolerance compared with HFpEF patients without PH (non-PH-HFpEF) [72]. It is likely that the pathophysiology of the reduced physical capacity in PH-HFpEF patients includes mechanisms determining exercise intolerance both in HFpEF and in PAH. A significant impact of pulmonary vascular disease on the pathophysiology of exercise intolerance in HFpEF was already proven in [72]. During symptom-limited peak exercise, CpcPH-HFpEF patients, compared with non-PH-HFpEF and isolated post-capillary PH, developed more dramatic increases in the right heart filling pressures. In CpcPH-HFpEF patients, an increased venous return during exercise resulted in an enhanced ventricular interdependence, which compromised the LV chamber filling. Together with the reduced RV contractile reserve, this led to decreases in SV and blunted ability to augment CO with exercise. These changes in haemodynamics were accompanied by marked limitation in aerobic capacity [72].

2.2. Review of previous clinical studies on rehabilitation

2.2.1. Previous clinical studies on pre-capillary PH rehabilitation

Previous single-centre clinical trials, mainly focusing on the rehabilitation of PAH and CTEPH patients, have demonstrated its safety and effectiveness when using different models of exercise training regimens [43–53]. Three meta-analyses and a Cochrane Database systematic review

including heterogeneous training methodologies and different designs of the trials showed exercise training to be beneficial for pre-capillary PH patients while revealing an improvement in 6MWD and peak VO_2 (ml/kg/min) [48, 49, 52, 121].

The ERS statement on exercise training and rehabilitation of patients with severe chronic PH summed up the findings of studies which enrolled 784 PH patients in total, including 6 single-centre RCT, 3 controlled trials, 10 prospective cohort studies, three case series, two retrospective cohort studies, four systematic reviews, and three meta-analyses [122]. According to this statement, training programs have been shown to significantly improve exercise capacity, muscular function, and the quality of life [122].

Most exercise training trials in PH rehabilitation focused on changes in exercise capacity. The only prospective RCT examining the effect on invasively measured haemodynamics at rest and during exercise revealed positive results: a significant increase in the cardiac index (+9.3% versus −6.5%; $p<0.001$), a decrease in the mean PAP (−7.3% versus +16.1%; $p=0.007$) and PVR (−19.3% versus +34.5%; $p<0.001$) at rest, and a significant increase in the cardiac index during maximal exercise (+19.5% versus −4.3%; $p=0.002$) in the training group, compared with the control group [51]. Interestingly, echocardiography showed no significant differences in the right heart areas and systolic PAP between the groups in this study [51]. Nevertheless, meta-analysis of seven PH rehabilitation studies showed exercise training to be associated with a decrease in systolic PAP (assessed invasively in exclusively one study) at rest from the baseline to the follow-up (−3.7 mmHg; 95% CI −5.4 to −1.9) [48].

Only a few adverse events (<5%) were reported with regards to exercise training in PH. As summarised in the ERS statement, out of 674 exercise-trained PH patients, adverse events were reported in 64 (9.5%), the most common of which were dizziness, desaturation, respiratory infections, and arrhythmia [122]. Exercise-related complications seemed to be more frequent in outpatient settings compared to inpatient settings (5.8% versus 4.3%) [104, 122–125]. Paroxysmal supraventricular arrhythmia, syncope, and pre-syncope during or shortly after workout were reported in <1% of all patients, and clinical worsening of HF was not observed in any study during exercise training [122]. The low incidence of adverse events in PH rehabilitation studies can be explained by the many precautions taken to ensure an optimal safety profile. Careful patient selection, appropriate settings, well-prepared multidisciplinary teams consisting of experienced PH and rehabilitation specialists, individualised exercise training protocols and close monitoring ensure a good safety profile in PH rehabilitation [122].

Previous studies of pre-capillary PH rehabilitation were single-centre; hence, multicentre RCT with a larger sample size was lacking so that to provide stronger evidence on the safety and efficacy of this treatment method.

2.2.2. Previous clinical studies of HFpEF rehabilitation

Consistent scientific data show that properly designed exercise interventions alone or as a component of a comprehensive cardiac rehabilitation programme for HF, improved patient's exercise capacity, symptoms, and health-related QOL reduced the risk of all-cause and HF hospitalizations [68, 126, 127]. Exercise-based cardiac rehabilitation is important in the holistic prevention and management of HFpEF [128, 129]. Exercise interventions for 12–24 weeks increased the functional capacity and quality of life in HFpEF in several single-centre randomised trials [130–136]. Meta-analyses showed exercise training to be effective in the improvement of the functional capacity change: a greater improvement in peak VO_2 was observed among HFpEF patients undergoing exercise training vs. the 'usual' care [58, 65–69], and 6MWD resulted in a mean difference of 32.1 m (95% CI 17.2 to 47.05; $p<0.0001$) with exercise vs. control [66, 67].

Training seemed to be beneficial for health-related QOL in HFpEF patients: the clinically meaningful improvement in *The Minnesota Living with Heart Failure Questionnaire* (MLWHF) total score was presented in the meta-analyses among HFpEF patients undergoing exercise training [58, 65–69].

Systematic reviews and meta-analyses of HFpEF rehabilitation clinical studies led to a conclusion that training of the patients was safe – no serious adverse events related to exercise training were registered, although minor events, including hypoglycaemia, palpitation, dyspnoea, and mild musculoskeletal discomfort, were reported [58, 65–68, 70, 71].

A limited number of echocardiography measurements were made in earlier studies, mostly the E/A, E/e′ ratios and E wave deceleration time, albeit with inconclusive results (Table 1) [58, 65–68].

Up to now, there are no data about the impact of rehabilitation on the functional capacity of PH-LHD or PH-HFpEF patients – none of the trials focused specifically on these patients; also, the presence of PH was not reported in the published trials, either.

Table 1. Results from meta-analyses of studies on HFpEF exercise training: changes of left ventricular function and morphology, comparing exercise training vs. control groups

Parameter	Result of meta-analysis with exercise versus control	Number of participants (training/ control)	Number of studies included[1]	Reference
E/e′	−0.9, 95% CI: −3.8 to 2.0, P=0.53*; random effect	102/38	3	[58]
	−2.3, 95% CI: −3.44 to −1.19, **P<0.0001**[*]; fixed effect	85/60	4	[66]
	−2.38, 95% CI: −3.47 to −1.28, **P<0.0001**[*], fixed effect	115/89	5	[67]
	−1.20, 95% CI: − 4.07 to 1.66, P=0.41[#], random effect	132/109	4	[68]
E/A	−0.02, 95% CI: −0.11 to 0.06, P=0.56[*]; fixed effect	84/45	3	[58]
	+0.08, 95% CI: −0.01 to 0.16, P=0.08[#]; fixed effect	82/81	4	[65]
	+0.07, 95% CI: 0.02 to 0.12, **P=0.005**[*]; fixed effect	56/52	3	[66]
	+0.07, 95% CI: 0.02 to 0.12, **P=0.006**[*], fixed effect	86/81	4	[67]
	+0.03, 95% CI: − 0.02 to 0.08, P=0.27[#]; random effect	128/124	5	[68]
e′ (cm/s)	+0.49, 95% CI: − 1.28 to 2.25, P=0.59[#]; random effect	102/79	3	[68]
DecT (ms)	+2.92, 95% CI: −18.56 to 24.41, P=0.79[#]; fixed effect	62/70	3	[65]
	−13.2, 95% CI: −19.8 to −6.5, **P=0.0001**[*]; fixed effect	56/52	3	[66, 67]
	− 2.04, 95% CI: −26.53 to 22.45, P=0.87[#]; random effect	62/69	3	[68]
LV EDV (ml)	+4.5, 95% CI: −1.8 to 10.9, P=0.16[*]; fixed effect	52/24	3	[58]
	− 0.03, 95% CI: − 0.28 to 0.21, P=0.78[#]; fixed effect	140/120	4	[68]
LV mass	+0.07, 95% CI: − 0.21 to 0.35, P= 0.61[#]; fixed effect	116/90	3	[68]
LV EF (%)	+0.02, 95% CI; −1.6 to 1.7, P=0.98[*]; fixed effect	96/44	5	[58]
	+1.26, 95% CI: −0.13% to 2.66%, P=0.08[#]; fixed effect	126/111	5	[65]
	+0.85, 95% CI: −0.128 to 1.83, P=0.09[#]; fixed effect	202/174	7	[68]

*mean difference; #weighted mean difference.

[1] All meta-analyses included RCTs only, except for Taylor et al. (2012) [58], where data from observational, non-RCTs, and RCTs were pooled.

2.3. Mechanisms of improvement in exercise capacity by rehabilitation

The mechanisms underlying the positive impact of exercise training on the functional capacity of PH and HFpEF patients seem to be complex and not fully established yet. In HFpEF patients, evidence suggests improvement in oxidative muscle metabolism and vascular function [137]. Several studies which investigated changes in the cardiac function reported little to no change in the LV volumes, systolic or diastolic function after training [64, 131, 132, 135, 138]. Two HFpEF studies demonstrated that increases in the VO_2 peak were secondary to the increased oxygen extraction, with no changes in the peak exercise SV or CO [139, 140], thus indicating the primary role of peripheral adaptations. Exercise training provides benefits at the molecular and physiological level while preventing muscle wasting and reduction in force generation [137].

The currently available data suggest that the exercise training of PAH patients may improve the function of the heart, lungs, and skeletal muscles, and can counteract oxidative stress, inflammation, vasoconstriction, vascular remodelling, and thrombosis [122, 123, 141–143]. Inspiratory muscle training and endurance exercises are able to reduce the sympathetic drive, thus potentially leading to an improved cardiac function in HF [142].

In animal PH models, there is some evidence, that exercise training may affect the pulmonary vasculature, which would result in vascular reverse remodelling [143]. A significant increase of lung perfusion in 20 human patients with PAH and CTEPH was detected after exercise training in contrast-enhanced magnetic resonance imaging [144].

3. PRE-CAPILLARY PH REHABILITATION STUDY (Publications I, II, III)

3.1. Methods of pre-capillary PH study

3.1.1. Ethical approval

This study was conducted following the *Declaration of Helsinki*, and the protocol was approved by *Vilnius Regional Biomedical Research Ethics Committee* (No.158200-16-867-381; Nov 08, 2016), according to the protocol of the European multicentre study *Implementation and effect of exercise and respiratory training on 6-minute walking distance in patients with severe chronic pulmonary hypertension: a randomized controlled multicentre trial in European countries*. The study was registered in clinicaltrials.gov under the identifier NCT03345212. All the involved patients gave their written informed consent before inclusion into the study.

3.1.2. Study design

This PhD study was a part of a prospective randomised controlled trial in eleven centres, including ten European countries (Austria, Belgium, Germany, Italy, Lithuania, the Netherlands, Portugal, the UK, Spain, and Switzerland). The data about the specialised PH rehabilitation program's impact on invasively measured parameters (PAC, SV) were generated by performing *post hoc* analyses of previous prospective RCT [51].

3.1.3. Study data source

In a multicentre trial (core centre in *Heidelberg University*, Germany), the participants were recruited in eleven Pulmonary Hypertension centres across ten European countries, including the centre of Vilnius University.

Candidate patients from the Vilnius centre were evaluated during consultations with a cardiologist at the *Pulmonary Hypertension Competence Centre of Vilnius University Hospital Santaros Klinikos*. The diagnosis of PH was established according to the ESC/ERS guidelines [6, 21].

The data for *post hoc* analyses were extracted from the database of *Heidelberg University*.

3.1.4. Study population

Twenty patients, diagnosed with pre-capillary PH (PAH and CTEPH), were invited to participate in the rehabilitation study during a 2-year recruitment period at the centre of Vilnius University (*from February 2017 to February 2019*). Thirteen of them provided informed consent for participation and were enrolled in the trial. The eligibility criteria for participation in the trial are presented in Table 2.

Table 2. Eligibility criteria for participation in pre-capillary PH rehabilitation study

INCLUSION CRITERIA	EXCLUSION CRITERIA
1. Female and male patients ≥18 years 2. WHO functional class II–IV 3. PH diagnosed by RHC, showing: a) mPAP ≥25 mmHg b) PVR ≥3 WU c) PAWP ≤15 mmHg 4. Patient is on optimised targeted PH therapy, stable for ≥2 months prior to study enrolment 5. Except for diuretics, medical treatment should not be expected to change during the entire 15-week study period 6. Able to understand and willing to sign the *Informed Consent Form*	1. PAH associated with: a) portal hypertension b) complex congenital heart disease c) HIV 2. Patients with pulmonary veno-occlusive disease 3. Patients with signs of right heart decompensation 4. Active myocarditis, acute coronary syndrome, exercise-induced ventricular arrhythmias, decompensated heart failure, active liver disease 5. Acute respiratory infection 6. Severe lung disease: FEV_1/FVC <0.5 and total lung capacity <70% of the normal value 7. Haemoglobin concentration of less than 75% of the lower limit of normal 8. Systolic blood pressure <85 mmHg 9. Any change in disease-targeted therapy within the previous 2 months 10. Any subject who is scheduled to receive an investigational drug during this study 11. Pregnancy 12. Walking disability 13. History or suspicion of inability to cooperate adequately

Abbreviations: WHO – World Health Organization; RHC – right heart catheterization; mPAP – mean pulmonary arterial pressure; PAWP – pulmonary arterial wedge pressure; PVR – pulmonary vascular resistance; WU – Wood Units; HIV – human immunodeficiency virus.

A total of 129 pre-capillary PH patients were enrolled in the multicentre study during a 4-year period (*from October 2015 to November 2019*).

Forty three pre-capillary PH patients from the prospective RCT who had complete haemodynamic examinations by right heart catheterization at baseline and after 15 weeks of follow-up period were included in the *post hoc* analysis.

3.1.5. Study randomisation procedure

After giving written informed consent for this study, the patients were randomly assigned to either a training group or a control group by using a permuted block randomisation procedure with sealed envelopes, stratified by each centre. After 15 weeks of the follow-up period, patients of the control group were offered to take part in the training programme as well (the waiting-group design).

The patients of the training group stayed in hospital for 10–30 days of the initial study period and continued exercising at home for a further 11–12 weeks. The patients of the control group stayed at home with their usual daily activity.

3.1.6. Description of specialised PH rehabilitation programme

At the Vilnius University centre, the specialised PH rehabilitation protocol from Heidelberg, as described in [43, 51, 54], was adapted to the local conditions, including the following characteristics:

1. In-hospital start of the rehabilitation (for 14–21 days), followed by continuation of exercising at home.
2. The programme consisted of:
    a. Interval ergometer training (20 minutes, 5 days a week).
    b. Respiratory therapy (30 minutes, 5 days a week).
    c. Dumbbell training of single muscle groups (30 minutes, 5 days a week).
    d. Guided walks, mental gait training (individually, at least 2 times a week).
    e. Conventional elements, such as massages, relaxation, psychological counselling, lectures, and patient education.

The initial training intensity was 40–60% of the peak workload achieved during the cardiopulmonary exercise test at baseline examination, and it was gradually increased within the in-hospital period, while aiming to achieve the maximal workload which was reached during baseline

assessment (maintaining 60–80% of the peak heart rate and avoiding desaturation <90%). Oxygen saturation, heart rate, right ventricular function at rest, and subjective load perception were considered for the establishment of the initial training intensity and training adjustment.

Training was closely supervised by dedicated physical therapists and physicians specialised in rehabilitation medicine, as well as by cardiologists with expertise in PH. Transcutaneous oxygen saturation and heart rate were monitored continuously throughout the workouts.

Before leaving the hospital, each patient received individualised written recommendations how to continue exercising at home, including detailed instructions with pictures for each exercise, recommended heart rate intervals during workouts, and contacts of a physiotherapist (specifically, the email address and the phone number).

In the multicentre trial, special effort was undertaken for the standardisation of the training program. Several meetings of the participating professionals were organised, and the 'train the trainer' principle was implemented. At least one PH expert and physiotherapist from each centre visited the PH centre and rehabilitation clinic in Heidelberg, Germany, where they had the possibility to receive first-hand experience on the set-up of the clinical examinations, evaluation of the exercise capacity, exercise training components, training adjustment, and monitoring, in order to harmonise the procedures across the involved countries as much as possible.

3.1.7. Outcomes

One of the purposes of this doctoral thesis was to assess the feasibility, safety and effectiveness of specialised exercise training for pre-capillary PH (PAH and CTEPH) patients.

The primary endpoint of this study was the effect of the specialised PH rehabilitation programme on the exercise capacity, assessed by the change in the six-minute walking distance (6MWD) from the baseline to 15 weeks.

Secondary endpoints included:

A. the change from the baseline to 15 weeks after rehabilitation in:
    a) the peak oxygen consumption (VO_2) based on cardiopulmonary exercise testing (CPET)
    b) the quality of life (by using short form health survey 36, SF-36 questionnaire) [146]
    c) calculated invasively measured haemodynamic parameters (PAC, SV)

d) safety parameters (adverse events defined according to the *International Conference of Harmonization Good Clinical Practice* were recorded) [147]

B. analysis of the barriers and prerequisites for launching the specialised PH rehabilitation programme service

3.1.8. Statistical analysis

The efficacy analysis and subject characterisation were performed by the use of the efficacy dataset including all patients with the baseline and follow-up assessment of the primary endpoint 6MWD. Data were given as mean values ± standard deviations, as well as the quartiles of the differences. For the description of the effects, changes in the absolute values were calculated. Differences between the changes of the intervention and the control group were calculated and expressed as the 'control-group corrected change'. The primary efficacy analysis was performed by a t-test with unequal variances (Welch tests) of changes between groups. Secondary endpoints were tested with two-sided Student's t-tests for unequal variances. For the analysis of categorical data, the chi-square test was used. No imputation strategy was implemented for the missing data. Safety was analysed descriptively. All the tests were two-sided, and p-values <0.05 were considered statistically significant. The analyses were carried out with *IBM SPSS V25* (*IBM Corp.*, Armonk, NY, USA).

3.2. Results of pre-capillary PH rehabilitation study

3.2.1. Results of pre-capillary PH rehabilitation at Vilnius University

Thirteen patients were enrolled in the study at Vilnius University; 6 of them were randomised to the training group, and 7 to the control group. After 15 weeks of follow-up, the patients of the control group were offered to take part in the rehabilitation program, and 3 of them accepted this offer. Hence, a total of 9 pre-capillary PH (PAH and CTEPH) patients were trained according to the specialised PH rehabilitation programme at our centre. The demographics, changes in the functional capacity, and the health-related quality of life within the 15 weeks of training in these patients are summarised in Table 3. The 6MWD and SF-36 scores improved in the majority of the patients. The median improvement on 6MWD was 14.5 m, whereas the median peak VO_2 increased by 1.2 mL/kg/min. The median of the 2 summation scores of SF-36 also advanced: the physical and mental summary scores improved by 80% and 25%, respectively.

Table 3. Demographics, changes in functional capacity and quality of life within 15 weeks of training in pre-capillary PH patients at Vilnius University

PARAMETERS												
Patient No.	**Sex**	**Age**	**mPAP (mmHg)**	**In-hospital rehab. duration (days)**	**6MWD baseline (m)**	**6MWD 15 weeks (m)**	**VO_2/kg peak baseline (ml/kg/min)**	**VO_2/kg peak 15 weeks (ml/kg/min)**	**Physical summary score baseline***	**Physical summary score 15 weeks***	**Mental summary score baseline***	**Mental summary score 15 weeks***
I	F	50	75	18	410	410	12.4	11.9	38.1	30.6	46.9	46.8
II	M	71	41	18	450	**	17.7	18.7	62.5	78.8	53.8	86.8
III	F	31	60	14	595	575	18.9	15.7	26.3	45.8	30.0	49.0
IV	F	54	64	14	420	480	12.0	14.0	50.6	72.5	83.8	84.0
V	F	42	78	20	446	470	12.0	14.0	28.8	76.9	42.0	77.3
VI	M	26	27	14	570	650	18.7	20.0	86.9	71.9	82.1	67.6
VII	M	75	65	20	420	400	12.3	14.0	43.1	68.8	55.8	65.6
VIII	F	55	53	18	535	530	13.6	14.8	33.1	60.0	84.4	86.6
IX	F	58	56	18	390	440	12.3	13.7	23.8	33.1	48.2	49.2

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Abbreviations: F – female; M – male; mPAP – mean pulmonary arterial pressure; 6MWD – 6-min walk test distance; VO_2, - oxygen uptake.

* Evaluated by the SF-36 questionnaire, a higher score indicating a better quality of life. ** The patient did not perform 6 MWTD 15 weeks after rehabilitation (severe gout pain).

3.2.2. Qualitative analysis of Vilnius University experience

Qualitative analysis of Vilnius University experience revealed 9 essential steps in establishing a specialised PH rehabilitation (Figure 1) and identified the main prerequisites and barriers for the set-up of such a kind of the programme (Table 4).

The preparation phase took about 14 months. The implementing and running of this programme required dedicated rehabilitation specialists to join, thus our regular multidisciplinary PH team was expanded by 2 qualified rehabilitation physicians, 3 physiotherapists, 1 occupational therapist, and 1 psychologist. Moreover, the involved healthcare professionals needed to gain special knowledge on exercise training in severely compromised patients – our cardiologists who were specialised in PAH/PH, together with rehabilitation physicians and physiotherapists, visited the *Thoraxklinik* at *Heidelberg University Hospital* and *Rehabilitation Clinic Königstuhl* (Germany), where they learned the methods, protocols, and components of the well-established exercise and respiratory training programme. In our rehabilitation clinic, most of the necessary equipment was already in place. For an individual PH patient workout, a cycle ergometer with an interval training opportunity, a pulse oximeter, and an oxygen tank were provided additionally.

To make the programme available to the patients, reimbursement was necessary. Although in-hospital rehabilitation for stable PH patients in Lithuania is not reimbursed routinely, it was possible due to the positive attitude of the *National Health Insurance Fund* (NHIF) to the requests for individual patients, each on the exceptional basis. The main eligibility criteria for the patients were their stable clinical status, optimal medical treatment, and the motivation to undergo the training.

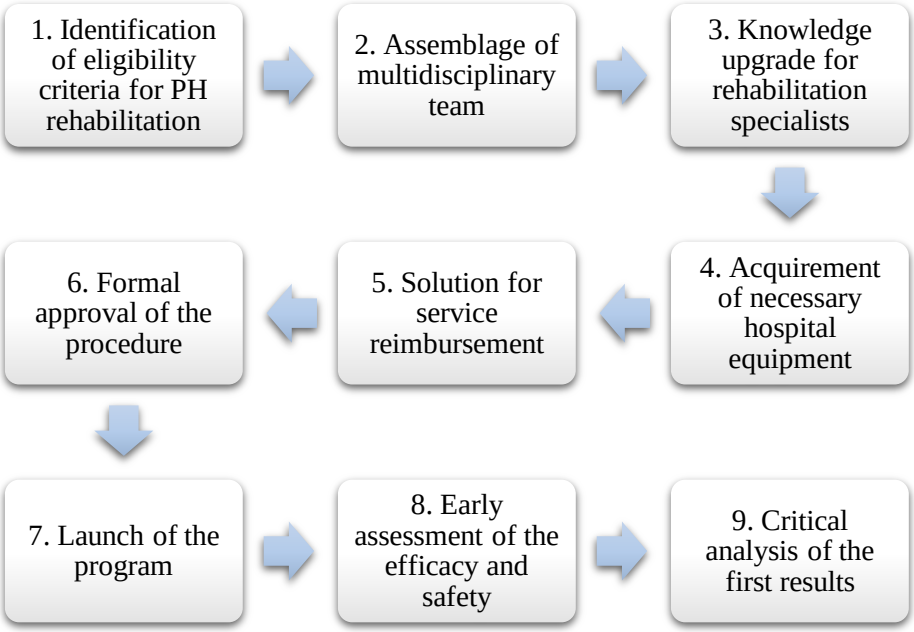

Figure 1. Essential steps in establishing a specialised PH rehabilitation programme at Vilnius University

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Table 4. Prerequisites and barriers for establishment of a specialised PH rehabilitation programme

PREREQUISITES	BARRIERS
PH SPECIALISTS	
● Specialised PH centre ● Multidisciplinary team ●Supervision of a more experienced centre in PH training	● Deficiency of local experience on PH treatment
REHABILITATION SPECIALISTS	
● Experienced rehabilitation team ● Special knowledge on exercise training in severely compromised patients ● Possession of hospital equipment (e.g. cycle ergometer, weights, pulse oximeter, mobile oxygen tank)	● Lack of experience for PH training ● Shortage of necessary equipment
PATIENTS	
● Personal abilities to train – no orthopaedic or other limitations ● Motivation	● Orthopaedic limitations/ comorbidities of the patient ● Loss of motivation over time ● Inability to continue at home ● Unstable status – worsening
HEALTHCARE SYSTEM	
● Availability of disease-targeted medications ● Established rehabilitation clinics/facilities ● Service reimbursement	● Lack of specific treatment ● Absence of rehabilitation clinics within the healthcare system ● No or limited reimbursement

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3.2.3. Results of pre-capillary PH rehabilitation in multicentre setting

In total, 116 patients (58 trained; 58 control) completed the multicentre study with the baseline and follow-up assessment of the primary endpoint 6MWD (Figure 2).

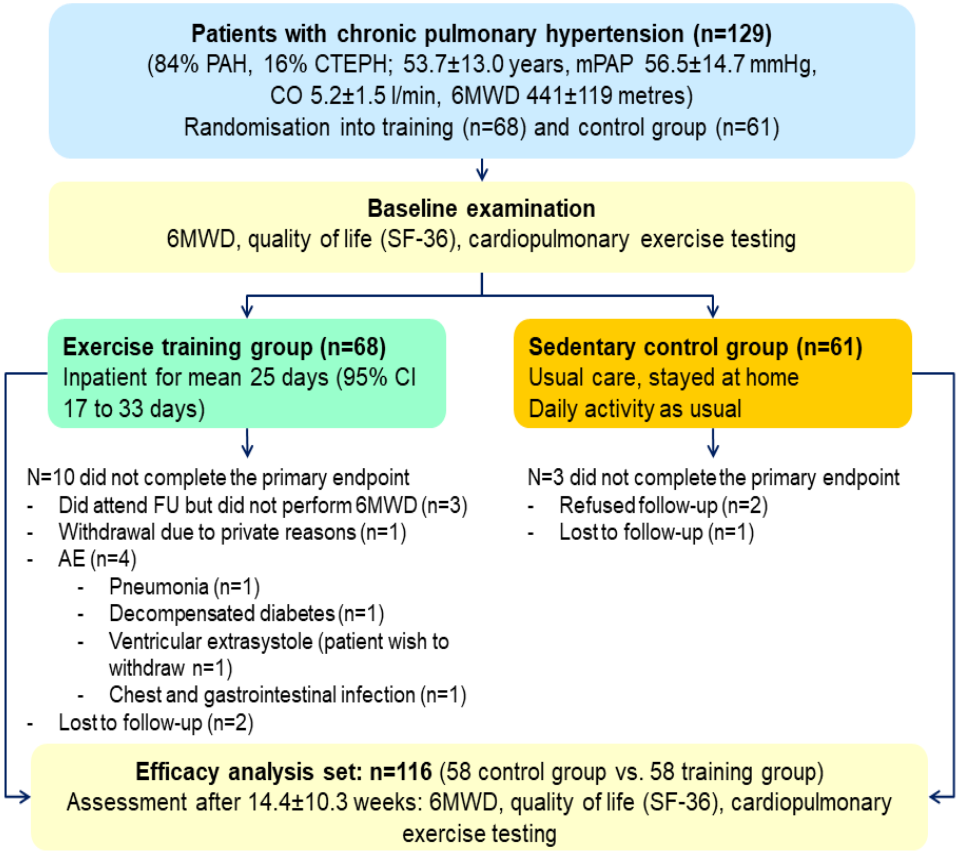

Figure 2. Multicentre pre-capillary PH study flow-chart and efficacy analysis set

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Abbreviations: 6MWD – 6-min walking distance; AE – adverse event; CI – confidence interval; CO – cardiac output; CTEPH – chronic thromboembolic pulmonary hypertension; FU – follow-up; mPAP – mean pulmonary artery pressure; PAH – pulmonary arterial hypertension.

The patients of the training group showed a significant improvement of 6MWD (30.7±57.9 meters), while 6MWD slightly decreased in the control group (-3.4±25.9 meters; control-group corrected change 34.1±8.3 meters; $p<0.0001$, Figure 3).

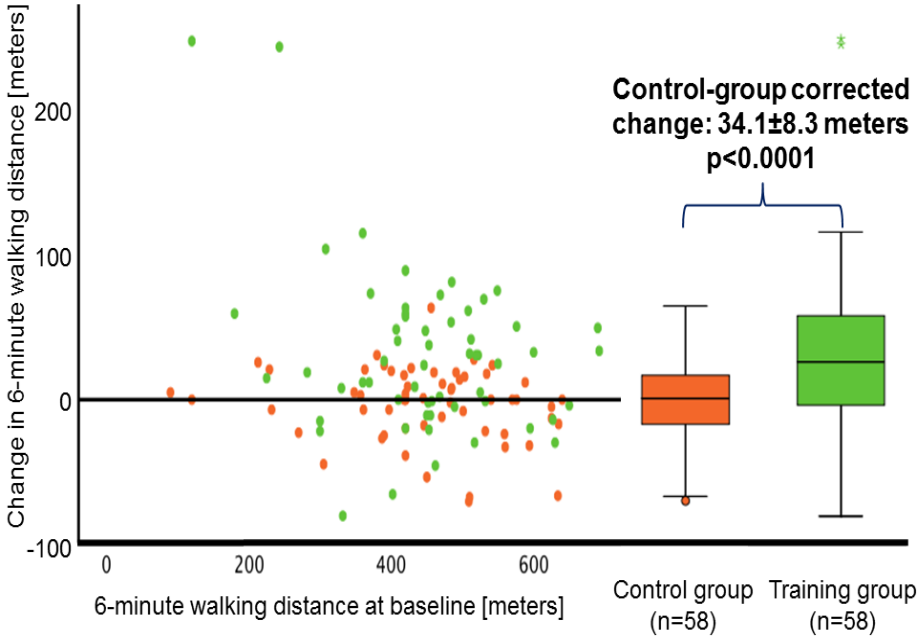

Figure 3. Changes of the primary endpoint 6-min walking distance in multicentre pre-capillary PH rehabilitation study. Patients of the training group significantly improved in 6MWD compared with the control group by 34.1±8.3m ($p < 0.0001$).

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In the cardiopulmonary exercise testing, the peak VO_2 significantly improved in the training group (control-group corrected change +0.9±0.3 ml/min/kg; p=0.048; Figure 4).

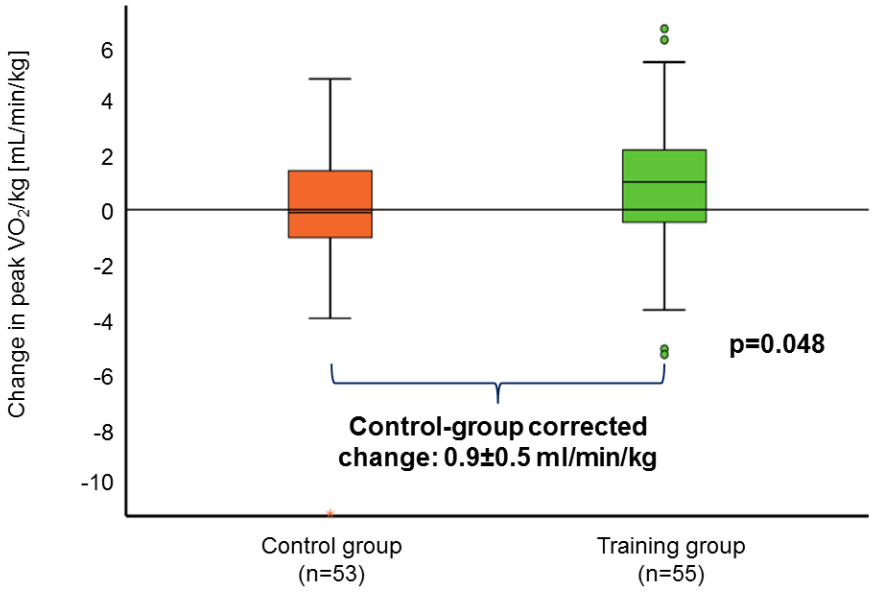

Figure 4. Changes of the peak oxygen consumption in the training group compared with the control group in multicentre pre-capillary PH rehabilitation study. VO_2/kg body weight significantly improved by 0.9±0.5 mL/min/kg in the training group compared with the control group (p = 0.048).

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The scores of health-related QOL (mental health) significantly improved in the training group compared to the control group (control-group corrected change 7.3±2.5; p=0.004), and trends for better physical (p=0.07) and social functioning (p=0.09) were also observed, as shown in Figure 5.

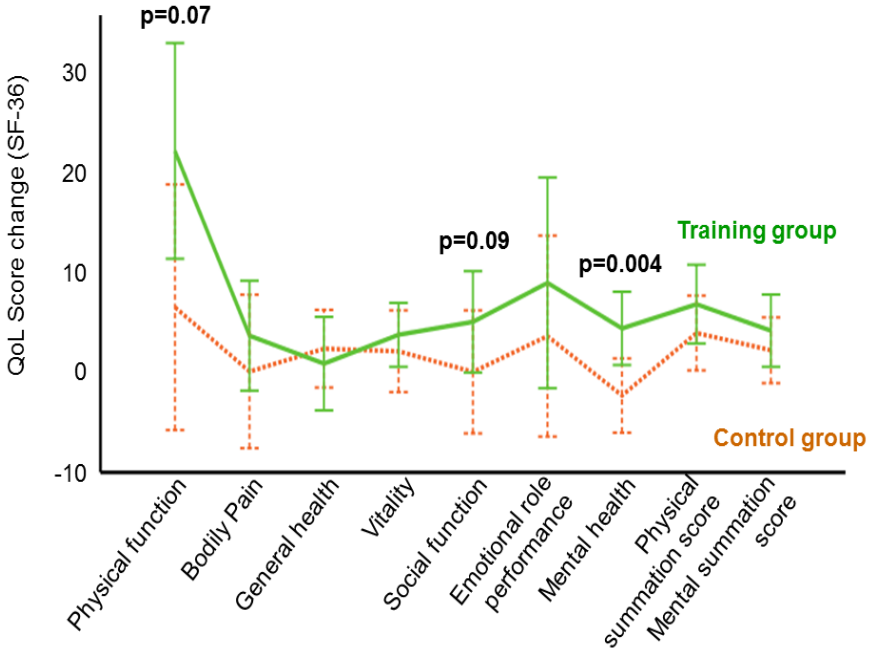

Figure 5. Quality of life (QoL) score (SF-36) changes comparing the training and control groups in multicentre pre-capillary PH rehabilitation study. QoL significantly improved in the subscale mental health in the training group compared with the control group (p=0.004). Two further subscales were significant in the trend (physical function p=0.07, social function p=0.09).

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Safety assessment was performed in 99 patients. In total, 52 adverse events (AEs) (27 attributed to training group, 25 to control group) were reported for 21 patients (13 participants of the training group and 8 of the control group). AEs with a frequency of ≥5% and serious AEs were comparable between the groups (Table 5). All serious AEs resulted in hospitalisations, but none of the AEs or serious AEs were related to the study intervention.

Table 5. Adverse events with occurrence of ≥ 5% and serious adverse events in multicentre pre-capillary PH rehabilitation study

Adverse Events	Group		
	Control (n=47)	**Training (n=52)**	**Total (n=99)**
Arrhythmia of any kind	5	3	8
Respiratory infection	3	4	7
Total	8	7	15
Serious adverse events			
Diabetes, decompensated	0	1	1
Aedema, generalised	0	1	1
Haemoptysis	1	0	1
Stroke	0	1	1
Total	1	3	4

3.2.4. Results of pre-capillary PH rehabilitation haemodynamic analysis

The data for the *post hoc* analysis of haemodynamics were extracted from previous RCT conducted from June 2010 to May 2015 (database of Heidelberg University) [51]. *Post hoc* haemodynamic analysis included 43 patients (24 in the training group, and 19 in the control group). Stroke volume (SV) and pulmonary arterial compliance (PAC) at rest significantly increased from the baseline to 15 weeks in the training group and was compared to the control group (Figure 6; Figure 7).

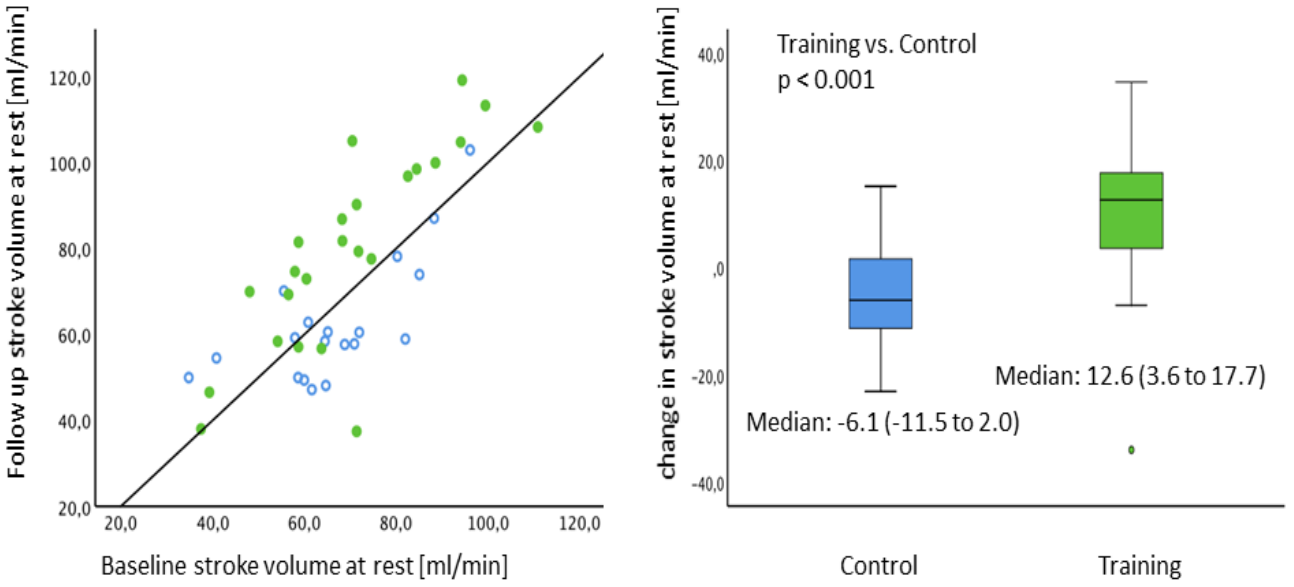

Figure 6. Change in stroke volume at rest after 15 weeks of the follow-up period in pre-capillary PH rehabilitation study

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Left graph: the abscissa shows baseline SV at rest, whereas the ordinate shows SV at rest after 15 weeks. The solid green points represent the patients of the training group, and the blue circles represent the patients of the control group.

Right graph: the boxplots on the right side show the distribution of changes between the baseline and the follow-up in the training and the control group. The changes were different between the training and the control group patients, $p<0.001$.

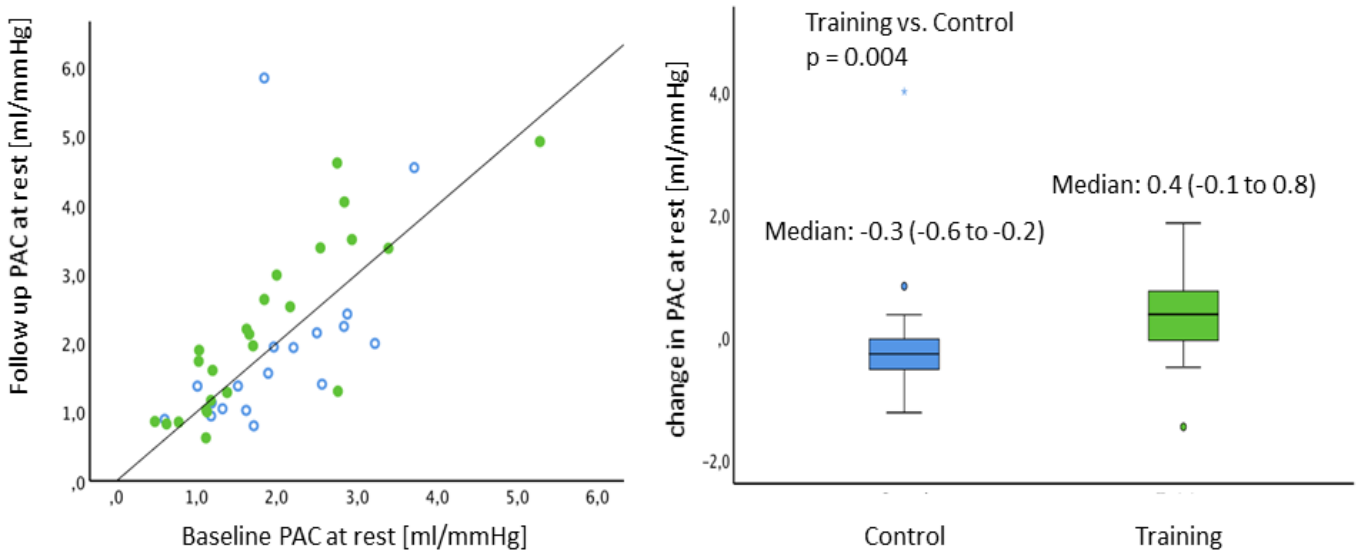

Figure 7. Change in pulmonary artery compliance at rest after 15 weeks of the follow-up period

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Left graph: the abscissa shows baseline PAC at rest, whereas the ordinate shows PAC at rest after 15 weeks. The solid green points represent the patients of the training group and, while the blue circles represent the patients of the control group.

Right graph: the boxplots on the right side show the distribution of the changes in PAC between the baseline and the follow-up. The changes are different between the training and the control patients, p=0.004.

4. POST-CAPILLARY PH REHABILITATION STUDY (Publication IV)

First, a systematic literature review on the impact of exercise and physiotherapy in HFpEF trials on cardiac morphological, functional, and pulmonary circulation parameters was conducted (Chapter 4.1.).

Primarily, we aimed to assess the effect of rehabilitation on PH-HFpEF patients, but we did not find any trials focusing specifically on this population. Our decision was to systematically review HFpEF training trials identifying whether and how different rehabilitation modalities alter the parameters of LV and RV diastolic and systolic function (E/e', LV EF, RV FAC, TAPSE, TV lateral s', strains), the volumes and dimensions of cardiac chambers (LAVI, LVMI, SVI, RV diameters, RA area), and the pressures of PA and RA. We expected this information to be useful in finding the optimal components of the rehabilitation programme for PH-HFpEF.

Next, the protocol for a prospective multicentre randomised controlled trial of a specialised rehabilitation programme investigating safety and efficacy for post-capillary PH (PH-HFpEF) was created, which was based on the pre-capillary PH rehabilitation experience and literature review (Chapter 4.2.). The pilot phase of the study was initiated at Vilnius University before the COVID-19 pandemic.

4.1. Systematic literature review of HFpEF rehabilitation studies

4.1.1. Methods

4.1.1.1. Study data source and outcomes

A comprehensive literature search was conducted in *Cochrane Library* and *MEDLINE/PubMed* bibliographic databases. We searched for all types of trials that evaluated the effects of various types of exercise training and/or physiotherapy in HFpEF patients (defined as LVEF ≥45%), including all papers published from December 1991 till March 2021. The search was limited to human studies only, adults (>18 years), and the results were filtered by 'Clinical Trial', 'Meta-Analysis', and 'Systematic Review'. Additionally, for any potentially eligible trials, we manually searched in *clinicaltrials.gov*, *Google Scholar* and the lists of references of the identified studies.

The main outcomes of interest were echocardiographic parameters (LV EF, E/e', LAVI, LVMI, SVI, RV diameters, RA area, RV FAC, TAPSE, TV lateral s', strains), as well as any reported MRI and invasively assessed haemodynamic measures.

Each title and abstract was independently evaluated by 2 reviewers, while following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [148]. If at least one of the reviewers considered the trial to be eligible, it was included in the primary analysis.

After the initial review, the full texts of the selected studies were assessed to verify the eligibility criteria. The same reviewers extracted data from the relevant articles by using pre-defined extraction forms. The data source selection process is shown in Figure 8.

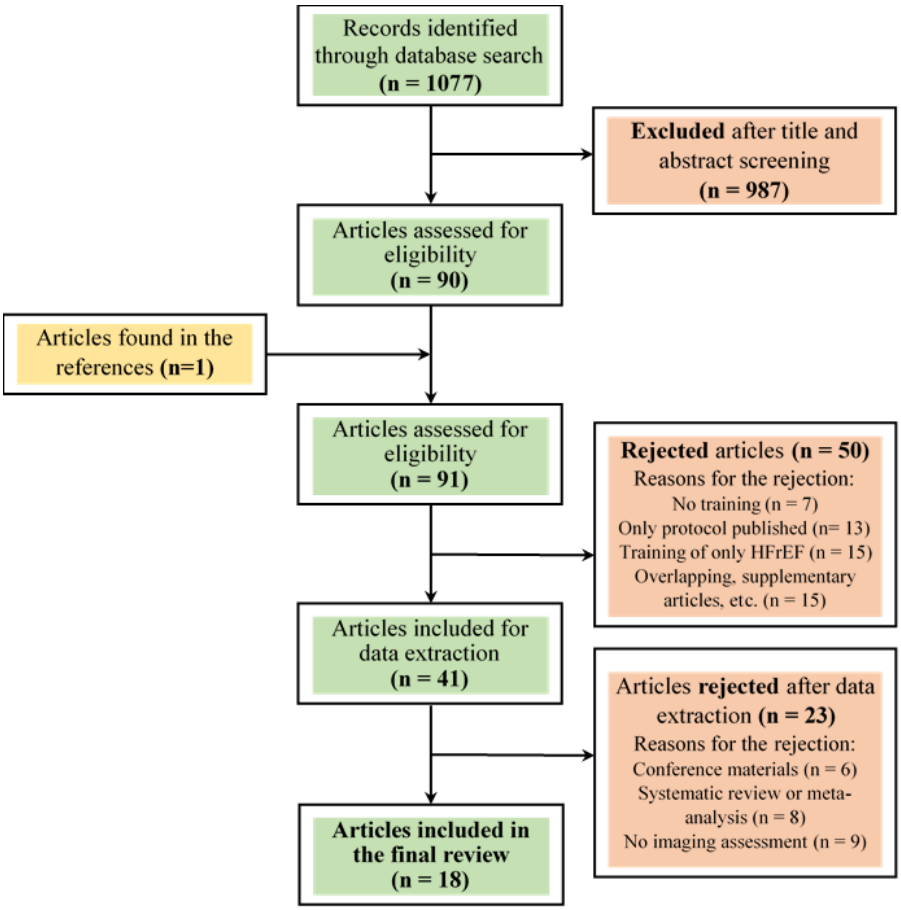

Figure 8. Flow diagram showing the selection of data source in systematic literature review

4.1.1.2. Description of rehabilitation program

Various protocols of exercise training and/or physiotherapy programs were used in different studies that were included in our systematic literature review. In all the considered studies, the training programs were conducted in out-patient settings, and, in most of them (16/18; 89 percent), the intervention was supervised by healthcare professionals. Eleven programmes consisted of endurance training alone, four combined endurance and resistance workouts, two studies applied resistance training, and in one of them, functional electric stimulation (FES) was added, and, in one trial, only FES was used.

