Cardiovascular and Respiratory Benefits From Regular Sauna Bathing and Its Role in Treating Disease

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Abstract

Cardiovascular disease (CVD) remains the leading cause of death worldwide. Most of our population is either directly affected or has a loved one that suffered the burden of cardiovascular disease. Given this, investigating all possible treatment strategies is crucial to alleviating this burden. Finnish sauna bathing is a form of whole-body passive thermotherapy that has shown promise in positively reinforcing our cardiovascular system. The affordable and easily accessible nature of sauna bathing makes it an attractive candidate to be utilized in the treatment of disease. The purpose of this review is to explore how sauna bathing benefits the heart and blood vessels in both physiological and diseased states. The therapeutic value of sauna bathing is evaluated in treating hypertension (HTN), coronary artery disease (CAD), congestive heart failure (CHF), and its usefulness in comorbidities of CVD such as metabolic syndrome and respiratory impairment. This literature review examines primary, peer-reviewed, and systematic review research from EMBASE, PubMed, and MEDLINE that link sauna bathing to improved cardiovascular and respiratory health. The positive effects on pathological states as well as the physiological mechanism responsible for these effects were investigated. Sauna bathing shows reduction in mean arterial pressure (MAP) in short-term as well as long-term studies through decreased arterial compliance and vasodilatory mechanisms. Studies have also shown positive effects of heat therapy in alleviating active CAD along with preventing disease by processes such as altering blood flow mechanics, supporting endothelial cell function, and attenuating metabolic risk factors. It has been deemed safe in the setting of stable CAD but is contraindicated in unstable CAD. In CHF, sauna's therapeutic properties include reducing heart size, preload, serum BNP as well as increasing left-ventricular ejection fraction (LVEF). Regular heat therapy also mitigated metabolic risk factors and aided concurrent pulmonary function. Whole-body passive thermotherapy shows a clinical benefit in preventing and treating cardiovascular disease. It has been shown to be safe in most patients, but it should be discussed with one's physician prior to use. Future work will include studying long-term outcomes and its beneficial role in other diseases that have cardiovascular consequences.

Categories: Preventive Medicine, Integrative/Complementary Medicine, Cardiology Keywords: peripheral arterial diseases, endothelial function, metabolic syndrome, copd, chf, hypertension, cardiovascular disease, finnish sauna, passive thermotherapy, sauna bathing

Introduction And Background

Sauna bathing is a passive thermotherapy technique that was invented in Finland over 2000 years ago for a variety of reasons such as promoting good hygiene and health along with social and spiritual enrichment. There are many forms of thermotherapy and ways to produce heat, however, the historic Finnish sauna baths are the most popular and will be the form of sauna bathing primarily reviewed in this study. Finnish sauna baths are usually short in duration (5 to 20 minutes) at temperatures between 80°C to 100°C. The humidity remains relatively low (less than 20%) but transient increases in humidity can be achieved by adding water to the heated rocks that serve as the primary heat source. Saunas are easily accessible and can be inexpensive as they are typically located in public exercise facilities, spas, hotels, and can also be purchased for private use. Sauna bathing already has well known health benefits such as skin rejuvenation, detoxification, metabolism stimulation, muscle recovery, pain reduction, enhanced immune function, decreased stress, and improved sleep. The proposed physiological mechanisms for these health benefits include reducing reactive oxygen species and inflammatory mediators, increasing nitric oxide levels, increasing insulin sensitivity, improving endothelial cell function and reactivity, and many more [1]. The postulated mechanism behind these effects is: heat-induced hypothalamic posterior and preoptic nuclei activation of the sympathetic nervous system which in turn modulate the hypothalamus-pituitary endocrine axis and the reninangiotensin-aldosterone system (RAAS). This manifests as systemic responses in the body like those seen during exercise. These physiological changes drastically affect the cardiovascular system, which highlights why the sauna should be considered in the management of hypertension, coronary artery disease, congestive heart failure, metabolic syndrome, and respiratory decline.

