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OptimEx is a collaborative project with experts from the European Union. Funded through the European Union’s Seventh Framework Programme (FP7-HEALTH-2013-INNOVATION-1), OptimEx project was officially launched in October 2013 and ran for 47 months. The project website can be found at https://www.ntnu.edu/OptimEx/

Heart failure with preserved ejection fraction (HFpEF) currently affects more than 7 million Europeans and is the only cardiovascular disease with increasing prevalence and incidence. At least 50% of the total HF population is considered to have HFpEF; indeed, as the population ages and the risk factors such as hypertension, diabetes, obesity, and inactive lifestyle, become more prevalent, the impact of this disease is set to rise considerably. Despite significant improvements in the treatment of HF, morbidity and mortality remain unacceptably high in HFpEF patients. A cardinal feature of the disease is substantially reduced exercise-tolerance associated with pathophysiological disturbances, both centrally and peripherally. The central hemodynamic disturbance is of cardiac origin and results from remodeling processes that include myocyte and non-myocyte components. In consequence, diastolic dysfunction ensues with impaired left ventricular (LV) relaxation, reduced LV compliance, failure of the Frank-Starling mechanism at rest and a rapid increase in left ventricular filling pressures even at low levels of physical activity. Furthermore, inadequate contractile reserve, leading to an insufficient increase in EF during exercise, and lower stroke volume, as well as chronotropic incompetence together contribute to lower peak cardiac output in HFpEF. The peripheral disturbance is characterized by impaired vasodilator reserve, which becomes explicit during exercise, as well as increased arterial stiffness and impaired skeletal muscle energy metabolism, both important determinants of exercise capacity. Blunting of the arterial-venous oxygen difference at peak exercise indirectly suggests peripheral vascular dysfunction, microvascular dysfunction and/or abnormal skeletal muscle oxygen utilization in HFpEF patients.

OptimEx translational approach studied similar training volumes in animal models prone to developing HFpEF (primary prevention) as well as animals and patients with established HFpEF (secondary prevention) focusing on exercise volume (optimal ‘dose-finding’ of exercise duration, frequency, and intensity). Assessing the underlying pathophysiology, OptimEx did not only concentrate on central adaptations in the heart but also took into account the contribution of peripheral factors (blood vessels and skeletal muscle) in this complex and multi-organ-involving disease of HFpEF. In addition, OptimEx addressed novel pathophysiological mechanisms that have not been investigated before but seem to be of relevance in the pathophysiology of HFpEF.

OptimEx sheds new light and provides new knowledge on exercise and HFpEF in both animal models and human subjects, data once available, will form a foundation for innovation in emerging science and technologies.
Summary Description of the Project Context and Objectives

A promising way to improve exercise intolerance in patients with low exercise capacity and cardiovascular risk factors is exercise training. In addition, exercise training may exert beneficial effects on a number of pathophysiological components in patients with HFrEF. Therefore, the concept of exercise training as a powerful strategy to fight HFrEF is progressively emerging, but clinical as well as pathophysiological data are still limited. From a pathophysiological point of view, exercise could by far outweigh any pharmacological intervention in HFrEF, since lifestyle-dependent risk factors, physical inactivity, and physical deconditioning largely contribute to the progressive development of this syndrome. Small-randomized trials in HFrEF patients showed improvements in peak\(\text{VO}_2\) of about 20%. Furthermore, a randomized controlled multi-center study, which OptimEx partners were also involved, demonstrated beneficial effects of exercise training on cardiac structure and diastolic function that directly translated into improved exercise capacity (Figure 1). However, neither mechanistic aspects, long-term effects, nor the optimum mode and dose of exercise interventions in HFrEF were addressed in any of these trials. Before recommendations for exercise in HFrEF can be given, the impact of exercise and exercise dose on pathophysiology as well as clinical outcomes have to be evaluated in a more comprehensive way in animal studies and larger human studies, both using comparable study designs. In particular, a number of important unresolved questions regarding the type of exercise that should be prescribed to HFrEF patients were addressed in OptimEx. These included:

1) Which exercise volume (duration, intensity, frequency,) was the most effective and beneficial in HFrEF?

2) Which were the leading pathophysiological mechanisms (central hemodynamic versus peripheral) that were modified by different exercise volumes?

3) How was adherence to exercise as well as longstanding changes in lifestyle assured? and

4) How were the mechanistic insights translated into future targeted therapies, including drug developments?

OptimEx focus on the cardiovascular effects of exercise training in primary and secondary prevention of HFrEF. We directed our research to find the optimal dose of exercise to improve pathophysiology, prevent disease development and reverse the disease state in HFrEF. OptimEx combined in vivo and in vitro preclinical and clinical studies in order to advance our understanding of fundamental cellular and molecular mechanisms underpinning dose-dependent exercise-induced changes in the heart, blood vessels, and skeletal muscles. In addition, a clinical European multicenter trial introducing exercise training besides best practice therapy was performed to enable us to determine the additional effect of exercise training beyond current treatment and guidelines.

In the primary prevention preclinical HFrEF study, a hypertensive model of HFrEF was used and assessment of the changes of defined physiological and molecular parameters in heart, skeletal muscle, and vascular tissue was performed, and the dose-dependent effect of exercise training on
morbidity and mortality was studied. Additionally, the animal studies were used to detect and test potential targets for prevention and treatment of HFPEF. To translate and compare the animal findings to the clinical scenario, a clinical secondary prevention study was performed in parallel in HFpEF patients. In the clinical trial, patients performed exactly the same training protocols as done in the animal studies. Dose-dependent exercise-induced effects on peakVO2, endothelial function, arterial stiffness and parameters of myocardial diastolic function were assessed. Beside these physiological parameters, safety and the impact on quality of life were also determined, and a telemedicine platform was developed to generate a feedback-loop to the patient via mobile phone to support adherence. This overall strategy, the combination of preclinical and clinical studies to investigate the dose-dependent effect of exercise training in HFpEF, provided physiological and molecular mechanisms elicited in different organs and the transferability into the clinical situation. In addition, the animal model provided a platform to test newly identified targets immediately, whereas the clinical study provided evidence for the safety of the exercise training regimes and whether they differed with regard to adherence.

The major objectives of OptimEx were:

a) to understand the effect of the volume (frequency x intensity x duration) of exercise interventions on structural and functional outcome parameters in animal models at risk for or with HFpEF
b) to gain mechanistic insight into pathophysiological pathways affected by exercise training in HFpEF
c) to establish the optimal volume of exercise training on structural and functional outcome in patients with established HFpEF in a prospective European multicenter trial
d) to introduce and investigate a novel telemedicine approach, in the context of exercise training in HFpEF in order to optimize adherence, supervision, and economic aspects of the intervention
e) to identify potential novel therapeutic targets for future pharmacotherapies for this syndrome

Primary Prevention
Primary prevention – rat model – major goals:
To optimize the dose-response relationship (optimal exercise volume=frequency x intensity x duration) of exercise intervention in order to prevent and/or delay HFpEF in a rat model and study cellular and molecular mechanisms in
- Heart (Cardiac function and structure, extracellular matrix environment, cardiomyocyte Ca2+/Na+ handling and excitation-contraction coupling, mitochondrial function)
- Blood vessels (Molecular determinants of vascular stiffness and endothelial dysfunction in arteries)
- Skeletal muscle (Determinants of exercise intolerance: mitochondrial function, capillary density, anabolic/catabolic pathways, modifications and expression of contractile proteins)

To identify and test potential novel candidates (e.g. mRNAs/miRs, signaling pathways) through which exercise training can influence the development of HFPEF

Secondary Prevention
Secondary prevention – rat model – major goals:
To optimize the dose-response relationship (optimal exercise volume=frequency x intensity x duration) of exercise as a therapeutic strategy in a rat model of established HFpEF on traditional and new cellular and molecular mechanisms related to HFPEF in

- Heart (Cardiac function and structure, extracellular matrix environment, cardiomyocyte Ca2+/Na+ handling and excitation-contraction coupling, mitochondrial function)
- Blood vessels (Molecular determinants of vascular stiffness and endothelial dysfunction in arteries)
- Skeletal muscle (Determinants of exercise intolerance: mitochondrial function, capillary density, anabolic/catabolic pathways, modifications and expression of contractile proteins)

To identify and test potential novel targets (e.g. mRNAs/miRs, signaling pathways) through which exercise training can influence established HFPEF
To quantify the impact of different exercise strategies on morbidity and mortality in HFPEF-rats and control rats.

**Secondary prevention – clinical study – major goals:**
To optimize dose-response relationship \( \text{optimal exercise volume} = \text{frequency} \times \text{intensity} \times \text{duration} \) to maximally improve objective parameters of exercise intolerance in patients with HFPEF.
To optimize exercise dose to reverse the underlying pathophysiology limiting exercise tolerance focusing on both cardiac and peripheral factors:

- **Heart** (Cardiac function and structure)
- **Blood vessels** (Peripheral arterial endothelial function and arterial stiffness)
- **Skeletal muscle** (Mitochondrial function, capillary density, anabolic/catabolic pathways, modifications and expression of contractile proteins).

To identify changes of different exercise volumes on currently established (e.g. NT-proBNP) and potential novel pathophysiological markers or therapeutic targets (e.g. collagen markers, Protein Kinase G, miRs).
To study the effect of different exercise volumes on the quality of life (QoL).
To assess adherence to different exercise volumes and effect on overall physical activity.
To develop a telemedicine platform for accelerometer data and automatic feedback loop to the patient and assess the potential influence on the adherence to the exercise intervention.
To calculate the potential impact of exercise training on cost for HFPEF (cost-benefit analysis).

