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ARTICLE

The effect of sauna on cardiac and skeletal muscle function in patients with HFpEF (SAUNA-HFpEF): rationale and design

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Abstract

Patients with heart failure with preserved ejection fraction (HFpEF) often experience dyspnea, fatigue, and exercise intolerance, which are closely linked to skeletal muscle dysfunction and structural abnormalities. The only proven intervention to enhance exercise capacity and quality of life in these patients is regular endurance exercise training. However, its long-term effectiveness is often limited due to poor patient adherence and mobility restrictions caused by sarcopenia, cachexia, or frailty. Therefore, novel therapeutic approaches targeting these unmet needs are urgently required. Sauna-HFpEF is an academic-led, mechanistic, prospective, single-arm, single-center pilot study designed to assess the safety, feasibility, and efficacy of intermittent hyperthermia (sauna therapy) in improving exercise capacity and quality of life in patients with heart failure with preserved ejection fraction (HFpEF), as well as to explore the underlying mechanisms. A total of 18 clinically stable outpatients with HFpEF were enrolled and participated in twice-weekly sauna sessions at 60°C over a 10-week period. Assessments were conducted at baseline and after the intervention, including: echocardiography, cardiopulmonary exercise testing, six-minute walk test, body composition analysis to assess skeletal muscle mass and fat tissue, isokinetic skeletal muscle strength measurement of the quadriceps, daily physical activity monitoring using wearable accelerometers for one week, blood biomarkers, including NT-proBNP, renal function, and inflammatory markers (GDF-15, IL-6), and quality-of-life questionnaires (SF-36, HADS, EQ-5D). Furthermore, to explore the underlying mechanisms of a potential sauna-induced effect, patients underwent two ultrasound-guided punch biopsies of the musculus vastus lateralis in the right quadriceps - one before and one after the intervention. The collected samples were analyzed for structural, metabolic, and mitochondrial changes to gain further insights into the physiological adaptations. Sauna-HFpEF is the first study to investigate the safety and efficacy of sauna therapy using a comprehensive bed-to-benchside approach within the same patient population. This study aimed to address the existing knowledge gap while providing a foundation for the design of a future randomized controlled trial.

Key words: sauna; skeletal muscle; heart failure with preserved ejection fraction; exercise capacity.

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Introduction

The main symptoms of patients with heart failure with preserved ejection fraction (HFpEF) are fatigue, exercise intolerance, and dyspnea.[1] While advances in medical and device therapies have reduced mortality in patients with heart failure with reduced ejection fraction (HFrEF), treatment options for HFpEF have been more challenging.[2-5] Only recently, large randomized clinical trials (RCT) in patients with HFpEF comparing sodium-glucose-cotransporter 2- inhibitors (SGLT2-I) to placebo have shown a reduction in the combined endpoint of hospitalization rate and cardiovascular mortality. Although patients with HFpEF have preserved ejection fraction (EF), there is still severe exercise intolerance primarily due to reductions in peak cardiac output (CO) and peripheral arterial-venous oxygen difference (A-VO_2 Diff),[6,7] as well as to a proposed impairment of skeletal muscle oxidative metabolism.[8] There is growing body of evidence showing that peripheral factors such as skeletal muscle function play a crucial role in explaining the reduced exercise capacity in patients with either HFrEF or HFpEF.[9,10] Some studies have shown that exercise intolerance persists for several months after heart transplantation and improvement of cardiac output.[11] Furthermore, exercise training improves exercise tolerance in patients with HF independent of improving cardiac function.[7] Skeletal muscle function may thus play a central role in explaining the limited exercise capacity in patients with HF.[12] As a result, more drugs or interventions are urgently needed to improve symptoms, quality of life, morbidity, and mortality in HF, in particular in the growing number of patients with HFpEF. Intermittent hyperthermia (sauna) seems to have a beneficial effect comparable to that of moderate sport, with many advantages especially for older patients with HFpEF. At least 20% of these patients suffer from sarcopenia and reduced mobility, which could limit traditionally recommended endurance training methods such as running or cycling. Thus, sauna could represent a suitable alternative to improve exercise capacity and muscle function in this group of patients.