The ACC/AHA has various degrees of hypertension (high blood pressure); beginning with "elevated blood pressure" when systolic blood pressure is between 120 mmHg and 129 mmHg. Stage 1 hypertension is

defined as a systolic blood pressure between 130 mmHg and 139 mmHg or a diastolic blood pressure between 80 mmHg and 89 mmHg. Hypertension can occur in solitary (primary or essential hypertension) or as a component of another disease (secondary hypertension) due to many pathologic manifestations. Coronary artery disease is defined as narrowing or blocking of coronary arteries resulting in a mismatch between myocardial oxygen supply and demand usually due to an atherosclerotic plaque. Heart failure is a complex disease process caused by a structural or functional abnormality of ventricular filling and/or ejection of blood usually from chronic myocardial injury. Congestive heart failure is a generalized clinical syndrome in which the heart is unable to pump enough blood to meet the needs of the rest of the body. Given this, the target population of this study is for patients diagnosed with these cardiovascular diseases or anyone with positive risk factors. Unmodifiable risk factors for cardiovascular disease are those a patient cannot change and include family history, ethnicity, male sex, and increasing age. However, many risk factors are modifiable such as smoking, diabetes mellitus, dyslipidemia, obesity, stress, alcohol, physical inactivity, and drug abuse.

Review

Methods

Overview

A systematic review of recent experimental and observational data was performed to explore the effects of regular sauna bathing on hypertension, coronary artery disease, congestive heart failure, as well as its effects in the management of metabolic syndrome and preventing respiratory consequences. The suggested physiological mechanisms responsible for the beneficial outcomes of heat therapy was also exposed.

Search Term Strategy

A variety of search terms were used to collect information from each database: "sauna bath, Finnish sauna bath, passive thermotherapy, cardiovascular disease, hypertension, coronary artery disease, congestive heart failure, endothelial function, metabolic syndrome, diabetes, COPD, pulmonary hypertension, arterial compliance, inflammation, nitric oxide" acquired most of the data that was analyzed.

Inclusion Criteria

Types of studies: The data reviewed include observational (longitudinal, cross-sectional, case-control, or retrospective cohort) studies, randomized controlled trials, and non-randomized controlled trials from the past decade that were published in the English language.

Types of participants: Studies that were examined were limited to human subjects with an emphasis on patients diagnosed with a cardiovascular, metabolic, or pulmonary disease such as hypertension, coronary artery disease, congestive heart failure, diabetes, hypercholesterolemia, and COPD. Any patient age was considered, however, most patients diagnosed with these diseases are over the age of 50. Healthy participants were also reviewed to assess the natural physiological consequences of sauna bathing.

Types of interventions: Many different forms of passive heat therapy were taken into consideration (e.g., infrared sauna, Waon therapy, hot water immersion) due to the similar physiological effects they have on the human body. However, Finnish sauna baths were the primary focus as they are the most widely used. Both single sauna sessions and repeated sauna sessions (3 to 4 times/week) were examined. All interventions took place in locations with medical supervision.

Types of outcome measures: In the purpose of studying solely direct cardiovascular consequences, objective measures included systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), cardiothoracic ratio (CTR) on chest X-ray (CXR), 6-minute walking distance (6 MWD), B-natriuretic peptide (BNP) levels, left ventricular ejection fraction (LVEF), electrocardiogram (ECG) changes, myocardial perfusion, mean pulmonary artery pressure, intracardiac pressures, peripheral vascular conductance, metabolic profiles, ankle/brachial index (ABI), and plasma levels of vascular endothelial growth factor (VEGF), nitric oxide (NO), pulmonary function tests (PFTs) such as forced vital capacity (FVC), forced expiratory volume at 1 second (FEV1), and pulmonary diffusion capacity . Multiple studies in this review also measured the many other physiological effects provided by sauna bathing.

Data Extraction

The abstracts of relevant studies were examined and selected for inclusion if they met the criteria above. The article's publication details, research design, key results, and conclusions were extracted (See Figure 1).

Data Analysis

Extracted data was comprehensively investigated and is shown accurately in the results and discussion

sections of this review. Effects of sauna bathing on hypertension is discussed first as it is a risk factor for both coronary artery disease and congestive heart failure. A review of the physiological mechanisms underlying these cardiovascular consequences was also conducted.