4.1.2. Results

We extracted the data from nine randomised controlled trials, five randomised parallel group trials (no control, all patients trained, but different training protocols were used), and four observational studies (one group, no control).

Our review included heterogeneous trials with various designs, populations, methodologies and interventions. Most studies were small in terms of their sample size – more than 25 patients were trained in only four of the eighteen trials. All the training programs were conducted in out-patient settings, and, in sixteen of them, the intervention was supervised by healthcare professionals. In total, 418 patients (mean age 60.0 to 75.0, 57% female, training duration 4 to 52 weeks) were trained. The components of exercise training and/or physiotherapy, together with other characteristics and results of these studies, are summarised in Table 6.

Table 6. Summary of articles selected and included in the systematic literature review [149]

Study (authors, year)	Duration of the training (weeks)	Intervention	Trained patients [N; Mean age, years; male gender, N (%)]	Assessed echocardiographic parameters	Significant changes of specific echocardiographic parameters
Randomised controlled trials (N=9)					
Kitzman et al., 2010 [132]	16	Outpatient, supervised, endurance training; 60 min. 3 times a week	N=26; age=70±6; male 6 (23.1%) *24 patients in the final analysis*	LV EF, E, A, E/A, DecT, IVRT, LVM, LVV, SV	No significant changes of the measured echocardiographic parameters
Edelmann et al., 2011 [130]	12	Outpatient, supervised, endurance training (supplemented with resistance training from the 5th week); 40 min. 3 times a week	N=44; age=64±8; male 20 (45.5%)	LV EF, e' (septal), E/e' (septal), S/D ratio, LAVI, LVMI, LVVI	↓**E/e'** from 12.8±3.2 to 10.5±2.5, change -2.3 (-3.0 to -1.6), p<0.001; between groups -3.2 (-4.3 to - 2.1) p< 0.001 ↑**e'** from 5.4±1.2 to 6.3±1.3, change 0.9 (0.6 to 1.1), p<0.001; between groups 1.2 (0.8 to 1.7) p < 0.001 ↓**LAVI** from 27.9±7.6 to 24.3±6.5, change -3.7 (-4.9 to -2.4), p<0.001; between groups -4.0 (- 5.9 to - 2.2) p< 0.001
Alves et al., 2012 [133]	26	Outpatient, supervised, endurance training; 35 min. 3 times a week	N=20; age=62.9±10.2; male 22 (71%) *mean age and gender distribution of all of the sample size (trained + control)*	LV EF, E/A, DecT, LV dimensions (EDD, ESD)	↑**EF** from 56.4 to 57.7, change 1.3% p=0.01 ↑**E/A** from 0.93 to 1.05, p<0.001 ↓**DecT** from 236.7 to 222.7, p <0.001
Smart et al., 2012 [135]	16	Outpatient, supervised, endurance training; 30 min. 3 times a week	N=12; age=67±5.8; male 7 (58.3%)	LV EF, E, A, E/A, E/e' (undetermined), DecT, s', e' (undetermined), SV, CO, LV-GLS, LV-GSR	↑**CO** from 5.7±2.7 to 7.1±3.1, change 1.4, p=0.04;
Haykowsky	17	Outpatient, supervised,	N=22; age=70±6;	LVV, SV, CO	No significant changes of the measured

et al., 2012 [140]		endurance training; 60 min. 3 times a week	male 4 (18.2%)		echocardiographic parameters		
Karavidas et al., 2013 [150]	6	Outpatient physiotherapy (functional electrical stimulation of the lower limb muscles); 30 min. 5 times a week	N=15; age=69.4±8.6; male 6 (40.0%)	E, A, E/A, E/e' (undetermined), DecT, LAV, A pulmonary − A mitral duration	No significant changes of the measured echocardiographic parameters		
Kitzman et al., 2013 [64]	16	Outpatient, supervised, endurance training; 60 min. 3 times a week	N=32; age=70±7; male 9 (28.1%) *24 patients in the final analysis*	LV EF, E, A, E/A, DecT, IVRT, LVV, SV	No significant changes of the measured echocardiographic parameters		
Palau et al., 2014 [151]	12	At home, unattended, inspiratory muscle training; 20 min. 2 times a day	N=14; age=68 [60–76]; male 7 (50.0%)	LV EF, e' (septal), E/e' (septal), LAVI, LVMI	No significant changes of the measured echocardiographic parameters		
Palau et al., 2017 [126]	12	Home, unattended, inspiratory muscle training; 20 min. 2 times a day Outpatient, physiotherapy (functional electrical stimulation of the lower limb muscles); 45 min. 2 times a week	IMT (baseline): N=15; age=75±10; male 7 (46.7%) FES (baseline): N=15; age=72±9; male 6 (40.0%) IMT + FES (baseline): N=16; age=73±10; male 8 (50%) *13 patients in each group in the final analysis*	E/e' (undetermined), LAVI	**IMT**: <u>After 12 weeks:</u> **↓E/e'** from 18.4 [14.4-28.0] to 17.2 [12.4-23.1], p=0.015 <u>After 24 weeks[3]:</u> **↓LAVI** from 39±11 to 31±11, p=0.008	**FES**: <u>After 12 weeks:</u> **↓E/e' from** 20.5 [12-26.4] to 15.7 [11.8-21.8], p=0.001 <u>After 24 weeks[3]:</u> No significant changes of the measured echocardiographic parameters	**IMT+FES:** <u>After 12 weeks:</u> No significant changes of the measured echocardiographic parameters <u>After 24 weeks[3]:</u> No significant changes of the measured echocardiographic parameters
Randomised parallel group trials (N=5)							

Yeh et al., 2013 [152]	12	Outpatient and home, endurance training compared with Tai Chi training; Supervised 60 min. 2 times a week + exercising at home 35 min. 3 times a week	AT: N=8; age=63±11; male 4 (50.0%) Tai Chi: N=8; age=68±11; male 4 (50.0%)	LV EF, E/A, E/e' (undetermined), LA dimension, LAV	**Tai Chi[#]**: ↓LA dimensions decreased more in Tai Chi (from 3.8±0.4 to 3.7±0.3) comparing with AT (from 3.7±0.3 to 3.8±0.3), p=0.04	**AT[#]**: ↓E⁄e' improved more in AT (from 17±4 to 14±4), comparing with Tai Chi (from 14±4 to 13±5), p=0.01
Angadi et al., 2015 [138]	4	Outpatient, supervised, endurance training; 45 min. 3 times a week	HIT: N=9; age=69.0±6.1; male 8 (88.9%) MI-ACT: N=6; age=71.5±11.7; male 4 (66.7%)	LV EF, E, A, e' (septal), E/A, E/e' (septal), DecT, IVRT, diastolic dysfunction grade[1], diastolic dysfunction grade distribution[2], LAVI	**HIIT:** ↓**Diastolic dysfunction grade*** from 2.1±0.3 to 1.3±0.7, p<0.01 ↓**E from** 0.9±0.3 to 0.8±0.3, p=0.02 ↑**DecT** from 194±55 to 225±40, p=0.02	**MI-ACT:** No significant changes of the measured echocardiographic parameters
Angadi et al., 2017 [127]**	4	Outpatient, supervised, endurance training; 45 min. 3 times a week	HIIT: N=9; age=69±6.1; male 8 (88.9%) MI-ACT: N=6; age=71.5±11.7; male 4 (66.7%)	LV EF, LVM, LVMI, SV, SVI, RV-GLS, RV-GSR, LV-GLS, LV-GSR	**HIIT:** ↑**RV-GLS** from -18.4±3.2 to -21.4±1.7, p=0.02	**MI-ACT:** No significant changes of the measured echocardiographic parameters
Silveira et al., 2020 [153]	12	Outpatient, supervised, endurance training; 38 min. (HIIT), 47 min. (MCT) 3 times a week	HIIT: N=10; age=60±10; male 3 (30.0%) MI-ACT: N=9; age=60±9; male 4 (44.4%)	LV EF, E, A, e' (average), E/A , E/e' (average), DecT, LV dimensions (EDD, ESD), LAVI, LVM, LVVI, LA diameter, SVI	**HIIT:** ↓**E/e'** from 13.3±3 to 11.1±2, p<0.001	**MI-ACT:** ↓**E/e'** from 14.2±4 to 11.6±3, p<0.001
Mueller et al., 2020 [154]	52	Outpatient, supervised (3 months), then continued at home, unattended (for the next 9 months),	HIIT: N=58; age=70±7; male 17 (29.3%) MI-ACT:	E/e' (septal), e' (septal), LAVI	No significant change of the measured echocardiographic parameters between HIIT, MI-ACT and the control group[#]	

		endurance training; 38 min. (HIIT), 47 min. (MCT) 3 times a week	N=58; age=70±8; male 23 (39.7%) *47 patients in the HIIT final and 52 in the MI-ACT final analysis*		
Observational trials (N=4)					
Smart et al., 2007 [155]	16	Outpatient, supervised, endurance training (supplemented with resistance training from the 8th week); 60 min. 3 times a week	N=18; age=65±5; male 9 (50.0%)	LV EF, E, A, s', e' (average), E/A, E/e' (average), DecT, LVV, LV-GLS, LV-GSR, SV	No significant changes of the measured echocardiographic parameters
Fujimoto et al., 2012 [156]	52	Outpatient, supervised, endurance training; 40 min. 3 times a week	N=7; age=74.9±6; male 3 (42.9%)	LV EF, E, A, e' (average), a', E/A, IVRT, LVV, LVVI	↑**E/A** from 0.75±0.11 to 0.89±0.14, p=0.03
Nolte et al., 2014 [157]*	24	Outpatient, supervised, endurance training (supplemented with resistance training from the 5th week); 30-35 min. 3 times a week	N=24; age=62±7; male 15 (62.5%)	LV EF, e' (septal), E/e' (septal), S/D ratio, LAVI, LVMI, LVVI	↓**E/e'** from 12.2±3.5 to 10.1±3.0, change -2.1 (-3.3 to -0.9), p=0.002 ↑**e'** from 5.9±1.3 to 6.8±1.4, change 0.9 (0.4 to 1.4), p=0.001 ↓**LAVI** from 30.0±7.9 to 25.1±8.7, change -4.9 (-6.7 to -3.2), p<0.001
Fu et al., 2016 [139]	12	Outpatient, supervised, endurance training**;** 30 min. 3 times a week	N=30; age=60.5±2.7; male 20 (66.7%)	LV EF, E/A, E/e' (septal), LV dimensions (EDD, ESD)	↓**E/e'** (septal) from 21.0±2.2 to 16.1±1.8, p <0.05

The data are expressed by number, mean ± standard deviation, median [interquartile range].

#p values compare the changes between the groups (changes before and after training in separate groups were not published).

[1]Four grades of diastolic dysfunction were used (0 – no diastolic dysfunction, 1 – abnormal relaxation pattern, 2 – pseudonormal pattern, 3 – restrictive filling pattern).

[2]Number of patients in each of the four diastolic dysfunction grades.

[3]Follow-up was extended to 24 weeks with the aim of exploring the sustainability of the 12-week training results.

*In this trial, the same patients who had participated in the study of Edelmann et al. (2011) (24) were enrolled. The authors presented the same data of the trained group changes after 12 weeks of training in both articles, but this article was supplemented with additional data after a longer exercise training period (24 weeks).
**In this study, the same patients who had participated in the study Angadi et al. 2015 (34) where assessed, but different echocardiographic parameters were measured – secondary analyses to explore the effects of HIIT on the biventricular strain characteristics were carried out.
Abbreviations: A (m/s) – late mitral inflow velocity; a' (m/s) – tissue Doppler mitral annular late diastolic velocity; AT – aerobic training; CO (l/min.) – cardiac output; DecT (ms) – mitral flow E wave deceleration time; E (m/s) – early mitral inflow velocity; e' (m/s) – tissue Doppler mitral annular early diastolic velocity; E/A – E and A ratio; EDD (mm) – end diastolic diameter; E/e' – E and e' ratio; FES – functional electrical stimulation; EF (%) – ejection fraction; ESD (mm) – end systolic diameter; HIIT – high-intensity interval training; IMT – inspiratory muscle training; IVRT (ms) – isovolumetric relaxation time; LA – left atrium; LA dimensions (cm) – the measurement was not clearly defined; LAV (ml) – left atrium volume; LAVI (ml/m^2) – left atrium volume index; LV – left ventricle; LV-GLS (%) – left ventricle global longitudinal strain; LV-GSR (s^{-1}) – left ventricle global longitudinal strain rate; LVM (g) – left ventricle mass; LVMI (g/m^2) – left ventricle mass index; LVV (ml) – left ventricle volume; LVVI (ml/m^2) – left ventricle volume index; MI-ACT – moderate-intensity aerobic continuous training; RV-GLS (%) – right ventricle global longitudinal strain; RV-GSR (s^{-1}) – right ventricle global longitudinal strain rate; s'(m/s) – tissue Doppler mitral annular systolic velocity; S/D – pulmonary vein peak systolic velocity and peak diastolic velocity ratio; SV (ml) – stroke volume; SVI (ml/m^2) – stroke volume index.

The quantity of studies assessing specific parameters along with the number of trained patients is shown in Table 7.

Table 7. Echocardiographic parameters assessed in the selected studies [149]

Echocardiographic parameter	Number of the studies with assessment of parameter	Number of trained patients with assessment of parameter
LV EF	14	292
E/e'	12	330
E/e' (septal)	6	211
E/e' (average)	2	37
E/e' (undetermined)	4	82
e'	9	261
e' (septal)	5	205
e' (average)	3	44
e' (undetermined)	1	12
LAVI	7	250
E/A	11	210
E	8	144
A	8	144
E wave DecT	8	144
LVMI	4	92
SV	6	113
LVVI	4	87
LV IVRT	4	80
SVI	3	46
LV GLS	3	45
LV GRS	3	45
CO	2	34
LV tissue S vel	2	30
RV GLS	1	15
RV GSR	1	15
Following parameters were NOT assessed in the included studies: RV diameter, SPAP, TV lateral s', TAPSE, RV FAC, RA area, RA pressure, IVC diameters		

Abbreviations: A (m/s) – late mitral inflow velocity; a' (m/s) – tissue Doppler mitral annular late diastolic velocity; CO (l/min.) – cardiac output; DecT (ms) – mitral flow E wave deceleration time; E (m/s) – early mitral inflow velocity; e' (m/s) – tissue Doppler mitral annular early diastolic velocity; E/A – E and A ratio; E/e' – E and e' ratio; EF (%) – ejection fraction; IVRT (ms) – isovolumetric relaxation time; LAVI (ml/m2) – left atrium volume index; LV – left ventricle; LV-GLS (%) – left ventricle global longitudinal strain; LV-GSR

(s-1) – left ventricle global longitudinal strain rate; LVMI (g/m2) – left ventricle mass index; LVVI (ml/m2) – left ventricle volume index; RA – right atrium; RV-GLS (%) – right ventricle global longitudinal strain; RV-GSR (s-1) – right ventricle global longitudinal strain rate; s' (m/s) – tissue Doppler mitral annular systolic velocity; SPAP (mmHg) – systolic pulmonary artery pressure; SV (ml) – stroke volume; SVI (ml/m2) – stroke volume index; TAPSE (mm) – tricuspid annular plane systolic excursion.

Five of nine RCTs, four of five randomised parallel group trials and three of four observational trials reported significant changes of different echocardiographic parameters by training, while the remaining studies detected no changes in the assessed parameters (Table 6).

Significant reduction of the mitral E/e' ratio after the training was reported in 5 out of 12 studies, ranging from -1.2 to -4.9; a significant decrease of LAVI was observed in 3 out of 7 trials, ranging from -3.7 to -8 ml/m^2. All but one study showed no significant change of LV EF after the intervention.

Furthermore, the impact of exercise training on the cardiac output (CO) was reported with inconsistent results, including an improvement of CO by 24.5% in one small (n=12), good quality study after 16 weeks of endurance exercise training [135]. Another moderate quality trial with older patients (n=22) demonstrated no significant changes of CO after similar duration endurance exercise training (60 minutes, 3 times a week) [140].

The effect of exercising on the RV function was assessed in one study [127]. The RV global longitudinal strain and strain rate were measured before and after 4 weeks of high intensity interval training (HIIT) (n=9) and moderate intensity aerobic continuous training (MI-ACT) (n=6). The HIIT group patients demonstrated an increase of the RV global longitudinal strain by 3% (from -18.4±3.2 to -21.4±1.7), p=0.02. The changes among MI-ACT group patients were non-significant.

None of the eighteen eligible studies assessed the impact of exercise rehabilitation on cardiac magnetic resonance imaging parameters.

Invasive haemodynamic measurements were performed only in one very small (n=7) poor quality study, which revealed that PAWP was unaffected by exercise training in HFpEF patients (16.1±5.6 mmHg before training vs. 15.2±3.6 mmHg after 12 months of training, p=0.65) [156].

4.2. Post-capillary PH rehabilitation study

4.2.1. Preparation of the protocol

4.2.1.1. Hypothesis and design

The research question we raised for the trial protocol under development: exercise training is safe, and it may improve the physical capacity, the health-related quality of life, the diastolic heart function, haemodynamics, and biomarkers in patients with PH-HFpEF.

We chose to design a prospective, randomised (1:1 randomisation), controlled, multicentre trial.

4.2.1.2. Outcomes

The primary endpoint of this study is to determine the effect of exercise training on the change of physical capacity, as measured by 6MWD (baseline vs. 15 weeks vs. control group) in the PH-HFpEF population.

The secondary outcome parameters shall include: parameters of echocardiography, cardiopulmonary exercise testing, *World Health Organization* (WHO) functional class, measurement of safety parameters, health-related QOL assessment (SF-36 questionnaire), anxiety and depression assessment (HADS scale), right heart catheterisation (RHC) at rest and during exercise, echocardiography during exercise, and cardiac magnetic resonance imaging (MRI). Considering that not all participating centres may have the opportunity to repeatedly perform cardiac MRI, echocardiography during exercise, and RHC at rest and during exercise, we decided to make these efficacy parameters optional.

The efficacy parameters in both groups shall be assessed at the baseline and after 15 weeks. The patients in the training group will additionally perform the MWD at the end of their in-hospital rehabilitation.

4.2.1.3. Population and sample size

The diagnosis of PH-HFpEF shall be established according to the ESC/ERS guidelines [5, 6, 21, 36] and shall be confirmed by invasively measured haemodynamic parameters. By virtue of being the ‘gold standard’ diagnostic tool for both – PH and HFpEF – invasive haemodynamic assessment shall ensure precise diagnosis of PH-HFpEF. Other eligibility criteria were selected considering the protocols of the most important pre-

capillary PH rehabilitation and HFpEF clinical trials [40, 41, 47, 51, 53, 54, 56, 59]; they are presented in Table 8.

In order to estimate the effect of exercise training on 6MWD, 90 patients are expected to be enrolled, who either receive exercise training or continue their daily lifestyle for 15 weeks. The sample size was calculated by the *G*Power 3.1* program. Based on the previous data and the inclusion criteria, we expect a clinically significant 6MWD mean increase of 35 metres with a standard deviation of difference of 50 metres. If the true treatment effect is a difference of at least 35 metres with an equal standard deviation of the difference of 50 metres, the two-sided Student's t-test at an alpha level of 0.05 has a power of 85% if 38 patients for each group are included. To account for a possible 15% dropout rate, we shall include 45 patients in each group – 90 patients in total.

Table 8. Inclusion and exclusion criteria for participation in post-capillary PH rehabilitation study

INCLUSION CRITERIA	EXCLUSION CRITERIA
1. Female and male patients ≥18 years 2. WHO functional class II–IV 3. Post-capillary PH confirmed by RHC, showing: a) mPAP ≥25mmHg at rest; b) mPAWP ≥15mmHg or LVEDP ≥16mmHg at rest and/or PAWP≥25mmHg during exercise 4. Preserved left ventricular ejection fraction ≥50% (measured by echocardiography or MRI) 5. Patient received optimised and stable for ≥1 month therapy 6. Except for diuretics, medical treatment should not be expected to change during the study period 7. Able to understand and willing to sign the *Informed Consent Form*	1. Pre-capillary pulmonary hypertension 2. Congenital or acquired severe valvular diseases (*severe aortic stenosis or insufficiency*, *severe mitral valve stenosis or insufficiency*) 3. Active myocarditis, unstable angina pectoris, exercise induced ventricular arrhythmias, active liver disease 4. Severe lung disease: FEV1/FVC <0.5 and total lung capacity <60% of the normal value 5. Subject who participates in an interventional study during this study 6. Walking disability or other orthopaedic limitations to exercise 7. Haemoglobin concentration less than 75% of the lower limit of normal 8. Systolic blood pressure < 85 mmHg 9. Pregnancy 10. History or suspicion of inability to cooperate adequately

4.2.1.4. Description of the rehabilitation program

Previous HFpEF rehabilitation trials used different models of exercise training regimens. Our systematic literature review did not allow us to draw conclusions about the potential benefits of specific training modality for PH-HFpEF; hence, we decided to use unmodified specialised PH rehabilitation programme from Heidelberg that was already described in Section 3.1.6.

The patients in the control group shall not receive exercise training and shall continue their regular treatment and daily activities for 15 weeks.

4.2.2. Results

The protocol for the PH-HFpEF rehabilitation study was created. The detailed timeline of the study protocol is shown in Figure 9.

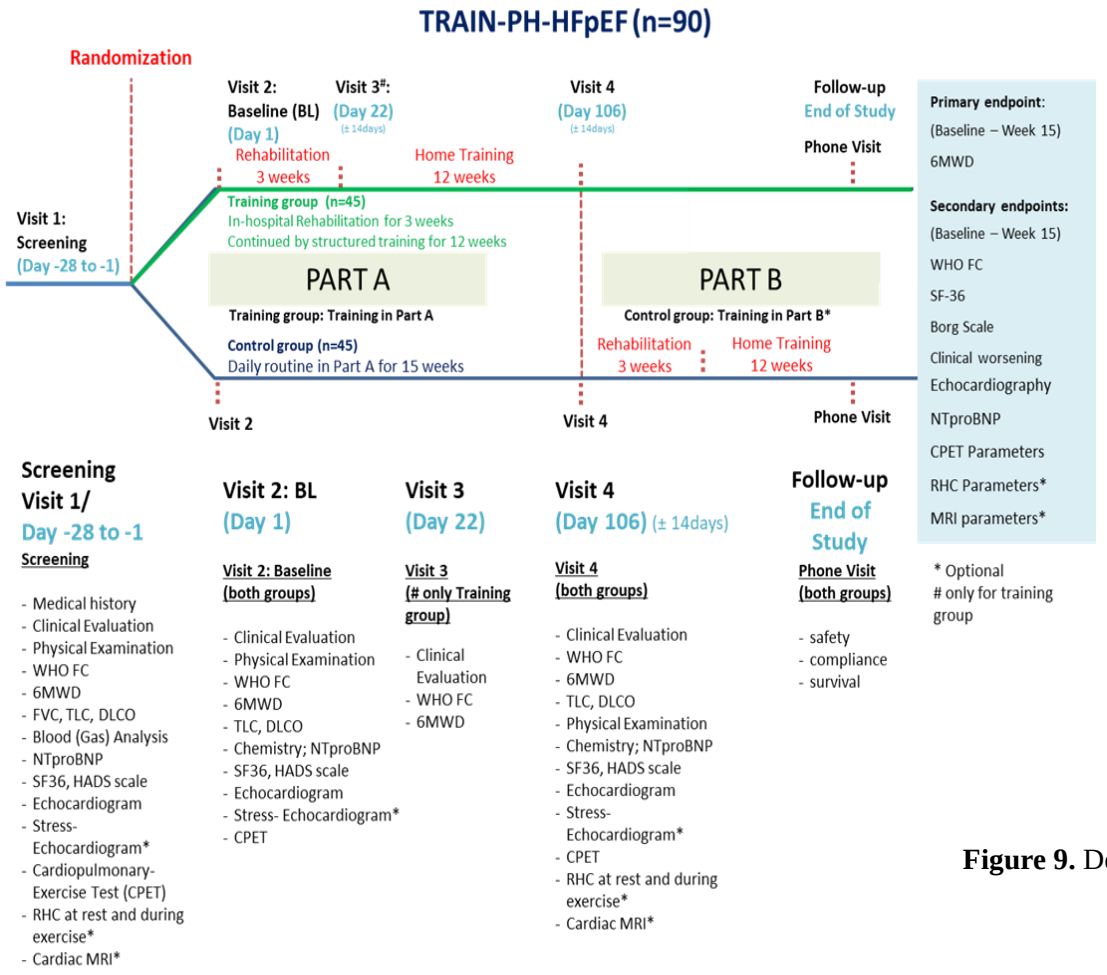

Figure 9. Detailed timeline of the study

4.2.3. Pilot phase of TRAIN-PH-HFpEF study

4.2.2.1. Ethical approval

The study was designed following the *Declaration of Helsinki*, and the protocol was approved by *Vilnius Regional Biomedical Research Ethics Committee* (No. 2019/4-1118-611) for the protocol *Effect of rehabilitation program on functional capacity of patients with pulmonary hypertension due to left heart failure*. All the participating patients gave their written informed consent before inclusion into the study.

4.2.2.2. Data source and study population

Candidate patients were selected during consultations with a cardiologist at the *Pulmonary Hypertension Competence Centre of Vilnius University Hospital Santaros Klinikos*. During the period of *July 2019 – March 2020*, 35 patients were suspected with PH-HFpEF based on echocardiography findings. They were screened regarding our inclusion and exclusion criteria (Table 8).

As shown in Figure 10, four patients were ultimately included in the study; subsequently, the trial had to be terminated due to the COVID-19 pandemic.

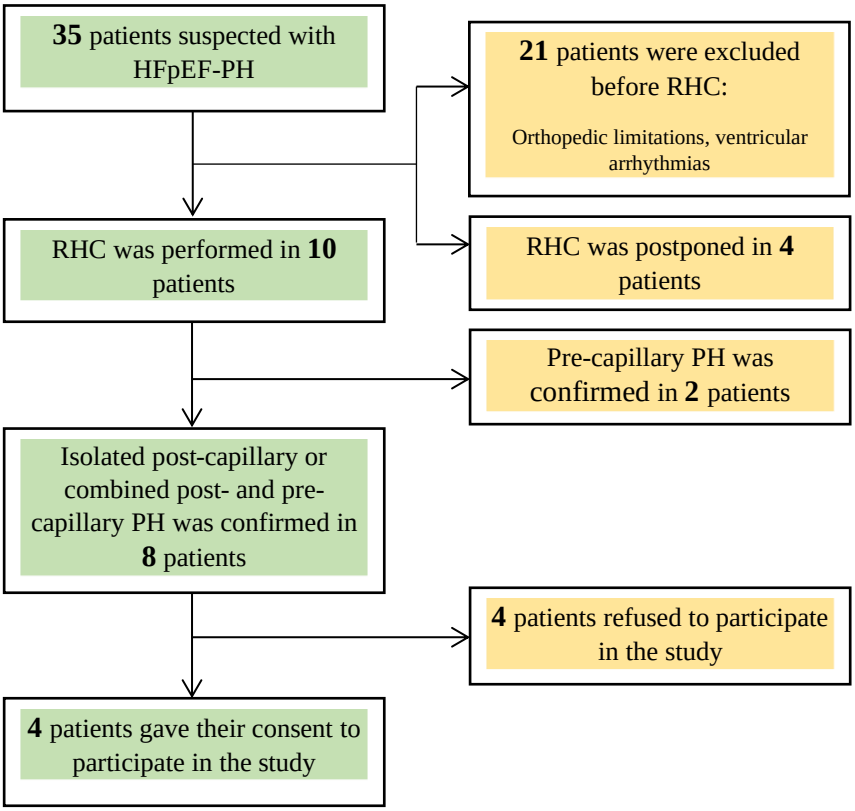

Figure 10. Selection of eligible patients in post-capillary PH rehabilitation study

4.2.2.3. Results

Our initial experience on the assessment of the newly created protocol at Vilnius University showed its potential to be safe (no adverse events related to the protocol procedures were observed) and realisable.

It is of note that the implementation of this protocol depends on the national healthcare system and the usual clinical practice of the study centre. As the rehabilitation efficacy evaluation is composite, and the secondary endpoints include different diagnostic tests performed by separate investigators, it was not easy to organise all assessments according to the provided timeline of the study. Moreover, the identification of the eligible patients was complicated as many (20 out of 35) potential candidates suffered from a walking disability or other orthopaedic limitations to exercise; exercise-induced ventricular arrhythmia as an exclusion criterion was met by only 1 patient.

Ultimately, four patients were included in the study. Two of them were randomised to the control group at first (*Patient 1* and *Patient 2*); the other two patients were randomised to the training group (*Patient 3* and *Patient 4*). After the 15 week-long follow-up period, both patients of the control group participated in the exercise training programme and became training group patients.

Patients of the intervention group

The initial in-hospital training phase in all but one individual continued for 18 days; *Patient 4* left the rehabilitation clinic after 15 days (upon request of the patient).

After the first in-hospital phase, the improvement of the physical exercise capacity was observed in all four trained persons: an increase of 6MWD was at least 10 meters (*Patient 3*), and, in three patients, it was >30 meters (Figure 11).

Before leaving hospital, each patient received individualised written recommendations on how to continue exercising at home. All the participants followed the advice, except for *Patient 4*, who trained at home for a few days only and stopped because of personal reasons and lack of motivation.

After 15 weeks of the follow-up, the three patients who continued exercising for all this period showed a further increase of 6MWD: + 43 meters (*Patient 1*), + 83 meters (*Patient 2*), + 42 meters (*Patient 3*) (Figure 11, Table 9). Moreover, all these patients estimated their dyspnoea by lower scores before and during the 6MWD test according to the 10-point Borg Scale compared with the baseline assessment (Table 9).

As *Patient 4* discontinued exercising, we asked her to come earlier – at week 11 of the follow-up. A reduction in the physical capacity was shown during 6MWD (Figure 11). Doses of diuretics were increased, and an additional visit was planned one month later, but the patient cancelled it due to the COVID-19 pandemic.

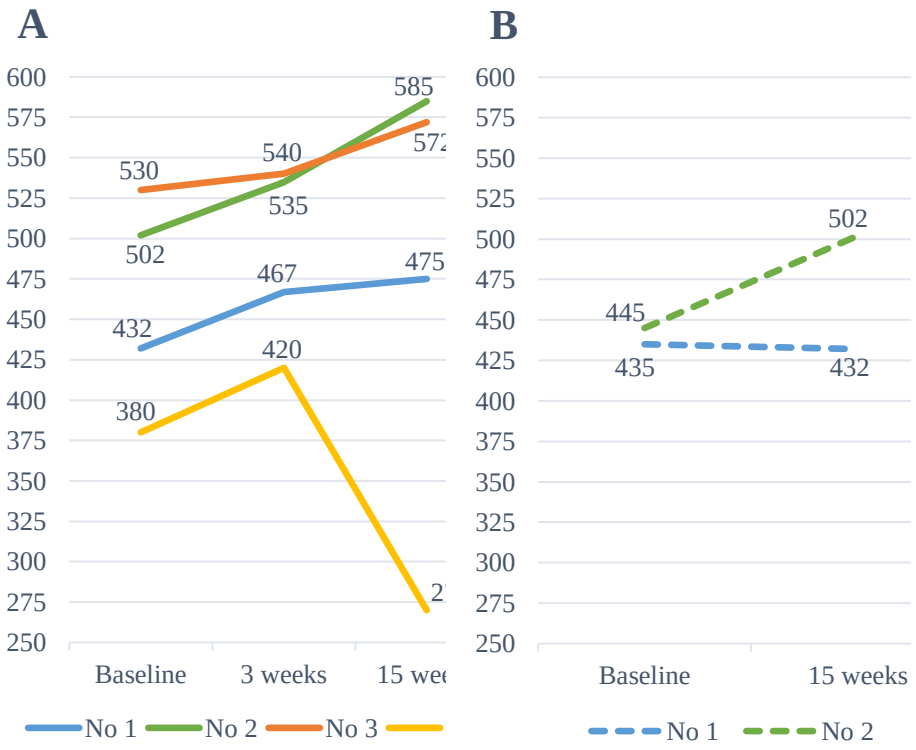

Figure 11. 6MWD change within the follow-up period (A – training group; B – control group)

* - after 11 weeks. Patient No. 4 discontinued exercising a few days after the in-hospital phase.

Table 9. Changes of functional capacity, BNP, echocardiographic parameters and quality of life within 15 weeks of the follow-up period

Randomisation group		**TRAINING**								**CONTROL**			
PATIENT		***Patient 1***		***Patient 2***		***Patient 3***		***Patient 4***		***Patient 1***		***Patient 2***	
		Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
Weight (kg)		108	107	74	71	72	69	125	-	105	108	72	74
BMI (kg/m^2)		37.8	37.5	28.2	27.0	29.6	28.4	52.0	-	36.8	37.8	27.4	28.2
WHO functional class		III	III	III	III	II	II	III	III	III	III	III	III
6MWT	*Distance (m)*	432	475	502	585	530	572	380	270[a]	435	432	445	502
	Borg dyspnoea score before walk	0.5	0	0	0	0.5	0	0.5	3[a]	0	0.5	0	0
	Borg dyspnoea score 1 minute after walk	3	2	3	2	4.5	2	5	8[a]	0.5	3	2	3
CPET	*Workload (Watts)*	104	113	78	85	107	118	74	-	98	104	72	78
	VO_{2peak} (ml/kg/min)	13.7 (55 %)	14.5 (58 %)	14.4 (72 %)	16.9 (85 %)	18.6 (73 %)	22.0 (87 %)	15.2 (52 %)	-	12.6 (51 %)	13.7 (55 %)	13.4 (66 %)	14.4 (72 %)
BNP (ng/l)		146.7	226.2	296.5	123.5	58.5	99.2	140.4	-	215.3	146.7	189.3	296.5
Echocardiography	*sPAP (mmHg)*	65	47	40	33	34	36	50	-	40	65	37	40
	RAP (mmHg)	10	10	5	5	3	3	-	-	5	10	5	5
	PAV AcT (ms)	61	95	103	69	142	137	42	-	54	61	94	103
	TAPSE (cm)	2.2	2.0	1.5	2.2	2.8	2.3	1.4	-	1.6	2.2	2.2	1.5
	TV annular S' (cm/sec)	15	13	11	15	15	13	11	-	16	15	12	11

	RV FAC (%)	40.1	41	37.8	37.5	49.7	50.7	30	-	43.2	40.1	38.2	37.8
	RA area (cm^2)	31.7	31.2	26.5	27.6	15.9	16.4	14.2	-	29.3	31.7	25.1	26.5
	LV EF (%)	57	56	56	56	68	62	57	-	57	57	58	56
	LAVI (ml/m^2)	41.7	52.9	113.0	92.6	38.4	44.1	35.0	-	43.6	41.7	115.0	113.0
	LVMI (g/m^2)	113.7	100.3	78.0	80.2	58.9	59.9	108.0	-	97.5	113.7	72.6	78.0
Quality of life (SF-36 physical)[b]		46.25	82.5	31.25	23.13	55.63	58.13	56.25	-	44.38	46.25	18.75	31.25
Quality of life (SF-36 mental)[b]		65.71	62.42	69.92	48.25	33.25	57.92	54	-	64.46	65.71	50	69.92
HADS (anxiety)[c]		0	2	8	8	11	6	8	-	4	0	8	8
HADS (depression)[c]		0	0	8	8	8	2	7	-	2	0	9	8

a – after 11 weeks;

b – each scale is directly transformed into a 0–100 scale on the assumption that each question carries equal weight, the lower is the score, the more severe is the disability;

c – score varying between 0 and 21 for each scale, 0–7 = normal, 8–10 = borderline abnormal, 11–21 = abnormal.

ABBREVIATIONS: 6MWD – 6-minute walk distance; CPET – cardiopulmonary exercise test; BMI – body mass index; BNP – brain natriuretic peptide; HADS – Hospital Anxiety and Depression Scale; LAVI – left atrial volume index; LV EF – left ventricular ejection fraction; LVMI – left ventricular mass index; PAV AcT – pulmonary arterial valve acceleration time; RA area – right atrial area; RAP – right atrial pressure; RV FAC – right ventricular fractional area change; SF-36 – 36-Item Short Form Survey; sPAP – systolic pulmonary arterial pressure; TAPSE – tricuspid annular plane systolic excursion; TV annular S' – tissue Doppler tricuspid annular systolic wave velocity; VO_{2peak} – peak oxygen uptake; WHO – World Health Organisation.

The cardiopulmonary exercise test also showed better exercise capacity after 15 weeks of training in all the three patients compared with the baseline: VO_{2peak} increased by + 0.8 ml/min/kg (*Patient 1*), + 2.5 ml/min/kg (*Patient 2*), + 3.4 ml/min/kg (*Patient 3*) (Figure 12; Table 9).

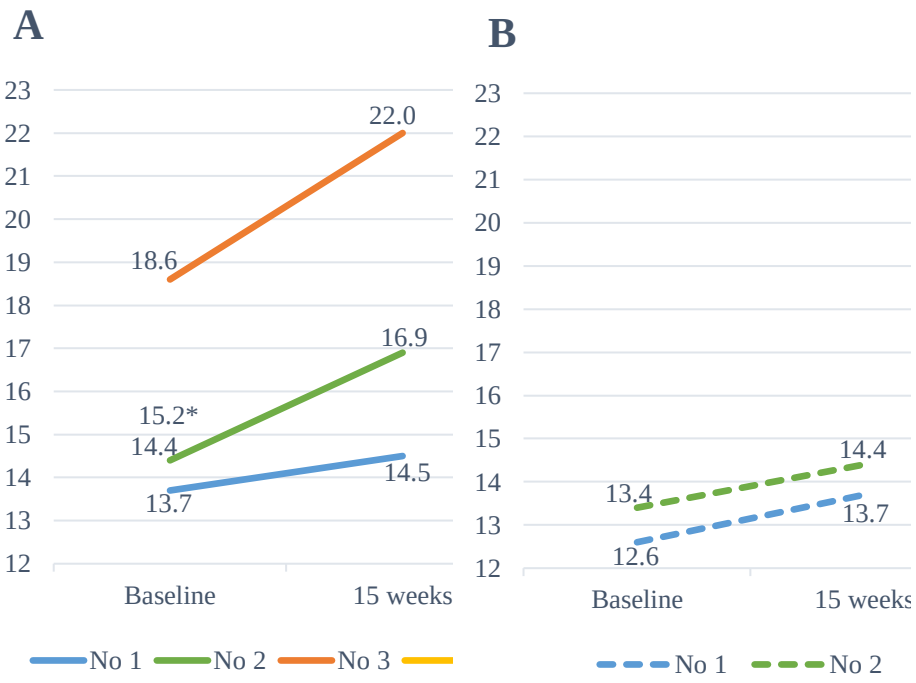

Figure 12. VO_2 peak change within follow up period (A- training group; B – control group)

* Patient No. 4 did not perform CPET after 15 weeks.

In echocardiography, a decrease in sPAP was observed in two patients and a slight increase (by 2 mmHg) in one. RV longitudinal contraction parameters (TAPSE and S') noticeably increased and improved in *Patient 2*, while, in the two other individuals, these parameters decreased but remained within the normal range. At the baseline, RV FAC was normal in all the three cases and did not change at all after the training (Table 9).

The subscales of the SF-36 questionnaire which were used for self-reported QoL assessment, changed variably in different participants. The physical summary score increased markedly in *Patient 1*, thus showing

better physical health, whereas the self-assessment of the mental health did not change significantly. At the same time, *Patient 3* pointed out an improvement in mental but not in physical health. *Patient 2* reported a decrease in both subscales of the SF-36 questionnaire, thus revealing a worsening QOL after 15 weeks of training (Table 9).

The anxiety and depression scores according to the HADS questionnaire were >7 in three patients at the baseline, thus indicating an abnormal level of anxiety and depression. After 15 weeks of rehabilitation, one of two patients reported normalisation of both scores; another patient did not show any changes (Table 9).

Patients of the control group

As already mentioned above, *Patient 1* and *Patient 2* were initially randomised to the control group. After 15 weeks of the follow-up period, 6MWD improved by 57 metres in *Patient 2*. This value did not change markedly (-2 meters) in *Patient 1* (Figure 11; Table 9).

Inconsistent changes were observed in the echocardiographic parameters and BNP levels in control patients (Table 9).

In *Patient 1*, the physical and mental scores according to the SF-36 questionnaire did not change markedly, and the HADS anxiety and depression scores remained normal. *Patient 2* reported better QoL in both scales after the follow-up period, and the HADS questionnaire showed an elevated level of anxiety and depression at the baseline, which did not change significantly after 15 weeks (Table 9).

5. DISCUSSION

5.1. Rehabilitation programme for pre-capillary PH

This PhD thesis is part of the first randomised controlled multicentre study on exercise training in patients with pre-capillary PH showing a significant improvement of the functional capacity measured by 6MWD. The findings of this trial confirm the positive results of the previous single-centre studies on exercise training in pre-capillary PH [48, 49, 52, 121, 122] in a multicentre setting. The large sample size and the adaptation of a standardised rehabilitation programme with an in-hospital start in 11 centres across 10 European countries are the unique features of this study.

The improvement of 6MWD by 34.1±8.3 metres after rehabilitation was clinically meaningful and lies above the suggested threshold of 33 meters for clinical importance in PAH [158]. The mean 6MWD improvement was also comparable to the results of the medication studies in PAH [159], and this value lies above the results of add-on medication in PAH with the mean improvements of 19.96 metres (95% confidence interval 15.35 to 24.57 m) [160].

Such secondary efficacy parameters as health-related QoL and VO_2 peak significantly improved in the training group compared with the control group. It is of note that the patients of the control group improved their VO_2 peak by more than 10% in 29% of the cases; this may possibly be attributed to the Hawthorne effect which describes the change of behaviour that occurs in clinical trials due to the awareness of being observed.

A specialised PH rehabilitation programme ensures the holistic approach of the therapy as exercise training is supplemented with mental gait training, relaxation, psychological counselling, and patient education. Improvements in the mental health parameters, together with a better physical function, enable deconditioned patients to extend their individual daily activity spectrum.

The assessment of pre-capillary PH invasive haemodynamics showed the positive impact of rehabilitation on the pulmonary arterial compliance (PAC) and stroke volume (SV). PAC has the prognostic importance in the clinical practice, and now it is being recommended to be obtained during RHC by the recently published ESC/ERS guidelines [1]. PAC has been shown to be a strong predictor of mortality in a study by Mahapatra et al. [161]. In this study, 109 PAH patients were assessed, and PAC was an independent predictor of mortality which is superior to PVR – in contrast to PAC, PVR was not associated with an increased mortality level

[161]. The same outcome was observed in PH-LHD patients [10, 28, 162, 163].

In Lithuania, a newly founded specialised rehabilitation programme for patients diagnosed with pre-capillary PH was safe and well-tolerated. The results of Vilnius University centre on the effect of 15-week PH rehabilitation programme on the patient's functional capacity and QOL were positive and in line with the results of the pooled data in a multicentre trial or other previously published single-centre studies [54, 122].

Thus, the specialised PH rehabilitation therapy successfully addressed all the important prognostic aspects of PAH/CTEPH by improving the exercise capacity (6MWD and peak VO_2), the RV function (CO, SV), the vascular elasticity (PAC), and the vascular remodelling (PVR) at once. This underlines the importance of the training therapy in severe but stable pre-capillary PH (PAH and CTEPH) patients as an add-on to the optimal medical therapy.

5.2. Establishment of specialised PH rehabilitation program

Although ESC/ERS 2015 guidelines advise to consider (*Class IIa level B recommendation*) the incorporation of rehabilitation into the care of PAH patients [2], this treatment intervention was unavailable in many European PH centres. The utilisation of exercise therapy was limited by gaps in the special expertise of healthcare professionals and the lack of rehabilitation standardisation (patient selection, the optimal methodology, the best intensity, duration of the training, etc.). Most data on the training effects in PH were based on the results from single-centre studies, and the most extensive trials used the *Heidelberg PH rehabilitation programme* characterised by a rather intense in-hospital initiation of exercise training [122].

Namely, the *Heidelberg PH rehabilitation programme* was adapted to the healthcare systems of Lithuania, as well as nine other European countries. An intensive in-hospital programme demands substantial resources of the personnel, time and reimbursement. However, as shown in a multicentre study for the first time, this specialised PH rehabilitation programme can be standardised and is feasible in different countries with different health care systems, while simultaneously being safe and effective.

Prior to this study, cardiac rehabilitation programs in Lithuania had mainly focused on the primary and secondary prevention of coronary heart disease [164–166]. Pulmonary rehabilitation for patients with chronic obstructive pulmonary disease or other chronic respiratory diseases [167–

169] had been underutilised. Since in-hospital rehabilitation clinics are established within the healthcare system in our country, the *Heidelberg PH rehabilitation programme* can be performed in the most secure way. In the framework of this doctoral study, a specialised PH rehabilitation programme was successfully established at Vilnius University Hospital.

This thesis is the first to precisely describe the process, the essential organizational steps, the barriers, and the prerequisites of the implementation of an exercise programme in Lithuania; it can thus be of interest for specialists worldwide and may be helpful in the establishment of specialised PH rehabilitation.

