Experimental Gerontology 154 (2021) 111509

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Review

Sauna use as a lifestyle practice to extend healthspan

Rhonda P. Patrick [a,*], Teresa L. Johnson [b]

[a] FoundMyFitness, LLC, PO Box 99785, San Diego, CA 92169, USA
[b] TLJ Communications, LLC, 36 Creek Harbour Blvd., Freeport, FL 32439, USA

ARTICLE INFO

Keywords:
Cardiorespiratory fitness
Cardiovascular disease
Heat shock protein
Heat stress
Hormesis
Hyperthermia

ABSTRACT

Sauna use, sometimes referred to as "sauna bathing," is characterized by short-term passive exposure to high temperatures, typically ranging from 45 °C to 100 °C (113 °F to 212 °F), depending on modality. This exposure elicits mild hyperthermia, inducing a thermoregulatory response involving neuroendocrine, cardiovascular, and cytoprotective mechanisms that work in a synergistic fashion in an attempt to maintain homeostasis. Repeated sauna use acclimates the body to heat and optimizes the body's response to future exposures, likely due to the biological phenomenon known as hormesis. In recent decades, sauna bathing has emerged as a probable means to extend healthspan, based on compelling data from observational, interventional, and mechanistic studies. Of particular interest are the findings from large, prospective, population-based cohort studies of health outcomes among sauna users that identified strong dose-dependent links between sauna use and reduced morbidity and mortality. This review presents an overview of sauna practices; elucidates the body's physiological response to heat stress and the molecular mechanisms that drive the response; enumerates the myriad health benefits associated with sauna use; and describes sauna use concerns.

1. Introduction

The evolving field of aging research has undergone dramatic shifts in recent decades, as the prevailing view of aging as a non-modifiable inevitability has given way to the possibilities of extending lifespan and, even more promising, healthspan. A widely accepted definition of healthspan is the period of one's life spent in good health, free from the chronic diseases and disabilities that commonly accompany aging (Kaeberlein, 2018). Healthspan extension compresses the time spent in ill health, shifting it to one's later years. Sauna use has emerged as a probable means to increase lifespan and extend healthspan.

Bathing oneself in heat for the purposes of purification, cleansing, and healing is an ancient practice, observed for thousands of years across many cultures. Variations of its use appear today in the banyas of Russia, the sweat lodges of the American Indians, and the saunas of Finland. Sauna use, sometimes referred to as "sauna bathing," is characterized by short-term passive exposure to high temperatures, typically ranging from 45 °C to 100 °C (113 °F to 212 °F), depending on modality. This exposure elicits mild hyperthermia, an increase in the body's core temperature that induces a thermoregulatory response involving neuroendocrine, cardiovascular, and cytoprotective mechanisms that participate in restoring homeostasis and conditioning the body for future stressors (Laukkanen et al., 2018a).

Compelling data from observational, interventional, and mechanistic studies support the assertions that sauna use extends healthspan, and multiple recent reviews have described the cardiovascular, neurological, and metabolic benefits associated with sauna use (Brunt and Minson, 2021; Ely et al., 2018; Hunt et al., 2019; Pizzey et al., 2021). Of particular interest are the findings from studies of participants in the Kuopio Ischemic Heart Disease (KIHD) Risk Factor Study. This ongoing

Abbreviations: ADHD, attention deficit hyperactivity disorder; BDNF, brain-derived neurotrophic factor; BPA, bisphenol A; CHF, congestive heart failure; CRP, C-reactive protein; CVD, cardiovascular disease; FOX, forkhead box protein; FOXO3, forkhead box protein O3; GLUT4, glucose transporter type 4; HRV, heart rate variability; HO-1, heme oxygenase-1; HSP, heat shock protein; IL-10, interleukin-10; IL-6, interleukin-6; KIHD, Kuopio Ischemic Heart Disease Risk Factor Study; LDL, low density lipoprotein; Nrf2, nuclear factor erythroid 2–related factor 2; PAD, peripheral artery disease; PVC, premature ventricular contraction; RH, relative humidity; SIRT1, sirtuin 1.