FIGURE 1: Identification of studies via databases and registers

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Results:

Hypertension

Sauna bathing has been demonstrated to have positive effects on blood pressure (BP) in many experimental and observational studies. In a recent study, systolic and diastolic blood pressures were evaluated in 102 subjects (56% men; age 32-75 years) before and after a typical 30-minute sauna session [2]. The mean systolic BP before the sauna was 137±16 mmHg and it decreased to 130±14 mmHg after. A reduction in diastolic BP was also recorded from 82±10 mmHg to 75±9 mmHg (P<.0001). The subject's BP 30 minutes after the sauna session remained lower than pre-sauna pressures. This reflects the positive modifications on arterial compliance. The mean carotid-femoral pulse wave velocity was 9.2±2.4 m/s before and decreased to 8.6±1.6 m/s after the sauna bath. Similarly, pulse pressure reduced from 42.7 mmHg before the sauna to 39.3 mmHg after a 30-minute recovery period. Gayda et al also assessed the change in total peripheral resistance (TPR; another parameter associated with HTN) [3]. 16 patients with stage 1 HTN that were not taking any medication had various hemodynamic measurements taken before and after an 8-minute sauna session at 87°C. TPR (dyne-sec/cm5) dropped from 896±430 before the sauna session to 773±255 fifteen minutes after the session, thus mitigating cardiac work to overcome afterload. Zaccardi et al conducted one of the few long-term studies of sauna bathing's effect on hypertension [4]. This prospective cohort study recruited 1621 men of ages 42 to 60 years old. These men took frequent sauna baths from 4-7 times/week. All men had normal blood pressures and were not taking any antihypertensives at the start of the study. When followed for 24.7 years, the hazard ratio for developing hypertension was .48 (0.26-0.87)

Coronary Artery Disease

The effects of sauna therapy in the setting of coronary artery disease are complex and has different uses in prevention in the pre-diseased state versus its application in already occluded coronary vasculature. 24

subjects, each with a history of chronic coronary occlusion and a percutaneous coronary intervention underwent passive heat thermotherapy to assess myocardial perfusion before and after sauna bathing [5]. Myocardial perfusion was measured with myocardial perfusion scintigraphy with adenosine infusion and peripheral perfusion changes were measured as flow-mediated vasodilation (FMD) using a linear array ultrasound transducer of the brachial artery. Each test was performed at baseline and immediately after sauna sessions along with a treadmill stress test after 3 weeks of daily sessions to assess cardiovascular performance. Due to sauna induced vasodilation distal to the stenosed coronary segment, ischemic (but reversible) changes were seen on myocardial perfusion scan following the session. FMD of the brachial artery improved from 4.1 ± 1.3 to $5.9 \pm 1.8\%$ suggesting improved circulation distally. The treadmill stress test at three weeks demonstrated prolonged exercise tolerance from 430 ± 185 to 511 ± 192 seconds. Similar results were demonstrated by Gravel H. et al after measuring the brachial artery diameter and blood flow velocity in 22 patients over 50 years old with a history of stable CAD [6]. Brachial artery diameter increased 1.21% and forearm vascular conductance increased .51 mL/min/mmHg after two 10-minute sauna sessions at 81°C separated by a single 10-minute break.

One of the many detrimental consequences of sustaining a myocardial infarction (MI) is the reperfusion injury to myocardial tissue once blood supply is restored either medically or surgically. The reintroduction of oxygenated blood into a previously ischemic area activates endothelial cells causing inflammatory cell infiltration and generation of free radicals and inflammatory cytokines that can damage the surrounding myocardial cells [5]. Reintroducing perfusion is also thought to overwhelm and flood endothelial cells with backed up inflammatory mediators and oxygen-derived free radicals. Additionally, consequent endothelial swelling can even further disrupt blood supply to the myocardium. A recent experiment was performed to evaluate how cultured endothelial cells respond to direct heat treatment and human subject's serum before and after they completed 8 weeks of passive heat therapy [7]. Human umbilical vein endothelial cells were cultured appropriately and exposed to a hypoxia-reoxygenation model like the events of a re-perfused MI four hours post-infarction. The experimental group of cells that were either heated directly to the level endured in a sauna session or with sauna-treated serum showed significant upregulated heat shock proteins (HSP) that are responsible for maintaining many proteins that support cardiovascular function. There was also a significant decrease in NF-KB activation, superoxide production, IL-6 release, and cytoplasmic heme oxygenase-1 (HO-1) protein, all of which reduce inflammatory and free radical damage. To further assess how effective passive heat therapy is at protecting against the development of CAD, it is important to note how it alters other cardiovascular risk factors as well, not just hypertension. Sauna's ability to dampen other CVD risk factors will be shown in the metabolic syndrome results below.