Burden of disease

HF is a major health, social, and economic problem affecting about 2% of the world population.[13] In the U.S. alone, the costs related to HF are expected to reach 70 billion U.S. dollars by 2030, an increase of 130% on current costs.[14-16] The 30-day readmission rate is a key indicator of hospital performance. Currently, 25% of patients with HF are readmitted within one month of discharge.[17,18] In Germany, over 3 million people are affected by this condition, with more than half of patients with HF presenting with HFpEF.[19,20] Incidence and prevalence are increasing,[21] in part due to an aging population and rising burden of comorbidities.[22-28]

Sauna as an intervention

Several observational studies have suggested potential beneficial effects of regular sauna bathing in cardiovascular, muscular, and neurological outcomes. In a large prospective population-based cohort-study in middle-aged men from Eastern Finland (n=2315 with a follow-up of 20.7 years), increased frequency and duration of sauna sessions were associated with reduced sudden cardiac death, coronary heart disease, and fatal cardiovascular disease.[29] Another small interventional study in healthy individuals found that daily locally-applied heat treatment to skeletal muscle during an immobilization period of 10 days prevented the loss of mitochondrial function, increased heat shock protein (HSP), and reduced skeletal muscle atrophy by 37% compared to a sham treatment group.[30] Sauna bathing was further suggested to enhance cognitive function and mental health. For instance, whole-body hyperthermia using hot water baths have been shown to significantly increase serum levels of brain-derived neurotrophic factor (BDNF) in healthy males.[31] BDNF is a protein that activates the growth of new neurons in both the peripheral and central nervous systems and has a potential role in modulating and improving anxiety and depression.[32] A small RCT of 28 patients with mild depression showed that compared with a control group that received bed rest, patients exposed to sauna had reduced symptoms of depression and anxiety, and reported improved appetite and reduced somatic complaints.[33]

As demonstrated in a meta-analysis of observational and randomized trials in a broad HF population, sauna bathing may be associated with short-term improvement of cardiac function.[34] Thus, the next logical step would be to investigate, whether an intervention such as sauna is safe, feasible, and effective in patients with HFpEF, and what effects sauna might have on blood pressure and exercise capacity in these patients. Figure 1 describes suggested effects.

Methods

Study design

SAUNA-HFpEF is a mechanistic pilot, prospective, single-arm, single center study to evaluate the safety, feasibility, and efficacy of intermittent hyperthermia (sauna) in improving exercise capacity in a cohort of patients with HFpEF. A follow-up is planned approximately 15 weeks after completing the intervention to assess the maintenance of any potential effects following the cessation of sauna sessions.

Study population

Eighteen clinically stable outpatients with HFpEF were enrolled and attended sauna sessions as described below. The diagnosis of HFpEF was confirmed based on the recommendations of the European Society of Cardiology-HF.[35,36] Inclusion and exclusion criteria are summarized in Table 1. Eligible patients who meet all criteria and give their consent will receive the tests listed in Table 2.

All study participants signed an informed consent prior to the enrollment into SAUNA-HFpEF. The protocol number 61/23 was approved by the ethic committee of the Otto-von-Guericke University in Magdeburg and fulfilled the principles of good clinical practice and the Declaration of Helsinki.

Clinical assessment

The following tests were performed and evaluated: echocardiography, cardiopulmonary exercise test (CPET), six-minute walk test (6-MWT), body composition to evaluate the skeletal mass and fat tissue, isokinetic skeletal muscle measurement of the quadriceps, accelerometer for one week, blood tests (NT-pro-BNP, renal function, and inflammatory biomarkers

such as GDF-15, IL6), as well as quality-of-life questionnaires (SF-36, HADS, EQ-5D).
Additionally, to investigate the underlying mechanisms of a potential effect from the sauna intervention, patients will undergo two ultrasound-guided punch biopsies of the musculus lateralis in the right quadriceps. The harvested samples will be analyzed