The novelty of the project is the combination of exercise intervention studies with equivalent protocols in animal and human studies investigating the optimal dose of exercise intensity on three different organ systems (heart, vasculature, skeletal muscle), also including novel analyses ranging from \textit{in-vivo} measurements all the way through to molecular targets. This translational research will form the basis to establish original and novel diagnostic and therapeutic tools for the prevention and treatment strategies of HFPEF (e.g. specialized exercise regimes as well as targets for molecular therapies), thus contributing to reduce the burden of lifestyle-related cardiovascular diseases.
Main Scientific and Technical Results

Work Plan Overview

OptimEx was divided into six work packages, two organizing and four scientific (Figure 2). Two work packages (WP1&2) used an animal model of HfPEF to investigate dose-dependent exercise-induced changes. Assessment of changes of defined physiological and molecular parameters in heart, skeletal muscle, and vascular tissue was performed, and the dose-dependent effect of exercise training on morbidity and mortality were studied. In addition, the animal studies were used to detect and test potential targets for prevention and treatment of HfPEF.

To translate and compare the animal findings to the clinical scenario, a clinical secondary prevention study was performed in parallel in HfPEF patients (WP3). During the clinical trial, patients performed exactly the same training protocols as done in the animal studies (moderate and high-intensity exercise training). Dose-dependent exercise-induced effects on peak oxygen uptake (peakVO2), endothelial function, arterial stiffness and parameters of myocardial diastolic function have been assessed. Beside these physiological parameters, safety and the impact on quality of life were also determined in the clinical study as well as a telemedicine platform (WP4) developed to generate a feedback-loop to the patient via mobile phone to support adherence.

The combination of preclinical and clinical studies to investigate the dose-dependent effect of exercise training in HfPEF has provided physiological and molecular mechanisms elicited in different organs and the transferability into the clinical situation. In addition, the animal model provided a platform to test new targets, whereas the clinical study has already provided evidence for the safety of the exercise training regimes and whether they differ with regard to adherence.

The work related to dissemination was undertaken in WP 5. Within WP 6, all activities related to management and coordination were combined. The communication and everyday work kept the project smoothly running and supported effective and prosperous research and cooperation.

![Figure 2. Schematic overview of the strategy of the work plan.](image-url)
WP 1: Primary Prevention – Rat Model

Work Undertaken

WP1 was divided into five tasks related to the work:

- Dose-response adaptations in left ventricular diastolic function (E/e') and peakVO₂ in a rat model prone to develop HFpEF.
- Dose-response adaptations on molecular and cellular alterations in the heart.
- Dose-response adaptations in endothelial function as well as cellular and molecular markers.
- Dose-response adaptations in skeletal muscle and the following cellular and molecular markers.
- Novel molecular targets for the prevention of HFpEF by exercise training.

Scientific and Technical Results

Dahl SS rats fed a high-salt diet (HS) had significantly higher blood pressure levels than those fed a low-salt diet (LS) from week nine, which was sustained until termination of the protocol. As illustrated in Figure 3, high-salt diet-induced diastolic dysfunction at week 28, assessed by the peak velocity of early filling to tissue Doppler early diastolic mitral annular velocity (E/E') (Figure 3A). EF was above 50% in all animals at the end of the study, although the group analysis showed HS had a slight decline of EF, reaching statistical significance versus LS at week 28 (Figure 3B). Hemodynamic data confirmed increased left ventricle (LV) end-diastolic pressure (LVEDP) (Figure 3C) and preserved systolic function in HS than LS group (Figure 3D). HFpEF was also confirmed by increased LV mass (Figure 3E) and elevated plasma levels of NT-proBNP (Figure 3F) in HS compared to LS rats.

Exercise training dose-response

Exercise training protocols and total weekly running time are illustrated in Figure 4. Exercise training was well tolerated by all animals and no deaths occurred during or immediately after a training session. The effect of all three protocols on running capacity, invasive and noninvasive assessment of cardiac function (systolic and diastolic), plasma NT-proBNP levels, and overall mortality were analysed and data will soon be available to the public.

Endothelial function

In Dahl SS rats, endothelium-dependent and -independent vasodilation was impaired when compared to control. This impairment was prevented by HIT-HV, whereas HIT-LV and MCT had no impact on endothelial dysfunction (Figure 5). Data already published (PMID:26229002).

Adaptation in skeletal muscle function

To measure maximal force generation of the soleus, EDL, and diaphragm, force-frequency relation was recorded. Performing these measures, an impairment of maximal force generation was obvious in the...
soleus and diaphragmatic muscle of the animals in HS (HFpEF) group when compared to the LS group (control animals). This difference in maximal force generation was not evident in the EDL muscle.

To evaluate the impact of different training modalities on muscle force generation, force frequency relations were recorded for all animals in the different groups. In the soleus muscle, all training modalities attenuated the loss of muscle force, whereas in the diaphragm only MCT and to a lesser extent HIT-HV were effective (Figure 6). In the EDL no significant impact of different training modalities on force generation was observed.

Besides force generation, muscle fatigability is another important parameter to describe physiological muscle function. Muscle fatigue was measured in all the muscles (soleus, EDL, and diaphragm) of the animals.

Comparing the initial force generated by the muscles after stimulation with the force after 2 min of the fatigue protocol (stimulation every sec with a frequency of 40 Hz) a significant difference was evident in the soleus and the diaphragm of the HS animals compared to the LS animals (soleus LS: 69.8±2.2 % of initial force vs. soleus HS: 56.1±2.3 % of initial force, p<0.05; Diaphragm LS: 56.3±2.6 % of initial force vs. diaphragm HS: 47.0±1.0 % of initial force, p<0.05). This increased fatigue of the HS group was not evident in the EDL muscle (LS: 27.0±7.0 % of initial force vs. HS: 27.1±6.6 % of the initial force, p=ns). Analysing the impact of different training modalities on muscle fatigue, all...
three training modalities (MCT, HIT-HV, and HIT-LV) attenuated muscle fatigue the soleus and diaphragm muscle (Figure 7). Data already available to the public (PMID:25655080).

Cardiac miR signature An unbiased high-throughput screening for miRs in cardiac tissue was performed and HIIT-HV group was prioritized among all training groups. Analysis of miR profile in cardiac tissue showed a range of miR with p-values <0.05. Manuscript in preparation and data will soon be available to the public.

Circulating miR signature We also tested whether the detection of miRs in the circulation could be used as a potential biomarker for experimental HFpEF. In order to identify circulating miRs, we performed an RT-qPCR screening in the plasma of the same cohort of Dahl SS animals. We found two miRs to be significantly altered in HS compared to LS group. We also determined the correlation coefficients (Pearson r) between plasma miRs levels and parameters of cardiac function and plasma NT-proBNP levels, the standard clinical biomarker of HFpEF. Interestingly, one of the circulating miRs levels correlated negatively with NT-proBNP, E/E', E/A, EF, LVEDP, and lung wet/dry ratio, but not with LAD. Differently, circulating levels of another miR correlated positively with E/E' and E/A ratios, LAD, and NT-proBNP, and negatively correlated with EF. We next performed a combined receiver operator characteristic (ROC) curve analysis for assessment of HFpEF classification to compare circulating levels of the two miRs we found to be significantly altered in HS compared to LS group and NT-proBNP, along with other functional parameters between HS and LS groups. We show that both miRs better distinguish HS from LS animals than classical HF biomarker NT-proBNP. Next, we tested whether HIIT-HV could influence the changes observed in the circulating miRs and, interestingly, HIIT-HV prevented changes in both miRs. Manuscript in preparation and data will soon be available to the public.

These data from an animal model of HFpEF provide evidence that all three-exercise regimens increased exercise capacity, with superior results found in HIIT-HV and MCT, as compared to HIIT-LV. HFpEF endothelium-dependent vasodilation of the aorta was prevented by HIT-HV, whereas HIT-LV and MCT have not shown a preventive effect on the endothelial dysfunction in HFpEF. In the soleus muscle, all three training modalities attenuated the loss of muscle force, whereas in the diaphragm only MCT and to a lesser extend HIT-HV were effective. Analysing the impact of different training modalities on muscle fatigue all three training modalities attenuated muscle fatigue the soleus and diaphragm muscle.

**HFpEF vs. HFrEF**

We used established animal models to reveal many novel findings in relation to the circulating miRs as well as to the molecular and cellular skeletal muscle alterations that exist between HFrEF and HFpEF.

**Circulating miR signature** Cardiac screening revealed four HFpEF-specific miRs compared to 79 HFrEF-specific miRs. Additionally, 13 miRs shared a common cardiac profile between HFpEF and HFrEF. We then performed Gene Ontology analysis (GOrilla) for all HFpEF, HFrEF and common
predicted target genes. Interestingly, miR target prediction for either HFpEF or HFrEF-specific miRs followed by enrichment analysis revealed several pathways of potential relevance in the disease management. Additionally, genes predicted to be targeted by both HFpEF and HFrEF cardiac miRs presented an enrichment in different pathways. Here, we uncovered distinctive cardiac miR signatures for HFpEF, which will contribute to future development of dedicated therapeutic targets and improved prognostication. Manuscript in preparation and data will soon be available to the public.