Congestive Heart Failure

Given the complexity of the clinical manifestations of CHF, there are numerous ways that recent literature has measured the therapeutic potential of sauna bathing. A meta-analysis analyzed the larger-scale physiologic effects sauna bathing has on a failing heart, such as the cardiothoracic ratio (CTR) and left-ventricular ejection fraction (LVEF) [8]. Patients were exposed to both infrared and Finnish style sauna bathing for 15-minute periods 5 times per week over the course of 2 to 4 weeks. All the participants had either grade II or III heart failure with a baseline ejection fraction under 40%. The studies in this meta-analysis demonstrated significantly higher LVEF in patients with sauna intervention compared to the controls, indicating improved myocardial contractility. The data also reported a significantly lower CTR in the experimental groups. CTR is a measure of heart size by taking the ratio of the maximal cardiac diameter to the maximal thoracic diameter seen on a CXR. These outcomes are very consistent with another meta-analysis that studied sauna's role in heart failure. These patients underwent typical Finnish sauna bathing daily for 2 weeks and were assessed on the overall grading of their disease. Improved NYHA (New York Heart Association) classification of disease just after 2 weeks compared to the control group [9]. Initially, participants had either grade III or IV heart failure and by the end of the two weeks most subjects showed grade II and III disease.

The degree of intracardiac pressures is also of high importance when evaluating and treating heart failure. A study of 32 patients with grade II to grade IV heart failure were evaluated before and after a single 15minute sauna bath [10]. ECG, echocardiogram, blood pressure, expiration gas, and intracardiac pressures were taken before, during, and 30 minutes after the sauna session. It was concluded that both pulmonary artery pressure, pulmonary capillary wedge pressure (corresponding to left atrial pressure), and right atrial pressure decreased during and after the single sauna bath, thereby alleviating peripheral or pulmonary fluid retention by a reduction in preload. The degree of preload and pressure overload of a failing ventricle is also represented by serum brain natriuretic peptide (BNP). This hormone is released by a stretched ventricle due to overwhelming preload and causes vasodilation and diuretic-like activities. A manuscript that reviewed heat therapy in the management of heart failure found that serum BNP levels are lowered in heart failure patients that regularly use the sauna [11]. A failing heart carries a higher risk of sudden cardiac death (SCD) than the normal population. It has been reported that the risk of SCD was 22% lower for biweekly sauna bathers and 63% lower for individuals who use the sauna 4-7 times per week compared to infrequent or zero sauna usage [12]. This is congruent with similar studies who found that the rate of premature ventricular contractions (PVCs) significantly decreased in avid sauna users [9]. Postulated mechanisms for these findings imply that sauna bathing improves cardiac autonomic nervous system balance by decreasing sympathetic tone and increasing vagal tone. This is supported by other data showing favorable cardiac

autonomic responses and heart rate variability following regular sauna use [13].

Metabolic Syndrome

A recent study studied the differences in various metabolic parameters in 1,297 patients with Type 2 Diabetes Mellitus (T2DM) who regularly used heat therapy, mostly in the form of hot-tub bathing. The data was grouped based on the frequency of heat therapy; group $1: \ge 4x$ per week, group $2: 1 \le and \le 4x$ per week, group 3: ≤ 1x per week. Group 1 was found to have the lowest recorded BMI, waist circumference, and HbA1c that indicated greater glycemic control [14]. These results are consistent with the data collected by Imamura M. et al [15], who designed a study consisting of 25 men with at least one cardiovascular risk factor but without evidence of CVD. These men underwent daily sauna sessions for two weeks. Fasting blood panels were taken immediately before and after the duration of the experiment, and the participants' diet was kept consistent with their pre-experimental routine and without any change in activity level. The data revealed mild, but statistically significant reductions in body weight, triglycerides, and plasma glucose. All of which are intimately linked to the development of CVD. It is also crucial to study the protective effects sauna bathing has on young adults as the pathological insult, commonly known as "fatty streaks", marks its presence all the way back to teenage years. To evaluate the protective effects sauna bathing has on young adults, 16 male subjects between the ages 20 and 23 years old underwent multiple sauna sessions held for 15 minutes at 90°C [16]. After 10 sauna sessions, a decrease in total cholesterol, LDL cholesterol, and triglycerides became statistically significant. Cardioprotective cholesterol (HDL) remained increased over this period. These changes in lipid profiles are what is to be expected after regular aerobic exercise paired with an optimal diet.