5.3. Rehabilitation programme for post-capillary PH (PH-HFpEF)

By taking into consideration the evidence about the positive impact of exercise training in PAH and HFpEF patients, we could expect it to be beneficial in PH-HFpEF patients as well. Given the heterogeneity of HFpEF, it is recommended to better discriminate among specific phenotypes [128]. PH-HFpEF patients differ in haemodynamics and exercise intolerance if compared with HFpEF without PH [72]. However, the safety, tolerability, and efficacy of rehabilitation in this specific PH-HFpEF population has never been evaluated so far. Most of the PH training studies excluded patients with post-capillary PH, and HFpEF trials did not focus on these severely ill patients.

Before creating a protocol for a multicentre trial of specialised rehabilitation for PH-HFpEF patients (post-capillary PH), we searched for evidence-based information. While expecting to find PH-HFpEF patients incorporated in HFpEF exercise training studies, we conducted systematic literature review in an attempt to find the most effective training methods for PH-HFpEF and accordingly adapt the *Heidelberg PH rehabilitation programme* which had previously been successfully used for pre-capillary PH patients. However, our literature review only confirmed gaps in the knowledge about PH-HFpEF exercise training as essentially not a single study analysed the specific right heart and pulmonary circulation parameters.

To the best of our knowledge, the study protocol for an exercise training programme precisely for the PH-HFpEF population has been created for the first time in the framework of this PhD thesis. We use the unmodified version of the *Heidelberg PH rehabilitation programme* as the intervention for this study protocol. Our first experience on the assessment of the newly created protocol at Vilnius University has shown its potential to be safe and realisable for properly selected PH-HFpEF patients.

Difficulties in finding eligible patients should be taken into consideration as the initial screening of our patients demonstrated a relatively large proportion of PH-HFpEF patients (21 of 35) with orthopaedic or other limitations regarding their capacity to exercise. A longer recruitment period, more participating centres, or the adaptation of exercises to patients with orthopaedic comorbidities could be useful in order to ensure a sufficient sample size for the study.

Positive outcomes from such a therapy only could be expected if the patient is sufficiently motivated and adherent. This rehabilitation programme is of low intensity, but the workouts should be done regularly and continuously. One of our patients discontinued exercising a few days after completing her in-hospital phase. She was highly motivated at the baseline and exercised daily with enthusiasm during the initial in-patient days, but a drop in motivation followed afterwards. This patient probably did not initially understand the personal effort required for workouts, as she had never exercised before, even when she was healthy. Moreover, the difficulties in training could also be associated with morbid obesity (the BMI of this patient was 52 kg/m^2). It is debatable, whether the patients with BMI ≥ 40 should be excluded and assessed separately to get more homogeneous data.

6. CONCLUSIONS

1. In a prospective randomised controlled multicentre study, a specialised PH rehabilitation programme in pre-capillary PH patients was safe and effective:
    a. Adverse events and serious adverse events were comparable between the training and the control groups.
    b. Beneficial effects of the programme on 6MWD, the quality of life, and the peak oxygen consumption were reported when comparing the training group versus the control group.
2. Local experts of pulmonary hypertension, the available targeted PAH medication therapy, supervision by an experienced centre, in-patient rehabilitation facilities, dedicated personnel, equipment, reimbursement, and the motivation of the patients themselves are essential for launching a specialised PH rehabilitation service.
3. The specialised PH rehabilitation programme improved the pulmonary arterial compliance and cardiac output in patients with pre-capillary PH.
4. No reliable data exist on the impact of exercise training on the left and right ventricular morphological, functional, and pulmonary circulation parameters in HFpEF. Some hypothesis-generating findings on the positive effects of rehabilitation on the marker of LV filling pressure E/e', left atrial size, cardiac output and right ventricular strain have been reported.
5. Our protocol for a multicentre trial of a specialised rehabilitation programme for PH-HFpEF patients (post-capillary PH) is based on the gaps in knowledge, eligibility criteria on the latest ESC/ERS guidelines, and the positive results of the *Heidelberg PH rehabilitation programme*. The initial data showed its potential to be safe and realisable. Although the COVID-19 pandemic interrupted the study, these insights give encouragement to resume the trial in the future.

7. PRACTICAL RECOMMENDATIONS

1. We recommend incorporating a specialised PH rehabilitation programme in the care of patients diagnosed with PAH and CTEPH as an add-on to medical therapy in dedicated PH expert centres and experienced rehabilitation clinics. The positive data obtained during a multicentre RCT (a part of this doctoral thesis) contributed to the updated recommendations for supervised exercise training in patients with PAH (*Class I level A recommendation*) in the 2022 ESC/ERS guidelines.
2. We suggest using the *Heidelberg PH rehabilitation programme* for the rehabilitation of patients diagnosed with PH.
3. We encourage the implementation of a specialised PH rehabilitation programme in a few dedicated PH expert centres per country. We suggest using our report on the essential organisational aspects, prerequisites and barriers as a helpful tool in the establishment of this important therapy program.
4. We recommend using a broader and more complex assessment of the parameters reflecting the cardiac function in the future HFpEF exercise training studies while supplementing evaluation with the right heart function and pulmonary circulation parameters in addition to the more precise assessment of the LV morphology and function.
5. We propose to resume the exercise training study within the PH-HFpEF population in the future.

8. LIMITATIONS OF THE STUDY

It is intrinsically impossible to implement the double blind protocol in an exercise training study. However, the investigators involved in the assessment procedures and data analysis were blinded to the patients' allocation group as far as possible.

As most of the patients in the prospective study were offered to participate in the exercise training programme after having finished their final examination, long-term and survival data for comparison between the exercise training and the control group were not available. Although specialised PH rehabilitation therapy successfully improved the important prognostic aspects of PAH/CTEPH (6MWD, peak VO_2, SV, PAC, and PVR), an additional purposeful study is needed to evaluate the effect of rehabilitation on PAH/CTEPH prognosis.

Daily physical activity measurements were not part of the prospective exercise training study protocol. Thus, it was not possible to quantify whether the general activity of the study patients actually increased after the exercise training.

The prospective exercise training study intervention and trial procedures are closely related to the in-hospital stay, which is generally associated with a higher risk of infection and as more difficult to organise during the COVID-19 pandemic. This was one of the reasons of the cessation of the post-capillary PH study.

9. SANTRAUKA LIETUVIŲ KALBA

Ši daktaro disertacija parengta mokslinių publikacijų, tolesniame tekste žymimų romėniškais skaitmenimis, rinkinio pagrindu:

I. Grünig E, MacKenzie A, Peacock AJ, Eichstaedt CA, Benjamin N, Nechwatal R, Ulrich S, Saxer S, Bussotti M, Sommaruga M, Ghio S, Gumbiene L, **Palevičiūtė E**, Jurevičienė E, Cittadini A, Stanziola AA, Marra AM, Kovacs G, Olschewski H, Barberà JA, Blanco I, Spruit MA, Franssen FME, Vonk Noordegraaf A, Reis A, Santos M, Viamonte SG, Demeyer H, Delcroix M, Bossone E, Johnson M. *Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial*. Eur Heart J. 2021 Jun 14;42(23):2284–2295. doi: 10.1093/eurheartj/ehaa696. PMID: 33232470.

II. **Palevičiūtė E**, Gumbienė L, Jurevičienė E, Šimbelytė T, Laucevičienė I, Laucevičius A, Barysienė J, Eichstaedt CA, Benjamin N, Grünig E, Čelutkienė J. *The Experience, Prerequisites, and the Barriers in Organizing a Specialized Rehabilitation Program for Patients with Pulmonary Hypertension.* Respiration. 2021;100(10):949–957. doi: 10.1159/000516331. Epub 2021 May 27. PMID: 34044412.

III. Nagel C, Benjamin N, Egenlauf B, Eichstaedt CA, Fischer C, **Palevičiūtė E**, Čelutkienė J, Harutyunova S, Mayer E, Nasereddin M, Marra AM, Grünig E, Guth S. *Effect of Supervised Training Therapy on Pulmonary Arterial Compliance and Stroke Volume in Severe Pulmonary Arterial Hypertension and Inoperable or Persistent Chronic Thromboembolic Pulmonary Hypertension*. Respiration. 2021;100(5):369–378. doi: 10.1159/000512316. Epub 2021 Mar 25. PMID: 33765679.

IV. **Palevičiūtė E**, Šimbelytė T, Eichstaedt CA, Benjamin N, Egenlauf B, Grünig E, Čelutkienė J. *The effect of exercise training and physiotherapy on left and right heart function in heart failure with preserved ejection fraction: a systematic literature review*. Heart Fail Rev. 2022 Jul 13. doi: 10.1007/s10741-022-10259-1. Epub ahead of print. PMID: 35831689.

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SANTRUMPOS

6 MĖT – 6 minučių ėjimo testas

DS – dešinysis skilvelis

DŠEM – dešiniųjų širdies ertmių manometrija

FES – funkcinė elektrinė stimuliacija

iIFŠN – išsaugotos išstūmio frakcijos širdies nepakankamumas

KPTI – kairiojo prieširdžio tūrio indeksas

KS – kairysis skilvelis

LTEPH – lėtinė trombinė embolinė plautinė hipertenzija

MŠT – minutinis širdies tūris

PAH – plaučių arterinė hipertenzija

$PA_{paslankumas}$ – plaučių arterijos paslankumas

PAPS – plaučių arterijos pleištinis spaudimas

PAS – plaučių arterinis spaudimas

PH – plautinė hipertenzija

PH-KŠP – PH, asocijuota su kairiosios širdies pusės patologija

PKP – plaučių kraujagyslių pasipriešinimas

RKT – atsitiktinių imčių kontroliuojamas tyrimas

SF-36 klausimynas – trumpa sveikatos apklausos forma 36

sIFŠN – sutrikusios išstūmio frakcijos širdies nepakankamumas

ŠN – širdies nepakankamumas

ŠSD – širdies susitraukimų dažnis

ST – smūginis tūris

VO_2 pikinis – didžiausias deguonies suvartojimas

ĮVADAS

Tyrimo aktualumas

Plautinė hipertenzija (PH) ir lėtinis širdies nepakankamumas (ŠN) yra sunkios širdies ir kraujagyslių sistemos būklės, kurioms išsivysčius ženkliai blogėja paciento fizinis pajėgumas, gyvenimo kokybė bei prognozė. Plaučių arterinė hipertenzija (PAH) – reta liga, tačiau PH sindromas pasireiškia 1 % pasaulio populiacijos (> 65 metų amžiuje iki 10 %) ir gali komplikuoti įvairias širdies ir kraujagyslių, kvėpavimo bei kitas sistemines ligas [1–3].

PH, asocijuota su kairiosios širdies pusės patologija (PH-KŠP), yra labiausiai paplitusi tarp skirtingų PH grupių ir sudaro 65–80 % visų PH atvejų [1, 3, 6–9]. Padidėjęs KS prisipildymo slėgis yra kairiosios širdies pusės ligos skiriamasis požymis, sąlygojantis dusulio atsiradimą [26], blogesnę fizinio krūvio toleranciją [27] ir lemiantis plaučių venų stazę bei antrinę pokapiliarinę PH *(2 grupės PH pagal PH klinikinę klasifikaciją)* [14]. Kad ir kokia būtų KS patologija, sąlygojusi PH atsiradimą, plaučių arterinio spaudimo (PAS) ir plaučių kraujagyslių pasipriešinimo (PKP) padidėjimas yra susijęs su sunkesne ligos našta ir blogesnėmis išeitimis [16–19]. PH dažnis tarp išsaugotos išstūmio frakcijos širdies nepakankamumo (iIFŠN) pacientų daugiausia yra pagrįstas echokardiografiniais duomenimis ir būna 36–83 % iIFŠN atvejų [14, 15].

Atsižvelgiant į invaziškai išmatuotą plaučių arterijos pleištinį spaudimą (PAPS), skiriami du pagrindiniai hemodinaminiai PH tipai:

a) Prekapiliarinė PH – PAPS yra ≤ 15 mmHg (būdinga PAH, LTEPH);
b) Pokapiliarinė PH – PAPS yra > 15 mmHg (būdinga PH-KŠP) [1].

Pastaraisiais dešimtmečiais, daugėjant mokslinių duomenų apie endotelino receptorių antagonistų, fosfodiesterazės 5 inhibitorių, tirpaus guanilato ciklazės stimuliatoriaus ir prostaciklinų bei jų analogų efektyvumą gydant šiuos pacientus, specifinė PAH ir LTEPH medikamentinė terapija progresyviai tobulėjo [30, 31]. Vis dėlto, nepaisant modernaus medikamentinio gydymo galimybių, dauguma PAH ir LTEPH sergančiųjų vis dar kenčia nuo ryškių klinikinių simptomų, sumažėjusios fizinio krūvio tolerancijos, prastos su sveikata susijusios gyvenimo kokybės ir ligos progresavimo [42].

Šiuo metu EKD/ERA gairėse siūloma taikyti kompleksinį PH gydymą, kurį sudaro į ligą orientuotas ir palaikomasis medikamentinis gydymas bei papildomos nemedikamentinės gydymo priemonės [1, 6]. Jau

2015 m. EKD/ERA rekomendacijose buvo patariama apsvarstyti atidžiai prižiūrimo fizinio treniravimo skyrimą kaip papildomą gydymo priemonę greta optimalaus medikamentinio gydymo pacientams, sergantiems stabilia PH *(IIa klasės B lygio rekomendacija)* [6]. Šis siūlymas buvo pagrįstas ankstesniais stebėsenos ir vieno centro atsitiktinių imčių kontroliuojamaisiais tyrimais (RKT), į kuriuos daugiausia buvo įtraukiami pacientai, sergantys išimtinai PAH ir LTEPH, naudotos skirtingos treniravimo programos ir buvo įrodyta, kad fizinė terapija yra saugi bei veiksminga šių pacientų funkciniam pajėgumui ir su sveikata susijusiai gyvenimo kokybei gerinti [43–55]. Vis dėlto iki šiol trūko didesnės imties, daugiacentrio RKT, kad būtų galima pateikti daugiau tvirtesnių įrodymų apie šio nefarmakologinio gydymo metodo saugumą ir veiksmingumą PH sergantiems pacientams.

Pažymėtina, kad PH-KŠP medikamentinės terapijos galimybės ribotos, ypač esant PH, asocijuotai su išsaugotos išstūmio frakcijos širdies nepakankamumu. Specifiniai PAH vaistai PH-KŠP gydymui nerekomenduojami – atlikti daugiacentriai atsitiktinių imčių tyrimai neįrodė jų naudos šiems ligoniams, negana to, buvo iškelta pagrįstų abejonių dėl minėtų vaistų saugumo PH-KŠP pacientų grupei [1, 5, 6, 32–35]. Įprasti ŠN gydymo būdai (medicininiai / intervenciniai) šiuo metu yra vienintelės įrodymais pagrįstos gydymo priemonės sergantiesiems PH-KŠP [1, 6, 36]. Sutrikusios išstūmio frakcijos širdies nepakankamumas (sIFŠN) ir išsaugotos išstūmio frakcijos širdies nepakankamumas (iIFŠN) pasižymi tam tikrais patofiziologijos, klinikinių charakteristikų, hemodinamikos, kardiopulmoninės sąveikos ir atsako į gydymą skirtumais [37–39]. iIFŠN, taigi ir PH-iIFŠN, pacientų gydymui skirtini tik natrio-gliukozės antrųjų vienakrypčių nešiklių (SGLT2) inhibitoriai, diuretikai ir gretutinių ligų (pvz., arterinės hipertenzijos, nutukimo, prieširdžių virpėjimo) gydymas [36, 40].

EKD širdies nepakankamumo diagnostikos ir gydymo gairės rekomenduoja fizinio treniravimo reabilitaciją visiems pacientams, kurie gali mankštintis, siekiant pagerinti fizinį pajėgumą ir gyvenimo kokybę, taip pat sumažinti hospitalizacijų dėl ŠN skaičių, kad ir kokia būtų KS išstūmio frakcija *(I klasės A lygio rekomendacija)* [36]. Tos pačios EKD rekomendacijos siūlo svarstyti galimybę taikyti atidžiai prižiūrimą, fiziniais pratimais pagrįstą kardiologinės reabilitacijos programą tiems ŠN pacientams, kurių liga yra labiau pažengusi, esant gausiai gretutinei patologijai *(IIa klasės C lygio rekomendacija)* – kaip tik tokie yra PH-KŠP ligoniai [36]. Vis dėlto pažymėtina, kad įrodymais pagrįstų rekomendacijų dėl fizinio krūvio terapijos PH-KŠP pacientams nėra. Nė vienas iš ankstesnių tyrimų nebuvo skirtas būtent PH-iIFŠN populiacijai, ankstesniuose iIFŠN

fizinio krūvio treniruočių tyrimuose dalyvavusių PH-iIFŠN ligonių skaičius nebuvo referuojamas, o dauguma PH fizinio treniravimo mokslinių tyrimų neįtraukė sergančiųjų pokapiliarine PH.

Nors EKD gydymo rekomendacijose pagrįstai siūloma į visapusišką PAH, LTEPH ir ŠN sergančių pacientų priežiūrą įtraukti fizinių pratimų terapiją, šio siūlymo įdiegimą į realią klinikinę praktiką riboja žinių apie optimalią reabilitacijos metodiką, saugiausią ir efektyviausią treniruočių intensyvumą, trukmę stoka, taip pat praktinės kliūtys – patirties trūkumas, gydymo išlaidų kompensavimo sunkumai ir kita. Daugelyje PH, ŠN ir bendrųjų kardiologijos centrų vis dar yra ribotas fizinio aktyvumo treniruočių prieinamumas. Iki šio tyrimo specializuota reabilitacijos programa PH sergantiems pacientams buvo neprieinama ir Lietuvoje.

Ši disertacija suskirstyta į dvi dalis, atsižvelgiant į tiriamąsias populiacijas: pirmoji susijusi su reabilitacijos programa, skirta pacientams, sergantiems prekapiliarine PH (PAH, LTEPH), antroji skirta reabilitacijos programai pacientams, sergantiems pokapiliarine PH (PH-iIFŠN).

Tyrimo hipotezė

Specializuota reabilitacijos programa, skiriama greta optimalaus medikamentinio gydymo, yra įmanoma, saugi ir veiksminga pacientams, sergantiems prekapiliarine ir pokapiliarine PH.

Disertacijos uždaviniai

1) Įvertinti specializuotos reabilitacijos programos saugumą ir efektyvumą pacientams, sergantiems prekapiliarine PH, atliekant atsitiktinių imčių kontroliuojamą tyrimą *(I ir II publikacijos)*.
2) Nustatyti ir aprašyti pagrindines kliūtis ir būtinuosius poreikius, diegiant specializuotą PH reabilitacijos programą *(II publikacija)*.
3) Įvertinti specializuotos reabilitacijos programos poveikį plaučių arterijų paslankumui ir smūginiam širdies tūriui pacientams, sergantiems prekapiliarine PH *(III publikacija)*.
4) Atlikti sisteminę literatūros apžvalgą, vertinant fizinio treniravimo ir fizioterapijos poveikį širdies morfologiniams ir funkciniams bei plaučių kraujotakos parametrams pacientams, sergantiems išsaugotos išstūmio frakcijos širdies nepakankamumu *(IV publikacija)*.
5) Sukurti daugiacentrio tyrimo protokolą, skirtą įvertinti reabilitacijos programos saugumą ir efektyvumą pacientams, sergantiems PH,

susijusia su išsaugotos išstūmio frakcijos širdies nepakankamumu (pokapiliarinė PH).

Tyrimo mokslinis naujumas

Šios daktaro disertacijos dalis apie prekapiliarinės PH reabilitaciją buvo vykdoma dalyvaujant pirmajame daugiacentriame ir iki šiol didžiausiame atsitiktinių imčių kontroliuojamame tyrime. Duomenys, surinkti Vilniaus universitete, buvo sujungti su kitų dešimties PH centrų iš skirtingų Europos šalių duomenimis ir tapo pagrindu sustiprinti PAH fizinio treniravimo rekomendacijas naujausiose 2022 m. EKD/ERA gairėse. Maža to, šis daugiacentris tyrimas pirmą kartą parodė, kad treniruočių programa gali būti standartizuota ir įgyvendinama skirtingose šalyse, kuriose yra skirtingos sveikatos priežiūros sistemos.

Iki šiol niekada nebuvo nagrinėti būtinieji poreikiai ir kliūtys, diegiant PH reabilitacijos programą. Surinkome ir aprašėme duomenis apie organizacinius aspektus, kurie užpildo žinių spragą ir skatina naudoti specializuotą PH reabilitaciją tam skirtuose PH centruose.

Prospektyvinio RKT *post hoc* analizėje pirmą kartą įvertintas reabilitacijos poveikis PAH ir LTEPH pacientų plaučių arterijos paslankumui ir smūginiam širdies tūriui.

Mūsų žiniomis, nė vienas ankstesnis reabilitacijos tyrimas nebuvo orientuotas į pokapiliarinės PH pacientus ir būtent į PH-iIFŠN populiaciją. Pirmieji atlikome sistemingą esamų duomenų literatūros apžvalgą, įvertindami mokslinius įrodymus apie treniravimo ir fizioterapijos poveikį iIFŠN pacientų širdies morfologiniams, funkciniams ir plaučių kraujotakos parametrų pokyčiams ir sukūrėme daugiacentrio mokslinio tyrimo protokolą, skirtą vertinti reabilitacijos poveikį ir saugumą PH-iIFŠN.

Disertacijos ginamieji teiginiai

1) Specializuota PH reabilitacijos programa, skiriama greta optimalaus medikamentinio gydymo, pagerina prekapiliarine PH (PAH ir LTEPH) sergančių pacientų:
    a. fizinį pajėgumą,
    b. su sveikata susijusią gyvenimo kokybę,
    c. plaučių arterijos paslankumą ir smūginį širdies tūrį.
2) Specializuota PH reabilitacijos programa, skiriama greta optimalaus medikamentinio gydymo prekapiliarine PH (PAH ir LTEPH) sergantiems pacientams, yra įgyvendinama ir saugi.

3) Fizinis treniravimas ir (ar) fizioterapija pagerina širdies ir plaučių kraujotakos morfologinius ir funkcinius parametrus pacientams, sergantiems iIFŠN.
4) Tikslinga organizuoti mokslinį tyrimą, vertinant specializuotos PH reabilitacijos programos saugumą ir veiksmingumą konkrečioje pokapiliarine PH (PH-iIFŠN) srgančių pacientų populiacijoje.

I. PREKAPILIARINĖS PH REABILITACIJOS TYRIMAS

Tyrimo metodai

Tyrimas buvo atliktas vadovaujantis Helsinkio deklaracija, protokolą patvirtino Vilniaus regioninis biomedicininių tyrimų etikos komitetas (Nr. 158200-16-867-381; 2016-11-08). Visi pacientai, prieš įtraukiant juos į tyrimą, davė raštišką informuoto asmens sutikimą. Daugiacentrė studija buvo užregistruota klinikinių tyrimų interneto svetainėje clinicaltrials.gov, identifikacinis numeris NCT03345212.

Prospektyvinė prekapiliarinės PH reabilitacijos tyrimo dalis buvo vykdoma kaip daugiacentris atsitiktinių imčių kontroliuojamas tyrimas. Pacientai buvo įtraukti vienuolikoje PH centrų, įskaitant Vilniaus universitetą, dešimtyje Europos šalių (Austrijoje, Belgijoje, Vokietijoje, Italijoje, Lietuvoje, Nyderlanduose, Portugalijoje, Škotijoje, Ispanijoje ir Šveicarijoje). PH diagnozė buvo nustatyta vadovaujantis EKD/ERA gairėmis [6, 21].

Duomenys specializuotos PH reabilitacijos programos poveikio analizei invaziniu būdu išmatuotiems išvestiniams parametrams ($PA_{paslankumui}$, ST) buvo gauti atlikus ankstesnio prospektyvinio RKT [51] *post hoc* analizę (Heidelbergo universiteto duomenų bazė).

Tyrimo populiacija

Per dvejus metus (2017 m. vasaris – 2019 m. vasaris) 20 prekapiliarine PH (PAH ir LTEPH) sergančių pacientų buvo pakviesti dalyvauti daugiacentriame specializuotos reabilitacijos tyrime Vilniaus universitete. Iš jų 13 sutiko dalyvauti ir buvo įtraukti. Dalyvavimo tyrime tinkamumo kriterijai pateikti **1 lentelėje.** Į visą daugiacentrį tyrimą per ketverius metus (2015 m. spalis–2019 m. lapkritis) buvo įtraukti 129 prekapiliarine PH sergantys pacientai. Tiriamieji atsitiktine tvarka buvo priskirti intervencijos (treniravimo) arba kontrolinei grupei. Po 15 savaičių

stebėjimo laikotarpio kontrolinės grupės pacientams taip pat buvo pasiūlyta dalyvauti treniruočių programoje *(laukiančiosios grupės modelis)*. Intervencijos grupės pacientai treniravosi pagal specializuotą reabilitacijos programą (10–30 d. stacionare, vėliau dar 11–12 sav. mankštinosi namuose), kontrolinės grupės pacientai užsiėmė jiems įprasta kasdiene veikla.

Į *post hoc* analizę buvo įtraukti 43 pacientai, dalyvavę ankstesniame prospektyviniame tyrime. Išsamūs jų invazinio hemodinamikos vertinimo duomenys buvo prieinami tiek įtraukiant pacientą į reabilitacijos programą, tiek po 15 sav. stebėsenos laikotarpio.

1 lentelė. Tinkamumo dalyvauti daugiacentriame prekapiliarinės PH reabilitacijos tyrime kriterijai

ĮTRAUKIMO KRITERIJAI	ATMETIMO KRITERIJAI
1. Moterys ir vyrai ≥ 18 metų. 2. PSO II–IV funkcinė klasė. 3. PH diagnozuota atlikus DŠEM: a) vid. PAS ≥ 25 mmHg; b) PKP ≥ 3 VV; c) PAPS ≤ 15 mmHg. 4. Pacientui taikomas optimalus ir ≥ 2 mėn. iki įtraukimo į tyrimą stabilus specifinis PAH gydymas. 5. Numanoma, kad medicininis gydymas neturėtų keistis per 15 sav. tyrimo laikotarpį (išskyrus diuretikus). 6. Gali suprasti ir sutinka pasirašyti informuoto asmens sutikimo formą	1. PAH, susijusi su: a) portine hipertenzija, b) sudėtinga įgimta širdies yda, c) ŽIV. 2. Pacientai, sergantys plaučių venų okliuzine liga. 3. Pacientai, turintys dešiniosios širdies pusės dekompensacijos požymių. 4. Aktyvus miokarditas, ūminis išeminis sindromas, fizinio krūvio sukeltos skilvelinės aritmijos, širdies nepakankamumo paūmėjimas, aktyvi kepenų liga. 5. Ūminė kvėpavimo takų infekcija. 6. Sunki plaučių liga: FEV1/FVC < 0,5 ir bendra plaučių talpa < 70 % normos. 7. Hemoglobino koncentracija mažesnė nei 75 % apatinės normos ribos. 8. Sistolinis kraujospūdis < 85 mmHg. 9. Bet koks specifinio PH gydymo pakeitimas per pastaruosius 2 mėn. 10. Pacientas, kuriam šio tyrimo metu planuojamas dalyvavimas vaisto studijoje. 11. Nėštumas. 12. Vaikščiojimo negalia. 13. Nesugebėjimas arba įtarimas, kad nesugebama tinkamai bendradarbiauti

Santrumpos: PSO – Pasaulio sveikatos organizacija; DŠEM – dešiniųjų širdies ertmių manometrija; vid.PAS – vidurinis plaučių arterijos spaudimas; PKP – plaučių kraujagyslių pasipriešinimas, VV – Vudo vienetai; PAPS – plaučių arterijos pleištinis slėgis; ŽIV – žmogaus imunodeficito virusas.

Specializuotos PH reabilitacijos programos aprašymas

Vilniaus universitete ir kituose dalvavusiuose centruose specializuotas Heidelbergo PH reabilitacijos protokolas [43, 51, 54] buvo pritaikytas vietos sąlygoms, išlaikant esmines ypatybes:

1) Reabilitacijos priemonės pradedamos taikyti ligoninėje (14–21 diena), vėliau treniruotės tęsiamos namuose.
2) Programą sudaro:
    a. intervalinės treniruotės dviračiu (20 min., 5 k./sav.);
    b. kvėpavimo mankšta (30 min., 5 k./sav.);
    c. jėgos treniruotės (30 min., 5 k./sav.);
    d. sąmoningo vaikščiojimo treniruotės (2–3 k./sav.);
    e. įprastiniai elementai, tokie kaip masažas, relaksacijos, socialinio darbuotojo, psichologo konsultacijos, paskaitos ir paciento mokymas (pagal poreikį).

Pradinis treniruočių intensyvumas siekė 40–60 % maksimalaus individualaus tiriamojo krūvio, pasiekto atliekant kardiopulmoninį fizinio krūvio mėginį pirminio ištyrimo metu. Reabilitacijos ligoninėje metu treniruočių intensyvumas buvo palaipsniui didinamas, stengiantis pasiekti maksimalų pirminio vertinimo metu toleruotą krūvį (išlaikant 60–80 % maksimalaus širdies susitraukimų dažnio (ŠSD) ir vengiant desaturacijos < 90 %). Treniruotes atidžiai prižiūrėjo specialiai paruošti kineziterapeutai ir fizinės medicinos bei reabilitacijos gydytojai, taip pat kardiologai, turintys PH gydymo patirties. Treniruočių metu buvo nuolat stebimas ligonio kraujo įsotinimas deguonimi (pulsoksimetru), ŠSD bei subjektyvūs paciento simptomai, atsižvelgiant į šiuos parametrus buvo nustatomas ir koreguojamas treniruočių intensyvumas.

Prieš išvykdamas iš ligoninės kiekvienas pacientas gavo individualias rašytines rekomendacijas, kaip toliau mankštintis namuose, įskaitant išsamias kiekvieno pratimo instrukcijas su paveikslėliais, rekomenduojamus ŠSD intervalus treniruočių metu ir kineziterapeuto kontaktus (el. pašto adresą ir telefono numerį).

Atliekant daugiacentrį tyrimą buvo dedamos ypatingos pastangos, siekiant reabilitacijos programą standartizuoti. Buvo organizuojami tyrime dalyvaujančių sveikatos priežiūros specialistų susitikimai, vykdyti specializuoti mokymai „apmokyk mokytoją“ principu. Norint kuo labiau suderinti įvairiose šalyse taikomas procedūras ir metodikas, bent vienas PH ekspertas ir kineziterapeutas iš kiekvieno dalyvaujančio centro apsilankė PH centre ir reabilitacijos klinikoje Heidelberge, Vokietijoje, kur turėjo

galimybę tiesiogiai susipažinti su fizinio pajėgumo vertinimu, taikomomis reabilitacijos programos priemonėmis, individualaus fizinio krūvio skyrimo ir dozavimo principais ir išmokti pacientų treniravimo metodikų.

Vertinamosios baigtys

Pirminė vertinamoji baigtis – reabilitacijos programos poveikis fiziniam pajėgumui, įvertintas pagal 6 minučių ėjimo testo (6 MĖT) distancijos pokytį per 15 stebėsenos savaičių, lyginant treniruojamą ir kontrolinę grupes.

Antrinės vertinamosios baigtys buvo šios:

A. Pradinių ir po 15 sav. stebėsenos laikotarpio gautų rodiklių pokytis, lyginant treniruojamą ir kontrolinę grupes:
   a. didžiausio deguonies suvartojimo (VO_2 pikinis), įvertinto kardiopulmoninio fizinio krūvio mėginio metu;
   b. su sveikata susijusios gyvenimo kokybės (panaudojant trumpą sveikatos apklausos formą 36 (SF-36 klausimynas) [146];
   c. plaučių arterijos paslankumo ir smūginio tūrio, išskaičiuotų iš invaziniu būdu išmatuotų hemodinaminių parametrų;
   d. saugumo parametrai (registruojami nepageidaujami reiškiniai, apibrėžti pagal Tarptautinės derinimo konferencijos gerąją klinikinę praktiką) [147].
B. Kliūčių ir būtinųjų poreikių įdiegti ir teikti specializuotos PH reabilitacijos paslaugą analizė.

Statistinė analizė

Kintamieji pateikti kaip vidurkis ± standartinis nuokrypis arba mediana ir tarpkvartiliniai intervalai. Poveikiui aprašyti buvo apskaičiuoti absoliučiųjų verčių pokyčiai. Skirtumai tarp intervencinės ir kontrolinės grupės pokyčių buvo apskaičiuoti ir išreikšti kaip „pagal kontrolinės grupės rodiklius koreguotas pokytis“. Pirminė veiksmingumo analizė atlikta naudojant t testą su nevienodomis pokyčių tarp grupių dispersijomis (Welcho testai). Antrinėms vertinamosioms baigtims įvertinti naudotas porinis Stjudento t testas. Kategorinių duomenų analizei naudotas chi kvadrato testas. Saugumas buvo analizuojamas aprašomuoju būdu. Visi testai buvo dvipusiai, o skirtumai laikomi statistiškai reikšmingais, kai

dvipusė p reikšmė buvo < 0,05. Analizė atlikta naudojant IBM SPSS V25 (IBM Corp. Armonk, Niujorkas, JAV).

REZULTATAI

Vilniaus universiteto duomenys

Tyrimo centre Vilniaus universitete (VU) dalyvavo 13 pacientų, 6 iš jų atsitiktinės atrankos būdu buvo priskirti intervencijos, 7 – kontrolinei grupėms. Po 15 sav. stebėsenos laikotarpio 3 buvę kontrolinės grupės pacientai pageidavo dalyvauti reabilitacijos programoje. Taigi VU tyrimo centre pagal specializuotą PH reabilitacijos programą iš viso buvo gydyti 9 prekapiliarine PH (PAH ir LTEPH) sergantys pacientai. Šių pacientų demografiniai duomenys, funkcinio pajėgumo ir su sveikata susijusios gyvenimo kokybės pokyčiai per 15 sav. stebėsenos laikotarpį apibendrinti **2 lentelėje**.

2 lentelė. Prekapiliarine PH sergančių pacientų demografiniai duomenys, funkcinio pajėgumo ir gyvenimo kokybės pokyčiai per 15 sav. Vilniaus universitete

PARAMETRAI												
Paciento Nr.	**Lytis**	**Amžius**	**Vid. PAS (mmHg)**	**Treniravimo trukmė stacionare (dienos)**	**6 MĖT pradinis (m)**	**6 MĖT 15 sav. (m)**	**VO_2/kg pikinis pradinis (ml/kg/min)**	**VO_2/kg pikinis 15 sav. (ml/kg/min)**	**Fizinės būklės vertinimo balas, pradinis***	**Fizinės būklės vertinimo balas, 15 sav.***	**Mentalinės būklės vertinimo balas, pradinis***	**Mentalinės būklės vertinimo balas. 15 sav.***
I	M	50	75	18	410	410	12,4	11,9	38,1	30,6	46,9	46,8
II	V	71	41	18	450	**	17,7	18,7	62,5	78,8	53,8	86,8
III	M	31	60	14	595	575	18,9	15,7	26,3	45,8	30,0	49,0
IV	M	54	64	14	420	480	12,0	14,0	50,6	72,5	83,8	84,0
V	M	42	78	20	446	470	12,0	14,0	28,8	76,9	42,0	77,3
VI	V	26	27	14	570	650	18,7	20,0	86,9	71,9	82,1	67,6
VII	V	75	65	20	420	400	12,3	14,0	43,1	68,8	55,8	65,6
VIII	M	55	53	18	535	530	13,6	14,8	33,1	60,0	84,4	86,6
IX	M	58	56	18	390	440	12,3	13,7	23,8	33,1	48,2	49,2

Perspausdinta leidus S. Karger AG, Bazelis (II publikacija).

SANTRUMPOS: M – moteris; V – vyras; vid. PAS – vidurinis plaučių arterijos spaudimas; 6 MĖT – 6 minučių ėjimo testas; VO_2 – didžiausias deguonies suvartojimas

* Vertinta pagal SF-36 klausimyną, kurio didesnis balas rodo geresnę gyvenimo kokybę.

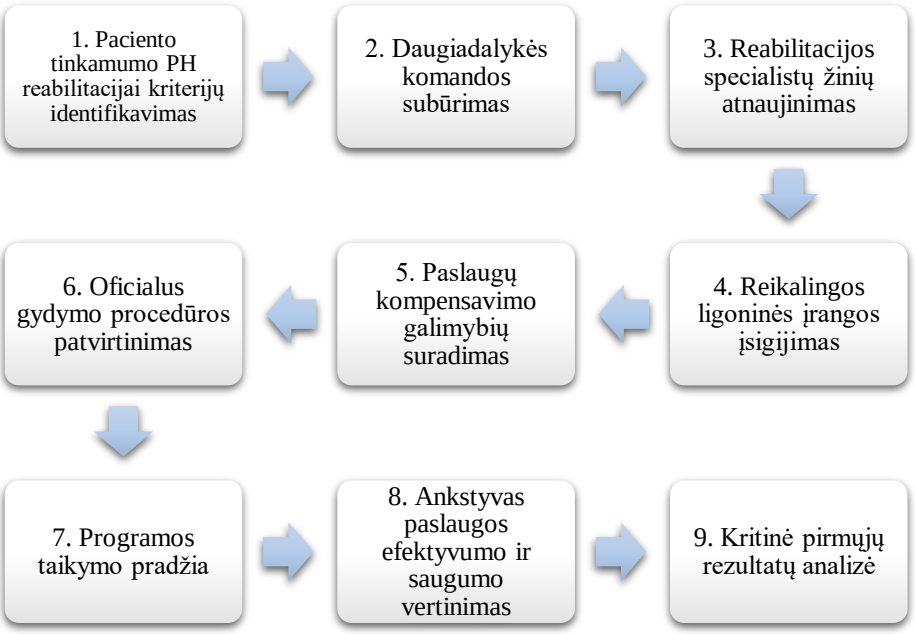
** Praėjus 15 sav. stebėsenos laikotarpiui pacientas neatliko 6 MĖT (podagros paūmėjimo sąlygotas pėdos skausmas).

Vilniaus universiteto patirties kokybinė analizė

Kokybinė Vilniaus universiteto patirties analizė atskleidė 9 esminius žingsnius, diegiant specializuotą PH reabilitacijos programą (1 paveikslas), taip pat nustatė pagrindinius poreikius ir kliūtis kuriant bei vykdant tokio pobūdžio gydymą (3 lentelė).

Pasirengimo etapas truko apie 14 mėnesių. Šiai programai įsteigti ir vykdyti reikėjo, kad prie įprastos daugiadalykės PH specialistų komandos prisijungtų specialiai apmokyti reabilitacijos srities profesionalai – komandą papildė 2 fizinės medicinos ir reabilitacijos gydytojai, 3 kineziterapeutai, 1 ergoterapeutas ir 1 psichologas. Be to, sveikatos priežiūros specialistams reikėjo įgyti tikslinių žinių apie sunkiai sergančių pacientų fizinį treniravimą – mūsų kardiologai, besispecializuojantys PH srityje, kartu su FMR gydytojais bei kineziterapeutais lankėsi Heidelbergo universitetinėje ligoninėje bei reabilitacijos klinikoje Königsstuhlio (Vokietija), kur mokėsi fizinių pratimų ir kvėpavimo treniruočių programos metodikos bei tinkamo fizinio krūvio dozavimo.

Kad programa būtų prieinama pacientams, reikėjo kompensuoti šios nemedikamentinės gydymo priemonės taikymo išlaidas. Nors Lietuvoje stabiliems PH sergantiems pacientams stacionarinės reabilitacijos paslaugos nėra finansuojamos įprasta tvarka, tačiau kompensaciją iš Valstybinės ligonių kasos pavyko užtikrinti dėl teigiamo VLK atsakymo į prašymą kompensuoti išlaidas išimties tvarka individualiems pacientams.



1 paveikslas. Esminiai žingsniai kuriant specializuotą PH reabilitacijos programą Vilniaus universiteto ligoninėje

Perspausdinta leidus S. Karger AG, Bazelis (II publikacija).

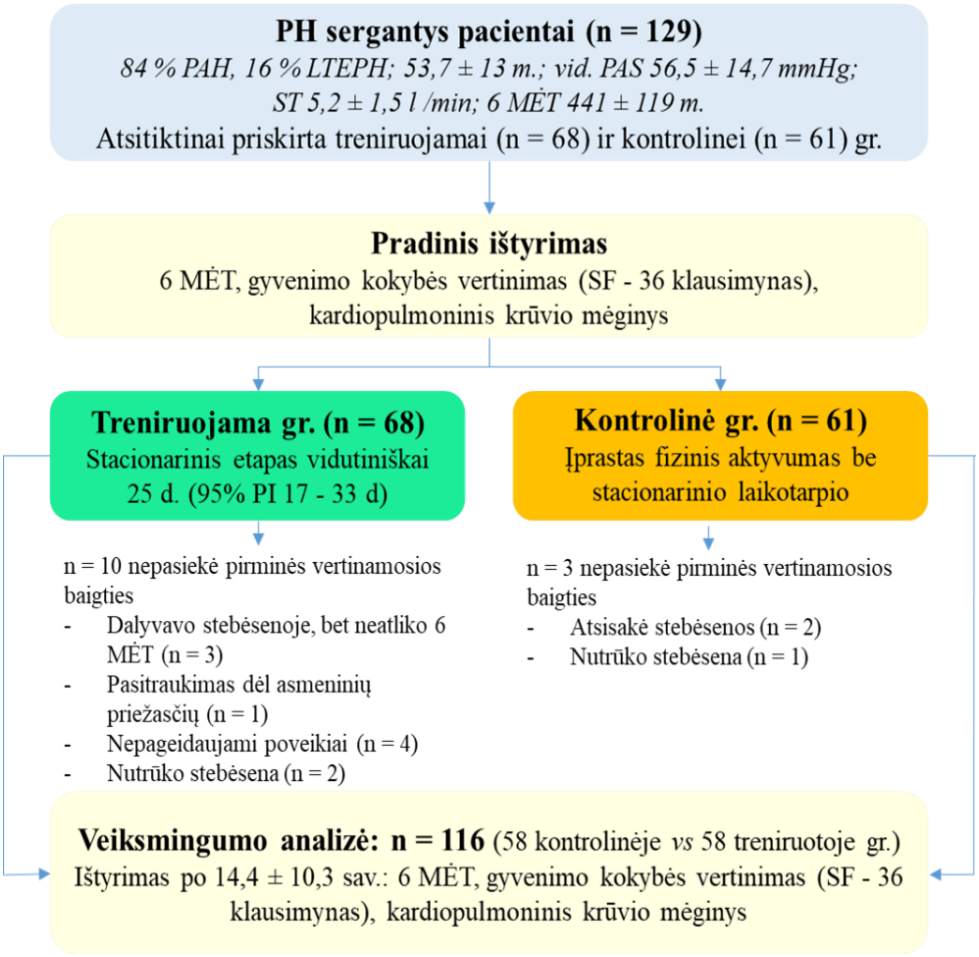
3 lentelė. Specializuotos PH reabilitacijos programos įdiegimo ir vykdymo pagrindiniai poreikiai bei kliūtys

BŪTINIEJI POREIKIAI	KLIŪTYS
PH SPECIALISTAI	
● Specializuotas PH centras ● Daugiadalykė komanda ● Taikant PH reabilitaciją labiau patyrusio centro priežiūra	● Vietinės patirties trūkumas, gydant PH pacientus
REABILITACIJOS SPECIALISTAI	
● Patyrusi reabilitacijos specialistų komanda ● Specializuotos žinios apie fizinį treniravimą labai sunkiai sergantiems pacientams ● Reikalingos įrangos užtikrinimas stacionare (pvz., veloergometras, svarmenys, pulsoksimetras, mobili deguonies talpykla)	● PH pacientų treniravimo patirties trūkumas ● Būtinosios įrangos stoka
PACIENTAI	
● Paciento gebėjimai treniruotis – ortopedinių ar kitų apribojimų nebuvimas ● Motyvacija	● Pacientų ortopedinės ir kitos gretutinės ligos ● Motyvacijos praradimas laikui bėgant ● Negalėjimas treniruočių tęsti namuose ● Nestabili būklė – ligos paūmėjimas
SVEIKATOS PRIEŽIŪROS SISTEMA	
● Ligai skirtų tikslinių vaistų prieinamumas. ● Įsteigtos reabilitacijos klinikos / įstaigos ● Paslaugų išlaidų kompensavimas	● Tikslinio gydymo trūkumas ● Reabilitacijos klinikų nebuvimas sveikatos priežiūros sistemoje ● Nėra arba ribotas paslaugų išlaidų kompensavimas

Perspausdinta leidus S. Karger AG, Bazelis (II publikacija).

Daugiacentrio tyrimo rezultatai

Į daugiacentrės studijos galutinę analizę įtraukta 116 pacientų (58 treniruoti ir 58 kontrolinės grupės) (2 paveikslas).

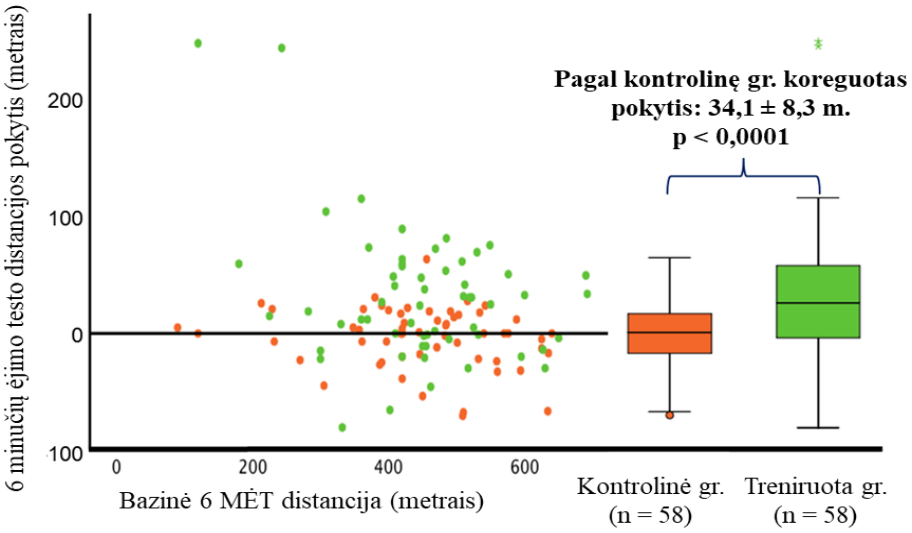


2 pav. Daugiacentrio prekapiliarinės PH tyrimo pacientų atrankos ir efektyvumo analizės srauto diagrama

Perspausdinta gavus Oxford University Press leidimą (I publikacija).