**Skeletal muscle** The main symptom observed in patients with HF is exercise intolerance, consequent not only to dyspnoea but also to severe skeletal muscle weakness (both in the limb and respiratory systems), with the latter being a robust predictor of quality of life and prognosis. Interestingly, initial evidence from independent studies indicates that some but not all skeletal muscle alterations are similar between HFrEF and HFpEF when compared with controls. OptimEx used established animal models to reveal many novel findings in relation to the different molecular and cellular skeletal muscle alterations that exist between HFrEF and HFpEF, which included:

1. Upregulation of markers of muscle atrophy in HFrEF (ie, MuRF1, calpain, and ubiquitin-proteosome) but unchanged or lower levels in HFpEF soleus.
2. Increased oxidative stress in HFrEF (ie, higher NADPH oxidase with lower antioxidative enzyme activities) but not in HFpEF soleus.
3. Impaired mitochondrial indices in HFrEF (ie, a lower SDH/LDH ratio and PGC-1α protein expression) but not in HFpEF soleus.
4. Muscle-dependent alterations between HFpEF and HFrEF limited to limb muscle (soleus), with respiratory muscle (diaphragm) remaining largely unaffected.
5. A distinctive circulating inflammatory cytokine response, with increased plasma concentrations of TNF-α in HFrEF but IL-1β and IL-12 in HFpEF.

Overall, therefore, our findings provide initial evidence that skeletal muscle alterations are exacerbated in HFrEF compared with HFpEF, which are mainly isolated to limb (soleus) rather than to respiratory (diaphragm) tissue, and that the different circulating inflammatory cytokines detected among phenotypes may be potentially mediating such effects (as summarized in Table 1). As such, our data provide novel insights into the different molecular alterations and potential treatment targets specific to HFpEF and HFrEF. Data already published and available to the public (PMID:27609832).

**TABLE 1. Skeletal Muscle Molecular Alterations in HFrEF and HFpEF Ejection Fraction Compared With Controls from the Limb (Soleus) and Respiratory (Diaphragm) Muscle, As Well As Measured Circulating Cytokines**

<table>
<thead>
<tr>
<th></th>
<th>Soleus</th>
<th>Diaphragm</th>
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</thead>
<tbody>
<tr>
<td><strong>Anabolic factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFpEF</td>
<td>Decreased ↓IGF-1</td>
<td>Decreased ↓IGF-1</td>
</tr>
<tr>
<td>HFrEF</td>
<td>Decreased ↓IGF-1</td>
<td>Decreased ↓IGF-1</td>
</tr>
<tr>
<td></td>
<td>Unchanged ↔IGF-1</td>
<td>Unchanged ↔IGF-1</td>
</tr>
<tr>
<td><strong>Catabolic factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFpEF</td>
<td>Increased ↑Murf1, ↑calpain/proteasome activity; ↑LC3,</td>
<td>Increased ↑Murf1, ↑calpain/proteasome activity; ↑LC3,</td>
</tr>
<tr>
<td>HFrEF</td>
<td>Decreased ↓Murf1, ↓calpain/proteasome activity; ↓LC3</td>
<td>Decreased ↓Murf1, ↓calpain/proteasome activity; ↓LC3</td>
</tr>
<tr>
<td></td>
<td>Unchanged ↔Murf1, ↔calpain/proteasome activity; ↔LC3</td>
<td>Unchanged ↔Murf1, ↔calpain/proteasome activity; ↔LC3</td>
</tr>
<tr>
<td><strong>Mitochondrial indices</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFpEF</td>
<td>Decreased ↓SDH/LDH ratio; ↓Pgc-1α; ↓CK</td>
<td>Decreased ↓SDH/LDH ratio; ↓Pgc-1α; ↓CK</td>
</tr>
<tr>
<td>HFrEF</td>
<td>Decreased ↓SDH/LDH ratio; ↓Pgc-1α; ↓CK</td>
<td>Decreased ↓SDH/LDH ratio; ↓Pgc-1α; ↓CK</td>
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<tr>
<td></td>
<td>Unchanged ↔SDH/LDH ratio; ↔Pgc-1α; ↔CK</td>
<td>Unchanged ↔SDH/LDH ratio; ↔Pgc-1α; ↔CK</td>
</tr>
<tr>
<td><strong>Oxidative stress</strong></td>
<td></td>
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<tr>
<td>HFpEF</td>
<td>Increased ↑NADPH oxidase, ↑GPX, ↑Cat; ↑SOD</td>
<td>Increased ↑NADPH oxidase, ↑GPX, ↑Cat; ↑SOD</td>
</tr>
<tr>
<td>HFrEF</td>
<td>Decreased ↓NADPH oxidase, ↓GPX, ↓Cat; ↓SOD</td>
<td>Decreased ↓NADPH oxidase, ↓GPX, ↓Cat; ↓SOD</td>
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<tr>
<td></td>
<td>Unchanged ↔NADPH oxidase; ↔GPX, ↔Cat; ↔SOD</td>
<td>Unchanged ↔NADPH oxidase; ↔GPX, ↔Cat; ↔SOD</td>
</tr>
<tr>
<td><strong>Plasma inflammatory cytokines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFpEF</td>
<td>Increased ↑TNF-α, IL-1; ↑IL-12, increased in HFpEF: TNF-α, IL-1; IL-12</td>
<td>Increased ↑TNF-α, IL-1; ↑IL-12, increased in HFpEF: TNF-α, IL-1; IL-12</td>
</tr>
</tbody>
</table>

↑ indicates increased; ↓, decreased; ↔ unchanged; CK, creatine kinase; GPX, glutathione peroxidase; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IL, interleukin; LC3, microtubule-associated protein 1 light chain 3; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; SOD, superoxide dismutase; and TNF, tumor necrosis factor.
WP 2: Secondary Prevention – Rat Model

Work Undertaken

WP2 was also divided into six tasks related to the work:

1. Dose-response adaptations in E/é and peakVO₂ in HFpEF rats.
2. Dose-response adaptations on molecular and cellular alterations in the heart.
3. Dose-response adaptations in endothelial function as well as cellular and molecular markers.
4. Dose-response adaptations in skeletal muscle as well as cellular and molecular markers.
5. Novel molecular targets to treat cellular defects in cardiomyocytes from rats with HFpEF.

Scientific and Technical Results

Obese diabetic Zucker fatty/spontaneously hypertensive HF F1 hybrid (ZSF1) rats (Charles River Laboratories; bought at 8 weeks of age) were used as a model to induce HFpEF, with this strain of rat previously shown to develop typical clinical signs of HFpEF at 20 weeks of age. While both lean and obese ZSF1 rats inherit the hypertension gene, only the obese ZSF1 rats inherit a mutation in the leptin receptor gene that drives weight gain and metabolic impairments. A schematic of the study design is presented in Figure 8. This cardiometabolic syndrome model developed diastolic dysfunction, despite a preserved systolic function, reduced effort tolerance when compared with both WKY and lean ZSF1 rats (Figure 9).

Dose-response adaptations in exercise capacity and diastolic function After randomization into either a sedentary, MCT, or HIIT intervention group, ZSF1 obese rats trained for 8 weeks as described in Figure 8. Exercise training independent of modality did not show an impact of LVEF, E/E’ and LVEDP when compared to the sedentary animals (Figure 10C, A, and B, respectively). Only HIIT was able to improve peakVO₂ when compared to the group of obese sedentary animals (Figure 10H). Data already published and available to the public (PMID:29066440).

Effects of exercise training on cardiomyocyte Ca⁺ handling LV cardiomyocyte Ca⁺ transient amplitude, Ca⁺ kinetics, and SR Ca⁺ content were studied in diabetic and hypertensive ZSF1 rats at 20 and 28 weeks of age. The effect of 8 weeks of exercise training (MCT and HIIT) on cardiomyocyte Ca⁺ homeostasis was also studied in ZSF1 rats. The manuscript is in preparation.

Dose-response adaptations in endothelial function as well as cellular and molecular markers Endothelial-dependent and endothelium-independent vasodilation was also studied in all animals before and after 8 weeks of exercise training (MCT and HIIT) intervention. Additionally, the molecular mechanisms underpinning altered endothelial function in HFpEF, which include eNOS and NAD(P)H oxidase expressions, were also studied before and after 8 weeks of exercise intervention and the data have been already analysed. The manuscript is in preparation.