Respiratory Function

Several lung function parameters were measured before and after a 4-week trial of repeated sauna sessions in 20 subjects with COPD, 10 being in the treatment group and 10 in the control groups [17]. Both groups were former smokers with similar pack years and other demographic characteristics. Each group was also receiving conventional therapy for COPD including $\beta 2$ agonists, anticholinergics, oral theophylline, inhaled glucocorticoids, systemic glucocorticoids, and pulmonary rehabilitation regimes. Vital Capacity (VC), Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), Peak Expiratory Flow (PEF), were all statistically larger in the treatment group than those in the control group. A significant improvement was noted in the Forced Expiratory Flow after 50% of expired FVC (FEF50). Longer walking distances were also noted in the treatment group. A nearly identical study was later performed. However, this time the investigators used echocardiography with continuous wave doppler to measure tricuspid regurgitation speeds and calculated pulmonary systolic pressure using Bernoulli's equation. In addition, right ventricular (RV) function was also assessed with the Tei Index [18]. Overall, significant improvements in RV function and in the Right Ventricular Positive dP/dt at Rest measured with doppler echocardiography were seen after 4-weeks of repeated sauna therapy. These parameters were also compared between the two groups during exercise. A significant drop in pulmonary arterial pressure was observed in the treatment group compared to those in the control group along with an increase in the lowest Sp02 during exercise. This is consistent with heightened exercise tolerance in subjects in this study and the one prior. A recent crossover study observed how a 30-minute sauna bath at 45°C while sitting in a chair for 10 consecutive days alleviated fluid overload. All subjects were defined as being in fluid overload since they carried an extra burden of >2 liters. All participants were receiving peritoneal dialysis and did not have active cardiopulmonary disease. Nonetheless, all subjects had retained fluid that threatens pulmonary function as seen in congestive heart failure. A significant decrease in extra fluid and body weight was seen in the intervention group, with a mean reduction of 0.7 ± 0.2 L, and .85 ± 0.1 kg. Significant improvements in the number of nocturnal awakenings were also observed [19].

Discussion

Endothelial cell health is quite often the root cause of most cardiovascular disease, especially in hypertension and the formation of atherosclerotic plaques which can lead to CAD. Multiple pathways that improve endothelial health are responsible for the data collected. One of which is the production of nitric oxide (NO), a powerful vasodilator. In normal conditions, NO is produced in the endothelium by endothelial nitric oxide synthase (eNOS). It then activates cyclic guanosine monophosphate (cGMP)-dependent enzymes that dephosphorylate myosin light chains causing relaxation of the smooth musculature inside blood vessels leading to vasodilation [20]. This mechanism is a feature of the endothelial cell's reactivity, which is commonly disturbed in diseases like HTN causing stiff, rigid, and non-compliant blood vessels. A major function of the NO released in response to sauna bathing is to direct blood away from the core and allow the dissipation of heat to maintain an appropriate core body temperature. Due to this acute fluctuation of blood pressure, sauna bathing should be used with caution if an individual is taking anti-hypertensive medication to avoid the risk of a hypotensive episode [21]. Another mechanism at the molecular level inside endothelial cells is the production of vascular endothelial cell growth factor (VEGF) by hypoxic cells [7]. VEGF is a signal protein that stimulates the formation of blood vessels. It has been shown that VEGF signaling is upregulated in thermal therapy. This can be beneficial to provide revascularization or even neovascularization to

ischemic myocardial tissue to compensate for any occlusion.