* Corresponding author.
E-mail addresses: rhonda@foundmyfitness.com (R.P. Patrick), teresa@tljcommunications.net (T.L. Johnson).

https://doi.org/10.1016/j.exger.2021.111509
Received 18 May 2021; Received in revised form 16 July 2021; Accepted 2 August 2021
Available online 5 August 2021

prospective population-based cohort study of health outcomes in more than 2300 middle-aged men from eastern Finland has identified associations between sauna use and reduced risk for age-related impairments, including cardiovascular disease, neurodegenerative disease, metabolic dysfunction, and immunological decline.

The KIHD findings revealed that among men who reported using the sauna 2–3 times per week, the risk of cardiovascular disease (CVD) mortality was 27% lower than among men who reported using the sauna only once weekly (Laukkanen et al., 2015b). Furthermore, these effects were dose-dependent: Among men who reported using the sauna 4–7 times per week, the risk of CVD mortality was 50% lower than among men who reported using the sauna only once weekly (Laukkanen et al., 2015b). In addition, the risk of all-cause mortality was 40% lower among frequent sauna users compared to infrequent users, independent of conventional risk factors (Laukkanen et al., 2015b).

Noncausal mechanisms, including socioeconomic status and reverse causation bias, have been proposed as contributors to the KIHD findings (Kivimaki et al., 2015). Although differences in socioeconomic status may influence sauna access and opportunities for use, the robust dose-dependent associations observed between sauna bathing and sudden cardiac death, coronary artery disease, and cardiovascular events in the KIHD studies are indicative of genuine inverse associations (Laukkanen et al., 2015a). Furthermore, the KIHD studies were conducted in Finland, where sauna use is deeply rooted in the culture, and saunas are readily accessible (Laukkanen et al., 2015a). Similarly, whereas reverse causation bias figures prominently in observational studies and is a valid concern when investigating links between cardiovascular disease and lifestyle, the KIHD findings were adjusted for potential biases, including lifestyle factors such as socioeconomic status, physical activity, and cardiorespiratory fitness (Laukkanen et al., 2015a).

The KIHD studies also revealed that frequent sauna use was associated with reduced risk of developing age-related neurodegenerative conditions such as dementia and Alzheimer's disease, in a dose-dependent manner. Men who reported using the sauna 4–7 times per week had a 66% lower risk of developing dementia and a 65% lower risk of developing Alzheimer's disease, compared to men who reported using the sauna only once weekly (Laukkanen et al., 2017). The health benefits associated with sauna use extended to other aspects of mental health, as well. Men participating in the KIHD study who reported using the sauna 4–7 times per week had a 77% reduced risk of developing psychotic disorders, even after adjusting for the men's energy intake, socioeconomic status, physical activity, and inflammatory status, as measured by C-reactive protein (Laukkanen et al., 2018c).

2. Sauna practices overview

The term “sauna” is a Finnish word, and it typically refers to an unpainted spruce- or pine-paneled room, with wooden benches made of aspen, spruce, or obeche (Hannuksela and Ellahham, 2001). The preponderance of research related to sauna bathing has been conducted in Finland or in regard to Finnish-style sauna practices. Not all saunas are Finnish style, however, and saunas may differ according to their heat source, relative humidity, and duration of use. Similarly, sauna practices may differ by modality.

2.1. Heat source

Historically, saunas were heated by wood fires, a practice still observed today in rural parts of Finland. Most modern saunas, however, are heated by electric conventional or infrared heaters. Conventional heaters warm the air to a high temperature, ranging from 70 °C to 100 °C (158 °F to 212 °F), optimally at 80 °C to 90 °C (176 °F to 194 °F) at the level of the user's face, and the heat of the warmed air transfers to the body (Hannuksela and Ellahham, 2001; Kukkonen-Harjula and Kauppinen, 2006). Infrared heaters emit thermal radiation, which heats the body directly. They operate at lower temperatures than traditional saunas, at 45 °C to 60 °C (113 °F to 140 °F) (Beever, 2009). Infrared heaters emit either near or far wavelengths. Near infrared heaters use incandescent bulbs to produce thermal radiation of varying wavelengths, ranging from near-infrared wavelengths (primarily) to middle-infrared wavelengths (to a lesser degree). Far infrared heaters use ceramic or metallic heating elements that emit energy in the far-infrared range, typically at wavelengths of approximately 10 μm (Beever, 2009).