Adaptation in diaphragm function This study, using a well-characterized rat model of HFpEF underpinned by multiple comorbidities and exercise intolerance (i.e., one that closely resembles the patient phenotype), provides the first evidence in rats that diaphragm alterations and dysfunction induced in overt HFpEF were not reversed following 8 weeks of aerobic exercise training (i.e., secondary prevention). This was observed for both the HIIT and MCT exercise training regimens, which indicates an apparent metabolic inflexibility of the diaphragm in HFpEF—a finding that opposes previous data where exercise training as primary prevention was beneficial in the period
preceding the development of HFpEF (Figure 6 and 7). As such, these data may have important clinical implications for treating respiratory muscle weakness in patients with HFpEF, suggesting that alternative therapeutic interventions may provide greater benefits compared with aerobic exercise training. Nevertheless, the finding that both training regimens still improved exercise capacity in HFpEF supports the current notion that exercise training is an effective treatment strategy for the HFpEF syndrome. Data already published (PMID:29066440)

Adaptation in soleus limb muscle

In addition, OptimEx secondary preclinical study also assessed alterations in the soleus limb muscle, both at 20 and 28 weeks, in order to provide a comparison to the diaphragm (Figure 11). At 20 weeks, while contractile function and fatigability remained unaltered (P>0.05) (Figure 11A and 11B), muscle atrophy was present in HFpEF rats with muscle mass reduced by 15% (P>0.05) (Figure 11C). Further assessment of the molecular alterations revealed that mitochondrial density, as measured by citrate synthase activity, tended (P=0.06) to be increased by 45% in the soleus of HFpEF rats (Figure 11D). Similarly, markers typically related to the atrophy process were also higher in HFpEF rats: protein expression of MuRF1 tended to be increased by 20% (P>0.05) (Figure 11F), while MuRF2 increased by 25% (P<0.05) (Figure 11G). Interestingly, at 28 weeks, sedentary HFpEF rats tended to generate higher maximal soleus forces (10% higher compared with the HIIT HFpEF rats; P<0.05) (Figure 11A), with exercise training also having no influence on soleus fatigability (P>0.05) (Figure 11B). In contrast, however, HIIT was able to attenuate the muscle atrophy induced by HFpEF (P<0.05) (Figure 11C), while molecular measures following exercise training tended to be improved, albeit not significant: citrate synthase activity (P=0.07) (Figure 11D) and PGC1-a protein content (P>0.05) (Figure 11E) tended to be 30% higher in trained animals, while levels of MuRF1 and MuRF2 were generally lower by 25% (P>0.05) (Figure 11F and 11G).

While we found no obvious functional deficits in the soleus muscle from the current group of obese HFpEF rats (i.e., contractile function and fatigue indices remained unchanged), we did reveal numerous tissue alterations such that at 20 weeks an 15% muscle atrophy was present and this was associated with an upregulation of atrogins (i.e., the MuRF1 and MuRF2), while mitochondrial
capacity (as inferred from citrate synthase activity) tended to be higher in HFP EF rats compared with controls. The latter may suggest a potential compensatory response to the obese phenotype attributable to a reduction in blood flow or consequent to an increase in weight-bearing load. Indeed, this suggestion is supported by previous data whereby obesity was shown to increase measures of oxidative capacity in numerous limb muscles. Yet, and in contrast, biopsies collected from limb muscle in patients with HFP EF recently reported that mitochondrial content and oxidative capacity were reduced. However, as this patient cohort were widely heterogeneous, older, and not primarily characterized by obesity, whether our current findings translate to patients remains to be determined. In addition, and similar to the diaphragm, the present study found that exercise training had limited benefits on most soleus tissue indices in HFP EF rats, although the HIIT intervention was clearly able to attenuate the muscle atrophy observed in sedentary HFP EF rats. This was associated with a trend for levels of atrogin (MuRF1 and MuRF2) to be reduced and mitochondrial markers (PGC1-α and citrate synthase) to be increased. Collectively, therefore, these data confirm that in an obese model of HFP EF, numerous alterations in limb skeletal muscle are induced, with evidence demonstrating that HIIT may provide an intervention to reverse potential underlying impairments, which, in turn, may contribute to improving exercise capacity following training. Alternatively, the primary mechanism that may have underpinned the increase in exercise capacity in HFP EF following the HIIT or MCT
regimens may be directly related to improvements in endothelial function. It is well established that HFpEF can induce endothelial dysfunction, with available evidence showing that this can be reversed by exercise training. While the inclusion of endothelial measurements was beyond the scope of the present study, where the main interest was to investigate the diaphragm, the potential for exercise training to improve peripheral endothelial function remains likely. The latter would be predicted to elevate O2 diffusion from capillary to myocyte, thereby driving improvements in subsequent exercise capacity—a finding that was observed in the present study following 8 weeks of exercise training. Data already published (PMID:29066440).

Detection and validation of novel molecular targets to treat HFpEF Coexisting conditions observed in ZSF1 obese rats (e.g., hypertension, obesity and diabetes) seem to lead to a systemic microvascular endothelial inflammation, which has been studied by this consortium. Furthermore, OptimEx also aimed to look for possible right ventricular (RV) structural changes and potential mechanisms related to inflammation in ZSF1 obese rats as well as whether improved exercise capacity can modify the development of adverse RV remodeling and HFpEF. Data have already been analysed and will soon be submitted for publication.

One of our major goals in OptimEx secondary prevention rat model was to quantify the impact of different exercise strategies on morbidity and mortality in HFpEF and control rats. Dahl SS rat and ZSF1 obese rat are the only two animal models that have been suggested in the literature to study molecular mechanisms underlying HFpEF. Considering the high mortality and the inconsistency of Dahl SS rat model used for the primary prevention, the hypertensive diabetic (ZSF1 obese) rat model...
was our rat model of choice for the secondary preclinical study. ZSF1 obese rat presented coexisting conditions (obesity, hypertension, and diabetes), which led to the development of HFrEF. However, no positive effect of either MCT or HIIT was observed on any of the parameters responsible for the development of HFrEF in ZSF1 obese rat model. Furthermore, mortality was not an issue in this model either. Therefore, a follow-up study in separate groups (sedentary and exercised at two different intensities, MCT and HIIT) of ZSF1 rats to investigate the development of clinical symptoms and mortality was not conducted. However, we feel confident in making several observations based on what we have learned so far:

1. ZSF1 obese rat model shows a very severe increased body weight over time, which would make it more difficult for the animals to perform HIIT for a long period;
2. There is no evidence of important mortality reported in the literature using ZSF1 rat model;
3. We believe that the most important physiological adaptations in response to MCT or HIIT were evidenced after a period of 8 weeks exercising.
WP 3: Secondary Prevention – Clinical

Work Undertaken

WP3 was divided into nine tasks related to the work:

1. Dose-response adaptations in the primary combined endpoint of E/é and peakVO2.
2. Dose-response adaptations on systolic and diastolic echocardiographic parameters.
3. Dose-response adaptations on aerobic and anaerobic exercise capacity as well as daily activity level.
4. Dose-response adaptations on quality of life.
5. Dose-response adaptations on endothelial function and repair mechanisms, arterial stiffness.
6. Dose-response adaptations on skeletal muscle including energetics and molecular adaptation.
7. Monitoring adverse and serious adverse events during the entire trial.
8. Dose-response adaptations on circulating biomarkers of hemodynamic load, inflammation, fibrosis and cell death/remodeling.

Scientific and Technical Results

In a prospective randomised multi-center study (OptimEx-CLIN), 180 patients with stable symptomatic HfPEF were randomised (1:1:1) to moderate intensity continuous training, high-intensity interval training, or a control group (Figure 12 and 13). The training intervention included three months supervised followed by nine months of telemedically monitored home-based training. The primary endpoint was changed in exercise capacity, defined as the change in peakVO2 after three months, assessed by cardiopulmonary exercise testing. Secondary endpoints included diastolic filling pressure (E/é) and further echocardiographic and cardiopulmonary exercise testing parameters, biomarkers, quality of life and endothelial function. Training sessions and physical activity were monitored and documented throughout the study with accelerometers and heart rate monitors developed on a telemedical platform for the OptimEx-CLIN study (PMID:25354950). For compelling statistical analysis, data acquisition of all 180 patients should be completed. No interim analysis was performed. Data presented here were not adjusted for group assignment, gender, age, NYHA class, or diastolic function parameters. Statistical analysis was done without the aforementioned adjustments, because the unplanned analyses of accumulating data from an ongoing trial to evaluate treatment efficacy can cause the overall Type I error (alpha level), generally fixed at the initial design stage, to become inflated. Therefore, the analysis of the primary and secondary endpoints will be completed when all data are
collected and cleaned. Data collection was completed in November 2017 and data analyses have already been started.

**Dose-response adaptations in the primary combined endpoint of E/é and peakVO2**
Change in E/e' was negatively correlated with changes in peakVO2 ($r=-0.3$, 95% CI:$-0.45$ to $-0.14$, $p<0.001$) for the whole study population (Figure 14). In line with the literature, in OptimEx, peakVO2 increased with exercise after first 3 months was associated with improvement in diastolic function (decrease E/e').

**Dose-response on diastolic echocardiographic parameters**
Of all echocardiographic parameters investigated, the LV filling index E/e' was identified as the best index to detect diastolic dysfunction in HFrEF in which the diagnosis of diastolic dysfunction was confirmed by conductance catheter analysis. A cardinal feature of HFrEF is severely impaired exercise capacity, objectively determined as peakVO2, which is one of the strongest prognostic markers in chronic HF. Change in EF was slightly negatively correlated with changes in peakVO2, but with no statistical significance ($r=-0.09$, 95% CI: $-0.27$ to $-0.09$, $p=0.34$). Change in e' septal was positively correlated with changes in peakVO2 ($r=0.19$, 95% CI: $0.02$ to $0.35$, $p<0.05$) (Figure 15), which could indicate an improvement in diastolic function.