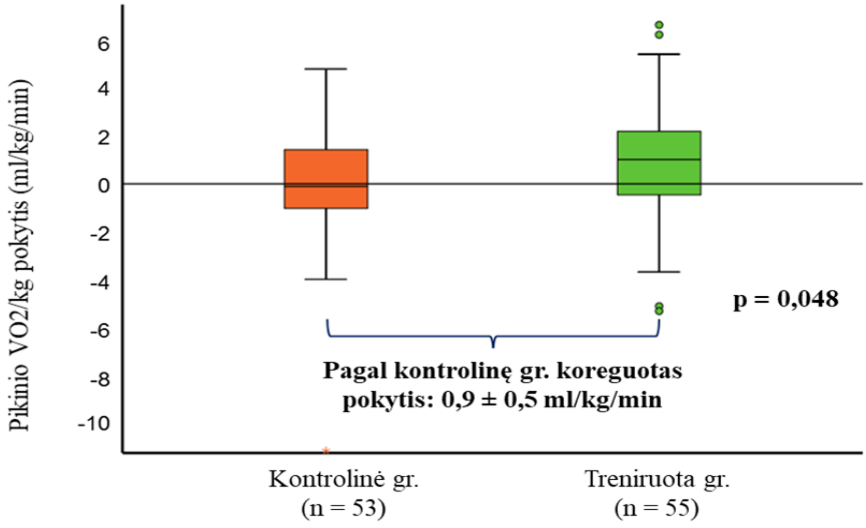
Po 15 sav. stebėsenos laikotarpio 6 MĖT metu nueitas atstumas treniruotų pacientų grupėje reikšmingai pagerėjo (30,7 ± 57,9 metro), o kontrolinėje grupėje šiek tiek sumažėjo (–3,4 ± 25,9 metro); pagal kontrolinę grupę koreguotas pokytis buvo 34,1 ± 8,3 metro; $p < 0,0001$ **(3 paveikslas)**.

Atliekant kardiopulmoninio krūvio mėginį pikinis VO_2 reikšmingai pagerėjo treniruotų pacientų grupėje (pagal kontrolinę grupę koreguotas pokytis +0,9 ± 0,3 ml/min/kg; $p = 0,048$; **4 paveikslas**).



3 pav. Pirminės vertinamosios baigties – 6 minučių ėjimo testo distancijos – pokyčiai daugiacentriame prekapiliarinės PH reabilitacijos tyrime

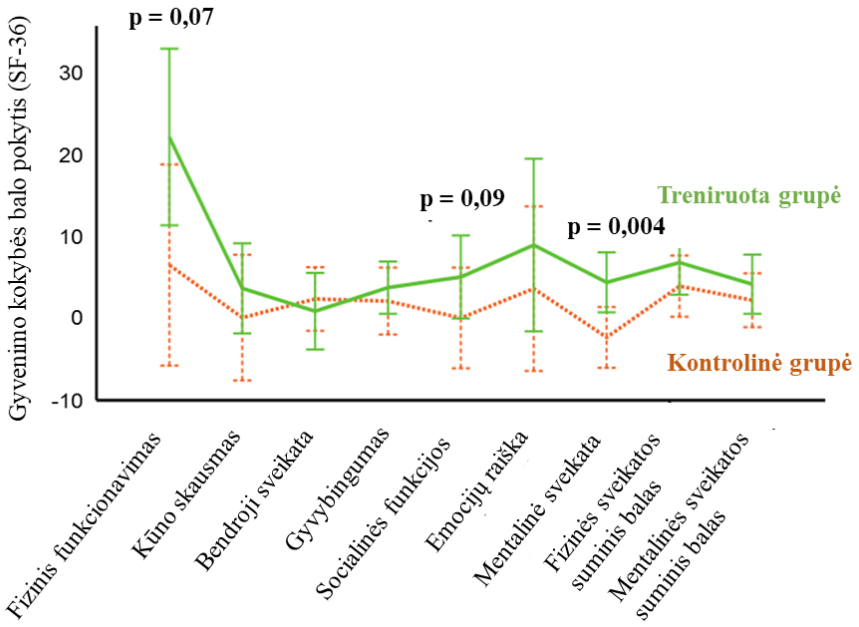
Perspausdinta gavus Oxford University Press leidimą (I publikacija).



4 pav. Didžiausio deguonies suvartojimo (VO_2) pokyčiai treniruotų pacientų grupėje, palyginti su kontroline grupe, daugiacentriame prekapiliarinės PH reabilitacijos tyrime

Perspausdinta gavus Oxford University Press leidimą (I publikacija).

Vertinant su sveikata susijusią gyvenimo kokybę SF-36 klausimynu, po 15 sav. stebėsenos laikotarpio treniruotų pacientų grupėje, palyginti su kontroline grupe, statistiškai reikšmingai labiau pagerėjo mentalinė sveikata (pagal kontrolinę grupę koreguotas pokytis 7,3 ± 2,5; p = 0,004), taip pat pastebėtos geresnio fizinio (p = 0,07) ir socialinio funkcionavimo (p = 0,09) tendencijos (**5 paveikslas**).



5 pav. Gyvenimo kokybės vertinimo skalių (SF-36 klausimynas) pokyčiai, lyginant treniruotą ir kontrolines grupes, daugiacentriame prekapiliarinės PH reabilitacijos tyrime

Perspausdinta gavus Oxford University Press leidimą (I publikacija).

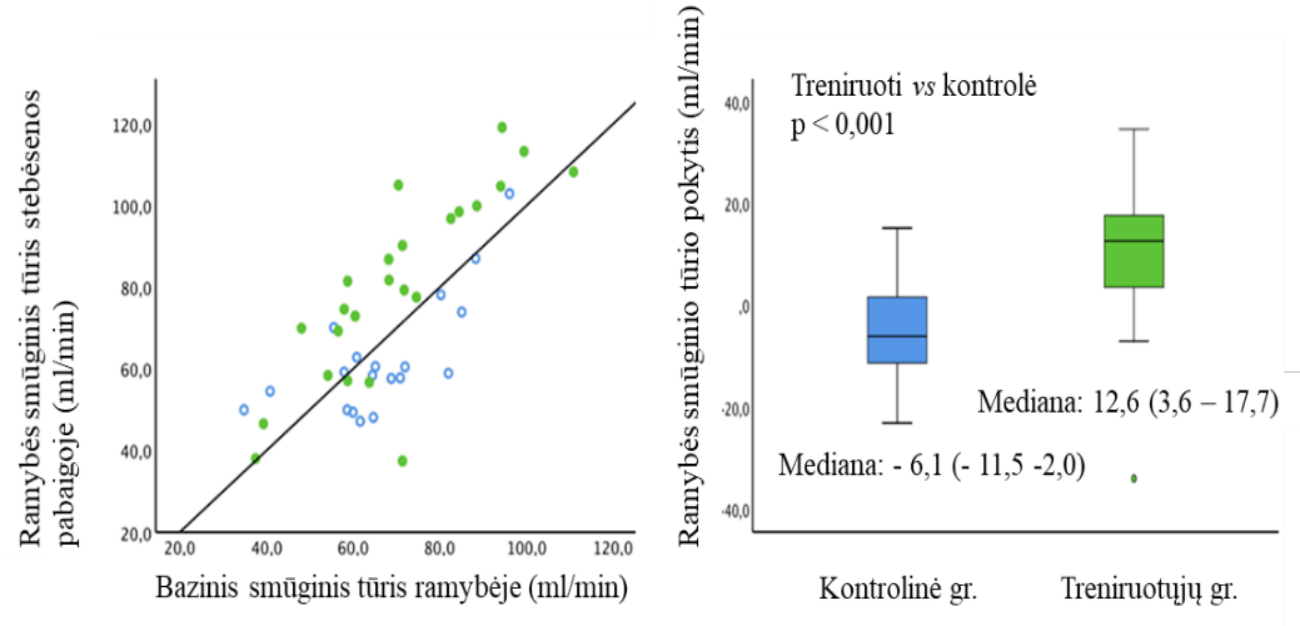
Į saugumo vertinimo analizę įtraukti 99 pacientai. Iš viso buvo stebėti 52 nepageidaujami reiškiniai (27 treniruočių ir 25 kontrolinėje grupėse) 21-am pacientui (13 iš treniruočių ir 8 iš kontrolinės grupių). Nepageidaujamų reakcijų, kurių dažnis ≥ 5 %, ir sunkių nepageidaujamų reakcijų dažnis abiejose grupėse buvo panašus (**4 lentelė**). Nė vienas nepageidaujamas poveikis nebuvo susijęs su tyrimo intervencija.

4 lentelė. Nepageidaujami poveikiai, kurių pasireiškimo dažnis ≥ 5 %, ir sunkūs nepageidaujami poveikiai

	Grupė		
Nepageidaujamas poveikis	**Kontrolinė (n = 47)**	**Treniruočių (n = 52)**	**Iš viso (n = 99)**
Bet kokia aritmija	5	3	8
Kvėpavimo takų infekcija	3	4	7
Iš viso	8	7	15
Sunkus nepageidaujamas poveikis			
Diabeto dekompensacija	0	1	1
Generalizuota edema	0	1	1
Hemoptizė	1	0	1
Insultas	0	1	1
Iš viso	1	3	4

Prekapiliarinės PH reabilitacijos hemodinaminės analizės rezultatai

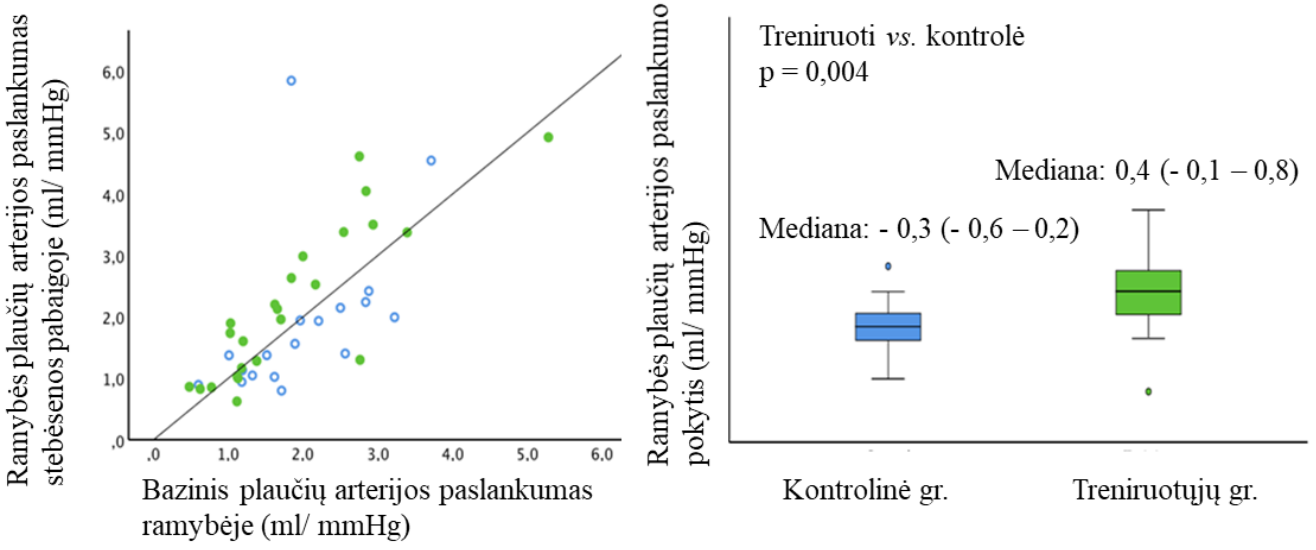
Duomenys išvestinių hemodinamikos rodiklių *post hoc* analizei buvo paimti iš ankstesnio RKT, vykdyto 2010 m. birželio–2015 m. gegužės mėnesiais (Heidelbergo universiteto duomenų bazė) [51]. Į šią *post hoc* analizę įtraukti 43 pacientai (24 iš treniruočių ir 19 iš kontrolinės grupių). Po 15 sav. stebėsenos laikotarpio ramybės smūginis tūris ir plaučių arterijos paslankumas reikšmingai labiau pagerėjo treniruotų pacientų grupėje, palyginti su kontroline grupe (**6 paveikslas; 7 paveikslas**).



6 pav. Smūginio tūrio pokytis ramybėje po 15 savaičių stebėjimo laikotarpio prekapiliarinės PH reabilitacijos tyrimo *post hoc* analizėje

Žalia spalva – treniruoti pacientai; mėlyna spalva – kontrolinė grupė.

Perspausdinta leidus S. Karger AG, Bazelis (III publikacija).



7 pav. Plaučių arterijos paslankumo pokytis ramybėje po 15 savaičių stebėjimo laikotarpio prekapiliarinės PH reabilitacijos tyrimo *post hoc* analizėje

Žalia spalva – treniruoti pacientai; mėlyna spalva – kontrolinė grupė.

Perspausdinta leidus S. Karger AG, Bazelis (III publikacija).

II. POKAPILIARINĖS PH REABILITACIJOS TYRIMAS

Pirmiausia atlikome sisteminę literatūros apžvalgą, siekdami įvertinti fizinio treniravimo / fizioterapijos poveikį pacientų, sergančių iIFŠN, širdies ir plaučių kraujotakos morfologiniams bei funkciniams parametrams. Tikėjomės, kad gauta informacija bus naudinga ieškant tinkamiausių PH-iIFŠN reabilitacijos programos komponentų.

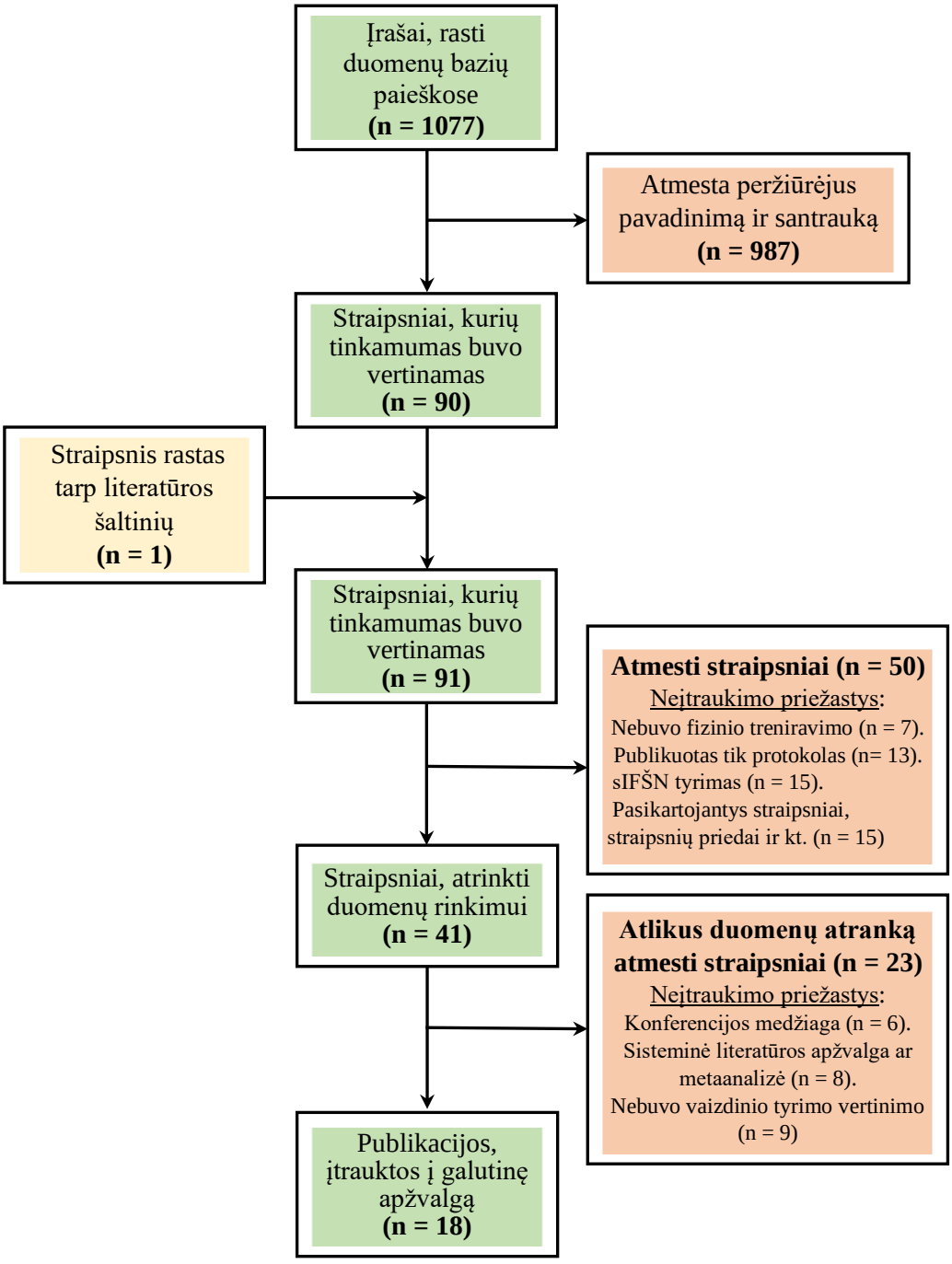
Kadangi neradome tyrimų, vertinusių fizinio treniravimo poveikį būtent PH-iIFŠN pacientų populiacijoje, nusprendėme sistemingai apžvelgti iIFŠN ligonių reabilitacijos studijas ir įvertinti, ar ir kaip skirtingos reabilitacijos priemonės bei metodikos keičia kairiojo skilvelio (KS) ir dešiniojo skilvelio (DS) diastolinės ir sistolinės funkcijos parametrus, širdies ertmių tūrius ir matmenis bei slėgį plaučių arterijoje ir dešiniajame prieširdyje.

Kitu etapu, remdamiesi prekapiliarinės PH reabilitacijos patirtimi ir iIFŠN sisteminės literatūros apžvalgos rezultatais, sukūrėme pokapiliarinės PH (PH-iIFŠN) reabilitacijos protokolą prospektyvinei daugiacentrei atsitiktinių imčių kontroliuojamai studijai. Protokolo bandomosios procedūros pradėtos Vilniaus universitete prieš COVID-19 pandemiją.

Sisteminė literatūros apžvalga

Cochrane Library ir *MEDLINE/PubMed* bibliografinėse duomenų bazėse atlikta išsami literatūros paieška. Ieškojome visų dizainų klinikinių tyrimų, publikuotų iki 2021 m. kovo mėnesio, kuriuose buvo vertinamas bet kokios rūšies fizinio treniravimo ir (ar) fizioterapijos poveikis iIFŠN (apibrėžtas kaip KS IF $\geq$ 45 %) sergančių pacientų echokardiografijos, širdies magnetinio rezonanso tomografijos ar invaziškai išmatuotiems hemodinamikos parametrams.

Kiekvieną publikacijos pavadinimą bei santrauką nepriklausomai vertino du recenzentai, vadovaudamiesi PRISMA (angl. *preferred reporting items for systematic reviews and meta-analyses*) pareiškimu [148]. Tie patys recenzentai, naudodami iš anksto parengtas duomenų rinkimo formas, surinko informaciją iš atitinkamų straipsnių. Duomenų šaltinių atrankos procesas schemiškai pavaizduotas **8 paveiksle**.



8 pav. Duomenų šaltinių atrankos į sisteminę literatūros apžvalgą srauto diagrama

Sisteminės literatūros apžvalgos rezultatai

Sisteminės literatūros apžvalgos analizei surinkome 9 atsitiktinių imčių kontroliuojamų tyrimų (RKT), 5 atsitiktinių imčių lygiagrečių grupių tyrimų (nekontroliuojamų, visi pacientai treniruoti, tačiau buvo naudojami skirtingi treniravimo protokolai) ir 4 stebėjimo tyrimų duomenis; iš viso įtraukta 18 publikacijų. Daugumos tyrimų imtis buvo nedidelė – tik keturiuose iš aštuoniolikos tyrimų buvo treniruoti > 25 pacientai. Iš viso į sisteminę apžvalgą įtraukta 418 treniruotų pacientų (vidutinis amžius nuo 60,0 iki 75,0 metų, 57 % buvo moterys, intervencijos trukmė svyravo nuo 4 iki 52 savaičių). Atskiruose klinikiniuose tyrimuose buvo naudojami skirtingi fizinio treniravimo ir (arba) fizioterapijos programų protokolai. Visose studijose aprašomas treniravimas vyko ambulatorinėmis sąlygomis ir daugumoje jų (16/18) treniruotes prižiūrėjo sveikatos priežiūros specialistai. Vienuolikoje publikuotų straipsnių nurodyta, kad atlikto tyrimo fizinio treniravimo programą sudarė tik ištvermės treniruotės, keturiuose ištvermės treniruotės derintos su jėgos treniruotėmis, dviejuose buvo taikomos pasipriešinimo treniruotės, viename iš šių pridėta funkcinė elektrinė stimuliacija (FES), o viename tyrime naudota tik FES. **5 lentelėje** apibendrinti atskirų publikuotų tyrimų rezultatai kartu su taikytomis reabilitacijos priemonėmis ir kitomis klinikinio tyrimo charakteristikomis. Studijų, kuriose buvo vertinamas konkretus echokardiografinis parametras, bei treniruotų pacientų skaičius nurodyti **6 lentelėje**.

Penkiuose iš devynių RKT, keturiuose iš penkių atsitiktinių imčių lygiagrečių grupių tyrimų ir trijuose iš keturių stebėjimo tyrimų nustatyta, kad fizinis treniravimas reikšmingai keitė skirtingus echokardiografinius parametrus, o likusiuose šešiuose tyrimuose echokardiografinių parametrų reikšmingų pokyčių nenustatyta **(5 lentelė).**

Reikšmingas mitralinio E/e' santykio sumažėjimas po treniruočių aptiktas 5 iš 12 tyrimų (nuo –1,2 iki –4,9); reikšmingas kairiojo prieširdžio tūrio indekso (KPTI) sumažėjimas nustatytas 3 iš 7 tyrimų (nuo –3,7 iki –8 ml/m2). Fizinio krūvio treniruočių poveikio minutiniam širdies tūriui (MŠT) vertinimas atskleidė prieštaringus rezultatus: viename nedidelės imties (n = 12), geros kokybės tyrime po 16 sav. ištvermės treniruočių MŠT pagerėjo 24,5 %[135], o kitas panašios trukmės ištvermės treniruočių taikymo, vidutinės kokybės, vyresnio amžiaus pacientų (n = 22) tyrimas reikšmingo poveikio MŠT neparodė [140].

Fizinio treniravimo įtaka DS funkcijai buvo vertinta tik viename tyrime [127]. Šiame tyrime DS globali išilginė deformacija (DS-GLS) ir

išilginės deformacijos greitis (DS-GSR) buvo vertinami prieš 4 sav. didelio intensyvumo intervalines treniruotes (DIIT) (n = 9) ir vidutinio intensyvumo tęstines treniruotes (VITT) (n = 6) ir po tokių treniruočių. DIIT grupės pacientų DS-GLS padidėjo 3 % (nuo –18,4 ± 3,2 iki –21,4 ± 1,7), p = 0,02. Šių parametrų pokyčiai VITT pacientų grupėje buvo nereikšmingi.

Nė viename iš aštuoniolikos tyrimų, atitikusių įtraukimo kriterijus, nebuvo vertinamas fizinės reabilitacijos poveikis širdies magnetinio rezonanso tomografijos parametrams.

Invaziniai hemodinaminiai matavimai buvo vertinti tik viename labai mažos imties (n = 7) prastos kokybės tyrime, kuris atskleidė, kad iIFŠN pacientams fizinio krūvio treniruotės neturėjo įtakos PPS (16,1 ± 5,6 mmHg prieš treniravimą *vs* 15,2 ± 3,6 mmHg po 12 mėnesių treniruočių, p = 0,65) [156].

5 lentelė. Atrinktų ir į sisteminę literatūros apžvalgą įtrauktų straipsnių apžvalga [149]

Tyrimas ***(autorius, metai)***	**Treniravimo trukmė** ***(sav.)***	**Intervencija**	**Treniruoti pacientai** ***(N; vidutinis amžius, metais; vyriškoji lytis, N (%))***	**Vertinti echokardiografiniai parametrai**	**Reikšmingi konkrečių echokardiografinių parametrų pokyčiai**
Atsitiktinių imčių kontroliuojami tyrimai (N = 9)					
Kitzman et al., 2010 [132]	16	Ambulatorinės, prižiūrimos ištvermės treniruotės; 60 min. 3 k./sav.	N = 26; amžius = 70 ± 6; vyrai 6 (23,1 %). *Galutinėje analizėje – 24 pacientai*	KS IF, E, A, E/A, DecT, IVRT, KSM, KST, ST	Reikšmingų vertintų echokardiografinių parametrų pokyčių nebuvo
Edelmann et al., 2011 [130]	12	Ambulatorinės, prižiūrimos ištvermės treniruotės (nuo 5 sav. papildytos pasipriešinimo treniruotėmis); 40 min. 3 k./sav.	N = 44; amžius = 64 ± 8; vyrai 20 (45,5 %)	KS IF, e' (medialinis), E/e' (medialinis), S/D santykis, KPTI, KSMI, KSTI	↓**E/e'** nuo 12,8 ± 3,2 iki 10,5 ± 2,5, pokytis –2,3 (–3,0 – 1,6), p < 0,001; skirtumas tarp grupių –3,2 (–4,3 – 2,1) p < 0,001 ↑**e'** nuo 5,4 ± 1,2 iki 6,3 ± 1,3, pokytis 0,9 (0,6 – 1,1), p < 0,001; skirtumas tarp grupių 1,2 (0,8 – 1,7) p < 0,001 ↓**KPTI** nuo 27,9 ± 7,6 iki 24,3 ± 6,5, pokytis –3,7 (–4,9 –2.4), p < 0,001; skirtumas tarp grupių –4,0 (–5,9 –2,2) p < 0,001
Alves et al., 2012 [133]	26	Ambulatorinės, prižiūrimos ištvermės treniruotės; 35 min. 3 k./sav.	N = 20; amžius = 62,9 ± 10,2; vyrai 22 (71 %). *Vidutinis amžius ir lyčių pasiskirstymas visoje imtyje*	KS IF, E/A, DecT, KS matmenys (GDS, GSS)	↑**KS IF** nuo 56,4 iki 57,7, pokytis 1,3 % p = 0,01 ↑**E/A** nuo 0,93 iki 1,05, p < 0,001 ↓**DecT** nuo 236,7 iki 222,7, p < 0,001
Smart et al., 2012 [135]	16	Ambulatorinės, prižiūrimos ištvermės treniruotės;	N = 12; amžius = 67 ± 5,8;	KS IF, E, A, E/A, E/e' (neapibrėžta), DecT, s',	↑**MŠT** nuo 5,7 ± 2,7 iki 7,1 ± 3,1, pokytis 1,4, p = 0,04

		30 min. 3 k./sav.	vyrai 7 (58,3 %)	e', ST, MŠT, KS-GLS, KS-GSR			
Haykowsky et al., 2012 [140]	17	Ambulatorinės, prižiūrimos ištvermės treniruotės; 60 min. 3 k./sav.	N = 22; amžius = 70 ± 6; vyrai 4 (18,2 %)	KST, ST, MŠT	Reikšmingų vertintų echokardiografinių parametrų pokyčių nebuvo		
Karavidas et al., 2013 [150]	6	Ambulatorinė fizioterapija (funkcinė apatinių galūnių raumenų elektrostimuliacija); 30 min. 5 k./sav.	N = 15; amžius = 69,4 ± 8,6; vyrai 6 (40,0 %)	E, A, E/A, E/e' (neapibrėžta), DecT, KPT	Reikšmingų vertintų echokardiografinių parametrų pokyčių nebuvo		
Kitzman et al., 2013 [64]	16	Ambulatorinės, prižiūrimos ištvermės treniruotės; 60 min. 3 k./sav.	N = 32; amžius = 70 ± 7; vyrai 9 (28,1 %). *Galutinėje analizėje – 24 pacientai*	KS IF, E, A, E/A, DecT, IVRT, KST, ST	Reikšmingų vertintų echokardiografinių parametrų pokyčių nebuvo		
Palau et al., 2014 [151]	12	Namuose, be priežiūros, kvėpavimo raumenų treniruotės; 20 min. 2 k./d.	N = 14; amžius = 68 [60–76]; vyrai 7 (50,0 %)	KS IF, e' (medialinis), E/e' (medialinis), KPTI, KSMI	Reikšmingų vertintų echokardiografinių parametrų pokyčių nebuvo		
Palau et al., 2017 [126]	12	Namuose, be priežiūros, kvėpavimo raumenų treniruotės (KvRT); 20 min. 2 k./d Ambulatorinė fizioterapija (funkcinė apatinių galūnių raumenų elektrostimuliacija); 45 min. 2 k./sav.	KvRT (įtraukiant): N = 15; amžius = 75 ± 10; vyrai 7 (46,7 %) FES (įtraukiant): N = 15; amžius = 72 ± 9; vyrai 6 (40,0 %) KvRT + FES	E/e' (neapibrėžta), KPTI	**KvRT**: <u>Po 12 sav.:</u> **↓E/e'** nuo 18,4 [14,4–28,0] iki 17,2 [12,4–23,1], p = 0,015. <u>Po 24 sav.[3]:</u>	**FES**: <u>Po 12 sav.:</u> **↓E/e'** nuo 20,5 [12–26,4] iki 15,7 [11,8–21,8], p = 0,001. <u>Po 24 sav.[3]:</u> Reikšmingų	**KvRT + FES:** <u>Po 12 sav.:</u> Reikšmingų pokyčių nebuvo. <u>Po 24 sav.[3]:</u> Reikšmingų

			(įtraukiant): N = 16; amžius = 73 ± 10; vyrai 8 (50 %). *Galutinėje analizėje kiekvienoje grupėje po 13 pacientų*		**↓KPTI** nuo 39 ± 11 iki 31 ± 11, p = 0,008	pokyčių nebuvo	pokyčių nebuvo
Atsitiktinių imčių lygiagrečių grupių tyrimai (N = 5)							
Yeh et al., 2013 [152]	12	Ambulatorinėmis ir namų sąlygomis vykdomos ištvermės treniruotės (AT) lygintos su Tai či treniruotėmis. Prižiūrimos 60 min. 2 k./sav. + treniruotės namuose 35 min. 3k./sav.	AT: N = 8; amžius = 63 ± 11; vyrai 4 (50,0 %). Tai či: N = 8; amžius = 68 ± 11; vyrai 4 (50,0 %)	KS IF, E/A, E/e' (neapibrėžta), KP matmenys, KPT	**Tai či**[#]: ↓KP matmenys labiau sumažėjo Tai či gr. (nuo 3,8 ± 0,4 iki 3,7 ± 0,3), palyginti su AT (nuo 3,7 ± 0,3 iki 3,8 ± 0,3), p = 0,04		**AT**[#]: ↓E/e' labiau pagerėjo AT gr. (nuo 17 ± 4 iki 14 ± 4), palyginti su Tai či gr. (nuo 14 ± 4 iki 13 ± 5), p = 0.01
Angadi et al., 2015 [138]	4	Ambulatorinės, prižiūrimos ištvermės treniruotės; 45 min. 3 k./sav.	DIIT: N = 9; amžius = 69,0 ± 6,1; vyrai 8 (88,9 %) VITT: N = 6; amžius = 71,5±11,7; vyrai 4 (66,7 %)	KS IF, E, A, e' (medialinis), E/A, E/e' (medialinis), DecT, IVRT, diastolinės disfunkcijos laipsnis[1], diastolinės disfunkcijos laipsnių pasiskirstymas[2], KPTI	**DIIT:** **↓Diastolinės disfunkcijos laipsnis*** nuo 2,1 ± 0,3 iki 1,3 ± 0,7, p < 0,01 **↓E nuo** 0,9 ± 0,3 iki 0,8 ± 0,3, p = 0,02 **↑DecT** nuo 194 ± 55 iki 225 ± 40, p = 0,02		**VITT:** reikšmingų pokyčių nebuvoa
Angadi et al., 2017 [127]**	4	Ambulatorinės, prižiūrimos ištvermės treniruotės; 45 min. 3 k./sav.	DIIT: N = 9; amžius = 69 ± 6,1; vyrai 8 (88,9 %)	KS IF, KSM, KSMI, ST, STI, DS-GLS, DS-GSR, KS-GLS, KS-	**DIIT:** **↑DS-GLS** nuo –18,4 ± 3,2 iki –21,4 ± 1,7, p = 0,02		**VITT:** reikšmingų pokyčių

			VITT: N = 6; amžius = 71,5±11,7; vyrai 4 (66,7 %)	GSR		nebuvo
Silveira et al., 2020 [153]	12	Ambulatorinės, prižiūrimos ištvermės treniruotės; 38 min. (DIIT), 47 min. (VITT) 3 k./sav.	DIIT: N = 10; amžius = 60 ± 10; vyrai 3 (30,0 %) VITT: N = 9; amžius = 60 ± 9; vyrai 4 (44,4 %)	KS IF, E, A, e' (vidutinis), E/A , E/e' (vidutinis), DecT, KS matmenys (GDS, GSS), KPTI, KSM, KSTI, KP skersmuo, STI	**DIIT:** **↓E/e'** nuo 13,3 ± 3 iki 11,1 ± 2, p < 0,001	**VITT:** **↓E/e'** nuo 14,2 ± 4 iki 11,6 ± 3, p < 0,001
Mueller et al., 2020 [154]	52	Ambulatorinės, prižiūrimos (3 mėn.), paskui tęsiamas namuose be priežiūros (kitus 9 mėn.) ištvermės treniruotės; 38 min. (DIIT), 47 min. (VITT) 3 k./sav.	DIIT: N = 58; amžius = 70 ± 7; vyrai 17 (29,3 %) VITT: N = 58; amžius = 70 ± 8; vyrai 23 (39,7 %). *Galutinėje analizėje: 47 pacientai DIIT, 52 pacientai VITT*	E/e' (medialinis), e' (medialinis), KPTI	Lyginant DIIT, VITT ir kontrolinę grupes, reikšmingų vertintų echokardiografinių parametrų pokyčių neaptikta [#]	
Stebėjimo tyrimai (N = 4)						
Smart et al., 2007 [155]	16	Ambulatorinės, prižiūrimos ištvermės treniruotės (nuo 8 sav. papildytos pasipriešinimo treniruotėmis); 60 min. 3 k./sav.	N = 18; amžius = 65 ± 5; vyrai 9 (50,0 %)	KS IF, E, A, s', e' (vidutinis), E/A, E/e' (vidutinis), DecT, KST, KS-GLS, KS-GSR, ST	Reikšmingų vertintų echokardiografinių parametrų pokyčių nebuvo	
Fujimoto et al., 2012 [156]	52	Ambulatorinės, prižiūrimos ištvermės treniruotės; 40 min. 3 k./sav.	N = 7; amžius = 74,9 ± 6; vyrai 3 (42,9 %)	KS IF, E, A, e' (vidutinis), a', E/A, IVRT, KST, KSTI	**↑E/A** nuo 0,75 ± 0,11 iki 0,89 ± 0,14, p = 0,03	

Nolte et al., 2014 [157]*	24	Ambulatorinės, prižiūrimos ištvermės treniruotės (nuo 5-os savaitės papildytos pasipriešinimo treniruotėmis); 30–35 min.; 3 k./sav.	N = 24; amžius = 62 ± 7; vyrai 15 (62,5 %)	KS IF, e' (medialinis), E/e' (medialinis), S/D santykis, KPTI, KSMI, KSTI	↓**E/e'** nuo 12,2 ± 3,5 iki 10,1 ± 3,0, pokytis –2,1 (–3,3 –0,9), p = 0,002 ↑**e'** nuo 5,9 ± 1,3 iki 6,8 ± 1,4, pokytis 0,9 (0,4 – 1,4), p = 0,001 ↓**KPTI** nuo 30,0 ± 7,9 iki 25,1 ± 8,7, pokytis –4.9 (–6,7 –3,2), p < 0,001
Fu et al., 2016 [139]	12	Ambulatorinės, prižiūrimos ištvermės treniruotės; 30 min. 3 k./sav.	N = 30; amžius = 60,5 ± 2,7; vyrai 20 (66,7 %)	KS IF, E/A, E/e'(medialinis), KS matmenys (GDS, GSS)	↓**E/e'** (medialinis) nuo 21,0 ± 2,2 iki 16,1 ± 1,8, p < 0,05

Duomenys pateikti skaičiumi, vidurkiu ± standartiniu nuokrypiu, mediana [tarpkvartilinis intervalas].

#p vertės, lyginant pokyčius tarp grupių (pokyčiai prieš intervenciją ir po jos atskirose grupėse nepublikuoti).

[1] Naudoti 4 diastolinės disfunkcijos laipsniai (0 – nėra diastolinės disfunkcijos, 1 – sutrikusi KS relaksacija, 2 – pseudonormali diastolinė f-ja, 3 – restrikcinis KS prisipildymas).

[2] Pacientų skaičius kiekvienoje iš 4 diastolinės disfunkcijos grupių.

[3] Siekiant įvertinti 12 sav. treniravimo rezultatų tvarumą, stebėjimas buvo pratęstas iki 24 savaičių.

*Į šią studiją įtraukti tie patys pacientai, kurie dalyvavo ankstesnėje studijoje Edelmann et al. (2011) (24). Autoriai abiejuose straipsniuose pateikė tuos pačius duomenis apie treniruojamos grupės pokyčius po 12 sav. treniruočių, tačiau šis straipsnis buvo papildytas duomenimis po ilgesnio treniruočių laikotarpio (24 sav.).

** Į šią studiją įtraukti tie patys pacientai, kurie dalyvavo ankstesniame tyrime Angadi et al., 2015 (34), bet analizė papildyta išilginės deformacijos parametrų vertinimu.

Santrumpos: A (m/s) – vėlyvasis mitralinis įtekėjimo greitis; a (m/s) – mitralinio žiedo vėlyvasis diastolinis greitis, įvertintas audinių dopleriu; AT – aerobinė treniruotė; CO (l/min.) – minutinis širdies tūris; DecT (ms) – mitralinės tėkmės E bangos lėtėjimo laikas; E (m/s) – ankstyvasis mitralinio įtekėjimo greitis; e' (m/s) – mitralinio žiedo ankstyvasis diastolinis greitis, įvertintas audinių dopleriu; E/A – E ir A santykis; GDS (mm) – galinis diastolinis skersmuo; E/e' – E ir e' santykis; FES – funkcinė elektrinė stimuliacija; KS – kairysis skilvelis; DS – dešinysis skilvelis; IF (%) – išstūmio frakcija; GSS (mm) – galinis sistolinis skersmuo; DIIT – didelio intensyvumo intervalinė treniruotė; KRT – kvėpavimo raumenų treniruotė; IVRT (ms) – izovoliuminės relaksacijos laikas; KP – kairysis prieširdis; KP matmenys (cm) – vertinimas nebuvo aiškiai apibrėžtas; KPT (ml) – kairiojo prieširdžio tūris; KPTI (ml/m^2) – KP indeksuotas tūris; KS-GLS (%) – KS globali išilginė deformacija; KS-GSR (s^{-1}) – KS globalus išilginės deformacijos greitis; KSM (g) – KS masė; KSMI (g/m^2) – KS masės indeksas; KST (ml) – KS tūris; KSTI (ml/m^2) – KS tūrio indeksas; VITT – vidutinio intensyvumo tęstinė treniruotė; DS-GLS (%) – DS globali išilginė deformacija; DS-GSR (s^{-1}) – DS globalus išilginės deformacijos greitis; s'(m/s) – audinių doplerio mitralinio žiedo sistolinis greitis; ST (ml) – smūginis tūris; STI (ml/m^2) – smūginio tūrio indeksas.

6 lentelė. Echokardiografiniai parametrai, vertinti į apžvalgą įtrauktuose tyrimuose

Echokardiografinis parametras	Tyrimų, kuriuose įvertintas šis parametras, skaičius	Treniruotų pacientų, kuriems įvertintas šis parametras, skaičius
KS IF	14	292
E/e'	12	330
E/e'(medialinis)	6	211
E/e' (vidutinis)	2	37
E/e' (neapibrėžta)	4	82
e'	9	261
e'(medialinis)	5	205
e' (vidutinis)	3	44
e'(neapibrėžta)	1	12
KPTI	7	250
E/A	11	210
E	8	144
A	8	144
E bangos DecT	8	144
KSMI	4	92
ST	6	113
KSTI	4	87
KS IVRT	4	80
STI	3	46
KS-GLS	3	45
KS-GRS	3	45
MŠT	2	34
KS s'	2	30
DS-GLS	1	15
DS-GSR	1	15
Parametrai, kurie tyrimuose <u>nebuvo vertinti</u>: DS diametras, PAS, TVŽPG, TVŽP, DS FPP, DP plotas, DP slėgis, ATV diametrai		

Santrumpos: A (m/s) – vėlyvasis mitralinis įtekėjimo greitis; a' (m/s) – mitralinio žiedo vėlyvasis diastolinis greitis, įvertintas audinių dopleriu; MŠT (l/min.) – minutinis širdies tūris; DecT (ms) – mitralinės tėkmės E bangos lėtėjimo laikas; E (m/s) – ankstyvasis mitralinio įtekėjimo greitis; e' (m/s) – mitralinio žiedo ankstyvasis diastolinis greitis, įvertintas audinių dopleriu; E/A – E ir A santykis; E/e' – E ir e' santykis; IF (%) – išstūmio frakcija; IVRT (ms) – izovoliuminės relaksacijos laikas; KP – kairysis prieširdis; KPTI (ml/m2) – KP indeksuotas tūris; KS-GLS (%) – KS globali išilginė deformacija; KS-GSR – KS globalus išilginės deformacijos greitis; KSMI (g/m2) – KS masės indeksas; KSTI (ml/m2) – KS tūrio indeksas; DS-GLS (%) – DS globali išilginė deformacija; DS-GSR – DS globalus išilginės deformacijos greitis; s'(m/s) – audinių doplerio mitralinio žiedo sistolinis greitis; ST (ml) – smūginis tūris; STI (ml/m2) – smūginio tūrio indeksas; DP – dešinysis prieširdis; PAS (mmHg) – plaučių arterijos spaudimas; TVŽPG (mm/s) – triburio vožtuvo žiedo poslinkio greitis; TVŽP (mm) – triburio vožtuvo žiedo poslinkis; FPP – frakcinis ploto pokytis; ATV – apatinė tuščioji vena.

PH – iIFŠN tyrimo protokolo kūrimas ir bandomosios procedūros

Nusprendėme sukurti protokolą prospektyviniam atsitiktinių imčių (1:1), įprasta gydymo taktika kontroliuojamam daugiacentriam tyrimui.

Tyrimo klausimas, kurį iškėlėme rengiamam studijos protokolui: ar fizinio treniravimo treniruotės yra saugios ir gali pagerinti fizinį pajėgumą, su sveikata susijusią gyvenimo kokybę, diastolinę širdies funkciją, hemodinamiką ir biožymenis pacientams, sergantiems PH-iIFŠN.

Šios studijos pirminė vertinamoji baigtis – treniravimo poveikis fizinio pajėgumo pokyčiui, išmatuotam pagal 6 MĖT distanciją (pradinis ir po 15 sav.), palyginti su kontroline grupe PH-iIFŠN pacientų populiacijoje.

Antrinės vertinamosios baigtys apims šiuos parametrus, lyginant treniruojamą ir kontrolinę grupes:

a. Echokardiografiniai parametrai.

b. Kardiopulmoninio krūvio mėginio rodikliai.

c. PSO funkcinė klasė.

d. Saugumo parametrai.

e. Su sveikata susijusi gyvenimo kokybė (panaudojant SF-36 klausimyną).

f. Nerimas ir depresija (panaudojant HADS vertinimo skalę).

g. Dešiniųjų širdies ertmių manometrijos rodikliai ramybėje ir fizinio krūvio metu.

h. Širdies magnetinio rezonanso tomografijos rodikliai.

Siekiant įvertinti fizinio treniravimo poveikį 6 MĖT distancijai, planuojama į tyrimą įtraukti 90 pacientų, kurie 15 sav. šalia optimalaus medikamentinio gydymo arba dalyvaus reabilitacijos programoje (intervencinė gr.), arba jų fizinis aktyvumas bus įprastas, be specifinių rekomendacijų (kontrolinė gr.). Imties dydis apskaičiuotas programa G*Power 3.1.

Efektyvumo parametrai abiejose grupėse bus vertinami pradžioje ir po 15 sav. stebėsenos laikotarpio. Intervencinės grupės pacientai papildomai atliks 6 MĖT stacionarinio reabilitacijos etapo pabaigoje.

PH-iIFŠN diagnozė bus nustatoma vadovaujantis EKD/ERA gairėmis [5, 6, 21, 36]. Kiti tinkamumo kriterijai pateikti **7 lentelėje**.