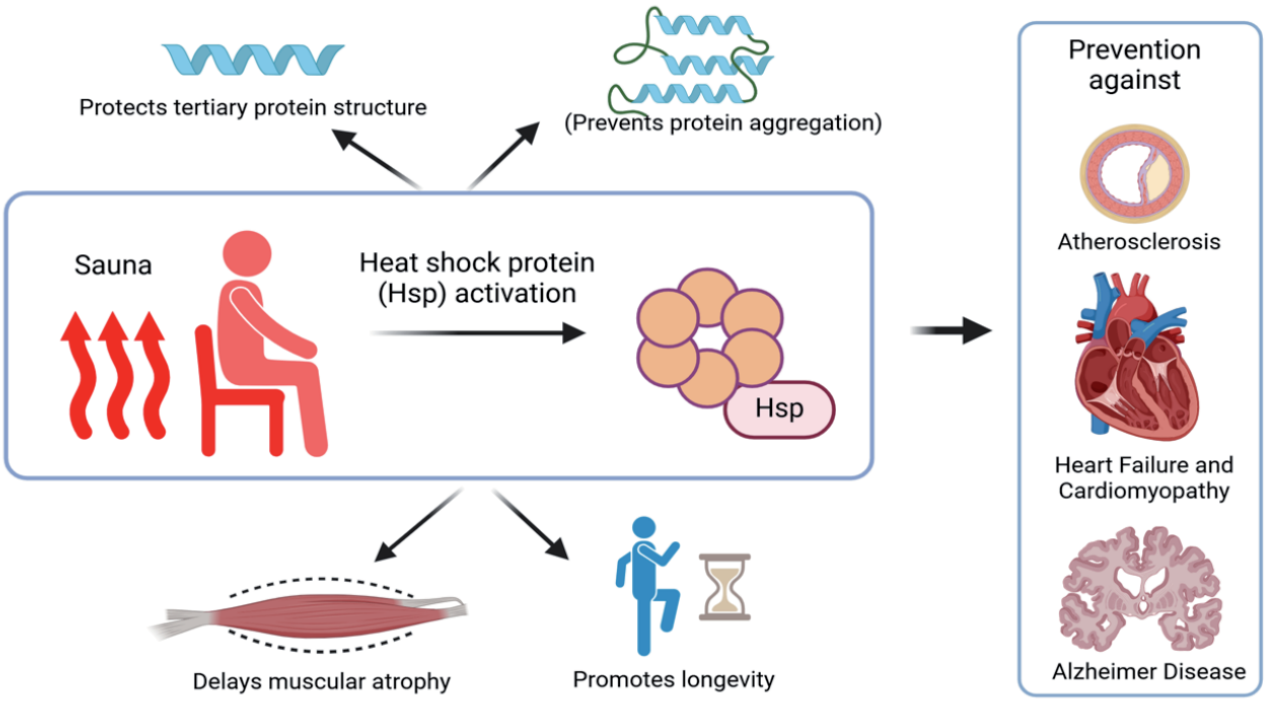

Figure 1. Illustration of possible heat shock protein-driven effects resulting from sauna exposure. Modified from Patrick RP, Johnson TL. Sauna use as a lifestyle practice to extend healthspan. Exp Gerontol 2021;154:111509; with permission.

Table 1. Selection criteria for SAUNA-HFpEF.

Inclusion criteria
• NYHA class II or III, clinically stable in the previous three months • Females and males, age ≥50 years • Left ventricular EF ≥50%, and at least 2 of the following: left atrial volume index (LAVI ≥34 ml/m2) or E/e' >9 or interventricular septal thickness >12 mm or pulmonary arterial pressure >35 mmHg (non-invasive measurement) for HFpEF as recommended by the ESC-HF-guidelines • Stable on standard HF medication according to the ESC-HF guidelines in the last 4 weeks
Exclusion criteria
• Major cardiovascular event or procedure such as myocardial infarction, percutaneous coronary intervention (PCI), aortocoronary bypass operation in the previous 3 months • Patients who have an indication for dual platelet inhibition • Stroke • Patients with mechanical heart valves or implanted cardiac devices • Pulmonary embolism or deep vein thrombosis • Patients with altered or reduced sweat function, such as in autoimmune diseases, spinal cord injuries or Fabry disease • Symptomatic hypotension regardless of the measured value and those with BP systolic <110 mm Hg • Patients on oral anticoagulation for other reasons than atrial fibrillation • Uncontrolled diabetes mellitus (HbA1c>8%), severe renal dysfunction (GFR<30 ml/min) or pulmonary disease (COPD GOLD ≥3) • Primary muscle disorder (e.g., muscular dystrophies) • Neurological disease (e.g., dementia or Parkinson syndrome) • Right ventricular dysfunction or uncontrolled arrhythmias • Any condition that in the opinion of the investigator could prohibit performance of 6-MWT

NYHA, New York Heart Association; EF, ejection fraction; COPD, chronic obstructive pulmonary disease; BP, blood pressure; 6-MWT, 6-minute walk test.

to identify specific structural, metabolic, or mitochondrial changes. The timetable of the study is shown in Table 2.