**Dose-response on aerobic capacity parameters and daily physical activity level**
Advances in telecommunication technologies have created new opportunities to provide telemedical care as an adjunct to medical management of patients with HF. To include telemedicine in lifestyle intervention strategies has been suggested to increase adherence to these programmes. However, telemedicine-based monitoring of and feedback on training adherence has not been tested in HFrEF patients yet. Also, the effects of different exercise training volumes particularly differing in intensity (MCT versus HIIT) on regular daily physical activity have not been tested before. In OptimEx-CLIN, the inclusion of telemedical strategies is important for assessing the relationship between different types of exercise intervention and adherence as well as their impact on daily activity. Average Steps between visit 1 (V1, baseline) and visit 2 (V2, 3 months later) was not correlated with changes in peakVO2 ($r=0.07$, 95% CI:$-0.10$ to $0.24$, $p=0.389$). The average Active time between V1 and V2 was also not correlated with changes in peakVO2 ($r=-0.00$, 95% CI:$-0.17$ to $0.17$, $p=0.999$).
Dose-response on health-related quality of life (HRQoL)

As patient-reported outcomes such as HRQoL and perceived symptoms represent important measures that can inform patients, clinicians, and policy-makers about morbidity, change in HRQoL was one of the secondary endpoints to evaluate the outcome of exercise training in the OptimEx trial. Significant effects of formal exercise training/exercise advice were observed among HFrEF, especially in disease-specific symptoms, physical limitations and quality of life domains, whereas symptom stability, social limitations, and mental health status remained unchanged. Among HFrEF patients who underwent formal exercise training/formal exercise advice, there were significant differences in the KCCQ scores before and after 3-month follow-up. The symptoms, physical limitations, quality of life domains, as well as the overall clinical score of the KCCQ showed significant improvement (all p<0.05), whereas symptom stability and social limitations remained unchanged (Table 2). Results for general quality of life and mental health at baseline and 3-months follow-up are given in Table 3. There was a significant improvement in self-reported overall health (visual analog scale (VAS) of the EQ-5D) after 3-months follow-up. No changes were observed in mental health status after 3 months (Table 3).

Dose-response on endothelial function

Retrospectively, four patients did not meet inclusion criteria and were excluded from analysis. Complete measurements were available in 66.6%, 19.4% and 60.0% of patients for reactive hyperemia index (RHI), pulse wave velocity (PWV) and endothelial progenitor cell (EPC), respectively (Table 4). At the time of writing, post-hoc analysis of flow-mediated dilation (FMD) measurements and angiogenic T cells was ongoing. Baseline characteristics are displayed in Table 5. Patients were predominantly female and overweighted. Blood pressure and heart rate were well-controlled.

Microvascular endothelial function (index of reactive hyperemia response (FRHI) did not significantly change between V1 and V2. When including body mass index (BMI) and gender in a multivariate linear mixed model for FRHI, an influence of these covariates was observed. FRHI was higher in females (β 0.27, p<0.001) and tended to be lower in patients with higher BMI (β -0.01, p=0.059). Arterial stiffness, assessed by PWV, showed a trend towards improvement over time (β -0.59, p=0.085). PWV increased with older age (β 0.16, p=0.024). These conclusions remained when using the corrected PWV, which is adjusted for differences in body size. In vitro endothelial repair mechanisms, assessed by a number of circulating EPC, did not differ between V1 and V2. Women had lower EPC numbers compared to men (β -24.0, p=0.001). Results are summarized in Table 6. Correlations between changes from V1 to V2 in different measures of vascular function were low (all rho <0.35, all p>0.05). At baseline, PWV correlated modestly with the number of EPC (rho 0.390, p=0.044). FRHI and EPC showed a small but significant correlation with baseline peakVO2 (FRHI rho 0.206, p=0.026; EPC rho -0.200, p=0.042, Figure 17). Vascular function measurements were not withheld as significant predictors of peakVO2 in a multivariate linear mixed model. Higher BMI, female gender, and older age were
associated with lower peakVO2 (BMI $\beta$ -0.43, p<0.001, gender $\beta$ -1.95, p=0.007, age $\beta$ -0.21, p<0.001).

Dose-response adaptations on skeletal muscle including energetics and molecular adaptation
Skeletal muscle biopsies from HFpEF patients randomized into a control group or the two different training groups (HIIT or MCT) were analysed at two different time point – at begin and 3 months after randomization (finishing the supervised training period). To assess the impact of different training regimes on skeletal muscle including energetics and molecular adaptation, the following analyses were performed (manuscript in preparation):

- **Metabolic enzymes:**
  - Glycolytic enzymes - hexokinase activity (responsible for phosphorylation of glucose when entering the cell), lactate dehydrogenase activity (pacesetter for anaerobic glycolysis) and pyruvate kinase activity (catalyzing the final step of glycolysis).
  - Fatty acid metabolism - the enzymatic activity of $\beta$-hydroxyacyl-COA dehydrogenase.
  - Mitochondrial energy metabolism and energy transfer from mitochondria to the contractile proteins - the enzymatic activity of citrate synthase, malate dehydrogenase, creatine kinase, succinate dehydrogenase, and mitochondrial complex I of the respiratory chain. Protein expression of the voltage anion channel of the outer mitochondrial membrane.

- **Superoxide dismutase expression** - superoxide dismutase.
- **Atrophy related pathways** - protein expression of MafBx.
- **PGC-1α expression**.
- **Quantification of satellite cells** – transcription factor paired box 7 (Pax-7) positive cells.
- **Functional analysis of satellite cells:**
  - The cell proliferation index.
  - Differentiation index.
TABLE 2. Disease-specific HRQoL at baseline and 3-month follow-up as measured by the KCCQ

<table>
<thead>
<tr>
<th>Variable</th>
<th>VISIT 1</th>
<th>VISIT 2</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (±SD)</td>
<td>Median</td>
</tr>
<tr>
<td><strong>KCCQ</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical limitation</td>
<td>155</td>
<td>65.17 (±24.46)</td>
<td>67.0</td>
</tr>
<tr>
<td>Symptom stability</td>
<td>171</td>
<td>50.44 (±16.21)</td>
<td>50.0</td>
</tr>
<tr>
<td>Symptom frequency</td>
<td>169</td>
<td>63.12 (±21.27)</td>
<td>67.0</td>
</tr>
<tr>
<td>Symptom burden</td>
<td>169</td>
<td>69.71 (±22.63)</td>
<td>75.0</td>
</tr>
<tr>
<td>Symptom total score</td>
<td>167</td>
<td>66.33 (±21.21)</td>
<td>71.0</td>
</tr>
<tr>
<td>Self-efficacy</td>
<td>169</td>
<td>64.54 (±25.83)</td>
<td>75.0</td>
</tr>
<tr>
<td>QoL</td>
<td>170</td>
<td>65.22 (±23.72)</td>
<td>67.0</td>
</tr>
<tr>
<td>Social limitation</td>
<td>123</td>
<td>40.83 (±16.63)</td>
<td>50.0</td>
</tr>
<tr>
<td>Overall sum score</td>
<td>107</td>
<td>59.06 (±18.75)</td>
<td>62.0</td>
</tr>
<tr>
<td>Clinical sum score</td>
<td>151</td>
<td>65.52 (±21.43)</td>
<td>68.0</td>
</tr>
</tbody>
</table>

**Physical fitness**

| VO2peak_1 | 176 | 18.82 (±5.32) | 18.3 | 155 | 19.49 (±5.62) | 19.4 | 0.004 |

* Non-parametric statistic (Wilcoxon Signed Rank Test).
Outcome measures that are statistically significant are presented in boldface.
HRQoL = health-related quality of life.
KCCQ = Kansas City Cardiomyopathy Questionnaire.
VAS = visual analogue scale.

TABLE 3. Generic quality of life and mental health at baseline and 3-month follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>VISIT 1</th>
<th>VISIT 2</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (±SD)</td>
<td>Median</td>
</tr>
<tr>
<td><strong>Generic QoL (EQ-5D)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td>172</td>
<td>1.39 (±0.50)</td>
<td>1.0</td>
</tr>
<tr>
<td>Self-care</td>
<td>171</td>
<td>1.09 (±0.31)</td>
<td>1.0</td>
</tr>
<tr>
<td>Usual activities</td>
<td>172</td>
<td>1.39 (±0.51)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pain discomfort</td>
<td>172</td>
<td>1.69 (±0.56)</td>
<td>2.0</td>
</tr>
<tr>
<td>Anxiety, depression</td>
<td>171</td>
<td>1.33 (±0.51)</td>
<td>1.0</td>
</tr>
<tr>
<td>Overall health (VAS)</td>
<td>166</td>
<td>64.84 (±18.4)</td>
<td>70.0</td>
</tr>
</tbody>
</table>

**Mental health**

| Depression (PHQ-9) | 168 | 5.35 (±4.57) | 4.0 | 154 | 5.01 (±4.81) | 4.0 | 0.18   |
| Anxiety (GAD-7)    | 165 | 4.60 (±4.50) | 3.0 | 148 | 4.41 (±4.41) | 3.0 | 0.51   |
| Negative affect (GMS) | 167 | 9.17 (±5.43) | 9.0 | 149 | 8.51 (±5.33) | 8.0 | 0.12   |
| Positive affect (GMS) | 164 | 13.37 (±4.31) | 14.0 | 148 | 13.76 (±4.04) | 14.0 | 0.62   |

* Non-parametric statistic (Wilcoxon Signed Rank Test).
Outcome measures that are statistically significant are presented in boldface.
EQ-5D = EuroQol-5D; VAS = visual analogue scale of the EQ-5D.
PHQ-9 = Patient Health Questionnaire.
GAD-7 = Generalized Anxiety Disorder scale.
GMS = Global Mood Scale.
Adverse and serious adverse events during the clinical trial