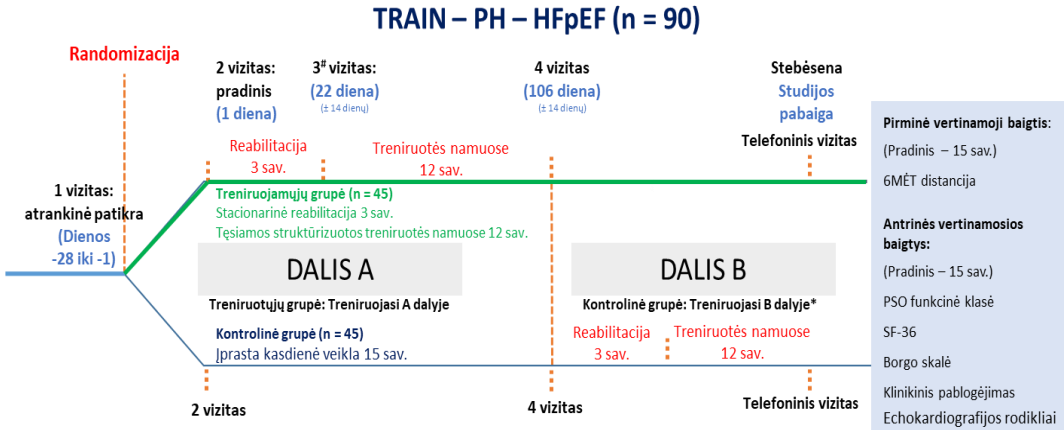
7 lentelė. Tiriamųjų įtraukimo į daugiacentrį pokapiliarinės PH reabilitacijos tyrimą tinkamumo kriterijai

ĮTRAUKIMO KRITERIJAI	ATMETIMO KRITERIJAI
1. Moterys ir vyrai ≥ 18 m. 2. PSO funkcinė klasė II–IV. 3. Pokapiliarinė PH diagnozuota pagal DŠEM rodiklius: a) Vid. PAP ≥ 25 mmHg; b) PPS ≥ 15 mmHg arba KSGDS ≥ 16 mmHg ramybėje arba PPS ≥ 25 mmHg fizinio krūvio metu. 4. Išsaugota KS sistolinė f-ja, KS IF ≥ 50 % (echokardiografiškai arba širdies MRT). 5. ≥ 1 mėn. iki įtraukimo į tyrimą taikomas optimalus medikamentinis gydymas. 6. Tikimasi, kad medikamentinio gydymo (išskyrus diuretikus) nereikės koreguoti per 15 studijos savaičių. 7. Pacientas geba suprasti ir sutinka pasirašyti informuoto sutikimo formą	1. Prekapiliarinė PH 2. Įgimtos arba įgytos reikšmingos vožtuvų ligos (*didelio laipsnio aortos vožtuvo stenozė ar nesandarumas, didelio laipsnio mitralinio vožtuvo stenozė ar nesandarumas).* 3. Miokarditas, ūmus koronarinis sindromas, fizinio krūvio provokuojami skilveliniai ritmo sutrikimai, aktyvi kepenų liga. 4. Sunki plaučių liga: FEV1/FVC < 0,5 ir TLC < 70 % normos. 5. Suplanuotas dalyvavimas kitoje intervencinėje studijoje. 6. Vaikščiojimo negalia. 7. Hemoglobino koncentracija < 75 % apatinės normos ribose. 8. Sistolinė hipotenzija < 85 mmHg. 9. Nėštumas. 10. Nujautimas, kad tiriamasis negebės tinkamai bendradarbiauti

Mūsų atlikta sisteminė literatūros apžvalga neleido padaryti patikimų išvadų apie konkrečios reabilitacinės priemonės didesnę naudą PH-iIFŠN sergantiems pacientams, todėl nusprendėme kaip tiriamąją intervenciją naudoti nemodifikuotą specializuotą Heidelbergo PH reabilitacijos programą (aprašyta pirmiau).

PH-iIFŠN rezultatai

Detali sukurto PH-iIFŠN tyrimo protokolo schema pateikta **9 paveiksle**.



Pirminė vertinamoji baigtis:
(Pradinis – 15 sav.)
6MĖT distancija

Antrinės vertinamosios baigtys:
(Pradinis – 15 sav.)
PSO funkcinė klasė
SF-36
Borgo skalė
Klinikinis pablogėjimas
Echokardiografijos rodikliai
NTproBNP
Kardiopulmoninio krūvio mėginio parametrai
DŠEM parametrai*
Širdies MRT rodikliai*

1 vizitas: atrankinė patikra
Dienos -28 iki -1
Atrankiniai tyrimai

- Medicininė anamnezė
- Klinikinis įvertinimas
- Fizinis ištyrimas
- PSO funkcinė klasė
- 6MĖT
- FVC, TLC, DLCO
- Kraujo dujų analizė
- NTproBNP
- SF36, HADS skalės
- Echokardiografija
- Krūvio echokardiografija*
- Kardiopulmoninis krūvio mėginys
- DŠEM ramybėje ir fizinio krūvio metu*
- Širdies MRT*

2 vizitas: pradinis ištyrimas (1 diena)

2 vizitas: pradinis (abi grupės)

- Klinikinis įvertinimas
- Fizinis ištyrimas
- PSO funkcinė klasė
- 6MĖT
- TLC, DLCO
- Vaistai, NTproBNP
- SF36, HADS skalės
- Echokardiografija
- Krūvio echokardiografija*
- Kardiopulmoninis krūvio mėginys

3 vizitas (22 diena)

3 vizitas (# tik Treniruotųjų grupė)

- Klinikinis įvertinimas
- PSO funkcinė klasė
- 6MĖT

4 vizitas (106 diena) (± 14 dienų)

4 vizitas (abi grupės)

- Klinikinis įvertinimas
- Fizinis ištyrimas
- PSO funkcinė klasė
- 6MĖT
- TLC, DLCO
- Vaistai, NTproBNP
- SF36, HADS skalės
- Echokardiografija
- Krūvio echokardiografija*
- Kardiopulmoninis krūvio mėginys
- DŠEM ramybėje ir fizinio krūvio metu*
- Širdies MRT*

Stebėsena Studijos pabaiga

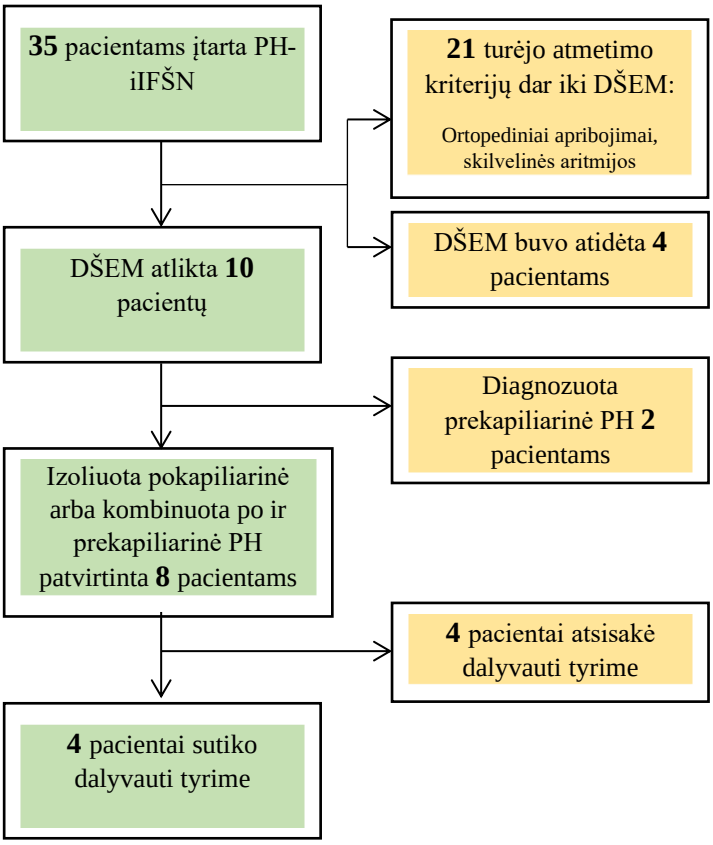
Telefoninis vizitas (abi grupės)

- Saugumas
- Rekomendacijų laikymasis
- Išgyvenamumas

9 paveikslas. Išsami tyrimo protokolo laiko juosta

PH-iIFŠN reabilitacijos bandomosios procedūros Vilniaus universitete atliktos vadovaujantis Helsinkio deklaracija, protokolą patvirtino Vilniaus regioninis biomedicininių tyrimų etikos komitetas (Nr. 2019/4-1118-611). Prieš įtraukiami į tyrimą visi pacientai davė raštišką informuoto asmens sutikimą.

Tyrimo kandidatai buvo atrinkti Vilniaus universiteto ligoninės Santaros klinikų Plautinės hipertenzijos kompetencijos centro gydytojo kardiologo konsultacijų metu. Nuo 2019 m. liepos– iki 2020 m. kovo 35 pacientams echokardiografiškai buvo įtarta PH-iIFŠN. Kaip parodyta **10 paveiksle**, keturi pacientai galiausiai buvo įtraukti į bandomąsias procedūras; vėliau tyrimas turėjo būti nutrauktas dėl COVID-19 pandemijos.



10 paveikslas. Tinkamų pacientų atranka pokapiliarinės PH reabilitacijos tyrime

Mūsų pradinė patirtis vertinant naujai sukurtą protokolą Vilniaus universitete parodė, kad jis gali būti saugus (nepastebėta jokių

nepageidaujamų reiškinių, susijusių su protokolo procedūromis) ir įgyvendinamas.

Pažymėtina, kad šio protokolo įgyvendinimas priklauso nuo nacionalinės sveikatos priežiūros sistemos ir įprastos klinikinės praktikos tyrimo centre. Kadangi reabilitacijos veiksmingumo vertinimas yra sudėtinis, o antrinės vertinamosios baigtys apima skirtingus diagnostinius tyrimus, kuriuos atliko atskiri tyrėjai, nebuvo lengva organizuoti visus tyrimus pagal numatytą tyrimo tvarkaraštį. Be to, atrinkti tinkamus pacientus taip pat nebuvo lengva, nes daugelis (20 iš 35) potencialių kandidatų turėjo vaikščiojimo negalią arba kitų ortopedinių apribojimų treniruotis; fizinio krūvio sukeltą skilvelinę aritmiją kaip atmetimo kriterijų atitiko 1 pacientas.

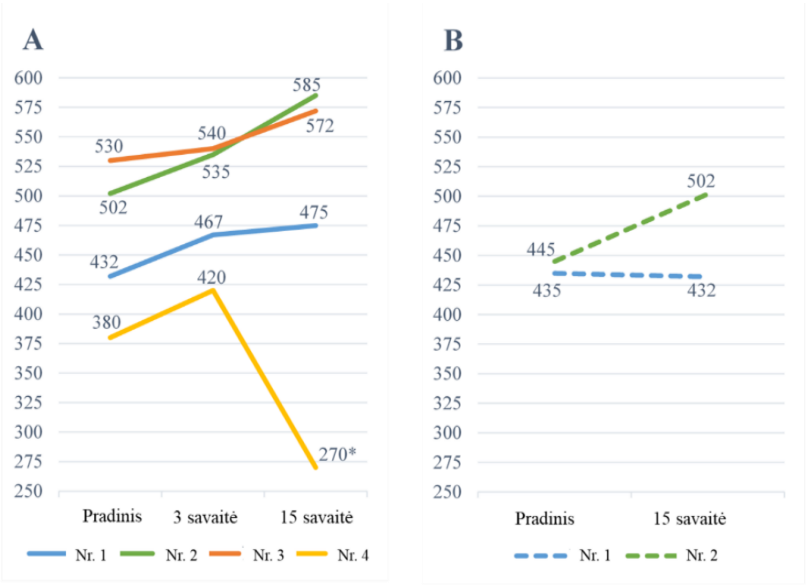
Į bandomąjį tyrimą buvo įtraukti keturi pacientai; du iš jų iš pradžių atsitiktinės atrankos būdu buvo priskirti kontrolinei grupei (*Pacientas Nr. 1* ir *Pacientas Nr. 2*), kiti du – intervencinei grupei (*Pacientas Nr. 3 ir Pacientas Nr. 4*). Po 15 sav. stebėjimo laikotarpio abu kontrolinės grupės pacientai dalyvavo treniruočių programoje ir tapo intervencinės grupės pacientais.

Intervencinės grupės pacientai

Pradinis reabilitacijos etapas stacionare visiems pacientams, išskyrus vieną, truko 18 d. *Pacientas 4* iš reabilitacijos klinikos išvyko po 15 d. (savo pageidavimu), be to, šis tiriamasis vienintelis nevykdė rekomendacijų mankštintis namuose – pristigus motyvacijos treniruotes nutraukė po kelių dienų gįžęs iš stacionaro.

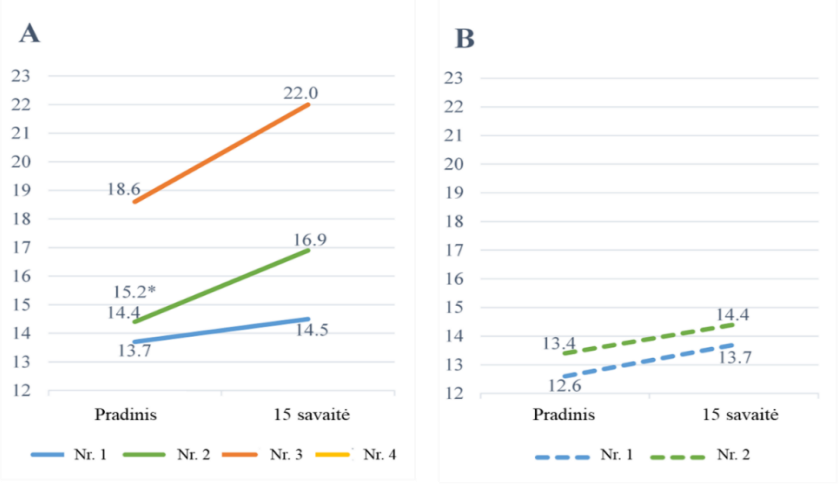
Jau pasibaigus pirmajam stacionariniam reabilitacijos etapui visų keturių treniruotų asmenų fizinis pajėgumas pagerėjo, o po 15 sav. stebėsenos laikotarpio pagerėjimas buvo dar didesnis tiems trims pacientams, kurie treniruotes tęsė ir namuose (11 paveikslas, 8 lentelė). Kadangi *Pacientas 4* namuose treniruočių netęsė, paprašėme jos atvykti anksčiau (11 stebėsenos sav.) – atlikus 6 MĖT stebėtas sumažėjęs fizinis pajėgumas (11 paveikslas), buvo padidintos diuretikų dozės ir suplanuotas papildomas vizitas po 1 mėn., tačiau prasidėjus COVID-19 pandemijai pacientė šį vizitą atšaukė.

Kardiopulmoninis fizinio krūvio mėginys taip pat parodė geresnį visų trijų pacientų fizinį pajėgumą po 15 sav. treniruočių (12 paveikslas; 9 lentelė).



11 paveikslas. 6 MĖT distancijos pokytis per stebėjimo laikotarpį (A – intervencinė grupė; B – kontrolinė grupė)

* – po 11 savaičių. *Pacientas 4* nustojo treniruotis praėjus kelioms dienoms po stacionarinio reabilitacijos etapo.



12 paveikslas. Pikinio VO_2 pokytis per stebėjimo laikotarpį (A – intervencinė grupė; B – kontrolinė grupė)

* *Pacientas 4 neatliko* kardiopulmoninio fizinio krūvio mėginio po 15 sav.

8 lentelė. Funkcinio pajėgumo, BNP, echokardiografinių parametrų ir gyvenimo kokybės pokyčiai 15 sav. stebėsenos laikotarpiu

Atsitiktinės atrankos grupė		INTERVENCIJA								KONTROLINĖ GRUPĖ			
PACIENTAS		*Pacientas 1*		*Pacientas 2*		*Pacientas 3*		*Pacientas 4*		*Pacientas 1*		*Pacientas 2*	
		Prieš	Po	Prieš	Po	Prieš	Po	Prieš	Po	Prieš	Po	Prieš	Po
Svoris (kg)		108	107	74	71	72	69	125	–	105	108	72	74
KMI (kg/m^2)		37,8	37,5	28,2	27,0	29,6	28,4	52,0	–	36,8	37,8	27,4	28,2
PSO funkcinė klasė		III	III	III	III	II	II	III	III	III	III	III	III
6 MĖT	*Distancija (m)*	432	475	502	585	530	572	380	270[a]	435	432	445	502
	Dusulio vertinimas pagal Borgo skalę prieš testą	0,5	0	0	0	0,5	0	0,5	3[a]	0	0,5	0	0
	Dusulio vertinimas pagal Borgo skalę 1 min, po ėjimo	3	2	3	2	4,5	2	5	8[a]	0,5	3	2	3
Ergospirometrija	*Maksimali apkrova (vatais)*	104	113	78	85	107	118	74	–	98	104	72	78
	Pikinis VO_2 (ml/kg/min ir %)	13,7 (55 %)	14,5 (58 %)	14,4 (72 %)	16,9 (85 %)	18,6 (73 %)	22,0 (87 %)	15,2 (52 %)	–	12,6 (51 %)	13,7 (55 %)	13,4 (66 %)	14,4 (72 %)
BNP (ng/l)		146,7	226,2	296,5	123,5	58,5	99,2	140,4	–	215,3	146,7	189,3	296,5
Echokardiografija	*sPAS (mmHg)*	65	47	40	33	34	36	50	–	40	65	37	40
	DP spaudimas (mmHg)	10	10	5	5	3	3	–	–	5	10	5	5
	PAV AcT (ms)	61	95	103	69	142	137	42	–	54	61	94	103
	TVŽP (cm)	2,2	2,0	1,5	2,2	2,8	2,3	1,4	–	1,6	2,2	2,2	1,5

	TVŽP greitis S' (cm/s)	15	13	11	15	15	13	11	–	16	15	12	11
	DS FPP (%)	40,1	41	37,8	37,5	49,7	50,7	30	–	43,2	40,1	38,2	37,8
	DP plotas (cm^2)	31,7	31,2	26,5	27,6	15,9	16,4	14,2	–	29,3	31,7	25,1	26,5
	KS IF (%)	57	56	56	56	68	62	57	–	57	57	58	56
	KPTI (ml/m^2)	41,7	52,9	113,0	92,6	38,4	44,1	35,0	–	43,6	41,7	115,0	113,0
	KSMI (g/m^2)	113,7	100,3	78,0	80,2	58,9	59,9	108,0	–	97,5	113,7	72,6	78,0
Gyvenimo kokybė (SF-36 fizinės sveikatos balas)[b]		46,25	82,5	31,25	23,13	55,63	58,13	56,25	–	44,38	46,25	18,75	31,25
Gyvenimo kokybė (SF-36 mentalinės sveikatos balas)[b]		65,71	62,42	69,92	48,25	33,25	57,92	54	–	64,46	65,71	50	69,92
HADS klausimynas (nerimas)[c]		0	2	8	8	11	6	8	–	4	0	8	8
HADS klausimynas (depresija)[c]		0	0	8	8	8	2	7	–	2	0	9	8

a – po 11 savaičių;

b – kiekviena skalė tiesiogiai transformuojama į skalę nuo 0 iki 100, darant prielaidą, kad kiekvienas klausimas turi vienodą svorį; kuo mažesnis balas, tuo didesnė negalia;

c – kiekvienos skalės balai nuo 0 iki 21; 0–7 = normalus, 8–10 = ribinis, 11–21 = padidėjęs.

SANTRUMPOS: 6 MĖT – 6 minučių ėjimo testas; KMI – kūno masės indeksas; HADS – nerimo ir depresijos skalė; KPTI – kairiojo pieširdžio tūrio indeksas; KS IF (%) – kairiojo skilvelio išstūmio frakcija; KS-GLS (%) – KS globali išilginė deformacija; KSMI (g/m2) – KS masės indeksas; PAV AcT (ms) – plaučių arterijos vožtuvo tėkmės pagreitėjimo laikas; DP – dešinysis prieširdis; DS – dešinysis skilvelis; FPP – frakcinis ploto pokytis; sPAP – sistolinis plaučių arterijos spaudimas; TVŽP (mm) – triburio vožtuvo žiedo poslinkis; TVŽPG (mm/s) – triburio vožtuvožiedo poslinkio greitis.

IŠVADOS

1. Prospektyvinė daugiacentrė atsitiktinių imčių studija atskleidė, kad specializuota reabilitacijos programa prekapiliarine PH sergantiems pacientams yra saugi ir efektyvi:

   a) Nepageidaujamų reiškinių ir sunkių nepageidaujamų reiškinių dažnis buvo panašus treniruotoje ir kontrolinėje grupėse.

   b) Palyginus treniruotą ir kontrolinę grupes, aptiktas teigiamas reabilitacijos programos poveikis šiems rodikliams: 6 MĖT distancijai, su sveikata susijusiai gyvenimo kokybei ir maksimaliam deguonies suvartojimui.

2. Norint įdiegti ir teikti PH reabilitacijos paslaugą, būtini vietiniai PH ekspertai, prieinamas optimalus PAH/PH gydymas, labiau šioje srityje patyrusių specialistų priežiūra, teikiamos stacionarinės reabilitacijos paslaugos, specialiai apmokytas personalas, gydymo išlaidų kompensacijos galimybė ir paciento motyvacija.

3. Specializuota PH reabilitacijos programa prekapiliarine PH sergantiems pacientams pagerina plaučių arterijų paslankumą ir smūginį širdies tūrį.

4. Nėra patikimų duomenų apie fizinio treniravimo poveikį KS, DS bei plaučių kraujotakos morfologiniams ir funkciniams parametrams iIFŠN sergantiems pacientams. Yra pradinių duomenų apie teigiamą reabilitacijos poveikį KS prisipildymo slėgio žymeniui E/e', kairiojo prieširdžio dydžiui, minutiniam širdies tūriui ir dešiniojo skilvelio deformacijai.

5. Mūsų sukurtas pokapiliarinės PH reabilitacijos daugiacentrio tyrimo protokolas yra pagrįstas esamu duomenų trūkumu, tiriamųjų tinkamumo kriterijais, nustatytais remiantis naujausiomis EKD/ERA gairėmis, ir teigiamais Heidelbergo prekapiliarinės PH reabilitacijos programos rezultatais. Pradiniai duomenys parodė, kad sukurtas protokolas gali būti saugus ir įgyvendinamas. Nors COVID-19 pandemija nutraukė tyrimą, šios įžvalgos skatina jį atnaujinti ateityje.

PRAKTINĖS REKOMENDACIJOS

1. Rekomenduojame PH reabilitaciją įtraukti į kompleksinę prekapiliarine PH (PAH ir LTEPH) sergančių pacientų priežiūrą, taikant treniravimą greta optimalaus medikamentinio gydymo, tam skirtuose PH ekspertų centruose ir patyrusiose reabilitacijos klinikose. Ši rekomendacija jau įtraukta į 2022 m. EKD/ERA gaires *(I klasės A lygio rekomendacija)*.

2. PH pacientų reabilitacijai siūlome naudoti standartizuotą „Heidelbergo PH reabilitacijos“ programą.

3. Skatiname diegti ir vykdyti PH reabilitacijos programą viename ar keliuose tam skirtuose centruose kiekvienoje šalyje. Siūlome naudoti mūsų ataskaitą apie esminius organizacinius aspektus, būtinuosius poreikius bei kliūtis kaip naudingą priemonę diegiant ir taikant šią svarbią gydymo programą.

4. Rekomenduojame būsimuose iIFŠN reabilitacijos moksliniuose tyrimuose naudoti platesnį ir kompleksiškesnį širdies funkciją atspindinčių parametrų vertinimą – analizę papildyti dešinės širdies pusės funkciją ir plaučių kraujotaką atspindinčiais parametrais, taip pat tikslesniu KS morfologijos ir funkcijos vertinimu.

5. Siūlome ateityje atnaujinti reabilitacijos tyrimą PH-iIFŠN populiacijoje.

10. PADĖKA

Esu labai dėkinga už žinias ir patirtį, kurias įgijau doktorantūros studijų metu, ir tikiu, kad jas panaudosiu ateityje. Norėčiau padėkoti visiems šiame darbe dalyvavusiems mokslininkams ir sveikatos priežiūros specialistams, kurie prisidėjo savo laiku, žiniomis ir įgūdžiais.

Esu labai dėkinga savo mokslinei vadovei *prof. Jelenai Čelutkienei* už tai, kad visada buvo kartu, atsakingai ir profesionaliai vadovavo visų doktorantūros studijų metu. Ačiū už įkvėpimą, skatinimą imtis mokslinės veiklos ir puikų lyderystės pavyzdį. Norėčiau nuoširdžiai padėkoti savo moksliniam konsultantui *prof. Ekkehard Grünig* už pagalbą kiekviename šio tyrimo etape, už įžvalgius pasiūlymus, paramą ir galimybę dalyvauti tarptautiniuose projektuose. Jūsų abiejų vizija, entuziazmas ir mano žinojimas, kad iškilus kliūtims galiu kreiptis pagalbos į Jus, suteikė man ramybės ir užtikrintumo jausmą, o šį tyrimą pavertė malonia ir naudinga patirtimi.

Nuoširdžiai dėkoju *doc. Linai Gumbienei* ir *dr. Elenai Jurevičienei* už paramą viso šio tyrimo metu, ypač jo pradžioje – už pirminę idėją, pagalbą inicijuojant tyrimą, vertingus patarimus ir praturtinusias pažintis.

Norėčiau nuoširdžiai padėkoti visiems bendraautoriams, ypač *prof. Christina Alessandra Eichstaedt* ir *Nicola Benjamin*. Dėkoju už šiltą bendravimą ir profesionalų bendradarbiavimą, taip pat už Jūsų svetingumą ir apmokymus apsilankymų *Thoraxklinic* Heidelberge metu.

Didžiulę padėką norėčiau išreikšti VUL Santaros klinikų Fizinės medicinos ir reabilitacijos centro darbuotojams. Už labai svarbią paramą diegiant ir vykdant PH reabilitacijos programą dėkoju *doc. Alfredui Rudžiui, prof. Alvydui Juocevičiui, dr. Ievai Laucevičienei, Jūratei Guogienei, Emilijai Šinkūnienei*. Ypač ačiū kineziterapeutėms *Vilmai Gaučytei, Barbarai Šemetienei* bei *Daivai Sakalauskienei* – Jūsų indėlis buvo esminis šio tyrimo sėkmei.

Nuoširdžiai dėkoju visiems tyrimo partneriams: VUL SK PH kompetencijos centro administratorei *Raimondai Jonaitienei*, kolegei *Tomai Kupei*, intervencinės kardiologijos komandai, ypač *Sigitui Čėsnai*, širdies echolaboratorijos darbuotojams, ypač *prof. Dianai Zakarkaitei*.

Esu dėkinga įkvepiantiems pacientams, kurie dalyvavo šiame tyrime su entuziazmu ir ryžtu.

Dėkoju disertacijos recenzentams: *dr. Egidijai Rinkūnienei, prof. Sigitai Aidietienei, prof. Pranui Šerpyčiui* už skirtą laiką, vertingas įžvalgas bei motyvuojantį paskatinimą.

Galiausiai norėčiau padėkoti savo brangiausiems ir artimiausiems – *tėvams Virginijai ir Vidui, broliui Laurynui, Ramūnui ir jo tėvams Onai ir Rimantui*, visiems laiko ir patirčių patikrintiems *draugams*. AČIŪ už Jūsų meilę, nuolatinį palaikymą, už tai, kad mane džiuginate, o labiausiai už tai, kad visada buvote ir esate kartu.

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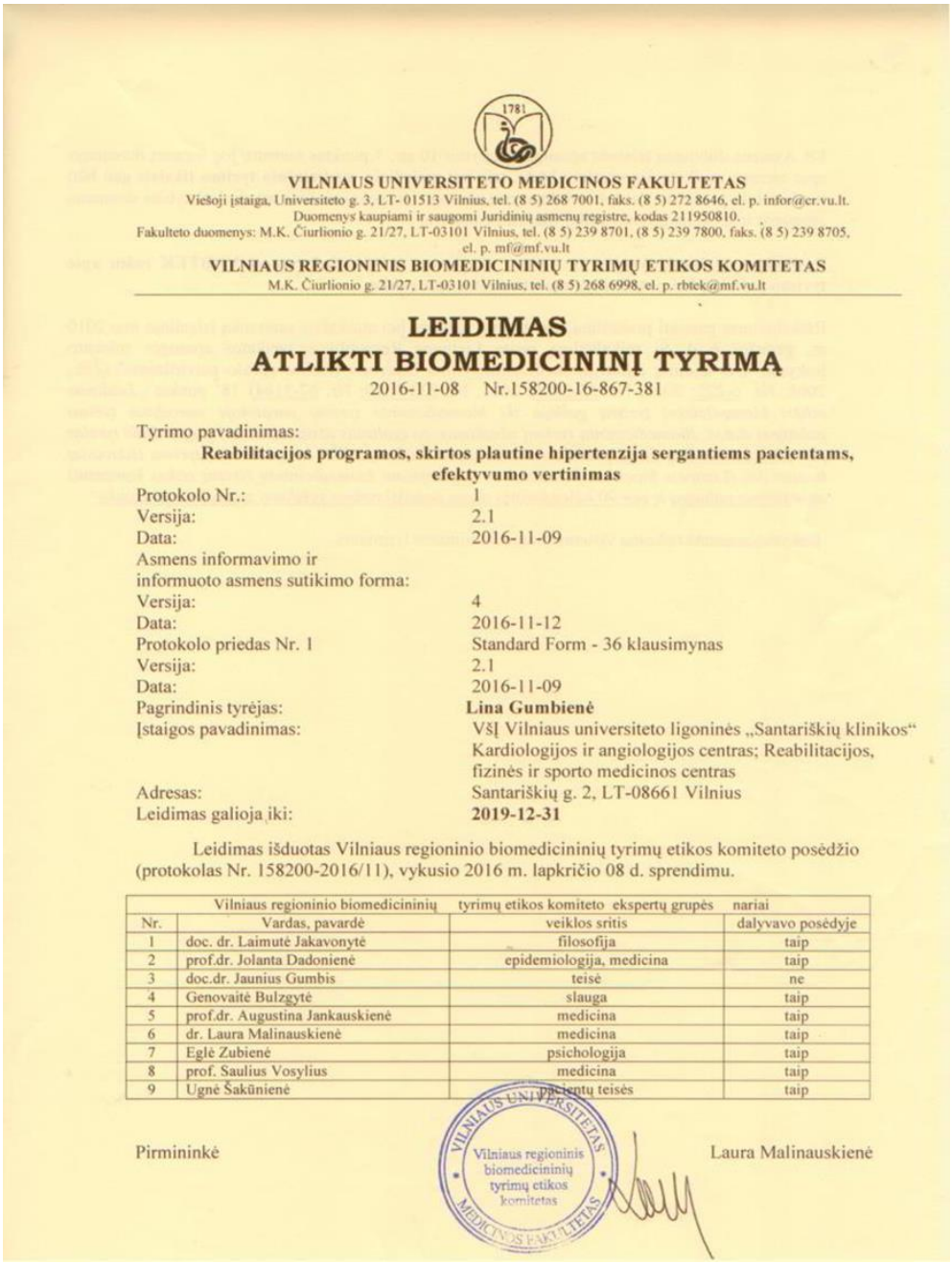
12. ANNEXES

AUTHORISATIONS OF VILNIUS REGIONAL BIOETHICS COMMITTEE



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Viešoji įstaiga, Universiteto g. 3, LT- 01513 Vilnius, tel. (8 5) 268 7001, faks. (8 5) 272 8646, el. p. infor@cr.vu.lt.
Duomenys kaupiami ir saugomi Juridinių asmenų registre, kodas 211950810.
Fakulteto duomenys: M.K. Čiurlionio g. 21/27, LT-03101 Vilnius, tel. (8 5) 239 8701, (8 5) 239 7800, faks. (8 5) 239 8705, el. p. mf@mf.vu.lt
VILNIAUS REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS
M.K. Čiurlionio g. 21/27, LT-03101 Vilnius, tel. (8 5) 268 6998, el. p. rbtek@mf.vu.lt

LEIDIMAS
ATLIKTI BIOMEDICININĮ TYRIMĄ

2016-11-08 Nr.158200-16-867-381

Tyrimo pavadinimas:
Reabilitacijos programos, skirtos plautine hipertenzija sergantiems pacientams, efektyvumo vertinimas

Protokolo Nr.:	1
Versija:	2.1
Data:	2016-11-09
Asmens informavimo ir informuoto asmens sutikimo forma:	
Versija:	4
Data:	2016-11-12
Protokolo priedas Nr. 1	Standard Form - 36 klausimynas
Versija:	2.1
Data:	2016-11-09
Pagrindinis tyrėjas:	**Lina Gumbienė**
Įstaigos pavadinimas:	VšĮ Vilniaus universiteto ligoninės „Santariškių klinikos" Kardiologijos ir angiologijos centras; Reabilitacijos, fizinės ir sporto medicinos centras
Adresas:	Santariškių g. 2, LT-08661 Vilnius
Leidimas galioja iki:	**2019-12-31**

Leidimas išduotas Vilniaus regioninio biomedicininių tyrimų etikos komiteto posėdžio (protokolas Nr. 158200-2016/11), vykusio 2016 m. lapkričio 08 d. sprendimu.

Vilniaus regioninio biomedicininių tyrimų etikos komiteto ekspertų grupės nariai			
Nr.	Vardas, pavardė	veiklos sritis	dalyvavo posėdyje
1	doc. dr. Laimutė Jakavonytė	filosofija	taip
2	prof.dr. Jolanta Dadonienė	epidemiologija, medicina	taip
3	doc.dr. Jaunius Gumbis	teisė	ne
4	Genovaitė Bulzgytė	slauga	taip
5	prof.dr. Augustina Jankauskienė	medicina	taip
6	dr. Laura Malinauskienė	medicina	taip
7	Eglė Zubienė	psichologija	taip
8	prof. Saulius Vosylius	medicina	taip
9	Ugnė Šakūnienė	pacientų teisės	taip

Pirmininkė Laura Malinauskienė

Vilniaus regioninis biomedicininių tyrimų etikos komitetas

VILNIAUS UNIVERSITETO
VILNIAUS REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS

LEIDIMAS
ATLIKTI BIOMEDICININĮ TYRIMĄ

2019-04-30 Nr.2019/4-1118-611

Tyrimo pavadinimas:

Specializuotos reabilitacijos programos efektyvumo vertinimas pacientams, sergantiems plautine hipertenzija dėl kairiosios širdies nepakankamumo

Protokolo Nr.:	1.0
Versija:	1.2
Data:	2019 04 18
Informuoto asmens sutikimo forma:	1.1 2019 04 18
Pagrindinis tyrėjas:	**Jelena Čelutkienė**
Įstaigos pavadinimas:	VšĮ Vilniaus Universiteto ligoninė Santaros Klinikos
Adresas:	Santariškių g. 2, Vilnius
Leidimas galioja iki:	**2022 05**

Leidimas išduotas Vilniaus regioninio biomedicininių tyrimų etikos komiteto posėdžio (protokolas Nr. 2019/4), vykusio 2019 m. balandžio 30 d. sprendimu.

Pirmininkas prof. dr. (HP) Saulius Vosylius

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LIST OF PRESENTATIONS

1. Arnas Rimkus, **Eglė Palevičiūtė**, Elena Jurevičienė, Lina Gumbienė. Effects of Exercise and Respiratory Training on Exercise Capacity and Quality of Life in Precapillary Pulmonary Hypertension: primary results of A Prospective, Randomized Controlled Study in Lithuania. *2nd Baltic and 3rd Lithuanian Pulmonary Hypertension conference,* Vilnius; 19 October 2018; Poster presentation;

2. Ekkehard Grünig, Martin Johnson, Alison MacKenzie, Christina Eichstaedt, Nicola Benjamin, Silvia Ulrich, Stéphanie Saxer, Maurizio Bussotti, Stefano Ghio, Lina Gumbiene, **Eglė Palevičiūtė**, Elena Jurevičienė, Antonio Cittadini, Anna A. Stanziola, Alberto M. Marra, Gabor Kovacs, Horst Olschewski, Joan-Albert Barberà, Isabel Blanco, Martin Spruit, Anton Vonk Noordegraaf, Abílio Reis, Mário Santos, Sofia Gonçalves Viamonte, Marion Delcroix, Eduardo Bossone, Andrew J. Peacock. Effect of exercise training on 6 minute walking distance in severe pulmonary hypertension – results from a European multicenter randomized controlled trial. *14th Pulmonary Vascular Research Institute (PVRI) Annual World Congress on Pulmonary Vascular Disease*, Lima (Peru); 31 January 2020; Poster presentation;

3. **Eglė Palevičiūtė**, Lina Gumbienė, Elena Jurevičienė, Toma Šimbelytė, Ieva Laucevičienė, Aleksandras Laucevičius, Jūratė Barysienė, Christina Eichstaedt, Nicola Benjamin, Ekkehard Gruenig, Jelena Čelutkienė. Specialized rehabilitation program for patients with pulmonary hypertension: the experience, prerequisites and the barriers of implementing this service. RSU 8th International Multidisciplinary Research Conference *Society. Health. Welfare*, 24–26 March 2021 Riga, Latvia; Oral presentation;

4. **Eglė Palevičiūtė**. Rehabilitation programs for pulmonary hypertension. *3rd Baltic Pulmonary Hypertension and Circulation Conference*, Tallinn (Estonia); 01 October 2021; Oral presentation;

5. **Eglė Palevičiūtė**, Jelena Čelutkienė. Not only medications matter for the optimal treatment of chronically ill patients: specialized rehabilitation program for patients with pulmonary hypertension and heart failure. *Joint International Meeting: 22nd EAA Congress, 15th ISGA Congress, 5th International Conference of Evolutionary Medicine*; 24 – 26 August 2022, Vilnius; Poster presentation.

ABOUT THE AUTHOR

Eglė Palevičiūtė obtained a Medical Doctor qualification at Vilnius University in 2011, and after four years of residency studies she became a cardiologist. Since 2015 she has been working as a junior researcher at Vilnius University, Faculty of Medicine, and since 2021 also as a lecturer. She started the Vilnius University doctoral study programme in 2018.

Since 2015 Eglė Palevičiūtė has been working as a cardiologist at Vilnius University Hospital Santaros Klinikos. Managing of patients with pulmonary hypertension and heart failure makes up a significant proportion of her daily clinical practice. Since 2016 she has developed the knowledge in rehabilitation of pulmonary hypertension and heart failure patients. In order to gain more practice in this field, for one year (2017 – 2018) she worked as a cardiologist at the Department of Physical Medicine and Rehabilitation at VUH Santaros Klinikos. In 2022 Eglė Palevičiūtė became a coordinator of Pulmonary Hypertension Competence Center at VUH Santaros Klinikos. As a researcher she participated in various international projects, authored publications and presented at international conferences.

Publication I

Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial.

Grünig E, MacKenzie A, Peacock AJ, Eichstaedt CA, Benjamin N, Nechwatal R, Ulrich S, Saxer S, Bussotti M, Sommaruga M, Ghio S, Gumbienė L, **Palevičiūtė E**, Jurevičienė E, Cittadini A, Stanziola AA, Marra AM, Kovacs G, Olschewski H, Barberà JA, Blanco I, Spruit MA, Franssen FME, Vonk Noordegraaf A, Reis A, Santos M, Viamonte SG, Demeyer H, Delcroix M, Bossone E, Johnson M.

Eur Heart J. 2021 Jun 14;42(23):2284-2295.
doi: 10.1093/eurheartj/ehaa696. PMID: 33232470.

ESC European Society of Cardiology

European Heart Journal (2021) **42**, 2284–2295
doi:10.1093/eurheartj/ehaa696

CLINICAL RESEARCH
Thrombosis and antithrombotic treatment

Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial

Ekkehard Grünig[1]*†, Alison MacKenzie [2†], Andrew J. Peacock [2], Christina A. Eichstaedt[1,3], Nicola Benjamin[1], Robert Nechwatal [4], Silvia Ulrich [5], Stéphanie Saxer [5], Maurizio Bussotti [6], Marinella Sommaruga [6], Stefano Ghio [7], Lina Gumbiene [8,9], Eglė Paleviciūtė[8,9], Elena Jurevičienė[8,9], Antonio Cittadini[10], Anna A. Stanziola[11], Alberto M. Marra [1,12], Gabor Kovacs [13,14], Horst Olschewski [13,14], Joan-Albert Barberà[15], Isabel Blanco[15], Martijn A. Spruit [16,17,18,19], Frits M.E. Franssen [20], Anton Vonk Noordegraaf[21], Abílio Reis [22], Mário Santos [22], Sofia Gonçalves Viamonte[23], Heleen Demeyer [24,25,26], Marion Delcroix [24], Eduardo Bossone [27‡], and Martin Johnson [2‡]

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See page 2296 for the editorial comment on this article (doi: 10.1093/eurheartj/ehaa780)

Aims This prospective, randomized, controlled, multicentre study aimed to evaluate efficacy and safety of exercise training in patients with pulmonary arterial (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).

Methods and results For the first time a specialized PAH/CTEPH rehabilitation programme was implemented in 11 centres across 10 European countries. Out of 129 enrolled patients, 116 patients (58 vs. 58 randomized into a training or usual care

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‡These authors shared last authorship.
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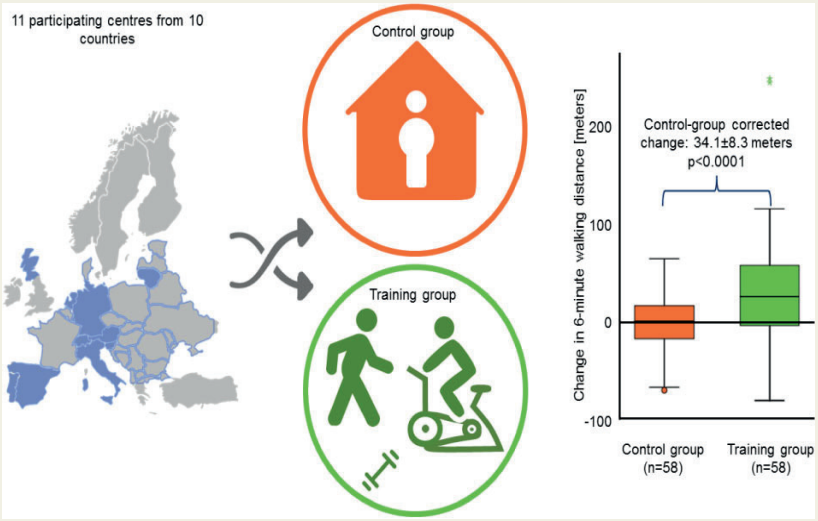
control group) on disease-targeted medication completed the study [85 female; mean age 53.6 ± 12.5 years; mean pulmonary arterial pressure 46.6 ± 15.1 mmHg; World Health Organization (WHO) functional class II 53%, III 46%; PAH $n = 98$; CTEPH $n = 18$]. Patients of the training group performed a standardized in-hospital rehabilitation with mean duration of 25 days [95% confidence interval (CI) 17–33 days], which was continued at home. The primary endpoint, change of 6-min walking distance, significantly improved by 34.1 ± 8.3 m in the training compared with the control group (95% CI, 18–51 m; $P < 0.0001$). Exercise training was feasible, safe, and well-tolerated. Secondary endpoints showed improvements in quality of life (short-form health survey 36 mental health 7.3 ± 2.5, $P = 0.004$), WHO-functional class (training vs. control: improvement 9:1, worsening 4:3; χ^2 $P = 0.027$) and peak oxygen consumption (0.9 ± 0.5 mL/min/kg, $P = 0.048$) compared with the control group.

Conclusion This is the first multicentre and so far the largest randomized, controlled study on feasibility, safety, and efficacy of exercise training as add-on to medical therapy in PAH and CTEPH. Within this study, a standardized specialized training programme with in-hospital start was successfully established in 10 European countries.

Graphical Abstract



Keywords Pulmonary rehabilitation • Pulmonary hypertension • Exercise programme

Introduction

Low-intensity exercise training for patients with pulmonary arterial (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) has been shown to increase quality of life (QoL), exercise capacity, lower limb muscle strength, and possibly haemodynamics.[1–3] Up to date, 6 randomized controlled trials have been published[2–7] as well as 14 further controlled trials or cohort studies.[8] Hence, the evidence is mounting that exercise training is a valuable add-on to targeted medical therapy. Currently, specialized low-dose exercise training holds a class IIa level B recommendation in the European Society of Cardiology/European Respiratory Society (ESC/ERS) pulmonary hypertension (PH) guidelines.[9–11]

Until the ESC/ERS-guidelines had been published, the sample sizes of the four randomized controlled studies in pre-capillary PH patients considered for recommendations on exercise training were quite small (ranging from 23 to 30 patients). After 2015, two further randomized controlled trials,[2,5] three meta- and one Cochrane

analysis[12–15] have shown that exercise training is highly beneficial for pre-capillary PH patients. In most previous studies, the initial training was highly supervised and conducted in an inpatient setting.[8,9] Therefore, PH guidelines recommended that exercise training programmes should be implemented by centres experienced in both—PAH patient care and rehabilitation of compromised patients. In addition, patients should be treated with the best standard of pharmacological treatment and in a stable clinical condition before embarking on supervised rehabilitation.[9] However, the access to such programmes is very limited and multicentre studies are lacking to assess the effect of exercise training in different countries with different healthcare systems. Before the start of this trial, rehabilitation was not available for PH patients in most European countries.

Therefore, the objective of this study was to perform a multicentre, randomized, controlled trial across Europe also including countries in which exercise training had so far not been available for PH patients to investigate its feasibility, safety, and efficacy. Furthermore, we aimed to develop and assess standardized settings, monitoring, and adjustment of exercise training which would be helpful to implement a validated, high-quality programme with a solid scientific evaluation.

Methods

Study population and design

All participating centres were members of a European Respiratory Society Task Force on exercise training in PH.[8] A common protocol was designed to conduct the first multicentre study on exercise training in PH. Eleven centres from 10 European countries (Austria, Belgium, Germany, Italy, Lithuania, the Netherlands, Portugal, Scotland, Spain, and Switzerland) participated.

Inclusion criteria were pre-capillary PH [PAH or non-operable or recurrent chronic thromboembolic PH (CTEPH)] diagnosed by right heart catheterization according to the ESC/ERS PH guidelines.[9] Study participants had to be ≥18 years of age, non-pregnant, in World Health Organization functional class (WHO-FC) II–IV and stable on optimized PAH targeted therapy for at least 2 months prior to study enrolment. Excluded were patients with PAH associated with portal hypertension, complex congenital heart disease,[16] HIV and patients with pulmonary veno-occlusive disease. Further exclusion criteria were clinically relevant lung or left heart disease, active liver disease, acute infection, walking disability, haemoglobin concentration below 75% of lower limit of normal values (individual age and gender adjusted normal values of haemoglobin), systolic blood pressure <85 mmHg, recent syncope and skeletal or muscle abnormalities prohibiting participation in an exercise programme. Patients with sustained supraventricular and ventricular arrhythmias at baseline were not enrolled into the study. Patients with mild non-sustained supraventricular or ventricular arrhythmias or with a history of arrhythmia, e.g. after cardioversion, were able to participate in the study. Targeted PAH or other medication was not to be altered within the training period. The study complies with the Declaration of Helsinki. All patients gave their written informed consent to the study. The study was approved by the ethics committee of the Medical Faculty of Heidelberg University, Germany (S-473/2015) and by each centre's respective ethics committee. The study was registered in clinicaltrials.gov under the identifier NCT03345212.