2.2. Humidity

Saunas are generally classified as either dry or wet. In a dry sauna, the relative humidity is low (10–20%) (Hannuksela and Ellahham, 2001). A common practice in Finland, called *löyly*, is to apply water to the heater's rocks to slightly increase the humidity. The term “wet sauna” is a misnomer, however, referring to a steam sauna, where the humidity is extremely high (typically greater than 50%), which impairs sweat evaporation (Pilch et al., 2014a). Due to its reduced evaporative cooling, a wet sauna may feel subjectively hotter than a dry sauna and elicits greater strains on the cardiovascular system (Pilch et al., 2014a).

2.3. Duration, temperature, and practices across modalities

Finnish-style sauna bathing involves 1–3 sessions of heat exposure lasting 5–20 min each, interspersed with periods of cooling (Kukkonen-Harjula and Kauppinen, 2006). Some cooling methods involve rolling in snow or immersing in cold water, further stressing the cardiovascular system (Vuori, 1988). The KIHD studies typically involved saunas that were heated to a temperature of at least 78.9 °C (174 °F), with an average duration of 14.5 min (range, 2 to 90 min). Sessions lasting 19 min or more elicited a more robust protective effect than 11 to 18 min on lowering mortality rate (Laukkanen et al., 2015b).

Infrared sauna sessions are typically 15 to 30 min in duration (Beever, 2009). A variant of infrared sauna use, called waon therapy, originated in Japan. Waon therapy involves a two-step process wherein participants engage in a 15- to 30-minute session of infrared heat exposure in a sauna heated to approximately 60 °C (140 °F), followed by a 30-minute session of lying supine (outside the sauna) while covered in warm blankets, to raise the core body temperature approximately 1.0 °C to 1.2 °C (1.8 °F to 2 °F) (Sobajima et al., 2015). Waon therapy is associated with improvements in multiple aspects of cardiovascular function (Miyata and Tei, 2010).

A clinical application of heat exposure that differs slightly from sauna use is called whole-body hyperthermia, a therapeutic strategy used to treat various medical conditions, including cancer, fibromyalgia, and others (Hoffmann et al., 2016; Romeyke et al., 2015; van der Zee, 2002). Emerging evidence suggests that whole-body hyperthermia is beneficial in treating depression (Janssen et al., 2016). Whole-body hyperthermia employs radiation, convection, or conduction and is typically administered in the clinical setting using a variety of methods, such as the use of direct contact with a heated liquid (such as water or wax), hot blankets or suits, heating coils, or specialized lamps that emit infrared-A radiation in a confined area or chamber (Jia and Liu, 2010; Milligan, 1984; Robins et al., 1994).

3. Physiological response to heat stress

Exposure to high temperature stresses the body, eliciting a rapid, robust response that affects primarily the skin and cardiovascular systems (Fig. 1). The skin heats first, rising to approximately 40 °C (104 °F), followed by changes in core body temperature, rising slowly from 37 °C to approximately 38 °C (98.6 °F to 100.4 °F) and then increasing rapidly to approximately 39 °C (102.2 °F) (Gravel et al., 2021; Kukkonen-Harjula and Kauppinen, 2006; Kunutsor et al., 2021; Mori et al., 2017; Smolander and Kolari, 1985; Sohar et al., 1976). Cardiac output may increase by as much as 60–70%, while the heart rate increases and the stroke volume remains stable (Hannuksela and Ellahham, 2001;