Until 30.09.2016, 108 adverse events occurred in 64 patients of all groups. Out of these, 35 events (in 23 patients) were of cardiovascular origin. Forty events were classified as severe adverse events. Criteria for serious adverse events are death, life-threatening, hospitalization, disability or permanent damage, or a required intervention to prevent one of these criteria. Out of the 40 serious adverse events, 19 events (in 14 patients) were of cardiovascular origin. The serious adverse events led to 42 cases of hospitalization in 25 patients. Out of these, 21 (in 14 patients) were of cardiovascular origin. Since some patients had several hospitalizations for the same serious adverse event and some patients were hospitalized for a primary diagnostically reason, not including any kind of therapy, only 14 (in 11 patients)

### TABLE 4. Available vascular function measurements

<table>
<thead>
<tr>
<th></th>
<th>TUM-Med</th>
<th>Berlin</th>
<th>UZA</th>
<th>Leipzig</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total included patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V1</td>
<td>72</td>
<td>24</td>
<td>36</td>
<td>44</td>
<td>176</td>
</tr>
<tr>
<td>V2</td>
<td>50</td>
<td>17</td>
<td>34</td>
<td>0</td>
<td>116</td>
</tr>
<tr>
<td>FRHI</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>24</td>
<td>105</td>
</tr>
<tr>
<td>PWV</td>
<td>13</td>
<td>13</td>
<td>32</td>
<td>32</td>
<td>104</td>
</tr>
<tr>
<td>EPC</td>
<td>13</td>
<td>13</td>
<td>32</td>
<td>24</td>
<td>104</td>
</tr>
</tbody>
</table>

### TABLE 5. Baseline characteristics of study cohorts

<table>
<thead>
<tr>
<th></th>
<th>FRHI</th>
<th>PWV</th>
<th>EPC</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total patients</strong></td>
<td>116</td>
<td>104</td>
<td>176</td>
<td></td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>69 (65-76)</td>
<td>75 (69-78)</td>
<td>71 (66-76)</td>
<td>71 (65-76)</td>
</tr>
<tr>
<td><strong>Gender (% Female)</strong></td>
<td>61.2</td>
<td>64.5</td>
<td>63.4</td>
<td>66.4</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>29.1 (26.1-32.1)</td>
<td>29.1 (27.0-32.7)</td>
<td>30.1 (26.5-34.4)</td>
<td>29.3 (26.5-33.2)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td>126 ± 15</td>
<td>123 ± 17</td>
<td>127 ± 15</td>
<td>128 ± 14</td>
</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td>64 ± 11</td>
<td>65 ± 12</td>
<td>66 ± 10</td>
<td>64 ± 10</td>
</tr>
</tbody>
</table>

### TABLE 6. Exercise capacity, vascular function and endothelial repair at baseline and after 3 months follow-up

<table>
<thead>
<tr>
<th></th>
<th>V1</th>
<th>V2</th>
<th>F-value time</th>
<th>p-value time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak VO₂ (ml/kg/min)</strong></td>
<td>18.8 ± 5.3</td>
<td>19.5 ± 5.6</td>
<td>6.489</td>
<td>0.012 <strong>††</strong></td>
</tr>
<tr>
<td><strong>FRHI (m/s)</strong></td>
<td>0.56 (0.28-0.95)</td>
<td>0.54 (0.18-0.89)</td>
<td>0.070</td>
<td>0.759 *†</td>
</tr>
<tr>
<td><strong>PWV (m/s)</strong></td>
<td>12.2 (10.3-14.6)</td>
<td>11.8 (10.3-14.0)</td>
<td>3.261</td>
<td>0.085 ‡</td>
</tr>
<tr>
<td><strong>Corrected PWV (m/s)</strong></td>
<td>9.8 (8.3-11.6)</td>
<td>9.4 (8.3-11.1)</td>
<td>3.322</td>
<td>0.082 ‡</td>
</tr>
<tr>
<td><strong>EPC (cells/10⁶ MNC)</strong></td>
<td>47 (25-74)</td>
<td>56 (29-89)</td>
<td>1.737</td>
<td>0.191 *</td>
</tr>
</tbody>
</table>

Values are mean ± SD or median (interquartile range). Linear mixed models adjusted for
*Gender, ‡BMI and/or †Age. HIIT= High intensity interval training; MCT= moderate continuous training; VO₂= oxygen uptake; FRHI= Framingham reactive hyperemia index; PWV= pulse wave velocity; EPC= endothelial progenitor cells; MNC= mononuclear cells.
hospitalizations for cardiovascular reasons required treatment. Two adverse events were associated with exercise sessions (during or less than 2 hours after training). In both cases, the event occurred during exercise and the patients had to stop the exercise session. In one case, the patient felt uncomfortable and had low blood pressure during exercise. No intervention was necessary and the patient was able to restart exercise training the next day. In the other case, the patient had to stop exercise training due to the onset of atrial fibrillation. The patient was subsequently successfully cardioverted and remained an active participant in the trial. None of the adverse events were associated with cardiopulmonary exercise testing (during or less than 2 hours after CPX testing). None of the patients died.

**TABLE 7: Incidence for Adverse Events, Serious Adverse Events and hospitalizations**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Incidence</th>
<th>No. of AEs</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular origin</td>
<td>35</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Directly associated with an exercise session</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serious Adverse Events</th>
<th>Incidence</th>
<th>No. of AEs</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular origin</td>
<td>18</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Including therapy</td>
<td>13</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Directly associated with an exercise session</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospitalizations</th>
<th>Incidence</th>
<th>No. of AEs</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular origin</td>
<td>21</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Including therapy</td>
<td>14</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Directly associated with an exercise session</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Until 30.09.2017, 108 adverse events (AE) occurred in 64 patients of all groups. Out of these, 35 events (in 23 patients) were of cardiovascular origin. Forty events were classified as severe adverse events (SAE). Out of the 40 serious adverse events, 19 events (in 14 patients) were of cardiovascular origin. The serious adverse events led to 42 cases of hospitalization in 25 patients. Out of these, 21 (in 14 patients) were of cardiovascular origin. Since some patients had several hospitalizations for the same serious adverse event and some patients were hospitalized for a primary diagnostically reason, not including any kind of therapy, only 14 (in 11 patients) hospitalizations for cardiovascular reasons required treatment. Two adverse events were associated with exercise sessions (during or less than 2 hours after training). In both cases, the event occurred during exercise and the patients had to stop the exercise session. In one case, the patient felt uncomfortable and had low blood pressure during exercise. No intervention was necessary and the patient was able to restart exercise training the next day. In the other case, the patient had to stop exercise training due to the onset of atrial fibrillation. The patient was subsequently successfully cardioverted and remained an active participant in the trial. None of the adverse events were associated with cardiopulmonary exercise testing (during or less than 2 hours after CPX testing). None of the patients died.

**Dose-response on circulating biomarkers of left ventricular wall stress**

Table 8 and Figure 18 (below) show that variations in peakVO₂ (changes from V1 to V2) do not correlate with the variations of all biomarkers analysed (NT-proBNP, hs-CRP, Gal-3, sST2).

**TABLE 8. Spearman correlation analysis of all biomarkers and VO₂peak variations after 3 months follow-up period in HFpEF patients.**

<table>
<thead>
<tr>
<th></th>
<th>Δ ln(NT-proBNP)</th>
<th>Δ ln(CRP)</th>
<th>Δ ln(Gal-3)</th>
<th>Δ ln(sST2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>113</td>
<td>112</td>
<td>112</td>
<td>112</td>
</tr>
<tr>
<td>r</td>
<td>-0.1267</td>
<td>0.0466</td>
<td>-0.01106</td>
<td>-0.07679</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>-0.3094 to 0.0649</td>
<td>-0.1457 to 0.2355</td>
<td>-0.2016 to 0.1803</td>
<td>-0.2639 to 0.1159</td>
</tr>
<tr>
<td>p value (one-tailed)</td>
<td>0.1811</td>
<td>0.6257</td>
<td>0.9078</td>
<td>0.4210</td>
</tr>
</tbody>
</table>

NT-proBNP, N-terminal pro B-type natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; Gal-3 indicates galectin 3; and sST-2, soluble suppressor of tumorigenicity-2.

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Variations in the circulating NT-proBNP levels show significant correlation with variations of circulating hs-CRP and sST2 (Figure 19A and 19B). It is already known that the presence of more severe HFpEF is generally indicated by higher levels of NT-proBNP and a direct relationship between sST2 and NT-proBNP, e.g., may be a good indication of a biomarker pattern associated with a more profibrotic milieu in HFpEF. Our preliminary analyses also show a significant correlation between the variation of circulating levels of sST2 and Gal-3 (Figure 19C), which may reinforce the profibrotic state mentioned above, in the circulating biomarkers of the HFpEF patients enrolled in OptimEx-CLIN.

Assessment of cost and operational savings due to exercise-improved health in HFpEF One of the most important aims of OptimEx-CLIN is to study the economic aspects exercise training and the impact on patients with HFpEF. The purpose is to use health economic models and health-related quality of life and mood models to assess the cost of HFpEF in both in terms of money and loss of health. Information on health-care costs was collected from all centers. Models include prediction of health-care costs for different patients’ profiles/risk and the nature of the cost incurred.

The study has intervention costs that stem from supervised training (salary) and some costs for home-based training. There are also some minor costs related to the calculating compliance to exercise training and giving feedback to patients. This also incurs costs for the control group. Totally training costs for patients in the intervention are estimated to be 1055 € per patient. Patients in control group have estimated costs to 87,50 € per patient.
Preliminary results (Figures 20A, B, and C) indicate a positive association between peakVO\textsubscript{2} and improved quality of life, and a negative association of hospitalizations and peakVO\textsubscript{2} as well as medications and peakVO\textsubscript{2}. The slight negative association regarding hospitalizations could indicate that an increased peakVO\textsubscript{2} could potentially imply large societal savings as hospitalizations have been shown in other studies to be the major cost driver.