In the setting of CAD, it is important to acknowledge the extent of an individual's perfusion deficits. In someone with unstable CAD, the occlusion blocks a majority of the coronary vessel and will precipitate angina with or without rest. Some experiments did show ECG changes and acute perfusion defects in subjects with unstable disease [22]. This is like what is seen on an adenosine based cardiac stress tests. The basis behind the interrupted perfusion following adenosine or in this case, sauna bathing, is the "coronary steal phenomenon". This phenomenon occurs when there is vasodilation of the coronary vasculature, an adjacent vessel with the same branch point "steals' blood flow from a stenotic vessel since the stenotic vessel is already maximally dilated for compensation. This will result in acute ischemic events of the distal myocardial tissue seen on nuclear imaging and ECG. The contraindication of sauna bathing due to an unstable cardiac occlusion reveals a weakness in this review as it lowers the number of clinical indications saunas can be used to treat. Additionally, this makes it necessary for a patient to discuss with their physician before use to avoid any adverse events.

Nevertheless, the therapeutic value of sauna bathing for CAD is strengthened due to its alterations in peripheral blood flow and more importantly, its protective component in respect to heart disease by mitigating risk factors. A frequent comorbidity to CAD is peripheral artery disease (PAD) as they are both a common manifestation of atherosclerotic plaques. Sauna's clinical benefit in the setting of PAD is appreciated by its improvements in subject's ankle/brachial indexes (ABI) and peripheral vascular conductance. Many patients that suffer from PAD have poor exercise tolerance due to painful ischemic events in their lower extremities. This ischemic pain occurs when the existing distal perfusion deficits are exacerbated by increased oxygen demand during activity. Improvements in peripheral circulation would allow patients to tolerate more aerobic activity to reduce complications seen in ischemic heart disease. Many of the modifiable risk factors to cardiovascular disease can be alleviated with heat therapy. Preventive effects of sauna bathing include improving cholesterol profiles, decreasing blood glucose, maintaining arterial compliance, decreasing stress, improving sleep, decreasing obesity, increasing heart rate variability (HRV), reducing inflammation, reducing oxidative stress, enhancing respiratory function, and overall supporting endurance and cardiovascular fitness [23]. Sauna-induced changes in respiratory function were assessed due to the high comorbidity of breathing related issues in cardiovascular compromised patients and that alterations in cardiovascular physiology have influences on pulmonary status and vice versa. For example, many of these patients were former smokers that developed heart failure because of either chronic obstructive pulmonary disease (COPD), atherosclerosis, or long-standing hypertension. Likewise, patients in uncompensated heart failure develop respiratory distress secondary to fluid congested lungs from the pulmonary circulation.

Given sauna bathing's protective profile, primary care physicians may find this review very helpful to limit the cardiovascular burden on their patients, especially their patients that have difficulty tolerating physical activity due to osteoarthritis or another disabling condition. Those that wish to begin incorporating sauna bathing into their lifestyle, it is important to utilize heat therapy safely. According to the American College of Sports Medicine, a temperature of at least 70°C is required to promote cardiometabolic health, and any temperature above 95°C is not recommended as it can cause cellular and protein damage [24]. Users should limit their initial sessions to about 10 to 15 minutes a couple times per week. Once an individual becomes more acclimated around their 6th to 7th session, they may increase the duration by 5 minutes every few sauna sessions. No sauna bathing session should last more than 45 minutes as data shows no further benefit beyond this duration.

Conclusions

Passive whole-body heat therapy shows promise in both the prevention and treatment of cardiovascular and respiratory illness and should be highly considered as a primary treatment modality given its affordable and accessible nature to the general population. It is also highly recommended in patients that have little capacity to tolerate exercise. The data presented shows that sauna bathing provides similar cardiovascular modifications to that of moderate aerobic exercise and typical cardiovascular pharmaceuticals. For most people, sauna bathing is deemed safe, however, it should be discussed with one's physician prior to use due to possible adverse events with more severe disease or certain medication. Some limitations encountered during this review include the lack of long-term outcomes, few studies on women subjects, and unclear adverse events when combined with various cardiovascular medications. The frequent use of male subjects in these studies is likely secondary to cardiovascular disease being male predominate. It would be informative to have more data on sauna bathing in females and the transgender population as heat therapy may have varying effects on different hormonal profiles and fertility. Future work regarding the beneficial effects of sauna therapy will also include evaluating patient's long-term outcomes and sauna's effects in other systemic diseases that have a cardiovascular consequence. It will be useful to compare the outcomes of patients that practice sauna bathing versus outcomes of patients only taking classic cardiovascular medication. This will be crucial to facilitate the addition of sauna bathing into the standard clinical care of cardiovascular medicine.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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