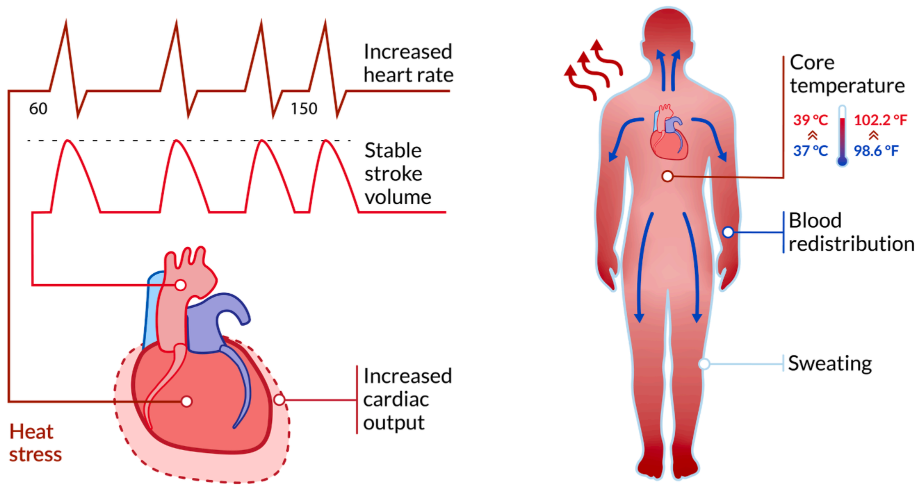

Fig. 1. Physiological response to heat stress.
Heat stress increases core body temperature, promotes blood redistribution, and increases sweat production. Heart rate and cardiac output increase, while stroke volume remains stable.

Kukkonen-Harjula and Kauppinen, 2006). Concurrently, approximately 50–70% of the body's circulation redistributes from the core to the skin to facilitate sweating, driving fluid losses at a rate of approximately 0.6 to 1.0 kg per hour, averaging approximately 0.5 kg during a moderate temperature (80 °C to 90 °C; 176 °F to 194 °F) Finnish-style sauna session (Gravel et al., 2021; Hasan et al., 1966; Kauppinen, 1989; Laukkanen et al., 2019a; Laukkanen et al., 2015b; Podstawski et al., 2014; Sohar et al., 1976; Vuori, 1988). Acute heat exposure also induces a transient increase in overall plasma volume to mitigate the decrease in core blood volume. This increase in plasma volume provides a reserve source of fluid for sweating, cools the body to prevent rapid increases in core body temperature, and promotes heat tolerance (Fortney and Miescher, 1994). Sweating also facilitates higher excretion of some heavy metals including aluminum (3.75-fold), cadmium (25-fold), cobalt (7-fold), and lead (17-fold), compared to elimination via urine (Genuis et al., 2011).

Repeated sauna use acclimates the body to heat and optimizes the body's response to future exposures, likely due to a biological phenomenon known as hormesis, a compensatory defense response following exposure to a mild stressor that is disproportionate to the magnitude of the stressor. Hormesis triggers a vast array of protective mechanisms that not only repair cell damage but also provide protection from subsequent exposures to more devastating stressors (Mattson, 2008). Exercise is a form of hormetic stressor (Goto and Radak, 2009; Ji et al., 2010; Radak et al., 2005, 2008a; Radak et al., 2008b; Radak et al., 2017). Interestingly, many of the physiological responses to sauna use (described in detail below) are remarkably similar to those experienced during moderate- to vigorous-intensity aerobic exercise, and sauna use has been proposed as an alternative to aerobic exercise for people who are unable to engage in physical activity due to chronic disease or physical limitations (Hoekstra et al., 2020; McCarty et al., 2009; Sobajima et al., 2013).

3.1. *Molecular mechanisms involved in the heat stress response*

The hormetic effects of heat stress are facilitated by molecular mechanisms that mitigate protein damage and aggregation and activate endogenous antioxidant, repair, and degradation processes. Many of these responses are also triggered in response to moderate- to vigorous-intensity exercise and include increased expression of heat shock proteins, transcriptional regulators, and pro- and anti-inflammatory factors.