Figure 20. Scatter of peakVO\textsubscript{2} and change in self-assessed health (A), number of medications (B) and hospital length of stay (C).
WP 4: eHealth tool

Work Undertaken

WP4 was divided into four tasks related to the work:

1. Integrate heart rate monitoring data and accelerometry (daily activity) into the established telemedicine database.
2. Develop an extension of the established telemedicine platform for an automatic feedback loop of scheduled exercise volumes to the trial sites and the patient via mobile phone.
3. Continuously record and monitor adherence to scheduled home-based exercise sessions and take appropriate measures to maintain compliance >70% of scheduled volumes.
4. Acquire and file physical activity data from accelerometry from all patients in a central database over the recording period (3 months) and provide these data for statistical analysis together with the data from OptimEx-CLIN that evaluated aerobic capacity and daily physical activity level.

Scientific and Technical Results

The SME “Vitaphone” developed a telemedicine platform in order to integrate heart rate and physical activity data assessed by heart rate monitor and accelerometers, respectively. This integration enabled OptimEx to more accurately interpret data on daily physical activity. In addition, Vitaphone has addressed vital aspects of the OptimEx study by ensuring compliance and adherence to intensity prescription during training. To accomplish this Vitaphone developed the OptimEx app. Vitaphone preconfigured personalized accounts on smartphones of all participants (installed OptimEx app, Fitbit app, and linkage with the portals) (Figure 21).

The OptimEx app – key points:

- **Main functions:**
  - Connecting to Polar H7 Bluetooth Smart strap using Bluetooth 4.0 Low Energy Heart Rate Service & Profile
  - Reading heart rate (HR) and RR interval data from Polar H7 Bluetooth smart strap
  - Secure communication of RR interval data to Moove server (including provisions for delayed upload when internet connection, not present)
  - Secured administration of target HR training zones for different exercise types (MCT and HIIT)

- **User interface components:**
  - Easy to use for elderly target group
  - Simplified HR monitor functions with display of HR, elapsed time enabled for duration of the exercise session
  - Results screen at end of exercise session with smiley scheme to show actual duration, intensity vs. target set by the administrator
  - Administration screens to set target training types & HR limits
We have made, tested, and finalized the technical solution for the transfer of accelerometer and HR monitor (HRM) data from the patient to telemedicine database. In addition, we have a working technical solution for automatic feedback of HRM data on the phone back to the patient. Compliance regarding exercise training was given if ≥ 70 % of the training sessions were performed (see Table 9). Each study center monitored training compliance of their patients throughout the whole study duration.

**TABLE 9: Definition of Compliance in OptimEx for both high intensity and moderate continuous training.**

<table>
<thead>
<tr>
<th></th>
<th>High Intensity Interval Training (HIIT)</th>
<th>Moderate Continuous Training (MCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>To reach Compliance:</strong></td>
<td>To reach 70% compliance, 110 out of 156 sessions must be completed. (Within 4 weeks: 9 out of 12 sessions must be completed)</td>
<td>To reach 70% compliance, 182 out of 260 sessions must be completed. (Within 4 weeks: 14 out of 20 sessions must be completed)</td>
</tr>
<tr>
<td><strong>To reach Training Requirements:</strong></td>
<td>Patient has spent at least 4 minutes &gt;80% HRR</td>
<td>Patient has spent at least 20 minutes between 35 and 50% of HRR</td>
</tr>
</tbody>
</table>

**Compliance with supervised training (week 1-13)**

The patient had to exercise supervised and the training log filled out during or after each training by the supervisor.

For MCT group (3 times/week supervised, 2 training sessions/week home-based): the home-based training was checked every week and the training log was filled out by the supervisor. If the patient was not able to reach compliance, he was allowed to extend the training phase up to 17 weeks (adding 4 weeks to training phase).

**Compliance during home-based training (week 14-52)**

Compliance during home-based training was checked every week and the training log was filled out by the supervisor.

Feedback by telemonitoring:
The HRs of every single training session were recorded via Bluetooth, the monitoring worked as a feedback-loop: the heart rate sensor sent the information about the training sessions to the OptimEx app on the phone. These data were then transmitted to the platform of Vitaliberty, where every center downloaded the data of their patients for monitoring and evaluating the training session (see Figure 22).

The study centers contacted their patients via telephone or SMS on the study phone
- if the patient had not trained for one week or
- if the compliance was < 70 % / week for a period of two weeks (with respect to the number of training sessions as well as the heart rate)
For calculating compliance, a Microsoft Excel-based program was designed: the Vitaminer program. This program uses the Excel exports (Figure 23) downloaded from the Vitaliberty platform and calculates for every session the time spent in each intensity (Figure 24).
Potential Impact and Main Dissemination Activities and Exploitation of Results

Potential impact of the project

The OptimEx project studied the effects of primary and secondary prevention of cardiovascular health using physical activity as a lifestyle intervention strategy. The research focus was to understand and optimise the dose-response relationship between exercise training and reduction of HFpEF. In today’s Europe, more than 14 million people suffer from HF, and HFpEF is present in half of those patients. Although the prognosis of HFpEF patients is slightly better than for those with HF with Reduced EF (HFrEF), the 3-year fatality rate approaches 25%. As a result, the economic, social and personal burden of HFpEF is enormous. This project, therefore, aimed to tackle one of the major health problems the developed world faces with increasing sedentarism, obesity, and aging, all of which are known to increase the prevalence of HFpEF and support sustainable health systems in EU member states through improvements in the clinical management of a common and disabling disease. OptimEx has had outputs addressing different aspects of HFpEF: providing and generating new knowledge on exercise and HFpEF in both animal models and human subjects, data that will potentially form a foundation for innovation in emerging science and technologies.

OptimEx combined in vivo and in vitro studies in rats and humans in serial experiments and advanced our understanding of fundamental cellular and molecular mechanisms underpinning dose-dependent exercise-induced changes in the heart, blood vessels, and skeletal muscles.

The impact of OptimEx on reducing the burden of HFpEF on European society is severalfold:

- OptimEx has already provided some results regarding the mechanistic insights and a better understanding of the development of HFpEF and its causes. The project will continue to analyze the vast amount of data collected and uncover new knowledge.
- OptimEx provided data, which will be available for design of new therapeutic and diagnostic algorithms supporting the translation of research into human health.
- OptimEx data form the basis of new diagnostic and preventive measures to promote healthy aging and human health.
- OptimEx has successfully implemented an eHealth platform, which created more convenient, and likely more cost-effective delivery of care. It allowed researchers to supervise patients remotely to ensure that they adhered to the training prescription.
- With partners from SMEs and industry given access to research of OptimEx, the competitiveness of European business and industry is supported.

Dissemination Activities and Exploitation of Results

We will continue to disseminate the results of the project even after its closure.

Main dissemination activities

The project has had the following stakeholders:

Patients, healthcare personnel, scientific public, the lay public, policymakers, and technology innovators.

Outreach to patients, lay public and policymakers have mostly been done using the OptimEx webpage as well as the social media (Facebook page) and the blog. The NTNU has a Norwegian (CERG, in Norwegian) as well as the international Facebook page (CERG International Page, in English), with 4643 and 7475 followers, respectively. Munich also has a Facebook page (Sportmritum, in German) with 1185 followers. The NTNU blog is written in lay language and it often reviews new scientific research on heart failure and training and shows the studies presented at different scientific symposia. To date, our blog has had 606,333 views from 197 countries around the world.

Internet and social media

- Norwegian University of Science and Technology, 2013-present, Trondheim, Norway
  https://OptimExblog.wordpress.com/category/animal-study/
- Norwegian University of Science and Technology, 2011-present, Trondheim, Norway
  https://cergntnu.wordpress.com/
Outreach to healthcare personnel was mostly done through the “Training as medicine national competence service center” established by the NTNU and St Olavs Hospital in Trondheim. The role of the “Training as medicine national competence service center” is to ensure that research backed knowledge about training as medicine has a maximum impact and reaches the patient through their healthcare provider. It informs the healthcare providers on the sound rationale for an effective training program for patients with heart failure. Outreach to healthcare personnel was also done through training sites at various network partner locations (Munich, Antwerp, Berlin). Six medical students were involved in the OptimEx project from various consortium partners, ensuring that the torch of knowledge is passed on to new medical students as well as their patients.

Outreach to the scientific community was mostly done through scientific publications and conference presentations. To date, the OptimEx group has published 5 manuscripts in high ranking scientific journals on the results of the projects pertaining to both animal studies and clinical trial. The OptimEx results were presented at more than 20 international scientific conferences, including the EuroPrevent and the ESC. The manuscript on the results of the OptimEx Clinical Trial will be submitted to the New England Journal of Medicine by the end of 2017. The OptimEx consortium will also present the final results of the OptimEx clinical trial at the Exercise in Medicine Conference in Trondheim, Norway in Dec 2017 and at the EuroPrevent conference Ljubljana, Slovenia, in April 2018. The Exercise in Medicine conference will also be attended by a representative from the New York Times.

Scientific publications


functional alterations in skeletal muscles of heart failure with preserved ejection fraction. Submitted to Int J Cardiol.