Echocardiography

The diameter, size, and function of all 4 chambers were measured through transthoracic echocardiography. Valve functions as well as the diastolic function will be evaluated. Strain analysis of the left and right ventricle and of the left atrial will also be performed.

Cardiopulmonary exercise testing

Exercise testing in association with air-gas-exchange is an optimal gauge of functional capacity. We performed cardiopulmonary exercise testing (CPET) in all participants using biking exercise with a 15 Watt/min ramp protocol on an electronically braked cycle ergometer.[37,38]

Questionnaire tools to complement functional assessment measurements

Several questionnaires that assess physical limitation, symptoms and quality of life (QOL) of patients with HF were used. The visual analogue scale (VAS), a component of the European Quality of Life-5 Dimensions (EQ-5D) questionnaire, was utilized to assess self-rated health status. The scale consists of a 20-cm vertical line, with 100 at the top representing the «best imaginable health state» and 0 at the bottom indicating the «worst imaginable health state”. EQ-5D (VAS) ratings are a quantitative measure and differences in this scale can be used as a measure of outcome, as judged by the individual respondents.[39]

In addition, a psychometric analysis was conducted to assess co-existing anxiety and depression by asking patients and healthy controls to complete the hospital anxiety and depression scale (HADS) questionnaire.[40] QoL was further assessed using the short-form 36 (SF-36, German Version 2.0) questionnaire. This tool comprises 36 items grouped into eight dimensions: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional health (RE), and mental health (MH). These eight dimensions were combined into two summary scores, representing mental and physical QoL, respectively.[41]

Six-minute walk test

The 6-MWT is a widely used clinical tool for assessing functional capacity in heart failure patients within a «real-life» setting, following standard methodology.[42] Patients were instructed to walk as quickly as possible along a 25-meter course for a duration of six min. The test results were recorded as the total distance covered, rounded to the nearest meter.

Accelerometer-based measures

Using the wearable device Actigraph wGT3X-BT, baseline and at final visit accelerometry characteristics including step count, steps per min, metabolic equivalent of tasks, total time in sedentary bouts, total of time in moderate or vigorous physical activity were measured.[43]

Body composition using bioelectric impedance analysis

Bioelectrical impedance analysis (BIA) is a non-invasive measurement of the body composition, i.e., muscle, fat, water. Measurements was performed using InBody 970 scale (Seoul, South Korea).[44]

Muscle function by isokinetic dynamometry

The *isokinetic strength test* was applied to the right leg (i.e., knee extension and flexion) using a Biodex dynamometer (Biodex System 4 Pro, Biodex Medical System, Inc., Shirley, NY, USA). The test was performed in the concentric mode at angular velocities of 60°/s and 180°/s.[45] Prior to the testing procedure, patients performed a standardized warm-up consisting of two submaximal sets and one maximal set of isokinetic knee extension and flexion at a velocity of 60°/s in the concentric mode (first set: 5 repetitions at approximately 50% of maximal strength, second set: 5 repetitions at approxi-

Table 2. Study timetable.

	Week 0 Visit 1	Week 1 Visit 2	Week 2-12	Week 13 Visit 3	Week 14 Visit 4	Week 30 Visit 5
Informed consent	x					
Echocardiography	x			x		x
Cardiopulmonary exercise test (CPET)	x			x		x
6-MWT		x			x	x
Blood tests	x	x		x	x	x
QoL-questionnaire	x			x		x
Accelerometer	x			x		x
Isokinetic skeletal muscle measurement	x			x		
Skeletal muscle biopsy		x			x	
Sauna intervention (twice weekly)			x			

mately 70% of maximal strength, third set: 2 repetitions at 100% of maximal strength). Afterwards, patients were asked to perform 5 repetitions with maximum force with an angular velocity of 60°/s. The attempt with the highest torque achieved in extension and flexion was selected to determine the maximum muscle strength of the knee extensors and flexors. Thereafter, a further warm-up was conducted including 1 set of 5 repetitions of knee extension and flexion at an angular velocity of 180° with maximum force. Patients were then asked to perform 15 repetitions with maximum force with an angular velocity of 180°/s. The sum of the areas under the curves of every repetition was calculated.