3.1.1. *Heat shock proteins*

One of the protective adaptive responses to heat stress is the increased expression of heat shock proteins (HSPs). Heat-shock proteins comprise a large, highly conserved family of proteins that are present in all cells. Heat-shock proteins are also present in the extracellular environment (Lyon and Milligan, 2019). They play prominent roles in many cellular processes, including immune function, cell signaling, cell-cycle regulation, and proteome homeostasis. Loss of proteome integrity is a hallmark of the aging process (Lopez-Otin et al., 2013), and intrinsically disordered or damaged, dysfunctional proteins are common features in age-related diseases such as cardiovascular and neurodegenerative diseases (Cheng et al., 2006). Increased expression of HSPs prevents protein disorder and aggregation by repairing proteins that have been damaged, and animal evidence suggests that HSPs may offer protection against neurodegenerative diseases (Leak, 2014) (Fig. 2). Heat shock proteins also moderate muscle atrophy (Fig. 2). Findings from a small intervention study in rodents demonstrated that local heat application during an immobilization period decreased muscle atrophy by 37% compared to a sham treatment. The muscle-sparing effects of heat exposure were attributed in part to marked increases in expression of HSP70 and HSP90 (25 ± 6.6 and 20 ± 7.4%, respectively), a finding that has been demonstrated in other work, as well (Hafen et al., 2019; Senf et al., 2008) (Fig. 2). Furthermore, HSPs are associated with human longevity. A population-based association study of Danish nonagenarians demonstrated that female carriers of single nucleotide polymorphisms (SNPs) in specific gene regions of the *HSP70* gene that increase the gene's stability and activity live approximately one year longer than non-carriers (Singh et al., 2010).

Under stressful environmental conditions, cellular proteins can unfold or become damaged, impairing their normal functions, and further increasing their vulnerability to change. During exposure to environmental stressors such as temperature extremes (Amorim et al., 2015; Sandstrom et al., 2009; Staib et al., 2007), reduced nutrient levels (Ehrenfried et al., 1996; Heydari et al., 1993; Raynes et al., 2012), bioactive dietary components (Moura et al., 2018), or hypoxia (Zhong et al., 2000), cells increase expression of HSPs to stabilize unfolded proteins and repair or re-synthesize damaged proteins.

Heat stress, in particular, robustly increases intracellular levels of HSPs in humans (Yamada et al., 2007) (Fig. 3). For example, after healthy men and women sat in a heat stress chamber for 30 min at 73 °C (163.4 °F), their HSP72 levels increased by 49% (Iguchi et al., 2012). In a different study, in which healthy men and women were exposed to deep tissue heat therapy for six days, participants' HSP70 and HSP90