Randomization and outcome measures

The study was a 15-week, randomized, controlled multicentre trial. After giving written informed consent for this study, patients were randomly assigned to either a 'training group' or a 'control group' using a permuted block randomization procedure with sealed envelopes, stratified by centre. Patients of the training group stayed in-house for the initial 10–30 days of the study period and continued with a programme at home for another 11–12 weeks. Patients of the control group stayed at home with usual daily activity. Efficacy parameters were assessed at baseline and after 15 weeks by investigators who were blinded to the clinical data.

The primary endpoint was the change in 6-min walking distance (6MWD) from baseline to 15 weeks between exercise training and control group. Six-minute walk test was carried out under standardized conditions.[17]

Secondary endpoints were the change from baseline to 15 weeks after rehabilitation in peak oxygen consumption based on a cardiopulmonary exercise testing (CPET), WHO-FC, N-terminal prohormone brain natriuretic peptide (NT-proBNP), QoL, and safety parameters. Echocardiography at rest and during exercise and CPET were performed in a smaller subset of centres. Assessment and analysis of QoL (short-form health survey 36, SF-36 questionnaire) and of other efficacy parameters were performed as described previously.[2] Adverse events, defined according to International Conference of Harmonization Good Clinical Practice, during the study period were recorded.

Exercise training programme

For standardization of the training programme great effort has been undertaken including several meetings of the participating professionals and the implementation of a train the trainer setting. At least one PH expert and physiotherapist from each centre spent several days at the PH expert centre and rehabilitation clinic in Heidelberg, Germany between November 2014 and April 2018 to receive first-hand experience on the set-up of the clinical examinations, patients' exercise capacity evaluation, training adjustment, monitoring, and exercise training components to assimilate procedures across countries as much as possible. The 6MWD as primary endpoint was performed standardized according to current recommendations.[18] Each centre performed a study entrance examination to assess baseline parameters, enabled an inpatient phase between 10 and 30 days followed by an outpatient phase until the final examination at 15 weeks.

The exercise and respiratory training was based on published procedures[2,3] and adapted by each country to achieve a feasible set-up which was similar to the described setting. The Heidelberg exercise training programme specifically developed for patients with PH was chosen as intervention due to the profound scientific evaluation of the programme and safety reasons (low intensity). The training programme consisted of respiratory therapy, cycle ergometer training, dumbbell training, guided walks, and mental training as described previously.[2] During the initiation period, exercise training was performed 5–7 times/week. During the continuation phase at home, training frequency was 3–7 times/week. Training intensity was 40–60% of the patients' achieved maximal workload during ergometer test at baseline. Oxygen saturation, heart rate, right ventricular function at rest and during exercise, and subjective perception were considered for initial training intensity and training adjustment. Right ventricular function during exercise was measured by echocardiography as visual estimation of pump function and as change of systolic pulmonary arterial pressure from rest to peak exercise measured during stress echocardiography as described previously.[19] Pump function was classified qualitatively as normal, mildly, moderately, or severely impaired. Training was closely supervised by physical therapists and physicians specialized in rehabilitation medicine and PH experts. Transcutaneous oxygen saturation and heart rate were monitored continuously throughout the training. Patients, who were on oxygen therapy 16–24 h/day before inclusion

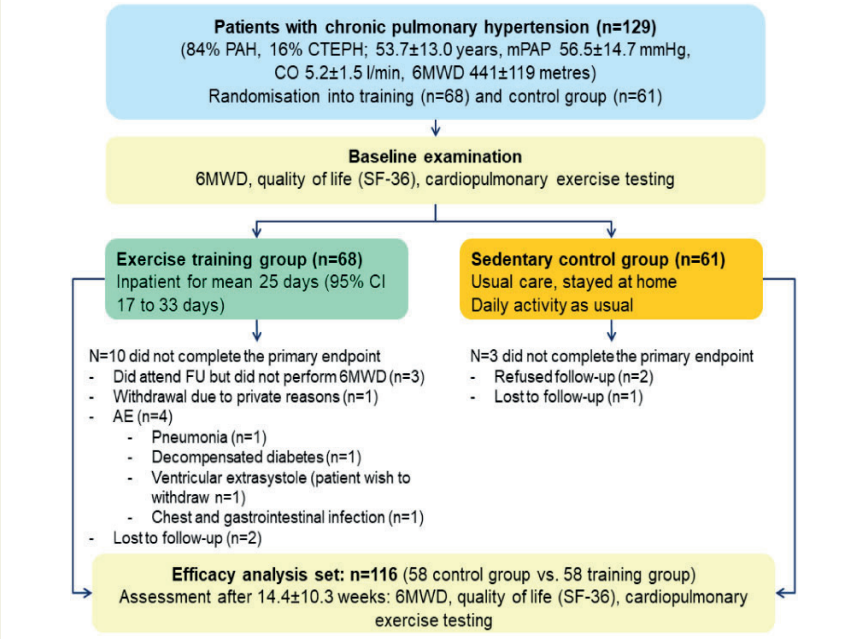


Figure 1 Study flow-chart. This flow-chart gives the course of the study, patient randomization, assessments, and definition of dropouts. 6MWD, 6-min walking distance; AE, adverse event; CI, confidence interval; CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; FU, follow-up; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension.

into this study remained on oxygen during the training programme. At discharge at the end of the inpatient phase, patients received an individualized training manual and organized a cycle ergometer for use at home.

Statistical methods

The analyses were performed by a statistician (N.B.). The efficacy analysis and subject characterization were performed by use of the efficacy dataset including all patients with baseline and follow-up assessment of the primary endpoint 6MWD. All patients who were enrolled and randomized into the study were included in the safety analysis. Data are given as mean values ± standard deviations. For the description of effects changes in absolute values were calculated. Differences between changes of the intervention and the control group were calculated and expressed as 'control-group corrected change'.

Calculation of sample size was based on the primary efficacy endpoint which was defined as the change in 6MWD between baseline and 15 weeks of exercise training between the training and the control group. To detect a control-group adjusted difference in 6MWD of 30 m, with an equal standard deviation of 53 m with a power of 80% and a two-sided significance level of 5%, it was calculated that 50 patients were required in each treatment arm. Under consideration of the assumed dropout rate of 20%, the sample size was increased to 63 patients in each group (total 126). The primary efficacy analysis was performed by a *t*-test with unequal variances (Welch tests) of changes between groups since the assumption for a covariance analysis was not fulfilled. The frequency of patients with increase of 6MWD ≥10% and the frequency of patients with increase above 440 m (low-risk category according to ESC/ERS risk stratification)[9] was analysed for interpretation of the primary endpoint.

Secondary endpoints were tested with two-sided student's *t*-tests for unequal variances. For analysis of categorical data, χ^2 test was used. No imputation strategy was implemented for missing data. A sensitivity analysis excluding outliers >1.5 of interquartile range was performed for the primary endpoint 6MWD and for peak VO_2.

Safety was analysed descriptively. Adverse events (AEs) during the study period included all AEs that started or worsened from baseline until the last visit (15 weeks). As one centre did not report AEs for the control group, patients from this centre were excluded from analysis of AEs. All tests were two-sided and *P*-values <0.05 were considered statistically significant. All analyses were carried out with IBM SPSS V25 (IBM Corp. Armonk, NY, USA).

Results

Study population

From October 2015 until November 2019, a total of 129 patients were enrolled into the study with 61 patients in the control group and 68 patients in the training group (*Figure 1*, Supplementary

material online, *Table S1*). Out of them, 116 completed the study with baseline and follow-up assessment of the primary endpoint 6MWD (58 vs. 58 patients; 73.3% female, 53.6 ± 12.5 years, 47.5% WHO-FC ≥3, mean pulmonary artery pressure 47 ± 15 mmHg, pulmonary vascular resistance 8.2 ± 5.0 WU; *Table 1*). One patient in the training group and one patient in the control group had mild impairment of left ventricular function. Right ventricular function was mildly impaired in 13 vs. 10, moderately impaired in 5 vs. 5, and severely impaired in 3 vs. 2 patients (training vs. control). Reasons for dropout are given in *Figure 1*. Mean inpatient training duration was 25 days [95% confidence interval (CI) 17 to 33 days]. Pulmonary hypertension-specific medication was not changed throughout the study period. Baseline parameters were well-balanced between groups (*Table 1*).

Primary endpoint 6MWD

Patients of the training group showed a significant improvement of the primary endpoint 6MWD (30.7 ± 57.9 m), while the control group slightly decreased in 6MWD (-3.4 ± 25.9 m; control-group corrected change 34.1 ± 8.3 m; $P < 0.0001$, *Table 1* and *Figure 2*). In the training group, 19 patients (32.3%) had a walking distance improvement ≥10%, compared with two patients (3.4%) in the control group. Twenty-five patients from the training group vs. one patient in the control group showed a 6MWD improvement above the threshold of clinically important difference ≥33 m.

Ten patients of the training group who presented with a walking distance <440 m at baseline improved their walking distance to ≥440 m during follow-up (ESC/ERS low-risk category), three patients showed deterioration of walking distance below this threshold. In comparison, one patient from the control group improved walking distance from <440 m to ≥440 m, while three patients showed deterioration below the threshold.

Secondary endpoints

Quality-of-life scores (mental health) significantly improved in the training group, compared with the control group (control-group corrected change 7.3 ± 2.5; $P = 0.004$) and improved in trend for physical functioning ($P = 0.07$) and social functioning ($P = 0.09$; *Figure 3*). With Bonferroni correction, *P*-values <0.005 remained statistically significant for QoL data. Other SF-36 scales and subscales did not significantly differ between groups.

In the training group, nine patients improved in WHO-FC, compared with one patient in the control group; four patients worsened in WHO-FC, compared with three patients in the control group (χ^2 $P = 0.027$).

In CPET peak oxygen consumption significantly improved in the training group [control-group corrected change +0.9 ± 0.3 mL/min/kg; $P = 0.048$; *Figure 4*; improvement equals 8.5 ± 17.6% in the training group vs. 1.0 ± 13.8% in the control group ($P = 0.015$)]. In the training group, 23 patients (41.8%) had a peak oxygen consumption improvement ≥10%, compared with 15 patients (28.3%) in the control group.

Patients in the training group had a significant decrease in systolic pulmonary arterial pressure (-4 mmHg) compared with the control group (+5.8 mmHg; difference 9.8 ± 3.1 mmHg, $P = 0.002$, *Table 2*). Other echocardiographic parameters did not show significant differences between respective changes compared with baseline.

Other parameters from CPET and change of NT-proBNP showed no significant differences between groups (*Table 2*).

Sensitivity analysis excluding outliers revealed that the primary endpoint 6MWD (difference 26.3 ± 6.5 m, $P = 0.0001$) and peak VO_2 (difference 0.75 ± 0.38 mL/min/kg, $P = 0.05$) still remained statistically significant.

Safety

The safety set comprised 99 patients, as AEs from one centre ($n = 30$), which only reported AE data for patients from the intervention group, were excluded. In total, 52 AEs (27 training group, 25 control group) were reported for 21 patients (13 training group and 8 control group). Adverse events with a frequency of ≥5% and serious AEs were comparable between groups (*Table 3*). The most frequent AEs were arrhythmia and respiratory infections. In the training group, three patients experienced a serious AE during the study period, compared with one in the control group (χ^2 $P = 0.38$). All serious AEs were classified as serious due to occurrence of hospitalization.

Patients of the training group showed a higher dropout rate for the efficacy dataset (χ^2 $P = 0.095$), though three patients successfully completed the study, but did not perform a 6MWD due to organizational issues. No patient in the control group vs. four patients in the training group did not complete the study due to AEs, out of which one was a serious AE (decompensated diabetes). However, none of the AEs or serious AEs were evaluated to be related to the study intervention.

Discussion

This is the first randomized controlled multicentre study on exercise training in patients with pre-capillary PH, performed in 11 centres in 10 European countries in a large patient population, showing a significant and clinically meaningful improvement of the primary endpoint 6MWD and of the secondary endpoints WHO-FC, QoL, and peak oxygen consumption. The study showed for the first time that a safe and effective exercise training programme can be standardized and is feasible in different countries with different healthcare systems. To make this therapy widely available for PH patients participating centres implemented this PH training programme mostly for the first time and successfully adapted it to their local healthcare system.

Significant improvement of primary endpoint 6MWD

The effects of exercise training have so far been investigated by only a few working groups, which raised the need for larger and multicentre studies to verify the results.[8,12,20]

Although the 6MWD as outcome parameter has been criticized, particularly in add-on treatments,[21] we chose this patient-relevant outcome to reflect patients' exercise capacity as it has been shown that the 6MWD highly correlates with daily activity, haemodynamics and prognosis in PH and is thus used for risk assessment. Change in 6MWD has been reported to be below the clinically relevant threshold in several studies, despite significant changes in other relevant outcomes.[21] In a meta-analysis, the 6MWD has shown limitations as surrogate endpoint for clinical worsening events in PAH, but still a

Table 1 Demographics and clinical characteristics of patients

Characteristic	Control group ($n = 58$)			Training group ($n = 58$)			Efficacy dataset ($n = 116$)		
	Mean ± SD or *n* and %	95% confidence interval	*n*	Mean ± SD or *n* and %	95% confidence interval	*n*	Mean ± SD or *n* and %	95% confidence interval	*n*
Age (years)	55.0 ± 12.7	(51.6 to 58.3)		52.3 ± 12.4	(49.1 to 55.6)		53.6 ± 12.5	(51.3 to 55.9)	
Height (cm)	164.6 ± 8.4	(162.4 to 166.8)		167.2 ± 9.9	(164.6 to 169.8)	57	165.9 ± 9.2	(164.2 to 167.6)	115
Weight (kg)	73.4 ± 12.9	(70.0 to 76.8)		77.7 ± 19.8	(72.4 to 82.9)	57	75.5 ± 16.8	(72.4 to 78.6)	115
Female sex number (%)	45 (77.6%)			40 (69.0%)			85 (73.3%)		
Pulmonary hypertension diagnosis									
Idiopathic or heritable PAH	34 (58.6%)			39 (67.2%)			73 (62.9%)		
Congenital heart disease-associated PAH	4 (6.9%)			5 (8.6%)			8 (6.9%)		
Connective tissue disease-associated PAH	8 (13.8%)			4 (6.9%)			12 (10.3%)		
Other type of PAH	1 (1.7%)			2 (3.4%)			3 (2.6%)		
PH due to lung disease	0			1 (1.7%)			1 (0.9%)		
Chronic thromboembolic pulmonary hypertension	11 (19.0%)			7 (12.1%)			18 (15.5%)		
PH-targeted drugs									
Calcium channel blockers	3 (5.2%)			9 (15.5%)			12 (10.3%)		
Phosphodiesterase 5-inhibitors	43 (74.1%)			45 (77.6%)			88 (75.9%)		
Endothelin receptor antagonists	49 (84.5%)			46 (79.3%)			95 (81.9%)		
Soluble guanylate cycle stimulator	8 (13.8%)			6 (10.3%)			14 (12.1%)		
Prostacyclin	10 (17.2%)			18 (31.0%)			28 (24.1%)		
IP receptor agonist	2 (3.5%)			2 (3.5%)			4 (3.5%)		
Medication combination treatment									
One drug	14 (24.1%)			12 (20.7%)			26 (22.4%)		
Two drugs	29 (50.0%)			24 (41.4%)			53 (45.7%)		
Three drugs	15 (25.9%)			21 (36.2%)			36 (31.0%)		
Four drugs	0			1 (1.7%)			1 (0.1%)		
Right heart catheterization									
Right atrial pressure (mmHg)	7.9 ± 4.5	(6.6 to 9.2)	51	6.5 ± 4.1	(5.4 to 7.7)	51	7.2 ± 4.3	(6.4 to 8.1)	102
Mean pulmonary arterial pressure (mmHg)	46.7 ± 14.9	(42.7 to 50.6)		46.5 ± 15.5	(42.4 to 50.6)	57	46.6 ± 15.1	(43.8 to 49.4)	115
Cardiac output (L/min)	5.2 ± 1.4	(4.8 to 5.6)	52	5.1 ± 1.5	(4.7 to 5.5)	53	5.2 ± 1.5	(4.9 to 5.45)	105
Cardiac index (L/min/m^2)	2.8 ± 0.7	(2.6 to 3.0)	52	2.7 ± 0.7	(2.5 to 2.9)	54	2.8 ± 0.7	(2.6 to 2.9)	106
Pulmonary arterial wedge pressure (mmHg)	9.9 ± 3.4	(9.0 to 10.9)	53	9.1 ± 3.7	(8.1 to 10.1)	55	9.5 ± 3.6	(8.8 to 10.2)	108
Pulmonary vascular resistance (WU)	7.7 ± 4.5	(6.4 to 9.0)	49	8.6 ± 5.5	(7.1 to 10.2)	52	8.2 ± 5.0	(7.2 to 9.2)	101

Continued

Table 1 *Continued*

Characteristic	Control group ($n = 58$)			Training group ($n = 58$)			Efficacy dataset ($n = 116$)		
	Mean ± SD or *n* and %	95% confidence interval	*n*	Mean ± SD or *n* and %	95% confidence interval	*n*	Mean ± SD or *n* and %	95% confidence interval	*n*
WHO-FC class number (%)									
I	0			1 (1.7%)			1 (0.9%)		
II	34 (58.6%)			26 (44.8%)			60 (51.7%)		
III	24 (41.4%)			30 (51.7%)			54 (46.6%)		
IV	0			1 (1.7%)			1 (0.9%)		
Laboratory									
NT-proBNP (ng/L)	332.5 ±480.6	(184.6 to 480.4)	43	686.0 ±1031.0	(342.2 to 1029.7)	37	460.0 ± 799.2	(318.2 to 673.8)	80
6-min walking test									
6MWD (m)	447.4 ±120.2	(415.8 to 479.0)		447.2 ± 117.7	(416.2 to 478.1)		447.3 ± 118.4	(425.5 to 469.1)	
Cardiopulmonary exercise testing (CPET)									
with stress echocardiography									
Heart rate at rest (/min)	78.7 ± 14.3	(74.3 to 83.2)	42	83.9 ± 14.0	(79.7 to 88.2)	44	81.4 ± 14.3	(78.3 to 84.4)	86
SaO_2 at rest (%)	95.4 ± 4.6	(93.9 to 96.8)	41	93.2 ± 11.8	(89.6 to 96.9)	42	94.3 ± 9.0	(92.3 to 96.2)	83
Peak heart rate (/min)	123.0 ± 23.3	(115.8 to 130.1)	43	134.1 ± 22.9	(127.2 to 141.1)	44	128.6 ± 23.6	(123.6 to 133.6)	87
Peak SaO_2 (%)	90.0 ± 7.2	(87.7 to 92.2)	41	90.5 ± 7.1	(88.3 to 92.7)	43	90.2 ± 7.1	(88.7 to 91.8)	84
Peak VO_2 (mL/min/kg)	15.3 ± 4.3	(14.2 to 16.5)	53	14.2 ± 5.2	(12.8 to 15.6)		14.7 ± 4.8	(13.8 to 15.6)	111
Peak VO_2 % predicted (%)	68.5 ± 20.8	(61.9 to 75.0)	41	68.7 ± 51.5	(52.9 to 84.6)	43	68.6 ± 39.4	(60.1 to 77.2)	84
Peak workload (W)	81.6 ± 30.2	(71.9 to 91.2)	40	81.2 ± 27.1	(79.3 to 89.4)	44	81.4 ± 28.4	(75.2 to 87.5)	84
Workload % predicted (%)	74.8 ± 30.4	(65.0 to 84.5)	40	65.3 ± 29.0	(56.4 to 74.2)	43	69.9 ± 29.9	(63.4 to 76.4)	83
V'E/VCO_2 slope	45.4 ± 11.1	(41.6 to 49.3)	35	46.2 ± 12.9	(41.6 to 50.7)	33	45.8 ± 11.9	(42.9 to 48.7)	68
Echocardiography									
sPAP (mmHg)	59.1 ± 23.3	(51.3 to 66.8)	37	65.6 ± 27.8	(56.8 to 74.3)	41	62.5 ± 25.8	(56.7 to 68.3)	78
TAPSE (mm)	2.1 ± 0.4	(2.0 to 2.3)	41	2.1 ± 0.4	(2.0 to 2.2)	43	2.1 ± 0.4	(2.0 to 2.2)	84
RA area (cm^2)	21.1 ± 9.0	(18.1 to 24.0)	38	21.6 ± 8.6	(18.9 to 24.3)	41	21.4 ± 8.8	(19.4 to 23.3)	79
RV area (cm^2)	23.3 ± 6.1	(21.0 to 25.6)	29	26.0 ± 7.9	(23.2 to 28.7)	33	24.7 ± 7.1	(22.9 to 26.5)	62
Quality of life (SF-36 Questionnaire)									
Physical summation score	45.6 ± 19.5	(40.1 to 51.1)	55	45.4 ± 19.0	(40.3 to 50.6)	50	45.5 ± 19.1	(41.8 to 49.2)	105
Mental summation score	56.9 ± 18.7	(51.6 to 62.2)	55	57.7 ± 21.3	(51.9 to 63.4)	50	57.3 ± 20.0	(53.4 to 61.2)	105
Physical functioning	53.7 ± 22.6	(47.5 to 59.9)	57	46.3 ± 24.5	(39.8 to 52.8)	53	49.9 ± 23.8	(45.4 to 54.4)	110
Physical role functioning	50.5 ± 40.9	(39.2 to 61.7)	57	39.9 ± 41.2	(29.0 to 50.8)	53	45.0 ± 45.0	(37.2 to 52.8)	110
Bodily pain	69.2 ± 29.6	(61.1 to 77.4)	57	71.0 ± 27.0	(63.8 to 78.2)	53	70.2 ± 70.2	(64.8 to 75.5)	110
General health perceptions	40.7 ± 19.7	(35.2 to 46.1)	57	46.6 ± 21.4	(41.0 to 52.3)	53	43.8 ± 20.7	(39.9 to 47.7)	110
Vitality	52.9 ± 20.2	(47.4 to 58.5)	57	54.7 ± 22.9	(48.7 to 60.8)	53	53.9 ± 21.6	(49.8 to 57.9)	110
Social role functioning	72.9 ± 25.6	(65.6 to 80.2)	57	69.8 ± 28.3	(62.2 to 77.3)	53	71.3 ± 27.4	(66.1 to 76.4)	110
Emotional role functioning	71.7 ± 37.8	(61.3 to 82.1)	57	66.1 ± 43.0	(54.7 to 77.5)	53	68.8 ± 40.5	(61.1 to 76.4)	110
Mental health	72.5 ± 17.6	(67.6 to 77.3)	57	72.0 ± 21.1	(66.4 to 77.6)	53	72.2 ± 19.4	(68.6 to 75.9)	110

In case of missing values, sample sizes are given in the column of *n*.
6MWD, 6-min walking distance; NT-proBNP, N-terminal pro brain natriuretic peptide; PH, pulmonary hypertension; RA, right atrial; RV, right ventricular; SaO_2, oxygen saturation; SD, standard deviation; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; V'E/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen consumption; WHO-FC, World Health Organization functional class.

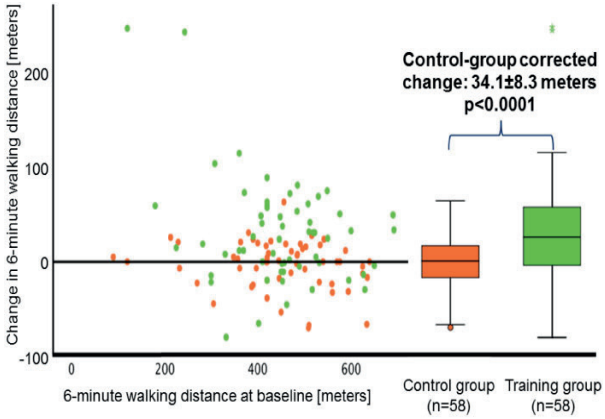


Figure 2 Primary endpoint 6-min walking distance. Patients of the training group significantly improved in 6MWD compared with the control group by 34.1±8.3 m ($P < 0.0001$).

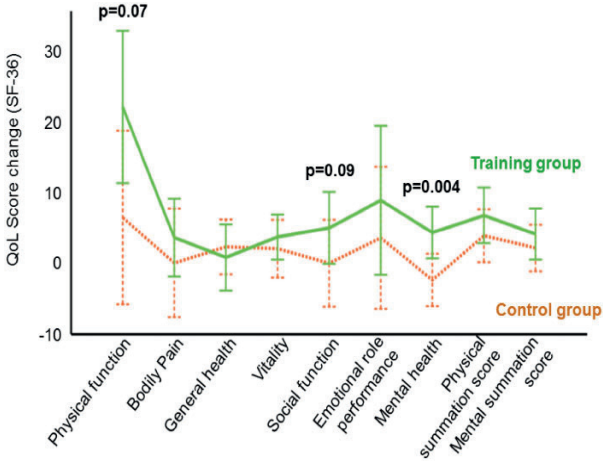


Figure 3 Secondary endpoints: quality of life. The secondary endpoint quality of life (QoL) significantly improved in the subscale mental health in the training group compared with the control group ($P = 0.004$). Two further subscales were significant in trend (physical function $P = 0.07$, social function $P = 0.09$).

difference of 22.4 m favoured active treatment.[22] In our study, clinically relevant improvement in 6MWD was supported by significant improvement of WHO-functional class and peak VO_2, which have both shown to be prognostically important and are included in the ERS/ESC risk stratification model for PAH. Though 6MWD may not be directly linked to clinical worsening events, it does represent physical exercise capacity and may, together with other parameters, be interpreted for risk stratification and QoL.[23]

Our findings are also in line with previous studies on exercise training in PH[8,12–15] and confirm the positive results in a multicentre setting

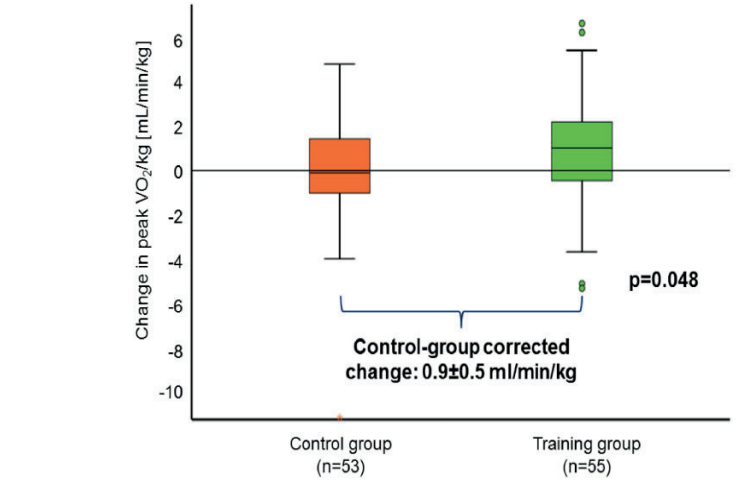


Figure 4 Secondary endpoints: peak oxygen consumption/kg. Peak oxygen consumption (VO_2)/kg body weight significantly improved by 0.9±0.5 mL/min/kg in the training group compared with the control group ($P = 0.048$).

with an inpatient start of exercise training. Moreover, this study is the largest trial of PH patients undergoing exercise rehabilitation, substantially increasing the number of patients with scientifically evaluated training effects. The improvement of 6MWD by 34.1 ± 8.3 m was clinically meaningful and lies above the threshold for clinical importance of 33 m in PH.[24] Ten patients of the training group (17.2%) improved walking distance to the low-risk category, according to ESC/ERS risk stratification. Mean 6MWD improvement was also comparable to results of medication studies in PAH,[25] and lies above the results of add-on medication in PAH with mean improvements of 19.96 m (95% CI 15.35–24.57 m).[26] The improvement of 6MWD is slightly lower than reported from other exercise training studies, which may also be attributed to the multicentricity of this study, the required adaptation of training protocols. It has already been shown that patients with high functional impairment, e.g. WHO-FC III and IV, show the most pronounced benefit by exercise training,[27] which may have influenced the results. As 25/58 patients of the training group and 26/58 patients of the control group already presented with 6MWD values ≥440 m at baseline, the improvement of walking distance may well be limited by a ceiling effect.[28] Furthermore, exercise training in PH was implemented for the first time in most of the centres, possibly resulting in suboptimal increase of training intensities, likely resulting in a lower training effect. To this end, the low number of AEs does support the focus on safety and tolerability of exercise training in this study.

Improvement of secondary endpoints

Secondary efficacy parameters such as QoL and peak oxygen consumption significantly improved in the training group compared with the control group. As peak oxygen consumption showed a significant increase, but workload and peak heart rate remained constant, the effect may be attributed to an economization of oxygen metabolism in the muscles. Patients of the control group improved peak VO_2 >10% in 29% of cases, which may possibly be attributed to the Hawthorne effect, which describes the change of behaviour that occurs in clinical trials due to the awareness of being observed. The improvement of physical and mental health parameters in this study underlines the holistic approach of exercise training to enable deconditioned PH patients to extend their individual daily activity spectrum. As NT-proBNP was not significantly increased in the training group, the exercise training also did not seem to have a negative impact on right heart insufficiency and ventricular load.

Implementation of exercise training in different countries

To implement the standardized training programme mostly for the first time in the respective European countries new collaborations were initiated between PH expert centres and rehabilitation centres, funding opportunities were sought as the in-hospital rehabilitation was not part of reimbursement schemes of most national insurance systems. Thus, this study was the first step to enable a permanent implementation of an exercise training programme for PH patients in the respective European countries.

Limitations

We cannot exclude a potential inclusion bias whereby patients who are willing to undertake an exercise intervention may reflect a more motivated and adherent group. Another limitation of this study is the amount of missing data including non-invasive haemodynamics. The number of values included for each parameter is reported to indicate

Table 2 **Changes in exercise testing and quality-of-life parameters**

Characteristic	Control group ($n = 58$)			Training group ($n = 58$)				Control-group corrected change		
	Mean ± SD or *n* and %	95% confidence interval	*n*	Mean ± SD or *n* and %	95% confidence interval	*n*	*P*-value*	Mean ± SD or *n* and %	95% confidence interval	*n*
Laboratory										
NT-proBNP (ng/L)	79.4 ± 195.5	(15.1 to 143.6)	38	16.5 ± 297.8	(-90.9 to 123.9)	32	0.31	62.9 ± 59.4	(-55.6 to 181.3)	70
6MWT										
6-min walking distance (m)	-3.4 ± 25.9	(-10.2 to 3.4)		30.7 ± 57.9	(15.4 to 45.9)		<0.0001	34.1 ± 8.3	(-50.6 to -17.5)	
Cardiopulmonary exercise testing (CPET)										
Heart rate at rest (/min)	-1.4 ± 12.4	(-5.3 to 2.4)	42	-0.1 ± 14.1	(-4.5 to 4.4)	39	0.64	1.4 ± 2.9	(-7.2 to 4.4)	83
SaO_2 at rest (%)	-0.1 ± 2.7	(-1.0 to 0.8)	39	2.3 ± 10.4	(-1.1 to 5.6)	41	0.17	2.4 ± 1.7	(-5.9 to 1.1)	78
Peak heart rate (/min)	4.9 ± 19.1	(-1.0 to 10.8)	43	3.6 ± 12.5	(-0.4 to 7.5)	40	0.70	-1.4 ± 3.5	(-5.6 to 8.3)	83
Peak SaO_2 (%)	-0.8 ± 5.7	(-2.7 to 1.1)	38	-0.5 ± 3.2	(-1.6 to 0.5)	38	0.80	0.3 ± 1.1	(-2.4 to 1.8)	78
Peak VO_2 (mL/min/kg)	0.0 ± 2.3	(-0.7 to 0.6)	53	0.9 ± 2.5	(0.3 to 1.6)	55	0.05	0.9 ± 0.5	(-1.9 to 0.0)	108
Peak VO_2 % predicted (%)	2.3 ± 8.0	(-0.2 to 4.9)	39	4.6 ± 10.2	(1.3 to 7.9)	39	0.28	-2.3 ± 2.0	(-6.4 to 1.9)	78
Peak workload (Watt)	3.7 ± 13.7	(-0.7 to 8.1)	40	4.6 ± 15.3	(-0.3 to 9.4)	41	0.80	0.8 ± 3.2	(-7.3 to 5.6)	81
Peak workload % predicted (%)	3.7 ± 12.5	(-0.3 to 7.7)	40	2.4 ± 10.8	(-1.1 to 5.8)	40	0.61	1.3 ± 2.6	(-3.9 to 6.5)	80
V'E/VCO_2 slope	-0.1 ± 5.6	(-2.1 to 1.9)	33	-1.9 ± 15.9	(-7.7 to 3.8)	32	0.55	1.8 ± 3.0	(-4.2 to 7.8)	65
Echocardiography										
sPAP (mmHg)	5.8 ± 14.2	(1.0 to 10.6)	36	-4.0 ± 12.5	(-8.1 to 0.1)	38	0.002	9.8 ± 3.1	(3.6 to 16.0)	74
TAPSE (mm)	3.2 ± 29.2	(-0.1 to 0.1)	41	5.5 ± 41.7	(-0.1 to 0.2)	38	0.77	-2.4 ± 8.2	(-18.6 to 13.9)	79
RA area (cm^2)	-0.2 ± 6.7	(-2.5 to 2.1)	36	0.4 ± 6.0	(-1.6 to 2.3)	39	0.70	-0.6 ± 1.5	(-3.5 to 2.4)	75
RV area (cm^2)	0.3 ± 2.1	(-0.5 to 1.1]	29	-0.3 ± 3.1	(-1.5 to 0.9]	28	0.41	0.6 ± 0.7	(-0.8 to 2.0]	57
Quality of life										
Physical summation score	3.9 ± 13.2	(0.2 to 7.7)	50	6.4 ± 14.4	(8.1 to 18.1)	49	0.37	2.5 ± 2.8	(-8.0 to 3.0)	99
Mental summation score	2.2 ± 11.6	(-1.1 to 5.5)	50	4.3 ± 11.7	(20.6 to 38.6)	49	0.38	2.1 ± 2.4	(-6.8 to 2.5)	99
Physical functioning	4.3 ± 13.2	(0.5 to 8.1)	48	8.1 ± 18.1	(3.0 to 13.3)	50	0.23	3.8 ± 3.2	(-10.2 to 2.5)	104
Physical role functioning	6.1 ± 42.2	(-5.5 to 17.8)	53	20.6 ± 38.6	(9.7 to 31.5)	51	0.07	14.5 ± 7.9	(-30.2 to 1.3)	104
Bodily pain	0.7 ± 26.7	(-6.7 to 8.1)	53	3.4 ± 18.3	(-1.8 to 8.5)	51	0.55	2.7 ± 4.5	(-11.6 to 6.2)	104
General health perceptions	3.0 ± 14.1	(-0.9 to 6.9)	53	0.6 ± 16.6	(-4.1 to 5.3)	51	0.23	-2.4 ± 3.0	(-3.6 to 8.4)	98
Vitality	2.5 ± 14.2	(-1.5 to 6.4)	53	4.6 ± 11.3	(1.4 to 7.8)	51	0.39	2.2 ± 2.5	(-7.2 to 2.9)	104
Social role functioning	0.1 ± 21.1	(-5.8 to 5.9)	53	6.6 ± 17.8	(1.6 to 11.6)	51	0.09	6.6 ± 3.8	(-14.1 to 1.0)	104
Emotional role functioning	4.7 ± 35.5	(-5.6 to 1.4)	53	8.5 ± 34.5	(1.7 to 8.7)	51	0.58	3.8 ± 6.9	(-17.4 to 9.8)	104
Mental health	-2.1 ± 12.8	(-5.6 to 1.4)	53	5.2 ± 12.5	(1.7 to 8.7)	51	0.004	7.3 ± 2.5	(-12.2 to -2.4)	104

In case of missing values, sample sizes are given in the column of *n*.
6MWT, 6-min walk test;NT-proBNP, N-terminal pro brain natriuretic peptide; O_2, oxygen; RA, right atrial; RV, right ventricular; SaO_2, oxygen saturation; SD, standard deviation; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; V'E/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen consumption.
**P*-value: significance of changes compared with baseline between groups.

Table 3 Adverse events with occurrence ≥5%

	Group		Total
	Control ($n = 47$)	Training ($n = 52$)	
Adverse events			
Arrhythmia of any kind	5	3	8
Respiratory infection	3	4	7
Total	8	7	15
Serious adverse events			
Diabetes, decompensated	0	1	1
Oedema, generalised	0	1	1
Haemoptysis	1	0	1
Stroke	0	1	1
Total	1	3	4

parameters which need to be interpreted with caution due to missing data. Especially for haemodynamic changes with exercise training in PH further data, preferably including right heart catheterization, are needed.

It is intrinsically not possible to blind a training study. However, investigators involved in data analysis were blinded as far as possible including clinical data and QoL assessments. Due to organizational reasons, not all centres were, however, able to perform blinded assessments of 6MWD, though the walking distance of previous assessments was not known to the investigators.

Total number of AEs did not differ between groups, though patients of the training group had a higher frequency of serious AEs and a higher dropout rate during the study. None of the AEs or serious AEs were stated to be related to the training intervention.

For safety concerns severely deconditioned patients with very restricted mobility range were not included in this study. Thus, we cannot exclude a selection bias towards more active patients.

As most of the patients in the control group were offered to participate in the exercise training programme after having finished their final examination, long-term data for comparison between exercise training and control group were not available. No daily physical activity measurements were part of the protocol. Thus, it is not possible to quantify whether general activity increased after the exercise training.

Conclusions

This is the first multicentre and the largest randomized, controlled study so far, reporting the beneficial effects of exercise training on 6MWD, QoL, and oxygen consumption in patients with PH. Study results are in line with previous studies. Exercise training was successfully implemented in all participating centres, including PH expert centres as well as experienced rehabilitation facilities. Further large multicentre studies are needed to investigate the haemodynamic effects of this intervention on different subtypes of PH.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Publication II

The experience, prerequisites, and the barriers in organizing a specialized rehabilitation program for patients with pulmonary hypertension.

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The Experience, Prerequisites, and the Barriers in Organizing a Specialized Rehabilitation Program for Patients with Pulmonary Hypertension

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Keywords
Pulmonary hypertension · Rehabilitation · Exercise program · Training · Implementation

Abstract
Background: Pulmonary hypertension (PH) is a severe progressive disease, associated with reduced exercise capacity and poor quality of life. Although scientific evidence supports the incorporation of specialized training in the treatment of PH, it is only available in a few countries. ***Objectives and Methods:*** This article aims to share the experience of implementing a PH rehabilitation program, to summarize the barriers and prerequisites for launching this service, and to assess its early effect. We retrospectively analyzed our pathway in organizing this program, by singling out essential steps. ***Results:*** The preparation phase took about 14 months. Establishing and running of a PH rehabilitation program required dedicated rehabilitation specialists to join the multidisciplinary PH expert team. Team members needed to gain special knowledge on exercise training in severely compromised patients; thus, supervision and education by experienced consultants was crucial. The main eligibility criteria for patients were stable status, optimal medical treatment, and motivation to undergo the training. The first results evaluating the effect of a specialized PH training program in 9 patients are promising. Seven of them improved their functional capacity over the period of 15 weeks. ***Conclusions:*** Despite a number of challenges and barriers, the implementation of a specialized rehabilitation program should be encouraged in a few dedicated PH expert centers per country, who are capable to fulfill all prerequisites and organizational aspects. Local PH experts, supervision by an experienced center, in-patient rehabilitation facilities, dedicated personnel, equipment, and patient motivation are essential.

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Introduction

Pulmonary hypertension (PH) is a severe progressive disease, associated with reduced exercise capacity, low quality of life, and poor survival. PH may complicate a majority of cardiovascular and systemic diseases [1]. PH is defined by pressure elevation in the pulmonary artery, and after the sixth World Symposium on Pulmonary Hypertension, mPAP >20 mm Hg (measured invasively) is considered to be abnormal [2].

The most recent guidelines, published jointly by the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), suggest complex treatment of precapillary PH, consisting of disease-targeted and supportive medical therapy with general measures. In this regard, physical activity and supervised rehabilitation, psychosocial support, and other nonpharmacological treatment strategies are advised [1]. At the same time, excessive physical activity that leads to distressing symptoms is not recommended for these patients, due to the risk of overexertion and increased shear stress on the pulmonary vascular walls, which could trigger the worsening of the disease. Exercise training should be considered in physically deconditioned PH patients under optimal medical therapy, and it should be supervised by PH experts [1].

Numerous clinical trials, mainly focusing on the rehabilitation of pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH) patients, have demonstrated its safety and effectiveness using different models of exercise training regimens [3–14]. The ERS statement on exercise training and rehabilitation of patients with severe chronic PH summed up the findings of studies, which enrolled 784 PH patients in total, including 6 randomized controlled trials (RCTs), 3 controlled trials, 10 prospective cohort studies, and 4 meta-analyses [15]. As summarized in this statement, training programs have been shown to significantly improve exercise capacity, muscular function, and quality of life [15]. The only prospective RCT examining the effect of specific training on invasively measured hemodynamics at rest and during exercise has also revealed positive results [11].

Importantly, practical experience shows that most PH patients are highly motivated to participate in a specialized rehabilitation program [16]. Limited availability and underutilization of exercise training remains a drawback in many specialized PH centers. A recent first multicenter RCT on feasibility, safety, and efficacy of exercise training on PH showed clearly positive results: the primary endpoint – change of 6-min walking distance – significantly improved by 30.7 ± 57.9 m in the training group, while it slightly decreased in the control group (−3.4 ± 25.9 m; $p < 0.0001$) [17]. Moreover, within this study, a standardized specialized training program, initiated in-hospital, was launched successfully in 10 European countries (including our center in Vilnius). Our aim was to share our experience in implementing a specialized PH rehabilitation program, identify and describe the prerequisites and barriers in organizing such service, and show the early effect of this newly created program.

Materials and Methods

We retrospectively analyzed our center's experience in initiating, organizing, and executing a specialized PH rehabilitation program, identifying the main prerequisites and the barriers for its establishment, finding practical solutions, and evaluating the first results. We assessed our practice in detail by singling out 9 necessary steps, shown in Figure 1.

Results

Identification of Eligibility Criteria for PH Rehabilitation

The Competence Centre for Pulmonary Hypertension in tertiary care Vilnius University Hospital was established in 2010. The specialized healthcare professionals see the patients with suspected and confirmed PH (most often PAH or CTEPH) daily. Moreover, all evidence-based disease-targeted treatment options, including combination therapy, are available and fully reimbursed in Lithuania. Per year, 110–140 patients are routinely managed with PAH- and CTEPH-specific drug therapies in this center. In the course of specific treatment, we realized that a part of them could be good candidates for a PH rehabilitation program. Moreover, some of them were greatly interested in the training, actively asked for the instructions of physical activity, or even performed exercises themselves without any professional recommendations or supervision. Identification criteria for patient's eligibility for the rehabilitation were optimal specific PH therapy, stable status, motivation to train, and no orthopedic or other limitations for exercising, such as acute heart failure, infection, and exercise-induced arrhythmia.

Assemblage of Multidisciplinary Team

Various healthcare professionals are involved in the diagnosis and treatment of PH patients: the key members of our multidisciplinary team were cardiologists, pulmo-

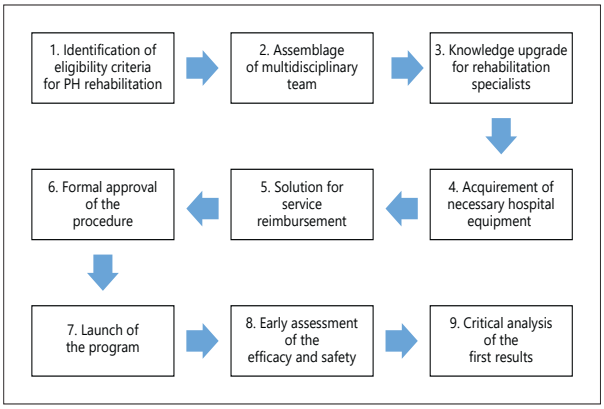

Fig. 1. Essential steps in establishing a PH rehabilitation program. PH, pulmonary hypertension.

nologists, radiologists, and nurses; we meet for the discussions every week or even more often, if necessary. For implementing the PH training program, our regular multidisciplinary team was expanded by 2 qualified rehabilitation physicians, 3 physiotherapists, 1 occupational therapist, and 1 psychologist.

Knowledge Upgrade for Rehabilitation Specialists

In Lithuania, in-hospital rehabilitation clinics are an established treatment option, but rehabilitation is mainly performed after acute disease and less in stable, but severely compromised state. Our choice was to profit from an experienced and established center in the rehabilitation of PH patients. Lithuanian cardiologists, who were specialized in PAH/PH, together with rehabilitation physicians and physiotherapists visited the Thoraxklinik at Heidelberg University Hospital and Rehabilitation Clinic Königstuhl, where they learned the methods, protocols, and components of the well-established exercise and respiratory training program. Though the nurses, working at our hospital in-patient rehabilitation department, were quite experienced in the care of rehabilitated patients with heart and respiratory failure, we additionally instructed them about PH patients, particularly focusing on the possible adverse events, signs of deterioration, and mitigation of side effects.

The training protocol from Heidelberg was adapted to local conditions, including the following characteristics: in-hospital start of rehabilitation (for 14–21 days) followed by continuation of the exercises at home, interval ergometer training (20 min, 5 days a week), respiratory therapy (30 min 5 days a week), dumbbell training of single muscle groups (30 min 5 days a week), guided walks, mental gait training (individually, at least 2 times a week), and conventional elements, such as massages, relaxation, lectures, and patient education as already described [3, 11, 14]. Training intensity was started at 40–50% of maximal patient's workload, reached during the ergometer test at baseline, and increased within the in-hospital period, trying to achieve the maximal baseline workload (maintaining 60–80% of the peak heart rate and avoiding desaturation <90%). Less than 21-day duration of the in-hospital phase in some patients (due to limited reimbursement) was the main difference of the Lithuanian program, compared with the Heidelberg protocol. Before leaving the hospital, each patient received individualized written recommendations and how to continue exercising at home, including detailed instructions with the pictures for each exercise and recommended heart rate interval during workouts. We did not specifically supervise our patients during their training at home, but each of them was provided with the contacts of the physiotherapist and cardiologist (e-mail and phone number) and could communicate in case of any questions or difficulties.