Skeletal muscle biopsies

Obtaining muscle tissue from all individuals will allow us to study the effect of sauna on skeletal muscle both structurally and functionally. Oral anticoagulation as a therapy for atrial fibrillation were withheld for two days (the day of the muscle biopsy and the day before). Patients laid comfortably in the supine position for biopsy of the vastus lateralis muscle in the right leg. Biopsy sites were prepped with betadine and 2% xylocaine (without epinephrine), with a small stab cut then completed with a blade scalpel. A 5 mm Bergstrom muscle biopsy needle were used to remove 100-200 mg muscle tissue. After harvesting the first sample, the needle was rotated 90°, and a second sample was extracted to maximize yield for analysis. The wound site was closed with steri-strips and a sterile pressure bandage.[46]

The intervention (sauna)

Patients were accompanied by study physicians for two sessions weekly, each between 8-15 minutes. We started the first 2 weeks with 8 minutes. Week 3-4: 10 min, week 5-6: 12 min, week 7-10: 12-15 min. Patients were given the freedom to leave the sauna session at any time if they experienced discomfort or were unable to tolerate it. Sessions were done in groups of 5 patients of men or women. The temperature of the sauna was 60°C. After each session, patients were asked to shower with moderate temperature of water and then rest for 20 min. Blood pressure and heart rate were measured prior to each session as well as directly after the sauna session and at the end of the rest time.

Statistics

All data and statistics will be reported as mean ± SD for continuous normally-distributed data or as median and interquartile range (IQR; 25-75%) for variables that were not normally distributed. Categorical data will be summarized by percentages. The chi-squared test will be used to look for trends for categorical variables and the Kruskal Wallis test will be applied for not normally distributed data, respectively. Analysis of variance (ANOVA), Pearson's or Spearman simple regression will be used as appropriate. A two-tailed *p*-value <0.05 indicates statistical significance. The Statistical Package for Social Sciences software (SPSS 26, IBM, Armonk, USA) will be used for all statistical analyses.

Study endpoints

The following explorative endpoints will be tested:

i. Feasibility, safety and tolerability of sauna
ii. The effect of the intervention on filling pressure (E/é)
iii. The effect of sauna on NT-pro-BNP levels
iv. The effect of sauna on peak VO2, 6-MWT and skeletal muscle strength
v. The effect of sauna on the structure and function of skeletal muscle including metabolic and mitochondrial function
vi. The effects of sauna on QoL and of cognitive function
vii. Accelerometer-based measures in order to identify significant changes in functional status or improvement in QoL.

Discussion

Until recent years, regular endurance exercise training was the only proven intervention to enhance exercise capacity and quality of life in patients with HFpEF.[47] However, emerging medical therapies, including SGLT-2 inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs), and non-steroidal mineralocorticoid receptor antagonists (nsMRAs), have demonstrated benefits in improving QoL in HFpEF patients and hold promise as additional therapeutic options. However, while GLP-1RAs and nsMRAs are not yet approved for the treatment of HFpEF,[48,49] exercise training also raises two key concerns: firstly, patient compliance and secondly, reduced mobility due to sarcopenia, cachexia or frailty, which are common in patients with HF.[10,50] Therefore, innovative interventions should take these conditions into account from the outset.

Intermittent hyperthermia such as sauna represents a potentially feasible intervention to address the above-mentioned limitations. Sauna could have a similar physiological effect as low- and moderate-intensity physical exercise training, during which heart rate may increase up to 100/min.[51,52]

As described, intermittent hyperthermia may improve exercise capacity and skeletal muscle function similar to endurance training. However, there is still uncertainty given that sauna as a treatment intervention has not been previously tested in patients with HFpEF. Proving safety of sauna will be of utmost importance to this study. Some previous studies have shown that sauna is safe and can improve endothelial function in patients with HF, leading to improvements in left ventricular ejection fraction and exercise capacity, as well as reductions in natriuretic peptides and arrhythmias.[53-55] SAUNA-HFpEF will also focus on potential adverse events that may arise after each sauna session and during the follow-up periods as well as on possible exercise capacity improvements on the mechanism beyond that.

Reducing the growing increasing burden of HFpEF has become a key goal in contemporary cardiovascular research. The results of this pilot study will therefore allow the design of a randomized trial to further evaluate the safety and efficacy of sauna as a potential therapeutic intervention to improve exercise capacity, dyspnoea, and skeletal muscle function in this particular group of patients.

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