Scientific presentations

- University of Leipzig, Exercise training: reversing molecular alterations in heart failure, 2014, Providence, RI, USA
- University of Leipzig, Impact of exercise training on striated muscle and endothelium in patients with cardiovascular disease, 2014, Rotterdam, Netherlands
- University of Antwerp, 35 years of cardiac rehabilitation UZA. To resist or to endure; which exercise mode is best to maintain vascular health?, 2014, Antwerp, Belgium
- Norwegian University of Science and Technology, High-Intensity Interval Training Partly Restores Thrombotic Microangiopathy in an Experimental Model of Hypertensive Renal Injury, 2014, San Francisco, USA
- Norwegian University of Science and Technology, Characterization of Dahl Salt Sensitive Rat Model for Heart Failure with Preserved Ejection Fraction Research: Defining Diagnostic Criteria, 2014, San Francisco, USA
- Norwegian University of Science and Technology, Trening ved kronisk nyresykdom: ein eksperimentell dyremodell ved hypertensiv nyreskade, 2014, Oslo, Norway
- University of Leipzig, High intensity interval training attenuates endothelial dysfunction in heart failure with preserved ejection fraction (HFpEF), 2015, Mannheim, Germany
- University of Leipzig, High intensity exercise training prevents diaphragm dysfunction induced by heart failure with preserved ejection fraction in rats, 2015, Lisbon, Portugal
- University of Leipzig, Influence of physical activity on vascular and skeletal function in HFrEF and HFrEF, 2015, Potsdam, Germany
- Charité Chronic heart failure (HFpEF and HFrEF), 2015, London, UK
- University of Antwerp, Is physical training an option in heart failure?, 2015, Antwerp, Belgium
- University of Antwerp, Effects of aerobic interval training and continuous training on cellular markers of endothelial integrity in coronary artery disease: A SAINTEX-CAD substudy, 2015, Lisbon, Portugal
- University of Antwerp, New exercise training modalities in heart failure, 2015, Seville, Spain
- University of Antwerp, Effect of gender and exercise intensity on the outcome of rehabilitation, 2015, London, UK
- Norwegian University of Science and Technology, Exercise Training Reduces Stroke Incidence in Heart Failure with Preserved Ejection Fraction Rats: role of miR-21 and let-7b in the circulation 2015, Oslo, Norway
- Norwegian University of Science and Technology, Deregulation of Circulating MicroRNA in an Experimental Model of Heart Failure with Preserved Ejection Fraction is Prevented by High-Intensity Interval Training, 2015, London, UK
- Norwegian University of Science and Technology, Exercise training reduces stroke incidence in heart failure with preserved ejection fraction rats: role of miR-21 and let-7b in the circulation, 2015, Trondheim, Norway
- University of Leipzig, Heart failure with preserved ejection fraction induces molecular, mitochondrial, histological, and functional alterations in rat diaphragm muscle, 2015, Boston, USA
- University of Leipzig, Exercise performance in HFpEF. Is it the heart or the muscle?, 2016, Lisbon, Portugal
- University of Leipzig, Sport bei Herzinsuffizienz: eine molekulare Sichtweise, 2016, Bad Oeynhausen, Germany
- University of Antwerp, Mechanisms for adaptation to exercise training, 2016, Leuven, Belgium
- University of Antwerp, How to train your heart failure patient?, 2016, Antwerp, Belgium
- Norwegian University of Science and Technology, Exercise in HFpEF preclinical evidence, 2016, Trondheim, Norway
- Norwegian University of Science and Technology  Animal models of HFpEF, 2016, Trondheim, Norway
- University of Antwerp, The road to the clinic: exercise in HFpEF patients, 2016, Trondheim, Norway
- Charité, Atrial and ventricular cellular Ca signaling at different stages in a rat model of heart failure with preserved ejection fraction, 2016, Les Diablerets, Switzerland
- University of Leipzig  Loss of muscle mass and muscle function in Heart Failure, 2017, St. Augustine, FL, USA
- University of Leipzig, Muskuläre und endotheliale Veränderungen bei Herzinsuffizienz: Einfluss von körperlicher Aktivität, 2017
- University of Leipzig, Impact of exercise training on cardiovascular disease and risk, 2017, Weimar, Germany
- University of Antwerp  Cardiac rehabilitation tailored for your patient, 2017 Antwerp, Belgium
- Charité, Amount or Intensity? Potential targets of exercise interventions in patients with heart failure with preserved ejection fraction, 2017, Munich, Germany
- Charité, Paulus criteria are useful for predicting outcome in patients with asymptomatic diastolic dysfunction, 2017, Munich, Germany
- University of Leipzig, Skeletal muscle alterations: HFrEF vs. HFpEF. Data from the animal study, 2017, Munich, Germany
- University of Leipzig, Impact of different training modalities of muscular alterations in HFpEF patients, 2017, Munich, Germany
- University of Leipzig, Impact of exercise training on satellite cells in HFpEF patients, 2017, Munich, Germany
- University of Leipzig, High-intensity interval training attenuates endothelial dysfunction in a Dahl salt-sensitive rat model of HFpEF, 2017, Munich, Germany
- University of Leipzig, Impact of exercise training (secondary prevention) on endothelial function in ZSF-1 animals, 2017, Munich, Germany
- University of Leipzig, High-intensity interval training prevents oxidant-mediated diaphragm muscle weakness in hypertensive mice, 2017, Munich, Germany
- University of Leipzig, Diaphragm alterations in a cardiometabolic obese rat model of HFpEF are not reversed by exercise training, 2017, Munich, Germany
- University of Leipzig, Heart failure with preserved ejection fraction induces molecular, mitochondrial, histological, and functional alterations in rat respiratory and limb skeletal muscle, 2017, Munich, Germany
- University of Leipzig, Relevance of VEGF for diaphragmatic function, 2017, Munich, Germany
- Norwegian University of Science and Technology, Uncover the cardiac microRNA signatures in heart failure with preserved versus reduced ejection fraction, 2017, Munich, Germany
- Norwegian University of Science and Technology, Exercise Training Reduces Stroke Incidence in Heart Failure with Preserved Ejection Fraction Rats: role of miR-21 and let-7b in the circulation, 2017, Munich, Germany
- Norwegian University of Science and Technology, Rodent models of heart failure with preserved ejection fraction and the reproducibility issues, 2017, Munich, Germany
- Norwegian University of Science and Technology, Exercise therapy in heart failure with preserved ejection fraction: preclinical evidence from the OptimEx Study, 2017, Munich, Germany
- University of Antwerp  A panel of circulating microRNA predicts response to exercise in HFpEF, 2017, Munich, Germany
- University of Antwerp, The OptimEx tele monitoring sub study - study design, 2017 Munich, Germany
- University of Antwerp, Impact of exercise training on exercise hemodynamics in HFpEF: insights from the OPTIMEX exercise echocardiography sub study, 2017, Munich, Germany
University of Antwerp, Prevalence of Exercise Oscillatory Ventilation in Heart Failure with Preserved Ejection Fraction: Factor Fiction?, 2017, Munich, Germany

Exploitation of results
Further dissemination
The OptimEx consortium will continue to disseminate the results of the project even after its closure. The manuscript on the results of the OptimEx Clinical Trial will be submitted to the New England Journal of Medicine by the end of 2017. The OptimEx consortium will also present the final results of the OptimEx clinical trial at the Exercise in Medicine Conference in Trondheim, Norway in December 2017 and at the EuroPrevent conference Ljubljana, Slovenia, in April 2018.

Outreach to technology innovators
We have several plans for further exploitation of the results: continued research in the field of exercise as medicine in HFpEF and further exploitation of the findings of OptimEx in the field of emerging science and technologies. Technology transfer is the movement of findings and knowledge to the patients and the general public. We have started this process through publications and education of students entering the research and healthcare professions, exchanges at conferences, and relationships with industry. However, it is also our goal to begin a technology transfer that refers to the formal licensing of technology to third parties, managed and administered by the technology transfer office. We have been in contact with the technology transfer office in order to explore our options and plan on getting potential biomarkers on the market. The value of biomarkers for HFpEF can only be realized once all the data from the OptimEx clinical study are available for analysis. It is our intent to validate the potential biomarkers in cell culture as well as animal models of disease. If successful, we have created a plan to patent the biomarkers in collaboration with potential industry partners.

The OptimEx clinical study would also provide us with the beat-to-beat data on heart rate for the entire duration of the intervention (12 months). Beat-to-beat variations in heart rate of individuals in sinus rhythm are termed heart rate variability. Heart rate variability is a non-invasive, easily obtained and reproducible measurement of cardiac autonomic nervous system function and its response to environmental changes. Lowered heart rate variability associates with poor prognosis in patients with heart failure. Data from OptimEx clinical study would enable us to analyze heart rate variability and the effect of different training modalities on heart rate variability in patients with HFpEF. This could then be used to understand the prognostic role of heart rate variability in patients with HFpEF and how and if it is affected by exercise. This knowledge could then be used to determine heart rate variability risk thresholds, which when incorporated into a wearable that monitors beat-to-beat heart rate, could alert both patients and the healthcare providers to potential hazard and ensure prompt medical check-up. All consortium partners, including Vitaliberty and other potential industrial partners, will be involved in exploitation possibilities, decide on patenting, draft license agreements, and involve other experts to assist in IP management, patenting and licensing.
Project Public Website and Contact

Project public website
The OptimEx website can be found at the following link:

https://www.ntnu.edu/OptimEx

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