Acquirement of Necessary Hospital Equipment

We composed a list of the equipment required for the training of PH patients – cycle ergometer, weights, gymnastic rubber, balls, and mats. Pulse oximeter and blood pressure monitor are necessary for the supervision of the patient's status. A mobile oxygen tank is mandatory, as

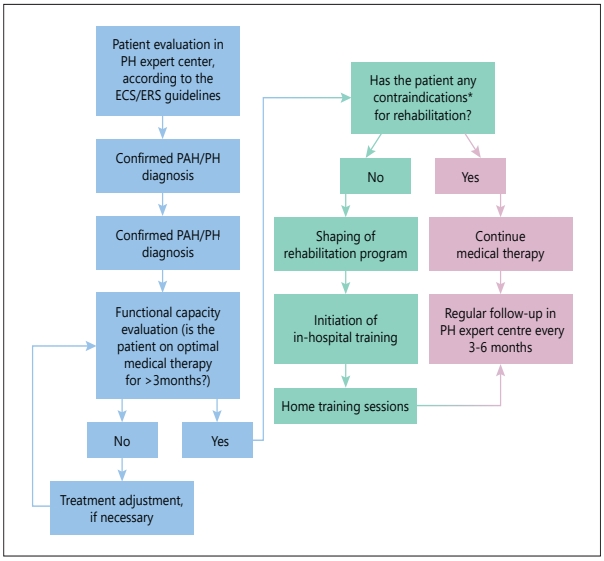

Fig. 2. Specialized PH rehabilitation scheme for an individual patient. PH, pulmonary hypertension. *The most common contraindications: unstable status, acute infection, severe anemia, orthopedic diseases, lack of patient's motivation, suspicion of patient's inability to cooperate adequately.

some patients need additional oxygen supply during exercise.

In our rehabilitation clinic, most of the necessary equipment was already in place. For an individual PH patient workout, a cycle ergometer with an interval training opportunity, pulse oximeter, and oxygen tank were provided additionally.

Solution for Service Reimbursement

In Lithuania, a standard reimbursement for in-hospital rehabilitation from the National Health Insurance Fund (NHIF) is ensured for the patients after acute cardiovascular diseases (e.g., myocardial infarction and stroke), trauma, or surgery. For stable patients with chronic heart diseases (e.g., chronic heart failure and PH), only an outpatient rehabilitation program, consisting of a limited number of procedures, is funded routinely. We have considered an outpatient PH rehabilitation service as an alternative to the inpatient program. The main factors that determined our choice to seek for opportunities of in-hospital service establishment were the endeavor of maximum safety, a sufficient number of training procedures, and patient convenience (only a very small number of such patients could arrive for exercising daily 5 days per week). In our center, the establishment of an in-hospital rehabilitation program for stable PH patients was possible due to the positive NHIF attitude to the requests for individual patients, each on an exceptional basis. For every patient separately, before the application to NHIF, we organized the multidisciplinary meeting. If the team recommended specialized training, the protocol and conclusions of the discussion, together with an official application, signed by the general director of the hospital, were referred to NHIF. Important factors for the NHIF decision were the subject's high motivation for exercise training and predicted potential of functional improvement based on clinical status. Moreover, NHIF decisions were not uniform in terms of the duration of the in-hospital rehabilitation period. Additional documentation filing separately for an individual patient was time consuming, so healthcare professionals planned the need of extra time.

Formal Approval of the Procedure

After the specialized PH rehabilitation team was trained, the necessary equipment was provided, and service reimbursement issues were resolved; we described the methodology of this service in accordance with the internal regulations and got approval from our medical institution.

Table 1. Patients' demographics, changes in functional capacity, and quality of life within 15 weeks of training

Patient No.	Parameters											
	sex	age	mPAP, mm Hg	in-hospital rehab. duration, days	6 MWT before, m	6 MWT after, m	peak VO_2/kg before, mL/kg/min	peak VO_2/kg after, mL/kg/min	physical summary score before*	physical summary score after*	mental summary score before*	mental summary score after*
1	F	50	75	18	410	410	12.4	11.9	38.1	30.6	46.9	46.8
2	M	71	41	18	450	**	17.7	18.7	62.5	78.8	53.8	86.8
3	F	31	60	14	595	575	18.9	15.7	26.3	45.8	30.0	49.0
4	F	54	64	14	420	480	12.0	14.0	50.6	72.5	83.8	84.0
5	F	42	78	20	446	470	12.0	14.0	28.8	76.9	42.0	77.3
6	M	26	27	14	570	650	18.7	20.0	86.9	71.9	82.1	67.6
7	M	75	65	20	420	400	12.3	14.0	43.1	68.8	55.8	65.6
8	F	55	53	18	535	530	13.6	14.8	33.1	60.0	84.4	86.6
9	F	58	56	18	390	440	12.3	13.7	23.8	33.1	48.2	49.2

F, female; M, male; mPAP, mean pulmonary arterial pressure; 6 MWT, 6-min walk test; VO_2, oxygen uptake. * Evaluated by the SF-36 questionnaire, a higher score indicating a better quality of life. ** The patient did not perform 6 MWT 15 weeks after rehabilitation (severe gout leg pain).

Launch of the Program

The process of the organization from the initial contact with the Heidelberg team until the enrollment of the first patient took about 14 months. Before starting the training program, each patient was carefully evaluated, including functional capacity assessment by a 6-min walking test (6 MWT) and cardiopulmonary exercise test (CPET), which were the basis for shaping an individualized training program. Nine PH patients participated in the newly established rehabilitation program, during a 2-year period (from February 2017 to February 2019). The specialized PH rehabilitation pathway scheme for an individual patient in Lithuania is shown in Figure 2. The prerequisites and the barriers that we identified during the organization of this program are summarized in Table 1.

Early Assessment of the Efficacy and Safety

To analyze the effect of this newly set up specialized rehabilitation program, functional tests (6 MWT and CPET) were repeated after 15 weeks of training. For the health-related quality of life estimation, we used the 36-item short-form health survey (SF-36) [18]. SF-36 scores were converted to a scale of 0–100, a higher score indicating a better quality of life.

Three men and 6 women participated in the program. Four of these patients were diagnosed with idiopathic PAH and 5 CTEPH (2 of them had residual PH after pulmonary endarterectomy). Eight patients were in the World Health Organization (WHO) functional class (FC) III and one in WHO FC II. All the patients were on optimized targeted PH therapy. Patients' demographics and changes in functional capacity and quality of life over 15 weeks are shown in Table 2.

The 6 MWT distance and SF-36 scores improved in the majority of patients. The median improvement on 6 MWT distance was 14.5 m, and median peak oxygen consumption (VO_2) on CPET increased by 1.2 mL/kg/min. The median of the 2 summation scores of the SF-36 also advanced: physical and mental summary score improved by 80 and 25%, respectively. During the in-hospital phase, no adverse events were detected, while during 15 weeks of continuation at home, 1 patient experienced severe leg pain, caused by acute attack of gout (the disease was known from his medical history).

Critical Analysis of the First Results

After the early assessment of the efficacy and safety of the specialized rehabilitation program, the first results were critically reviewed. The changes in functional capacity and quality of life were positive in our patients; however, the improvement was less significant compared to the results of the core center in Heidelberg. To improve our skills, Vilnius team members visited Heidelberg for a second time, to relearn the subtleties of specialized PH rehabilitation, paying particular attention to the appropriate selection of training intensity for each patient, individualized mental gait training methodologies, and the technique of 6 MWT. An additional coaching in Heidelberg gave us more confidence to be less conservative in

Table 2. Prerequisites and barriers for establishment of a specialized PH rehabilitation program

Prerequisites	Barriers
PH specialists	
Specialized PH center	Deficiency of local experience on PH treatment
Multidisciplinary team	
Supervision of more experienced center in PH training	
Rehabilitation specialists	
Experienced rehabilitation team	Lack of experience for PH training
Special knowledge on exercise training in severely compromised patients	
Possession of hospital equipment (e.g., cycle ergometer, weights, pulse oximeter, and mobile oxygen tank)	Shortage of necessary equipment
Patients	
Personal abilities to train – no orthopedic or other limitations	Orthopedic patient's limitations/comorbidities
Motivation	Loss of motivation over time
	Inability to continue at home
	Unstable status – worsening
Healthcare system	
Availability of disease-targeted medications	Lack of specific treatment
Established rehabilitation clinics/facilities	Absence of rehabilitation clinics within the healthcare system
Service reimbursement	No or limited reimbursement

PH, pulmonary hypertension.

gradual increase of the exercise intensity and to achieve the maximal workload that was reached at baseline cardiopulmonary exercise test in all further cases within the in-hospital period (yet, avoiding desaturation and too high heart rate, as described earlier).

We also looked at the feedback and adherence to the physical training of our patients. All patients were satisfied with the program and reported that they continued training at home for at least 15 weeks. All, except one, continued aerobic training with a cycle ergometer; 1 patient switched from bicycle workout to daily walking (he was instructed about walking loads by the rehabilitation team before finishing the in-patient phase of the program). While most of the patients continued intensive rehabilitation daily for about 9–12 months, later we observed a drop of motivation. The reasons for cessation were diverse: changes in personal life, disease progression, and most often decrease in interest after time. Though not continuing daily exercise, most of the patients at least sometimes performed the respiratory workout and implemented skills, gained during mental gait training, into their daily activities. Some of the patients, especially with the progressing disease, expressed their will to repeat this specialized rehabilitation program, starting in the hospital again.

Discussion/Conclusion

The establishment of a new treatment strategy requires additional organizational efforts that are mostly dependent on the national healthcare system and financing models. Given the limited availability of special rehabilitation service for PH patients in many countries, this analysis, describing the process, barriers, and prerequisites of the implementation of an exercise program in Lithuania, can be of interest for PH specialists worldwide.

To the best of our knowledge, this is the first detailed description of the processes and steps that may help in the establishment of PH rehabilitation. Though this report is not intended to be used as a guide, it provides information about essential organizational steps for this important therapy.

The implementation of such programs in different countries has been limited by several factors, such as lack of experience, specialists, clinical facilities, and often hardly accessible reimbursement for this kind of treatment. Importantly, Lithuanian NHIF was flexible enough to fully cover the cost of the specialized rehabilitation program for individual PH patients, starting with an in-hospital stay. That allowed us to treat patients without any additional charges.

Before 2015, many European countries, such as the United Kingdom, Ireland, Spain, and others, had no dedicated exercise training programs for PH patients, and some of them had no possibilities for an in-hospital start of PH rehabilitation, which is preferable [16]. Meanwhile, the experience in PH rehabilitation of the Heidelberg program is >15 years. After a large European RCT, with a core center in Heidelberg, exercise training for PH was started in 11 centers across 10 European countries, including our center [17].

Since in-hospital rehabilitation clinics are established within the healthcare system in Lithuania, the program can be performed in the most secure way. Until now, the rehabilitation programs in our country mostly have been focused on the primary and secondary prevention of coronary heart disease [19–21]. Pulmonary rehabilitation for patients with chronic obstructive pulmonary disease or other chronic respiratory diseases [22–24] is underutilized here.

Our results on the effect of 15-week PH exercise training on patients' functional capacity and quality of life are positive and in line with the data published earlier [15, 17]. Moreover, the program was safe and well tolerated, and no arrhythmia or other serious adverse events occurred during the 12-month follow-up period. Of note, for one of the patients (who did not show any positive result after 15 weeks of training), specific PAH medical treatment had to be enhanced (adding subcutaneous treprostinil) after 6 months. The possible reason for the need of additional treatment might be nonoptimal PAH therapy before the enrollment in the rehabilitation program.

The learning curve of the rehabilitation team should be acknowledged, which in our case was much more experienced in the training of patients after myocardial infarction or cardiac surgery and less in the rehabilitation of stable, but severely affected patients with poor functional capacity. Moreover, rehabilitation of PH patients demands specific skills and knowledge on shaping the appropriate individualized low-intensity physical training. The knowhow of gradually increasing the exercise intensity is also very important, as too high intensity comes with the risk of complications; on the other hand, if the training intensity is too low, the training may be less effective. Therefore, a more conservative increase of training intensities was applied, which could be one of the reasons for a lower training effect at the initial stage.

The effectiveness of such a treatment is highly dependent on patient's adherence to given recommendations and daily training. We enrolled only those patients, who were motivated to participate in this program, but we did not make any special assessment of their adherence. We also did not use any specific tools for the encouragement – the main motivator for the patient to continue was increasing individual functional capacity and better well-being after exercising.

For effective maintenance of physical activity, repeated consultations of rehabilitation specialists (e.g., every 3 months) could be useful. During such consultations, rehabilitation physicians or physiotherapists could evaluate the dynamics of the subject's functional capacity and, if necessary, adjust the training modes, encouraging the patient to continue training.

Despite a number of challenges and barriers, the implementation of a specialized rehabilitation program should be encouraged in the dedicated PH expert centers. Since PAH is a rare disease, it is crucially important to bundle the expertise and provide this advanced service in the most secure and effective way. Local PH experts, supervision by an experienced center, in-patient rehabilitation facilities, dedicated personnel, equipment, and patient motivation are essential.

Limitations

The main aim of this article was to share our experience of implementing a PH rehabilitation program, summarizing the barriers and prerequisites. We used the assessment of the effect for the patients as an additional tool for verification of this newly created program. The numbers of the patients are low, so the results might be prone to bias.

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Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Vilnius Regional Bioethics Committee in Lithuania approved the study (No. 158200-16-867-381; 2016-11-08). Each patient gave his/her written informed consent before inclusion in this study.

Conflict of Interest Statement

Eglė Palevičiūtė has no conflicts of interest to declare. Lina Gumbienė has received speaker's fees from Actelion and Pfizer and served on the Actelion advisory board. Elena Jurevičienė has no conflicts of interest to declare. Toma Šimbelytė has no conflicts of interest to declare. Ieva Laucevičienė has no conflicts of interest to declare. Aleksandras Laucevičius has no conflicts of interest to declare. Jūratė Barysienė declares personal fees from Bayer, Pfizer, Servier, Novartis, and Boehringer Ingelheim. Christina A. Eichstaedt has no conflicts of interest to declare. Nicola Benjamin received speaker fees from Actelion/Janssen and Bayer/MSD outside this study. Ekkehard Grünig has received honoraria for consultations and/or speaking at conferences from Bayer/MSD, Actelion/Janssen, GWT-TUD, OMT/United Therapeutics, and GSK. Jelena Čelutkienė declares personal fees from Novartis, Boehringer Ingelheim, AstraZeneca, Amgen, and Sanofi.

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Author Contributions

E.G., C.A.E., and N.B. initiated the program and prepared the protocol. E.P., L.G., E.J., and I.L. were the main persons in organizing the pulmonary hypertension rehabilitation program in Lithuania. E.P., J.C., L.G., E.J., E.G., C.A.E., and N.B. interpreted the data and drafted the manuscript. E.P. and J.C. prepared the figure. All authors contributed to writing and editing the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Publication III

Effect of supervised training therapy on pulmonary arterial compliance and stroke volume in severe pulmonary arterial hypertension and inoperable or persistent chronic thromboembolic pulmonary hypertension.

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Effect of Supervised Training Therapy on Pulmonary Arterial Compliance and Stroke Volume in Severe Pulmonary Arterial Hypertension and Inoperable or Persistent Chronic Thromboembolic Pulmonary Hypertension

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Keywords
Pulmonary hypertension · Pulmonary arterial hypertension · Pulmonary arterial compliance · Training · Stroke volume · Right heart catheter

Abstract
Background: Pulmonary arterial compliance (PAC) is a prognostic parameter in pulmonary arterial hypertension (PAH) reflecting the elasticity of the pulmonary vessels. ***Objectives:*** The objective of this post hoc analysis of a prospective randomized controlled trial (RCT) was to assess the effect of exercise training on PAC and stroke volume (SV) in patients with PAH and persistent/inoperable chronic thromboembolic pulmonary hypertension (CTEPH). ***Method:*** From the previous RCT, 43 out of 87 patients with severe PAH ($n = 29$) and CTEPH ($n = 14$) had complete haemodynamic examinations at baseline and after 15 weeks by right heart catheterization and were analysed (53% female, 79% World Health Organization functional class III/IV, 58% combination therapy, 42% on supplemental oxygen therapy, training group $n = 24$, and control group $n = 19$). Medication remained unchanged for all patients. ***Results:*** Low-dose exercise training at 4–7 days/week significantly improved PAC (training group 0.33 ± 0.65 mL/mm Hg vs. control group −0.06 ± 1.10 mL/mm Hg; mean difference 0.39 mL/mm Hg, 95% confidence interval [CI] 0.15–0.94 mL/mm Hg; $p = 0.004$) and SV (training group 9.9 ± 13.4 mL/min vs. control group −4.2 ± 11.0 mL/min; mean difference 14.2 mL, 95% CI 6.5–21.8 mL; $p < 0.001$) in the training versus control group. Furthermore, exercise

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training significantly improved cardiac output and pulmonary vascular resistance at rest, peak oxygen consumption, and oxygen pulse. ***Conclusions:*** Our findings suggest that supervised exercise training may improve right ventricular function and PAC at the same time. Further prospective studies are needed to evaluate these findings.

Introduction

Pulmonary arterial hypertension (PAH) and inoperable or persistent chronic thromboembolic pulmonary hypertension (CTEPH) are devastating and progressive pulmonary vascular diseases that lead to right heart failure and premature death. Mortality for PAH and inoperable or persistent CTEPH remains high despite therapeutic advances in the last 2 decades [1]. To assess prognosis and to guide therapy, current guidelines recommend a combination of treatment targets including haemodynamic measurements by right heart catheter, transthoracic echocardiography at rest, biomarkers, and exercise testing [2], which were predominantly derived from large registries like Compera [3], REVEAL [4], and the French registry [5]. To further improve risk assessment, therapy-guidance and patient outcome, new prognostic markers are needed.

Pulmonary Arterial Compliance

Pulmonary arterial elasticity maintains low pulse pressure and low pulsatile afterload for the right ventricle. Pulmonary arterial compliance (PAC) is calculated as

$$PAC = \frac{SV}{PP} = \frac{\left(\frac{CO}{heart\ rate}\right)}{sPAP - dPAP}$$

which is the simplest and most practical method for estimating pulmonary arterial elasticity [6]. It plays a key role in accommodating much of the SV of the right ventricle due to passive arterial expansion and in maintaining diastolic pulmonary blood flow due to arterial recoil. PAC decreases in pulmonary hypertension (PH) [6] and correlates with PH severity [7]. The increase in pulmonary arterial stiffness is associated with accumulation of collagen and loss of elastin in the proximal pulmonary arteries [8–12]. There is even further evidence suggesting that loss of PAC may actually initiate PH [13]. Decreased PAC increases right ventricular pulsatile afterload [12,14,15], which leads to decreased CO over time and finally to right heart failure [12, 16]. It has been shown that decreased PAC is independently associated with RV failure, dilatation, and hypertrophy [17], regardless of improvements of pulmonary vascular resistance (PVR) achieved under targeted PH therapy [14, 16, 18].

The aim of this post hoc analysis was to assess, whether supervised training could also improve vascular stiffness by increasing PAC and RV function by increasing SV apart from improving PVR, CO, and cardiac index as classic predictors of outcome.

Methods

The full design and methodology of the initial randomized controlled trial (RCT) has been published previously [19]. This prospective RCT, conducted from June 2010 (first patient, first visit) to May 2015 (end of study), was a 15-week study investigating the effects of supervised exercise training in patients with severe but stable PAH and inoperable or persistent CTEPH. Patients were randomized to either training therapy or a control group. Primary end point was the change in peak VO_2. Secondary end points included changes in haemodynamics at rest and during exercise, biomarkers, and echocardiography parameters as previously described [19].

Post hoc Analysis and Statistical Methods

The analyses were performed by 2 statisticians (N.B. and C.F.). Data are given as mean values ± standard deviations. We performed a post hoc analysis of the study by Ehlken et al. [19] focussing on SV and PAC. SV was calculated as

$$SV = \left(\frac{CO}{heart\ rate}\right)$$

PAC was calculated according to the formula

$$PAC = \frac{SV}{PP} = \frac{\left(\frac{CO}{heart\ rate}\right)}{sPAP - dPAP}$$

To enhance interpretation of PAC, further parameters reflecting RV load were calculated. RV afterload can be described as the sum of RV pressures throughout RV ejection. Effective arterial elastance (EA) is a lumped measure of RV afterload [20] and integrates pulsatile and resistive loading of the RV. EA is calculated as

$$EA = \frac{end - systolic\ pressure}{SV} = \frac{sPAP}{SV}$$

For further interpretation of the primary research question, change of clinical parameters including 6-min walking distance (6MWD), haemodynamic parameters, parameters of cardiopulmonary exercise testing, and N-terminal pro brain natriuretic peptide (NT-proBNP) were analysed. Descriptive analyses of these parameters include mean and standard deviation of baseline measurements and difference between baseline and 15 weeks of exercise training as well as quartiles of the differences. Non-parametric Mann-Whitney U tests have been performed to assess the differences of

Table 1. Baseline characteristics

	Control	Training	*p* value
Patients, *n*	19	24	
Gender male/female, *n*	8/11	12/12	0.606
Age, years	58±14	55±15	0.506
Height, cm	171±9	170±10	0.736
Weight, kg	80±18	78±17	0.711
WHO functional class, *n* (%) baseline			
II	3 (15.8%)	4 (16.7%)	
III	14 (73.7%)	19 (79.2%)	0.519
IV	1 (5.3%)	0 (0.0%)	
Diagnosis, *n* (%)			
PAH	10 (52.6%)	19 (79.1%)	0.065
CTEPH	9 (47.4%)	5 (20.9%)	
NT-proBNP, pg/mL	1,453±1,658	1,233±2,586	0.765
Right heart catheterization			
Mean pulmonary arterial pressure, mm Hg	38.1±10.8	40.4±12.5	0.529
PVR, WU	5.76±2.62	7.36±3.26	0.090
Central venous pressure, mm Hg	6.9±4.3	7.3±3.6	0.742
Pulmonary arterial oxygen saturation, %	63.2±9.0	64.6±11.5	0.678
Pulmonary arterial wedge pressure, mm Hg	10.2±4.5	8.7±2.4	0.168
Cardiac index, L/min/m^2	2.5±0.4	2.7±0.7	0.294
PAH-targeted medication, *n* (%)			
Endothelin receptor antagonist	11 (57.9%)	17 (70.8%)	0.377
Phosphodiesterase-5 inhibitor	12 (63.25%)	18 (75.0%)	0.401
Prostanoids inhaled	4 (21.1%)	3 (12.5%)	0.451
Prostanoids oral	0 (0%)	1 (4.2%)	0.368
Calcium channel blockers	2 (10.5%)	3 (12.5%)	0.841
Imatinib	1 (5.3%)	0 (0%)	0.368
Soluble guanylate cyclase stimulator	2 (10.5%)	3 (12.5%)	0.841
Combination therapy, *n* (%)			
Monotherapy	9 (47.4%)	9 (37.5%)	
Dual therapy	8 (42.1%)	10 (41.7%)	0.939
Triple therapy	2 (10.5%)	5 (20.8%)	
Oxygen therapy, yes/no, *n*	9/10	9/15	0.515

Values are presented as mean ± standard deviation unless specified otherwise. *p* values were derived from χ^2 tests or two-sided unpaired Student's *t* tests. WHO functional class was missing for 1 patient in each group. NT-proBNP at baseline was missing for 3 patients in the control group. Pulmonary arterial oxygen saturation was missing for 1 patient in the control group and 3 patients in the training group. Cardiac index was missing for 1 patient in each group. NT-proBNP, N-terminal pro brain natriuretic peptide; PAH, pulmonary arterial hypertension; WHO, World Health Organization; PVR, pulmonary vascular resistance; WU, Wood units; CTEPH, chronic thromboembolic pulmonary hypertension.

the changes between training and control group. To correct for haemodynamic imbalances between groups, differences of changes between groups were compared by analysis of covariance with baseline mean pulmonary arterial pressure and PVR as covariates. All analyses have been performed using IBM SPSS 25 (SPSS Statistics V25, IBM Corporation, Somers, NY, USA).

Statement of Responsibility

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Study Population and Randomization

Forty-three out of 87 patients with severe PAH ($n = 24$) or inoperable or persistent CTEPH ($n = 19$) had complete haemodynamic examinations at baseline and after 15 weeks by right heart catheterization and were analysed per protocol. Medication remained unchanged for all patients. Twenty-four patients were analysed from the training group, and 19 from the control group. The con-

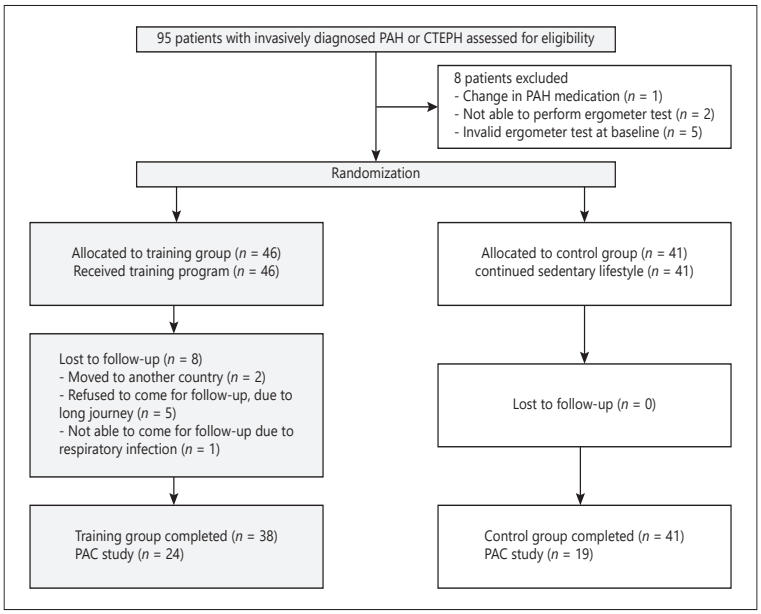

Fig. 1. Study design. The flow chart shows the number of patients for each study group, the number and reasons for exclusion, and the number of patients valid for PAC analysis. PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; PAC, pulmonary arterial compliance.

trol and training groups were well balanced in their baseline characteristics, disease severity, and medication (Table 1). Mean age in the training group was 55 ± 15 years and 58 ± 14 years in the control group. Nineteen patients in the training group had PAH (79.1%) versus ten patients in the control group (52.6%). Five patients in the training group had CTEPH (20.96%) versus 9 patients in the control group (47.4%, Fig. 1).

Main Outcomes: Change in SV and PAC at Rest

Both SV (training group 9.9 ± 13.4 mL vs. −4.2 ± 11.0 mL in the control group, mean difference 14.2 mL, 95% confidence interval [CI] 6.5–21.8 mL, $p < 0.001$; Fig. 2) and PAC (training group 0.33 ± 0.65 mL/mm Hg vs. control group −0.06 ± 1.10 mL/mm Hg, mean difference 0.39 mL/mm Hg, 95% CI 0.15–0.94 mL/mm Hg, $p = 0.004$; Fig. 3; Table 2) at rest significantly increased from baseline to 15 weeks. Analysis of covariance with baseline mean pulmonary arterial pressure and PVR as covariates led to consistent results for both SV ($p < 0.0001$) and PAC ($p = 0.031$). The training and the control group showed an increase of sPAP, dPAP, and PP in the control group and a decrease in the training group. Together with PAC and SV, EA improved significantly in the training group compared to the control group (−0.16 ± 0.35 mm Hg/mL vs. 0.14 ± 0.31 mm Hg/mL). No significant changes were found in right atrial pressure between both groups. The training group showed significant improvements in SV (increase, $p = 0.001$) and PAC (increase, $p = 0.014$).

Change in Mean Pulmonary Artery Pressure, CO, and PVR at Rest

Resting mean pulmonary artery pressure (mPAP) decreased in the training group after 15 weeks by −5 ± 11 mm Hg versus increase of 5 ± 7 mm Hg in the control group (mean difference training vs. control −8.9 mm Hg; 95% CI −14.3 to −3.6 mm Hg). CO at rest significantly improved in the training group by 0.6 ± 0.9 L/min versus −0.2 ± 0.8 L/min in the control group (mean difference training vs. control 0.8 L/min; 95% CI 0.3–1.3 L/min). PVR at rest changed in the training group after 15 weeks by −1.18 ± 2.13 Wood units (WU) versus 0.83 ± 1.13 WU in the control group

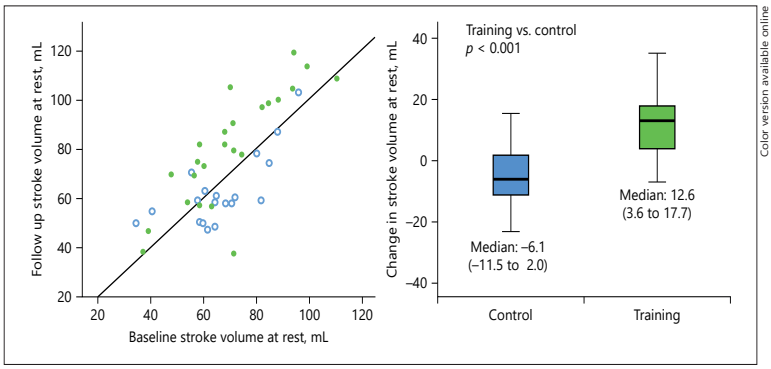

Fig. 2. Change in stroke volume. Left graph: the abscissa shows baseline stroke volume at rest, and the ordinate shows stroke volume at rest after 15 weeks. The solid points represent patients of the training group and the circles represent patients of the control group. Right graph: boxplots at the right side show the distribution of changes between baseline and follow-up in the training and control group. The changes were different between training and control patients, $p < 0.001$, Mann-Whitney U test.

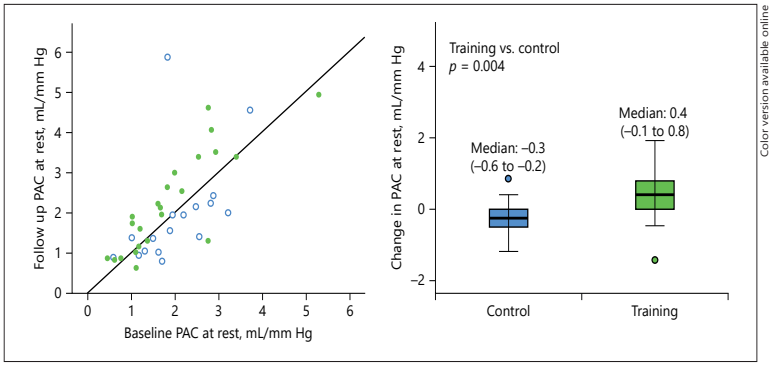

Fig. 3. Change in PAC. Left graph: the abscissa shows baseline PAC at rest, and the ordinate shows PAC at rest after 15 weeks. The solid points represent patients of the training group, and the circles represent patients of the control group. Right graph: boxplots at the right side show the distribution of changes in PAC between baseline and follow-up. The changes are different between training and control patients, $p = 0.004$, Mann-Whitney U test. PAC, pulmonary artery compliance.

(mean difference training vs. control −2.01 WU; 95% CI −3.05 to −0.96 WU, Table 2). The training group significantly improved in PVR (decrease, 0.001), mPAP at rest (decrease, 0.011), and CO at rest (increase, $p = 0.002$).

Change in mPAP, CO, and PVR during Exercise

Patients of the training group showed a lower increase of mPAP during exercise after 15 weeks than patients of the control group (2.2 ± 9.8 mm Hg vs. 6.7 ± 10.1 mm Hg) (mean difference training vs. control −4.5 mm Hg; 95% CI −11.4 to 2.4), although the training group had a higher increase in maximum workload after 15 weeks (16.1 ± 22.7 Watts vs. 1.6 ± 10.0 Watts, mean difference training vs. control 14.5 Watts; 95% CI 3.4 to 25.6 Watts). CO during exercise markedly and significantly increased in the training group by 1.5 ± 2.4

Table 2. Change of clinical outcome parameters

Characteristic	Training group		Control group		Training – control		
	baseline	change baseline to 15 weeks	baseline	change baseline to 15 weeks	difference of changes[#]		
	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean	95% CI	*p* value
Main parameters SV and PAC							
SV at rest, mL	70.3±18.5	9.9±13.4	66.8±15.3	−4.2±11.0	14.2	6.5 to 21.8	<0.001
PAC at rest, mL/mm Hg	1.86±1.09	0.33±0.65	1.95±0.83	−0.06±1.10	0.39	0.20 to 0.98	0.004
Mean 6MWD, m	442±80	26±51	402±66	−9±51	35.1	0.7 to 69.5	*
Laboratory parameter							
NT-proBNP, pg/mL	1,233±2,586	−394±1,390	1,453±1,659	−105±386	−289	−950 to 372	
Cardiopulmonary exercise testing							
Peak VO_2/kg, mL/min/kg	12.9±3.5	2.9±1.8	12.0±4.0	0.5±2.8	2.4	0.9 to 3.9	*
Peak VO_2, mL/min	993±315	216.0±123.0	974±255	13.5±157.2	203	112 to 293	*
Oxygen pulse, mL/beat	8.3±2.6	0.76±0.82	7.9±2.1	0.29±1.1	0.46	−0.18 to 1.1	*
HR rest, min^{-1}	73±10	1.3±9.8	73±10	−7.5±11.5	8.7	−2.0 to 15.5	
HR max, min^{-1}	131±17	11±11.9	131±38	−0.1±10.4	11.1	−4.0 to 18.1	
BP sys at rest, mm Hg	114±19	−5.3±19.7	111±15	−0.42±15.1	−4.9	−15.7 to 5.9	
BP dia at rest, mm Hg	72±11	−3.4±11.5	73±10	−2.5±11.3	−0.77	−7.9 to 6.4	
BP sys max, mm Hg	152±30	8.2±24.7	156±34	−5.5±22.2	13.7	−1.1 to 28.5	
BP dia max, mm Hg	89±12	1.6±14.7	78±11	1.2±10.5	0.43	−7.6 to 8.4	
Workload max, W	70±26	16.1±22.7	64±12	1.6±10.0	14.5	3.4 to 25.6	*
Right heart catheter at rest							
Right atrial pressure, mm Hg	7.3±3.6	0.3±3.9	6.9±4.3	0.9±4.3	0.6	−2.1 to 11.4	
mPAP, mm Hg	40.4±12.5	−4.5±10.5	38.1±10.8	4.5±6.7	−8.9	−14.3 to −3.6	*
Pulse pressure	45.4±15.9	−1.5±12.4	39.6±14.5	2.9±9.9	4.4	−2.7 to 11.4	
EA	1.19±0.61	−0.16±0.35	0.99±0.38	0.14±0.31	0.30	0.09 to 0.50	*
Cardiac output, L/min	5.0±1.0	0.6±0.9	4.8±7.5	−0.2±0.8	0.8	0.3 to 1.3	*
Cardiac index, L × min × m^{-2}	2.7±0.7	0.2±0.6	2.5±0.4	−0.1±0.4	0.27	−0.06 to 0.60	
PAWP, mm Hg	8.7±2.4	2±3	10.2±4.5	−0.1±4.1	3.2	0.9 to 5.5	*
PVR, WU	7.36±3.35	−1.18±2.13	5.76±2.63	0.83±1.13	−2.01	−3.05 to −0.96	*
Right heart catheter during exercise							
mPAP, mm Hg	69±20	2.2±9.8	56±16	6.7±10.1	−4.5	−11.4 to 2.4	
Cardiac output, L/min	10.0±2.8	1.5±2.4	8.7±2.0	−0.3±1.4	1.8	0.4 to 3.3	*
Cardiac index, L × min × m^{-2}	5.2±1.6	0.7±1.2	4.5±1.0	−0.1±0.7	0.8	0.2 to 1.5	*
PAWP, mm Hg	15.1±5.5	−0.3±6.0	16.4±7.9	0.5±4.5	−0.8	−4.4 to 2.9	
PVR, WU	6.05±2.65	−0.28±1.91	5.03±2.49	0.80±1.75	−1.08	−2.36 to 0.20	

PAC analysis set (n = 43; 24 training vs. 19 control). Values are mean ± standard deviation; * denotes CI not including 0. CI, confidence interval; SV, stroke volume; PAC, pulmonary artery compliance; 6MWD, 6-min walking distance; HR, heart rate; BP, blood pressure; sys, systolic; dia, diastolic; mPAP, mean pulmonary arterial pressure; EA, effective arterial elastance; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; peak VO_2, peak oxygen consumption; WU, Wood units; NT-proBNP, N-terminal pro brain natriuretic peptide; *p* values are calculated with the Mann-Whitney U test. [#] A positive difference denotes higher values in the training group; a negative difference denotes lower values in the training group.

L/min versus −0.3 ± 1.4 L/min in the control group (mean difference training vs. control 1.8 L/min; 95% CI 0.4–3.3). PVR during exercise significantly decreased in the training group after 15 weeks by −0.28 ± 1.91 WU versus 0.80 ± 1.75 WU in the control group (mean difference training vs. control −1.08 WU; 95% CI −2.36 to 0.20 WU) (Table 2). Peak CO significantly improved from baseline to follow-up in the training group (increase, p = 0.008); peak mPAP did not significantly differ between baseline and follow-up.

Change of NT-proBNP

NT-proBNP changed in the training group after 15 weeks by −394 ± 1,390 pg/mL versus −105 ± 386 pg/mL in the control group (mean difference training vs. control −289 pg/mL; 95% CI −950 to 372 pg/mL) (Table 2).

Cardiopulmonary Exercise Testing and 6MWD

Peak VO_2 in the training group increased by 216.0 ± 123.0 mL/min in the training group versus 13.5 ± 157.2 mL/min in the control group (mean difference training vs. control 203 mL/min; 95% CI 112–293 mL/min). Peak VO_2 per kg increased by 2.9 ± 1.8 mL/min/kg in the training group versus 0.5 ± 2.8 mL/min/kg in the control group (mean difference training vs. control 2.4 mL/min/kg; 95% CI 0.9–3.9 mL/min/kg). Oxygen pulse improved in the training group by 0.76 ± 0.82 mL/beat versus 0.29 ± 1.1 mL/beat (mean difference training vs. control 0.46 mL/beat; 95% CI −0.18 to 1.1 mL/beat). 6MWD changed in the training group after 15 weeks by 26 ± 51 m versus −9 ± 51 m in the control group (mean difference training vs. control 35.1 m; 95% CI 0.7–69.5) (Table 2).

Discussion

To our knowledge, this post hoc analysis is the first analysis of an RCT showing the impact of a supervised exercise training therapy on PAC and SV. Exercise training significantly improved vascular stiffness and RV function. Though patients of the training group seemed more severely affected with higher mPAP and PVR at baseline, they showed a significant improvement of PAC and SV compared to the control group.

PAC and PVR follow a predictable inverse, hyperbolic relationship. Any change in PVR meets an inverse change in PAC [20]. Therefore, the RC time (the product of resistance × compliance) in the pulmonary vasculature is constant and provides physiologically a time constant for the pulmonary arterial diastolic pressure decay [20]. In contrast to the pulmonary circulation, compliance can change independently of resistance in the systemic circulation and the RC time is not constant. Mean PVR in our training group was 7.36 ± 3.35 WU and 5.76 ± 2.63 WU in the control group at baseline and therefore moderately high. According to the PAC-PVR relationship [20], an increase or decrease in PVR above 10 WU results in a smaller change in PAC than below 10 WU and vice versa. SV increased in our training group, while PP decreased at the same time, and therefore the improvement of PAC was due to an improvement of both components. With an increase in PAC, PVR decreased to keep a constant RC time in the pulmonary circulation. Presumably, the improvement in vascular stiffness (PAC) resulted in a significant reduction in RV afterload (EA).

Prognostic Importance of PAC

PAC has been shown to be a strong predictor of mortality in a landmark study by Mahapatra et al. [6]. They assessed 109 patients with PAH. In this study, PAC was an independent predictor of mortality and superior to PVR, which is the most common haemodynamic parameter to characterize the resistance of the pulmonary vascular bed. In contrast to PAC, PVR was not associated with increased mortality in this study [6]. The hazard ratio of PAC was higher than that of established haemodynamic parameters like mPAP and cardiac index [6]. The same was observed in patients with PH due to heart failure with preserved ejection fraction [21] and in patients with PH due to left heart failure (World Health Organization Group II) [21–24], underlining the importance of PAC in clinical practice. Furthermore, increased pulmonary artery stiffness measured by cardiac MRI was associated with increased mortality in patients with PAH [25].

Change of PAC under Medical PAH/CTEPH Therapy

At present, current PH therapies are mainly directed at dilatation of small pulmonary arteries to reduce PVR and have only little effect on long-term survival of severe PAH patients [12, 26–28]. In a small single-center study by Brittain et al. [29], PAC improved minimally with parenteral prostacyclin therapy, but not with oral therapies. This was associated with an improvement in exercise capacity measured by 6MWD. Apart from parenteral prostacyclin, no other currently available targeted medical PAH therapy showed an improvement of PAC [29]. Ventetuolo et al. [30] pooled 4 RCTs in PAH and showed a small yet significant improvement of PAC of 0.2 mL/mm Hg but without a reduction in short-term clinical outcomes after 12 weeks of targeted PH medication therapy. Our supervised training therapy successfully addressed all important prognostic aspects of PAH/CTEPH therapy by improving pulmonary artery pressures (mPAP), RV function (CO, cardiac index, and SV), vascular elasticity (PAC), vascular remodelling (PVR), and exercise capacity (6MWD and peak VO_2) at once. This underlines the importance of supervised training therapy in severe but stable PAH and inoperable or persistent CTEPH.

Predictive Value of PAC at Baseline versus Change of PAC over Time

In a retrospective study of 109 patients with severe PAH, Medrek et al. [31] demonstrated for the first time that a decrease of PAC over time was an even better predictor of outcome than PAC at baseline with a hazard ratio of 4.21 (CI 1.77–10.02, $p = 0.004$) in the multivariate analysis. Longitudinal change of PAC was a highly prognostic parameter in this study. Although significant, PVR at baseline only had a hazard ratio of 1.003 ($p = 0.015$). Chemla and colleagues [32] found out that baseline pulmonary artery stiffness did not independently predict outcome in untreated incident idiopathic PAH. In their study, the great dispersion of the PVR × PAC product implied that PVR and PAC were differently affected by the disease process. Our training group showed significant improvements in both parameters at the same time: PAC and PVR. Due to the prognostic meaning of PAC both as assessment at a singular timepoint, as well as of changes due to treatment, the calculation of PAC based on routine right heart catheterization assessments could serve clinical estimation of prognosis and help to optimize and adapt treatment.

Effect on RV Function and Peak Oxygen Uptake

In a study by Ehlken et al. [19], training significantly improved RV function, one of the major predictors of outcome in PH, as measured by an increase in CO and cardiac index as well as SV. Peak VO_2 increased at the same time to levels above 11.4 mL/min/kg, which have been detected to be prognostically relevant by Grünig et al. [33]. Grünig et al. [33] identified two independent prognostic parameters in the multivariate analysis of 124 PAH patients for long-term survival: PASP increase during exercise >30 mm Hg as a correlate for RV contractility and output reserve, and peak VO_2 >11.4 mL/min/kg. Both independent prognostic parameters were improved by our supervised exercise therapy.

Current data raise the possibility that PAC is a critical factor that must be treated in order to improve outcomes for PH patients [7, 15, 17, 25]. There is an unmet need for novel approaches to improve PAC as a promising new parameter and RV function as major predictor of long-term survival in PAH.

Limitations

Our study has several limitations. First, this is a post hoc analysis of the initial RCT that was published previously [19]. As right heart catheterization was an optional assessment in the initial study [19], we only analysed participants with a complete haemodynamic measurement of two right heart catheterizations. Therefore, a referral bias might have occurred. However, both groups were well balanced in their baseline characteristics, with the training patients being slightly more severely affected than patients of the control group.

We received patients from many PH centres throughout Germany, but the training study was performed as a single-center study in Heidelberg. As patients of the control group were also offered to take part in the training program after having completed the study, we are not able to provide long-term and survival data of this cohort.

Conclusion

The findings of this post hoc analysis of our randomized controlled study suggest that supervised exercise training may improve RV function and reduce pulmonary arterial stiffness at the same time as major prognostic parameters of survival in PH, as well as CO, cardiac index, and PVR.

Acknowledgements

We would like to thank all patients who participated in this study, the patient organization PH e.V. for their support, and all physicians, therapists, and physiotherapists of the Rehabilitation Clinic Koenigstuhl, Heidelberg, who took part in the rehabilitation program.

Statement of Ethics

The original RCT and the post hoc analysis were conducted in accordance with Good Clinical Practice (GCP) and the current version of the revised Declaration of Helsinki (WMA Declaration of Helsinki). The Ethics Committee of the University of Heidelberg, Germany, did not have any objections against the conduct of the RCT. The study was registered at clinicaltrials.gov (NCT01394367). Written informed consent was obtained from each patient prior to enrolment.

Conflict of Interest Statement

C.N. reports honoraria for lectures and participation in clinical trials from Actelion, Bayer/MSD, Novartis, speaker honoraria from Boehringer, Astra Zeneca, and Berlin Chemie and participation in clinical trials from GSK, United Therapeutics outside the submitted work. N.B. received speaker honoraria and travel support from Actelion and Bayer outside the submitted work. B.E. has nothing to disclose. C.A.E. has nothing to disclose. C.F. has noth-

ing to disclose. E.P. has nothing to disclose. J.C. reports honoraria for lectures and participation in clinical trials from Novartis, Amgen, speaker honoraria from Boehringer, Astra Zeneca, and Berlin Chemie outside the submitted work. S.H. received travel support from Actelion and OMT outside the submitted work. E.M. reports non-financial support from the German Centre for Lung Research, during the conduct of the study; personal fees from Actelion Pharmaceuticals, Bayer, Pfizer, GSK, and MSD outside the submitted work. M.N. has nothing to disclose. A.M.M. has received personal fees from Bayer outside the submitted work. E.G. received advisory board member and speaker honoraria from Actelion, Bayer/MSD, GSK, United Therapeutics, Novartis, Pfizer, and OrphaSwiss GmbH outside the submitted work. S.G. reports non-financial support from the German Centre for Lung Research during the conduct of the study and personal fees from Actelion Pharmaceuticals, Bayer, Pfizer, and GSK outside the submitted work.

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Author Contributions

E.G., C.N., S.G., E.M., N.B., and C.F. made substantial contributions to the conception and design of the work. C.N., N.B., B.E., S.H., E.M., A.M.M., E.G., and S.G. acquired the data. N.B. and C.F. analysed the data. All authors were involved in data interpretation. E.G., C.N., and N.B. drafted the work. All authors were involved in manuscript revision, approved the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Publication IV

The effect of exercise training and physiotherapy on left and right heart function in heart failure with preserved ejection fraction: a systematic literature review.

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The effect of exercise training and physiotherapy on left and right heart function in heart failure with preserved ejection fraction: a systematic literature review

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Abstract
The impact of exercise training and physiotherapy on heart function and pulmonary circulation parameters in heart failure with preserved ejection fraction (HFpEF) patients is uncertain. Hence, we performed a systematic review of published trials studying physical training in HFpEF population, with a focus on exercise and physiotherapy effect on left ventricular (LV), right ventricular (RV) morphological, functional, and pulmonary circulation parameters. We searched Cochrane Library and MEDLINE/PubMed for trials that evaluated the effect of exercise training and/or physiotherapy in adult HFpEF patients (defined as LVEF ≥ 45%), including publications until March 2021. Our systematic review identified eighteen articles (n = 418 trained subjects, 4 to 52 weeks of training) and covered heterogeneous trials with various populations, designs, methodologies, and interventions. Five of twelve trials revealed a significant reduction of mitral E/e' ratio after the training (− 1.2 to − 4.9). Seven studies examined left atrial volume index; three of them showed its decrease (− 3.7 to − 8 ml/m^2). Findings were inconsistent regarding improvement of cardiac output, E/A ratio, and E wave DecT and uncertain for RV function and pulmonary hypertension parameters. For now, no reliable evidence about rehabilitation effect on HFpEF cardiac mechanisms is available. There are some hypotheses generating findings on potential positive effects to parameters of LV filling pressure (E/e'), left atrium size, cardiac output, and RV function. This encourages a broader and more complex assessment of parameters reflecting cardiac function in future HFpEF exercise training studies.

Keywords Exercise training · Physiotherapy · Heart failure with preserved ejection fraction · Cardiac imaging · Diastolic function

Introduction

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of all heart failure (HF) patients and its burden is increasing [1]. A definite diagnosis of HFpEF can be made by right heart catheterization with pulmonary arterial wedge pressure (PAWP) ≥ 15 mmHg or left ventricular end diastolic pressure (LVEDP) ≥ 16 mmHg at rest in presence of preserved left ventricular systolic function. The hallmark of HFpEF is an elevation in left-sided filling pressures. In some patients, this leads to secondary pulmonary hypertension (PH). Pulmonary arterial pressure (PAP) is a marker of the severity and chronicity of pulmonary venous congestion/hypertension in HFpEF, and, if present, PH is associated with more pronounced symptoms and a poorer outcome [2, 3]. Consistent scientific data show that properly designed exercise interventions alone or as a

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component of comprehensive cardiac rehabilitation program for HF improved patients' exercise capacity, symptoms, and health-related quality of life (QOL) and reduced the risk of all-cause and HF hospitalizations [4–7]. Of note, patients with HF with reduced ejection fraction (HFrEF) were predominant in most of the studies. European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF recommend exercise rehabilitation not only to improve exercise capacity and QOL, but also to reduce HF hospitalizations, regardless of LV systolic function (Class I recommendation) [4].

The positive impact of exercise training on the functional capacity of HF patients is complex and can be determined by different pulmonary, cardiovascular, skeletal muscle, and metabolic adaptations that increase oxygen delivery and energy production [8]. As shown in several meta-analyses of randomized controlled trials (RCT), aerobic exercise training, especially long-term duration (≥ 6 months), reverses left ventricular (LV) remodeling in clinically stable patients with HFrEF [9–11]. Exercise training was associated with a significant improvement in LV ejection fraction (LV EF), when data from all RCT were pooled in the first meta-analysis (articles were published in 1966–2006; 14 trials; 812 patients) [9]. Later, this finding was confirmed in two updated meta-analyses (including articles published in 2006–2011: 16 trials with 813 patients, and 2007–2017: 18 trials with 1077 patients) [10, 11]. Moreover, in two meta-analyses, aerobic training led to significant improvements in LV end diastolic volume (EDV) (5 trials with 371 patients and 12 trials with 573 patients) and LV end systolic volume (ESV) (5 trials with 371 patients and 11 trials with 548 patients) [10, 11]. There are limited data on the effects of HFrEF patients exercising on more precise structural and functional echocardiographic parameters, such as myocardial velocities, strain and strain rate, stroke volume, right ventricular 3D ejection fraction, estimated systolic pulmonary arterial pressure, and size and collapsibility of inferior vena cava. This knowledge gap is even wider in HFpEF patients.

Earlier HFpEF rehabilitation systematic reviews and meta-analyses demonstrated positive impact of exercise training on functional capacity change, by improving peak oxygen uptake [12–17] and six-minute walk test distance [14, 15]. Moreover, HFpEF training seemed to be safe [12–16, 18, 19] and beneficial for the QOL of patients [12–17]. Five previous meta-analyses assessed the influence of exercising on only several echocardiographic parameters, mostly the mitral E/A ratios, E/e′ ratios, and E wave deceleration time (DecT), and their results were inconsistent [12–16]. Neither of prior systematic reviews evaluated the changes of right ventricular (RV) and pulmonary circulation parameters after the training. The summary of their findings is presented in Table 1.

A single center exercise invasive hemodynamic study revealed that patients with HFpEF, complicated with PH and pulmonary vascular disease, demonstrate unique hemodynamic limitations during exercise that constrain aerobic capacity, including impaired recruitment of LV preload due to excessive right heart congestion (due to afterload) and blunted RV systolic reserve [20]. These conditions are leading to RV and pulmonary artery (PA) uncoupling with further limitation of exercise capacity and poor outcome [21].

In healthy subjects, intensive exercise has already shown to cause potentially deleterious remodeling of the RV [22, 23]. As pointed out by Arena et al. there may thus be an exercise training volume/intensity which may be detrimental to the RV in patients with HF and concomitant PH [24].

It is not clear whether changes of heart function and pulmonary circulation parallel improvement in cardiorespiratory fitness, or maybe exercise training may lead to harmful effects or worsening of the disease. We aimed to systematically review existing data on the impact of exercise and physiotherapy in HFpEF trials on LV, RV morphological, functional, and pulmonary circulation parameters.

Methods

We prepared this article by following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [25].

We conducted a Cochrane Library and MEDLINE/PubMed search for all types of trials that evaluated the effects of various types of exercise training and/or physiotherapy in adult (> 18 years) HFpEF patients (defined as LVEF ≥ 45%), including all papers published from December 1991 to March 2021. Studies that merely enrolled patients with other cardiac or respiratory diseases were excluded. HFpEF data was extracted from studies if various parameters were included and reported separately. The main outcomes of interest were any reported echocardiographic, MRI, and invasive hemodynamic parameters.

For each database search, we used two groups of keywords and their synonyms for participants and intervention. The search strategy for MEDLINE/PubMed can be found in the Supplementary Material (Table S1). We modified search strategies according to each database to achieve the broadest research.

The search was limited to human studies only, adults (> 18 years), and the results were filtered by "Clinical Trial," "Meta-Analysis," and "Systematic Review." Additionally, for any potential eligible trials, we manually searched in clinicaltrials.gov, Google Scholar, and the references of the identified studies.

Each title and abstract were independently evaluated by 2 reviewers. If at least one of the reviewers considered the trial to be eligible, it was obtained for primary analysis.

Table 1 Results from previous HFpEF exercise training meta-analyses: the changes of left ventricular function and morphology, comparing exercise training vs. control groups

Meta-analysis	Designs of included studies, *n*	Participants (*n*) (training/control)	Results of specific echocardiographic parameter meta-analysis with exercise versus control
Taylor et al. [12]	1 –observational 1 – non-RCT 1 – RCT	102/38	E/e′: – 0.9, 95% *CI*: – 3.8 to 2.0, $P = 0.53^{*}$; random effect
	1 –observational 1 – non-RCT 1 – RCT	84/45	E/A: – 0.02, 95% *CI*: – 0.11 to 0.06, $P = 0.56^{*}$; fixed effect
	1 –observational 1 – RCT	52/24	LV EDV (ml): 4.5, 95% *CI*: – 1.8 to 10.9, $P = 0.16^{*}$; fixed effect
	1 –observational 2 – RCT	96/44	LV EF (%): 0.02, 95% *CI*; – 1.6 to 1.7, $P = 0.98^{*}$; fixed effect
Pandey et al. [13]	4 – RCT	82/81	E/A: 0.08, 95% *CI*: – 0.01 to 0.16, $P = 0.08^{\#}$; fixed effect
	3 – RCT	62/70	DecT (ms): 2.92, 95% *CI*: – 18.56 to 24.41, $P = 0.79^{\#}$; fixed effect
	5 – RCT	126/111	LV EF (%): 1.26, 95% *CI*: – 0.13 to 2.66%, $P = 0.08^{\#}$; fixed effect
Dieberg et al. [14]	4 – RCT	85/60	E/e′: – 2.3, 95% *CI*: – 3.44 to – 1.19, $\mathbf{P < 0.0001}^{*}$; fixed effect
	3 – RCT	56/52	E/A: 0.07, 95% *CI*: 0.02 to 0.12, $\mathbf{P = 0.005}^{*}$; fixed effect
	3 – RCT	56/52	DecT (ms): – 13.2, 95% *CI*: – 19.8 to – 6.5, $\mathbf{P = 0.0001}^{*}$; fixed effect
Chan et al. [15]	5 – RCT	115/89	E/e′: – 2.38, 95% *CI*: – 3.47 to – 1.28, $\mathbf{P < 0.0001}^{*}$, fixed effect
	4 – RCT	86/81	E/A: + 0.07, 95% *CI*: 0.02 to 0.12, $\mathbf{P = 0.006}^{*}$, fixed effect
	3 – RCT	56/52	DecT (ms): – 13.2, 95% *CI*: – 19.8 to – 6.5, $\mathbf{P = 0.0001}^{*}$, fixed effect
Fukuta et al. [16]	4 – RCT	132/109	E/e′: – 1.20, 95% *CI*: – 4.07 to 1.66, $P = 0.41^{\#}$, random effect
	5 – RCT	128/124	E/A: 0.03, 95% *CI*: – 0.02 to 0.08, $P = 0.27^{\#}$; random effect
	3 – RCT	102/79	e′ (cm/s): 0.49, 95% *CI*: – 1.28 to 2.25, $P = 0.59^{\#}$; random effect
	3 – RCT	62/69	DecT (ms): – 2.04, 95% *CI*: – 26.53 to 22.45, $P = 0.87^{\#}$; random effect
	4 – RCT	140/120	LV EDV: – 0.03, 95% *CI*: – 0.28 to 0.21, $P = 0.78^{\#}$; fixed effect
	3 – RCT	116/90	LV mass: 0.07, 95% *CI*: – 0.21 to 0.35, $P = 0.61^{\#}$; fixed effect
	7 – RCT	202/174	LV EF: 0.85, 95% *CI*: – 0.128 to 1.83, $P = 0.09^{\#}$; fixed effect

*Mean difference; $^{\#}$weighted mean difference

After initial review, the full texts of selected studies were assessed to verify eligibility criteria.

Two reviewers assessed methodological quality of studies using modified Downs and Black Quality checklist, which is meant to assess the quality for both randomized and non-randomized trials [26]. The sub-domain, estimating the power, was modified (if the study conducted a power analysis to determine the sample size needed to detect a significant difference in effect size, 1 point was added, if not – 0 point). The maximum score in this checklist was 28. The studies were rated as excellent, good, moderate, and poor, based on the percentage of the total score achieved: > 95% (≥ 25), 75–95% (21–24), 55–74% (16–20), and < 55% (≤ 15).

The same reviewers extracted data from the relevant articles, using pre-defined extraction forms, including the aspects of study population, such as mean age and sex, study design, intervention characteristics, follow-up period, and main outcomes. Any disagreements in data extraction were discussed until consensus was reached.

Results

Study identification and selection

A flow diagram showing the selection of eligible studies is presented in Fig. 1. Initially, our searches in databases identified 1077 relevant publications; after primary review of titles and abstracts, 90 articles were eligible, and one extra paper was later found in the references. After full-text reading, 50 articles were rejected, thus the data were extracted from the rest 41 publications. The reasons for the rejection are described in Fig. 1.

Among these 41 papers, 6 were conference materials and 8 were meta-analyses and (or) systematic reviews—they were removed from the final analyses—leaving 27 articles. Nine from 27 articles did not analyze cardiac imaging parameters at all resulting in a final data set of 18 articles for our systematic review (Fig. 1, Table 2). We contacted the corresponding authors of selected trials asking about any additional findings of echocardiographic, MRI, or

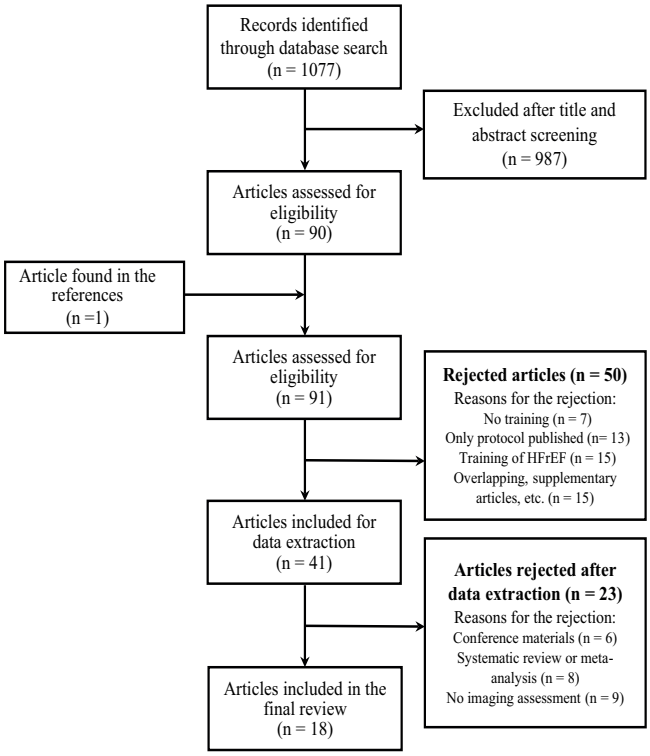

Fig. 1 Study flow diagram. This flow diagram shows the selection process of eligible studies

invasive measurement parameters; nobody could provide any unpublished data.

Characteristics of included studies and patients

We extracted the data from nine randomized controlled trials, five randomized parallel group trials (no control, all patients trained, but different training protocols were used), and four observational studies (one group, no control).

All studies included stable patients, diagnosed with HFpEF. The trials were performed in different years (1994–2018) and the definition of HFpEF used in each study varied, but in all trials, LV EF of the participants was ≥ 45%. Echocardiography was applied to measure LV EF in all studies: 7 trials used Simpson biplane, 1—Teichholz method (by M-mode echocardiography), and the remaining 10 studies did not specify the methodology. Detailed information about HFpEF definition used in each study is provided in Supplementary Material (Table S2). All incorporated studies measured at least one cardiac imaging parameter, reflecting LV diastolic function, RV function, or pulmonary hemodynamics.

Our study covered heterogeneous trials with various designs, populations, methodologies, and interventions. The majority of studies were small in sample size—more than 25 patients were trained in only four of the eighteen trials. All training programs were held out-patient, and in sixteen of them, intervention was supervised by healthcare professionals. Eleven programs consisted of endurance training alone, and four, endurance and resistance workouts in combination. Two studies applied resistance training, and in one of them, functional electric stimulation (FES) was added. Only FES was used in a single trial. Various research appraised multifarious echocardiographic parameters and none of them provided random variability in the data for these outcomes. In the selected trials, overall 418 patients (mean age 60.0 to 75.0, 57% female, training duration 4 to 52 weeks) were trained. The components of exercise training and (or) physiotherapy, together with other characteristics and results of these studies, are summarized in Table 2.

Table 2 Summary of articles selected and included in the review

Study (author, year)	Duration of the training (weeks)	Intervention	Trained patients [*N*; mean age, years; male gender, *N* (%)]	Assessed echocardiographic parameters	Significant changes of specific echocardiographic parameters
Randomized controlled trials (*N* = 9)					
Kitzman et al. [68]	16	Outpatient, supervised, endurance training; 60 min 3 times a week	*N* = 26; age = 70 ± 6; male 6 (23.1%) *24 patients in the final analysis*	LV EF, E, A, E/A, DecT, IVRT, LVM, LVV, SV	No significant changes of measured echocardiographic parameters
Edelmann et al. [30]	12	Outpatient, supervised, endurance training (supplemented with resistance training from the 5th week); 40 min 3 times a week	*N* = 44; age = 64 ± 8; male 20 (45.5%)	LV EF, e' (septal), E/e' (septal), S/D ratio, LAVI, LVMI, LVVI	↓**E/e'** from 12.8 ± 3.2 to 10.5 ± 2.5, change − 2.3 (− 3.0 to − 1.6), $p < 0.001$; between groups − 3.2 (− 4.3 to − 2.1) $p < 0.001$ ↑**e'** from 5.4 ± 1.2 to 6.3 ± 1.3, change 0.9 (0.6 to 1.1), $p < 0.001$; between groups 1.2 (0.8 to 1.7) $p < 0.001$ ↓**LAVI** from 27.9 ± 7.6 to 24.3 ± 6.5, change − 3.7 (− 4.9 to − 2.4), $p < 0.001$; between groups − 4.0 (− 5.9 to − 2.2) $p < 0.001$
Alves et al. [31]	26	Outpatient, supervised, endurance training; 35 min 3 times a week	*N* = 20; age = 62.9 ± 10.2; male 22 (71%) *mean age and gender distribution of all of the sample size (trained + control)*	LV EF, E/A, DecT, LV dimensions (EDD, ESD)	↑**EF** from 56.4 to 57.7, change 1.3% $p = 0.01$ ↑**E/A** from 0.93 to 1.05, $p < 0.001$ ↓**DecT** from 236.7 to 222.7, $p < 0.001$
Smart et al. [27]	16	Outpatient, supervised, endurance training; 30 min 3 times a week	*N* = 12; age = 67 ± 5.8; male 7 (58.3%)	LV EF, E, A, E/A, E/e' (undetermined), DecT, s', e' (undetermined), SV, CO, LV-GLS, LV-GSR	↑**CO** from 5.7 ± 2.7 to 7.1 ± 3.1, change 1.4, $p = 0.04$;
Haykowsky et al. [28]	17	Outpatient, supervised, endurance training; 60 min 3 times a week	*N* = 22; age = 70 ± 6; male 4 (18.2%)	LVV, SV, CO	No significant changes of measured echocardiographic parameters
Karavidas et al. [69]	6	Outpatient physiotherapy (functional electrical stimulation of the lower limb muscles); 30 min 5 times a week	*N* = 15; age = 69.4 ± 8.6; male 6 (40.0%)	E, A, E/A, E/e' (undetermined), DecT, LAV, a pulmonary – a mitral duration	No significant changes of measured echocardiographic parameters
Kitzman et al. [70]	16	Outpatient, supervised, endurance training; 60 min 3 times a week	*N* = 32; age = 70 ± 7; male 9 (28.1%) *24 patients in the final analysis*	LV EF, E, A, E/A, DecT, IVRT, LVV, SV	No significant changes of measured echocardiographic parameters
Palau et al. [71]	12	At home, unattended, inspiratory muscle training; 20 min 2 times a day	*N* = 14; age = 68 [60–76]; male 7 (50.0%)	LV EF, e' (septal), E/e' (septal), LAVI, LVMI	No significant changes of measured echocardiographic parameters
Palau et al. [32]	12	Home, unattended, inspiratory muscle training; 20 min 2 times a day Outpatient, physiotherapy (functional electrical stimulation of the lower limb muscles); 45 min 2 times a week	IMT (baseline): *N* = 15; age = 75 ± 10; male 7 (46.7%) FES (baseline): *N* = 15; age = 72 ± 9; male 6 (40.0%) IMT + FES (baseline): *N* = 16; age = 73 ± 10; male 8 (50%) *13 patients in each group in the final analysis*	E/e' (undetermined), LAVI	**IMT**: After 12 weeks: ↓**E/e'** from 18.4 [14.4–28.0] to 17.2 [12.4–23.1], $p = 0.015$ After 24 weeks[3]: ↓**LAVI** from 39 ± 11 to 31 ± 11, $p = 0.008$ **FES**: After 12 weeks: ↓**E/e' from** 20.5 [12–26.4] to 15.7 [11.8–21.8], $p = 0.001$ After 24 weeks[3]: No significant changes of measured echocardiographic parameters **IMT + FES:** After 12 weeks: No significant changes of measured echocardiographic parameters After 24 weeks[3]: No significant changes of measured echocardiographic parameters

Table 2 (continued)

Study (author, year)	Duration of the training (weeks)	Intervention	Trained patients [*N*; mean age, years; male gender, *N* (%)]	Assessed echocardiographic parameters	Significant changes of specific echocardiographic parameters	
Randomized parallel group trials (*N* = 5)						
Yeh et al. [72]	12	Outpatient and home, endurance training compared with Taichi training; supervised 60 min 2 times a week + exercising at home 35 min 3 times a week	AT: *N* = 8; age = 63 ± 11; male 4 (50.0%) Tai Chi: *N* = 8; age = 68 ± 11; male 4 (50.0%)	LV EF, E/A, E/e' (undetermined), LA dimension, LAV	**Tai Chi**[#]: ↓LA dimensions decreased more in the Tai Chi (from 3.8 ± 0.4 to 3.7 ± 0.3) comparing with AT (from 3.7 ± 0.3 to 3.8 ± 0.3), $p = 0.04$	**AT**[#]: ↓E/e' improved more in the AT (from 17 ± 4 to 14 ± 4), comparing with the Tai Chi (from 14 ± 4 to 13 ± 5), $p = 0.01$
Angadi et al. [33]	4	Outpatient, supervised, endurance training; 45 min 3 times a week	HIT: *N* = 9; age = 69.0 ± 6.1; male 8 (88.9%) MI-ACT: *N* = 6; age = 71.5 ± 11.7; male 4 (66.7%)	LV EF, E, A, e' (septal), E/A, E/e' (septal), DecT, IVRT, diastolic dysfunction grade[1], diastolic dysfunction grade distribution[2], LAVI	**HIIT:** ↓**Diastolic dysfunction grade*** from 2.1 ± 0.3 to 1.3 ± 0.7, $p < 0.01$ ↓**E from** 0.9 ± 0.3 to 0.8 ± 0.3, $p = 0.02$ ↑**DecT** from 194 ± 55 to 225 ± 40, $p = 0.02$	**MI-ACT:** No significant changes of measured echocardiographic parameters
Angadi et al. [29]**	4	Outpatient, supervised, endurance training; 45 min 3 times a week	HIIT: *N* = 9; age = 69 ± 6.1; male 8 (88.9%) MI-ACT: *N* = 6; age = 71.5 ± 11.7; male 4 (66.7%)	LV EF, LVM, LVMI, SV, SVI, RV-GLS, RV-GSR, LV-GLS, LV-GSR	**HIIT:** ↑**RV-GLS** from − 18.4 ± 3.2 to − 21.4 ± 1.7, $p = 0.02$	**MI-ACT:** No significant changes of measured echocardiographic parameters
Silveira et al. [36]	12	Outpatient, supervised, endurance training; 38 min (HIIT), 47 min (MCT) 3 times a week	HIIT: *N* = 10; age = 60 ± 10; male 3 (30.0%) MI-ACT: *N* = 9; age = 60 ± 9; male 4 (44.4%)	LV EF, E, A, e' (average), E/A, E/e' (average), DecT, LV dimensions (EDD, ESD), LAVI, LVM, LVVI, LA diameter, SVI	**HIIT:** ↓**E/e'** from 13.3 ± 3 to 11.1 ± 2, $p < 0.001$	**MI-ACT:** ↓**E/e'** from 14.2 ± 4 to 11.6 ± 3, $p < 0.001$
Mueller et al. [73]	52	Outpatient, supervised (3 months), then continued at home, unattended (for the next 9 months), endurance training; 38 min (HIIT), 47 min (MCT) 3 times a week	HIIT: *N* = 58; age = 70 ± 7; male 17 (29.3%) MI-ACT: *N* = 58; age = 70 ± 8; male 23 (39.7%) *47 patients in the HIIT final and 52 in the MI-ACT final analysis*	E/e' (septal), e' (septal), LAVI	No significant change on measured echocardiographic parameters between HIIT, MI-ACT, and control group[#]	
Observational trials (*N* = 4)						
Smart et al. [74]	16	Outpatient, supervised, endurance training (supplemented with resistance training from the 8th week); 60 min 3 times a week	*N* = 18; age = 65 ± 5; male 9 (50.0%)	LV EF, E, A, s', e' (average), E/A, E/e' (average), DecT, LVV, LV-GLS, LV-GSR, SV	No significant changes of measured echocardiographic parameters	
Fujimoto et al. [37]	52	Outpatient, supervised, endurance training; 40 min 3 times a week	*N* = 7; age = 74.9 ± 6; male 3 (42.9%)	LV EF, E, A, e' (average), a', E/A, IVRT, LVV, LVVI	↑**E/A** from 0.75 ± 0.11 to 0.89 ± 0.14, $p = 0.03$	
Nolte et al. [34]*	24	Outpatient, supervised, endurance training (supplemented with resistance training from the 5th week); 30–35 min; 3 times a week	*N* = 24; age = 62 ± 7; male 15 (62.5%)	LV EF, e' (septal), E/e' (septal), S/D ratio, LAVI, LVMI, LVVI	↓**E/e'** from 12.2 ± 3.5 to 10.1 ± 3.0, change − 2.1 (− 3.3 to − 0.9), $p = 0.002$ ↑**e'** from 5.9 ± 1.3 to 6.8 ± 1.4, change 0.9 (0.4 to 1.4), $p = 0.001$ ↓**LAVI** from 30.0 ± 7.9 to 25.1 ± 8.7, change − 4.9 (− 6.7 to − 3.2), $p < 0.001$	

Table 2 (continued)

Study (author, year)	Duration of the training (weeks)	Intervention	Trained patients [*N*; mean age, years; male gender, *N* (%)]	Assessed echocardiographic parameters	Significant changes of specific echocardiographic parameters
Fu et al. [35]	12	Outpatient, supervised, endurance training; 30 min 3 times a week	$N = 30$; age = 60.5 ± 2.7; male 20 (66.7%)	LV EF, E/A, E/e'(septal), LV dimensions (EDD, ESD)	↓**E/e '** (septal) from 21.0 ± 2.2 to 16.1 ± 1.8, $p < 0.05$

Data are expressed by number, mean ± standard deviation, median (interquartile range)

A (m/s) late mitral inflow velocity, *a' (m/s)* tissue Doppler mitral annular late diastolic velocity, *AT* aerobic training, *CO (l/min.)* cardiac output, *DecT (ms)* mitral flow E wave deceleration time, *E (m/s)* early mitral inflow velocity, *e' (m/s)* tissue Doppler mitral annular early diastolic velocity, *E/A* E and A ratio, *EDD (mm)* end diastolic diameter, *E/e'* E and e' ratio, *FES* functional electrical stimulation, *EF (%)* ejection fraction, *ESD (mm)* end systolic diameter, *HIIT* high-intensity interval training, *IMT* inspiratory muscle training, *IVRT (ms)* isovolumetric relaxation time, *LA* left atrium, *LA dimensions (cm)* the measurement was not clearly defined, *LAV (ml)* left atrium volume, *LAVI (ml/m^2)* left atrium volume index, *LV* left ventricle, *LV-GLS (%)* left ventricle global longitudinal strain, *LV-GSR (s^{-1})* left ventricle global longitudinal strain rate, *LVM (g)* left ventricle mass, *LVMI (g/m^2)* left ventricle mass index, *LVV (ml)* left ventricle volume, *LVVI (ml/m^2)* left ventricle volume index, *MI-ACT* moderate-intensity aerobic continuous training, *RV-GLS (%)* right ventricle global longitudinal strain, *RV-GSR (s^{-1})* right ventricle global longitudinal strain rate, *s'(m/s)* tissue Doppler mitral annular systolic velocity, *S/D* pulmonary vein peak systolic velocity and peak diastolic velocity ratio, *SV (ml)* stroke volume, *SVI (ml/m^2)* stroke volume index

[#]*p* values comparing the changes between the groups (changes before and after training in separate groups were not published)

[*]In this trial, the same patients that participated in the study of Edelmann et al. [30] were enrolled. Authors presented the same data of trained group changes after 12 weeks of training in both articles, but this article was supplemented by additional data after longer exercise training period (24 weeks); **In this study, the same patients that participated in the study Angadi et al. [33] were assessed, but different echocardiographic parameters were measured—secondary analyses to explore the effects of HIIT on biventricular strain characteristics was carried out

[a]Four grades of diastolic dysfunction were used (0—no diastolic dysfunction, 1—abnormal relaxation pattern, 2—pseudonormal pattern, 3—restrictive filling pattern)

[b]Number of patients in each of the four diastolic dysfunction grades

[c]Follow-up was extended to 24 weeks with the aim of exploring the sustainability of the 12-week training results

Table 3 The quality assessment of included studies by modified Downs and Black Quality checklist

	Study type	Reporting (11)	External validity (3)	Internal validity		Power (1)	Total (28)	Quality*
				Bias (7)	Confounding (6)			
Kitzman et al. [70]	RCT	10	3	6	5	1	25	Excellent
Donelli da Silveira et al. [36]	Randomized parallel group	10	3	6	5	1	25	Excellent
Mueller et al. [73]	Randomized parallel group	10	3	6	5	1	25	Excellent
Kitzman et al. [68]	RCT	10	2	6	4	1	23	Good
Edelmann et al. [30]	RCT	10	1	6	5	1	23	Good
Alves et al. [31]	RCT	10	1	6	5	1	23	Good
Smart et al. [27]	RCT	9	3	5	5	1	23	Good
Palau et al. [71]	RCT	9	2	6	5	1	23	Good
Karavidas et al. [69]	RCT	8	3	5	5	1	22	Good
Palau et al. [32]	RCT	9	1	5	5	1	21	Good
Yeh et al. [72]	Randomized parallel group	9	1	6	5	0	21	Good
Angadi et al. [29]	Randomized parallel group	9	1	5	5	1	21	Good
Haykowsky et al. [28]	RCT	10	1	5	4	0	20	Moderate
Angadi et al. [33]	Randomized parallel group	8	1	4	5	1	19	Moderate
Smart et al. [74]	Observational	10	0	5	1	0	16	Moderate
Nolte et al. [34]	Observational	9	1	5	4	0	19	Moderate
Fu et al. [35]	Observational	9	1	6	3	1	20	Moderate
Fujimoto et al. [37]	Observational	9	1	3	2	0	15	Poor

RCT randomized controlled trial

*Evaluated by the total score number: ≥ 25 – excellent, 21–24 – good, 16–20 – moderate, ≤ 15 – poor. Studies with no significant changes of assessed echocardiographic parameters after the intervention are marked in gray

The methodological quality of trials, assessed by modified Downs and Black Quality checklist, varied between excellent ($n=3$), moderate ($n=5$), good ($n=9$), and poor ($n=1$), as summarized in Table 3.

Echocardiographic assessment

All included studies analyzed the changes of echocardiography as secondary endpoints. Various studies appraised multifarious echocardiographic parameters (Table 2). The quantity of studies that assessed specific parameters along with the number of trained patients is shown in Table 4.

As it is shown in Table 2, different studies demonstrated controversial results of the training impact on echocardiographic change. Variations of echocardiographic measurements of trained patients before and after intervention were published in sixteen articles (two trials declared only the changes comparing different training modalities). LV EF and E/e' were parameters most frequently analyzed—in 14 and 12 studies, respectively.

Five of nine RCTs, four of five randomized parallel group trials, and three of four observational trials reported significant changes of different echocardiographic parameters by training, while the other studies detected no changes in the assessed parameters (Table 2). Significant reduction of mitral E/e' ratio after the training was reported in 5 of 12 studies, ranging from − 1.2 to − 4.9; significant decrease of LAVI was observed in 3 of 7 trials, ranging from − 3.7 to − 8 ml/m^2. All but one study showed no significant change of LV EF after the intervention.

Inconsecutive findings were also reported for the change of E/A ratio (9/11 studies showed no change, two statistically significant increase) and E wave DecT (8 studies, one significant increase, one significant decrease).

Furthermore, the impact of exercise training on cardiac output (CO) was reported with inconsistent results, including improvement of CO by 24.5% in one small ($n=12$), good quality study, after 16 weeks of endurance exercise training, organized 30 min 3 times a week [27]. Another moderate quality trial with older patients ($n=22$) demonstrated no significant changes of CO after similar duration endurance exercise training, 60 min 3 times a week [28].

The effect of exercising on RV function was assessed in one study [29]. RV global longitudinal strain and RV global longitudinal strain rate were measured before and after 4 weeks of high intensity interval training (HIIT) ($n=9$) and moderate intensity aerobic continuous training (MI-ACT) ($n=6$). HIIT group patients demonstrated the increase of RV global longitudinal

Table 4 The echocardiographic parameters, assessed in selected studies

Echocardiographic parameter	Number of the studies with assessment of parameter	Number of trained patients with assessment of parameter
LV EF	14	292
E/e'	12	330
E/e' (septal)	6	211
E/e' (average)	2	37
E/e' (undetermined)	4	82
e'	9	261
e' (septal)	5	205
e' (average)	3	44
e'(undetermined)	1	12
LAVI	7	250
E/A	11	210
E	8	144
A	8	144
E wave DecT	8	144
LVMI	4	92
SV	6	113
LVVI	4	87
LV IVRT	4	80
SVI	3	46
LV GLS	3	45
LV GRS	3	45
CO	2	34
LV tissue S vel	2	30
RV GLS	1	15
RV GSR	1	15

Following parameters were NOT assessed in the included studies: RV diameter, SPAP, TV laterals', TAPSE, RV FAC, RA area, RA pressure, and IVC diameters

A (m/s) late mitral inflow velocity, *a' (m/s)*, tissue Doppler mitral annular late diastolic velocity, *CO (l/min.)* cardiac output, *DecT (ms)* mitral flow E wave deceleration time, *E (m/s)* early mitral inflow velocity, *e' (m/s)* tissue doppler mitral annular early diastolic velocity, *E/A* E and A ratio, *E/e'* E and e' ratio, *EF (%)* ejection fraction, *IVRT (ms)* isovolumetric relaxation time, *LAVI (ml/m2)* left atrium volume index, *LV* left ventricle, *LV-GLS (%)* left ventricle global longitudinal strain, *LV-GSR (s-1)* left ventricle global longitudinal strain rate, *LVMI (g/m^2)* left ventricle mass index, *LVVI (ml/m^2)* left ventricle volume index, *RA* right atrium, *RV-GLS (%)* right ventricle global longitudinal strain, *RV-GSR (s-1)* right ventricle global longitudinal strain rate, *s'(m/s)* tissue doppler mitral annular systolic velocity, *SPAP (mmHg)* systolic pulmonary artery pressure, *SV (ml)* stroke volume, *SVI (ml/m^2)* stroke volume index, *TAPSE (mm)* tricuspid annular plane systolic excursion

strain by 3% (from -18.4 ± 3.2 to -21.4 ± 1.7), $p = 0.02$. The changes between MI-ACT group patients were insignificant.

As it is shown in Table 4, any other right heart and pulmonary hypertension parameters were not evaluated in the included trials.

Not all studies were well-balanced by the gender of trained participants (Table 4) and neither of them compared echocardiographic changes after the intervention according to sex. However, the majority of trials that revealed significant changes of specific echocardiographic parameters (E/e', LAVI, DecT, CO, EF, RV-GLS) included predominantly males, or males amounted at least 45% (Table 4) [27, 29–35]. The study of Silveira et al. was the only one with female predominance (63.2%) and significant decrease of E/e'; in this study, a multivariate model was created to adjust E/e' differences for age, BMI, and sex; the effect of training on E/e' remained statistically significant after the adjustment [36].

Invasive hemodynamic assessment

Invasive hemodynamic measurements were performed in only one very small ($n = 7$) poor quality study [37]. Right heart catheterization was performed at baseline and after a year of endurance exercise training. The results revealed

that pulmonary artery wedge pressure (PAWP) was unaffected by exercise training in HFpEF patients (16.1 ± 5.6 vs. 15.2 ± 3.6 mmHg, $p = 0.65$). A year of training had no effect on Starling curves (stroke volume index/PAWP) or stroke work-LVEDV relations (as a parameter of LV contractile function), suggesting no change in LV filling and contractile function.

Cardiac magnetic resonance imaging

None of the eighteen eligible studies assessed the impact of exercise rehabilitation to cardiac magnetic resonance imaging parameters.

Discussion

To the best of our knowledge, this is the first systematic literature review, which investigated the exercise training and physiotherapy impact not only on LV, but also RV morphology, function, and pulmonary circulation parameters in HFpEF patients. The results of our extended literature review were inconsistent. Eleven of 18 (61.1%) of the considered studies reported a positive impact of exercise training on at least one left and/or right heart function echocardiographic parameter. In seven of all eligible studies (38.9%, five RCTs), no significant changes were observed. Neither of the trials revealed negative effects of exercise training or physiotherapy on heart function (the outcome was positive or indifferent). These findings are in line with previous meta-analyses reporting inconsistent effects of exercise training in HFpEF [12–16].

LV diastolic dysfunction in HFpEF

Twelve studies assessed mitral E/e′ ratio, and significant decrease of it was observed in five of them [30, 32, 34–36]. Mitral E/e' ratio is the measure widely accepted as an index of LV filling pressure, but it also has limitations that are relevant in clinical practice, and it is not recommended to use as a single follow-up echocardiographic parameter in HFpEF [38–41].

LAVI is a further echocardiographic parameter, reflecting LV filling pressure, which is crucially important to measure, when assessing LV diastolic function [41]. We found seven articles with published LAVI assessments; three of these studies revealed statistically significant decrease of LAVI after the intervention [30, 32, 34]. Two out of three studies observed significant decrease of LAVI together with substantial decrease of mitral E/e' ratio, strengthening the tendency of positive training impact to LV diastolic function. When these two parameters were evaluated together, no significant differences of mitral E/e' ratio or LAVI changes were identified, when comparing the usual care (control) group with any of active treatment groups (IMT; FES; IMT + FES). However, when the analysis of each interventional group was performed separately, significant changes were observed [32]. After 12 weeks of IMT, statistically significant decrease of median mitral E/e' ratio was observed, while the change of median LAVI was insignificant. After 24 weeks follow-up period, statistically significant decrease of median LAVI was noticed, but the decrease of median mitral E/e' ratio became insignificant, comparing with the baseline data [32]. These findings could either be explained by the necessity of longer time for the remodeling of LA, as LAVI reflects the cumulative effects of increased LV filling pressures over time [41], or it could be an accidental finding, due to small sample size.

Improvements in mitral E/e' ratio were more often detected in the trials with larger sample size, which may be a hint that the other studies were underpowered for the effect size of E/e' changes. Significant decrease in LAVI was more common in studies with a longer follow-up period, which supports the theory of a longer period required to induce reverse atrial remodeling.

Some studies of our systematic review appraised intervention impact on LV diastolic function by evaluating the changes of mitral E wave, A wave, E/A ratio. However, the increase of mitral E wave or E/A ratio can be associated both with improvement and deterioration of diastolic function (a shift from impaired relaxation pattern to normal diastolic function, but also with a shift from normal diastolic function or pseudonormalized pattern to the restrictive filling pattern). For the same reasons and bidirectional interpretation, the changes of mitral E wave DecT and IVRT should not be used for pooled data analysis as well. A solution could be the graduation of LV diastolic function, as it was done by Angadi et al. [33], or use of unidirectional LV diastolic function indices such as mitral e' and E/e' ratio.

RV dysfunction and pulmonary hypertension in HFpEF

Though LV diastolic dysfunction is considered to be the cornerstone of HFpEF, the pathophysiology of the disease is complex. It consists not only of variable contributions of diastolic dysfunction, but also of impaired atrial function, impaired contractile reserve, ventriculo–arterial uncoupling, RV dysfunction, and pulmonary hypertension (PH) [42–44]. Despite variable reports, methods, and criteria, the best available current data indicate that RV dysfunction is present in up to 30–50% of HFpEF. It appears to be present in 18%, 28%, and 21% of HFpEF patients using RV FAC, TAPSE, and RV S' measurements, respectively [45, 46]. Increased LV filling pressure (> 12 mmHg) in HFpEF promotes symptoms of dyspnea [47], impairs exercise capacity [48],

and leads to pulmonary venous congestion and secondary PH, which are associated with worse symptoms and overall prognosis of HFpEF [2]. PH is common in HFpEF—a population-based study reported echocardiographic signs of PH in 83% of HFpEF patients [2]. In a prospective invasive hemodynamic assessment study, 77% of HFpEF patients were diagnosed with PH, and 12% of them had combined post- and pre-capillary PH (CpcPH) [49]. According the recent recommendations to define PH as mean pulmonary artery pressure > 20 mmHg is considered to be abnormal [50]; these numbers probably are even higher.

As LV diastolic dysfunction parameters are not the only ones that are relevant to the symptoms and prognosis of HFpEF patients [2, 44–47, 51, 52], we believe that evaluating effectiveness of exercise training on cardiac mechanisms should not be limited by the estimation of LV function single parameters. Instead, it should be more inclusive, by additionally assessing structural and functional measurements of both atria (LAVI, RA area, RA pressure), LV (LVMI, EDV, ESV, SV), RV, and pulmonary circulation (RV area, RV FAC, TAPSE, RV S', estimated PAP) and using more precise methods, including 3D and speckle tracking echocardiography. Even applying extended inclusion criteria for the trials, we found very few studies assessing change of indicated LA and LV echocardiographic parameters after the training; almost no studies analyzed specific right heart and pulmonary circulation parameters. This implies the need to evaluate them in the future HFpEF rehabilitation studies.

Impact of exercise training on HFpEF with PH

There are scientific insights on heterogeneity of HFpEF patients, recommending to look for specific phenotypes [53]. Previously, PH was considered to be limited to the end-stage HFpEF patients, but the study by Borlaug BA et al. revealed abnormalities in PA vasodilation and dynamic RV-PA coupling even in the earliest stages of HFpEF [43]. HFpEF patients with PH (HFpEF-PH) differ in hemodynamics and exercise intolerance, compared with HFpEF patients without PH. Phenotyping HFpEF patients according to the presence of PH in the exercise training studies could be beneficial in gaining a better understanding of the workouts' role on pulmonary circulation changes and finding the optimal exercise training modality for an individual patient. Significant impact of pulmonary vascular disease on the pathophysiology of exercise intolerance was already proven. During symptom limited peak exercise, CpcPH-HFpEF patients, comparing with non-PH-HFpEF and isolated post capillary PH, demonstrated greater increase in right atrial pressure, enhanced ventricular interdependence, and displayed an inability to enhance cardiac output together with blunted augmentation in RV systolic performance; these changes were coupled with marked limitation in aerobic capacity [20].

Extra-cardiac mechanisms of exercise intolerance in HFpEF and PH

Though major reasons for reduced physical capacity in many patients with HFpEF seem to be cardiac, non-cardiac factors are also very important. Reduced peripheral oxygen extraction during exercise in these patients was observed [54–56] that can be related to adverse changes in leg muscle mass and volume [57]. The role of extra-cardiac mechanisms of exercise intolerance in PH is probably even more prominent; they include respiratory muscle weakness, dynamic hyperinflation and mechanical constraints [58], poor skeletal muscle and cerebral oxygenation, hyperventilation, and enhanced sympathetic drive [59–61]. Skeletal muscles represent the largest pool of proteins in the organism, and its proper function is essential for locomotion and breathing [62]. Loss of skeletal muscle mass, that is characteristic in advanced HFpEF and PH, directly contributes to exercise intolerance. Exercise training provides benefits at the molecular and physiological level preventing muscle wasting and reduction in force generation [62, 63].

Limitations

Our systematic review included trials that were conducted in different years (1994–2018). The definition of HFpEF used in each study was not the same. The lowest limit of LV EF in this review was 45%, and according to the very recent ESC guidelines, one of the definition criteria for HFpEF diagnosis is LV EF ≥ 50%, while LV EF 41–49% is considered to be a diagnostic criteria for HFmrEF [4]. Involving a lot of studies with different designs and various statistics, we did not perform a meta-analysis, but previous systematic reviews and meta-analyses of RCT revealed controversial echocardiographic changes after exercise training [12–16]. Potential reasons for these inconsistent results could be related with pooled evaluation of studies with different populations, methodologies, and protocols, when different exercise training modalities and durations of training period and unequal HFpEF diagnostic criteria were used, as well as small sample sizes of the trials. Moreover, the mechanisms of exercise intolerance in HFpEF are complex and the improvement of cardiorespiratory fitness after exercise training might be mediated by cardiac and extra-cardiac mechanisms, being only partially dependent on LV function [28, 64, 65].

Future research

Our work encourages future HFpEF rehabilitation trials to be supplemented by right heart function and pulmonary circulation evaluation in addition with more precise assessments

of LV parameters. Further studies that consider echocardiographic changes after exercising according to sex could be beneficial. Moreover, estimation of specialized rehabilitation influence in HFpEF-PH phenotype would be useful, as until now we have no information about training safety and effectiveness in these patients, while the effectiveness of standardized exercise training in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension was already demonstrated [66, 67].

Conclusions

This systematic literature review that aimed to evaluate and summarize existing data of exercise training and physiotherapy impact on LV, RV morphological, functional, and pulmonary circulation parameters in HFpEF revealed a gap in this area. There are some hypotheses generating findings on potential positive effects on parameters of LV filling pressure (E/e'), left atrial size, cardiac output, and right ventricular function (RV-GLS). However, no reliable evidence about rehabilitation effect to HFpEF cardiac mechanisms is available for now. This encourages a broader and more complex assessment of parameters reflecting cardiac function in the future HFpEF exercise training studies.

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Declarations

Ethics approval Due to the design of the trial (literature review), the study was exempted from requiring ethics approval.

Competing interests The author E.P. reports speaker honoraria fees from Johnson and Johnson and Medis Pharma outside this work. The authors T.Š., C.A.E, N.B., and B.E. have no competing interests to declare. The author E.G. reports research grants and speaker honoraria/consultancy fees from Actelion, Janssen, Bayer, MSD, Merck, and Ferrer and research grants to the institution from Acceleron, Actelion, Bayer, MSD, Janssen, Liquidia, United Therapeutics, and OMT outside the submitted work. The author J.Č. reports personal fees from AstraZeneca, Boehringer Ingelheim, Pfizer, Bayer, and Novartis outside this work.

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