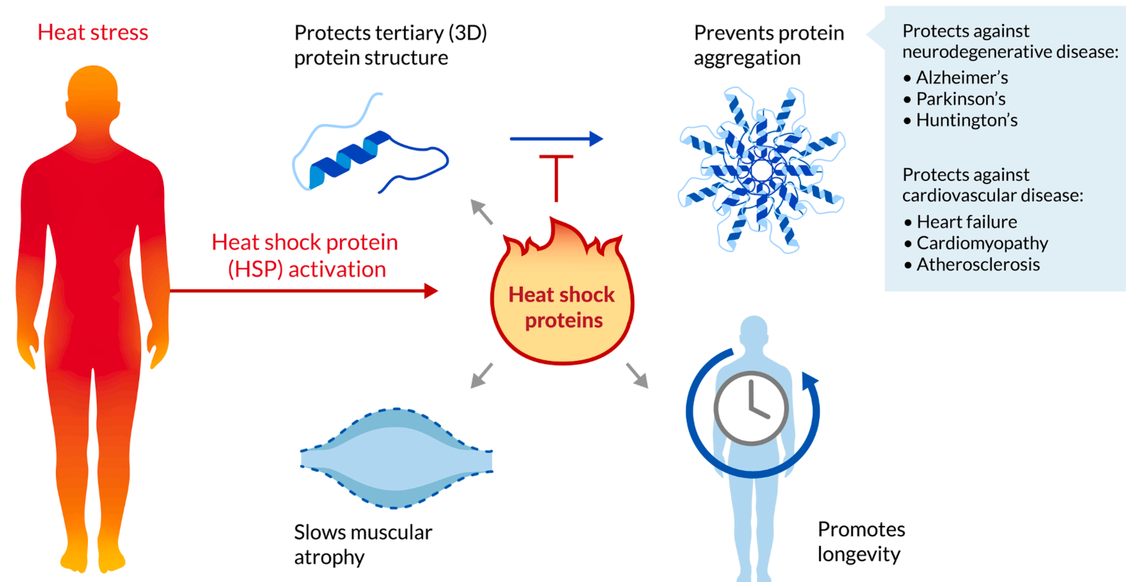

Fig. 2. Heat shock proteins provide protection against cellular stress.
Heat stress promotes increased expression of heat shock proteins (HSPs), which prevent protein disorder and aggregation by repairing proteins that have been damaged, providing protection against chronic diseases. Increased expression of HSPs also slows muscle atrophy and promotes longevity.

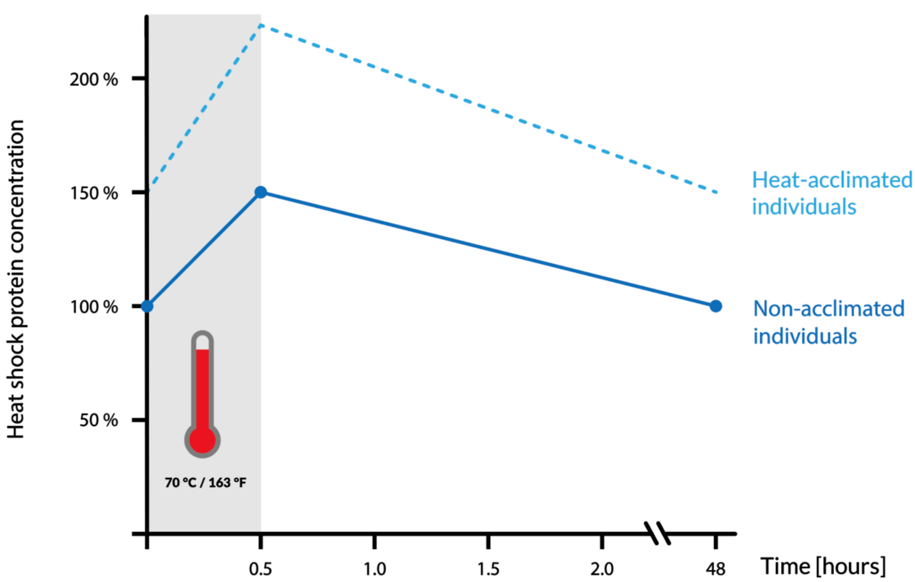

Fig. 3. Heat stress activates heat shock proteins.
Heat stress robustly activates heat shock proteins (HSP), resulting in higher intracellular concentrations of HSPs. This activation occurs within 30 min of heat exposure and is sustained over time. Basal HSP concentrations are higher in heat-acclimated individuals, suggesting that heat acclimation induces whole-body adaptations that increase heat tolerance, resulting in protective cellular adaptations.

levels increased 45% and 38%, respectively (Hafen et al., 2018). In addition, their mitochondrial biogenesis biomarkers improved, and their mitochondrial respiratory capacity increased by 28%, compared to baseline levels. Increased levels of HSPs are sustained over time and occur more rapidly in heat acclimated individuals, suggesting that heat acclimation induces whole-body adaptations that increase heat tolerance, resulting in protective cellular adaptations (Yamada et al., 2007).

3.1.2. *Nuclear factor erythroid 2–related factor 2*

Nuclear factor erythroid 2–related factor 2 (Nrf2) is a key regulator of the cellular antioxidant response. Upon activation, Nrf2 translocates from the cytoplasm to the nucleus, leading to the orchestrated regulation of a vast network of genes with cytoprotective, antioxidant, and anti-inflammatory functions and providing protection against oxidative stress, electrophilic stress, and chronic inflammation, the underlying causes of many age-related chronic diseases (Pawelec et al., 2014; Vomund et al., 2017). Application of whole-body hyperthermia (which would elicit effects similar to those encountered with sauna use) increased Nrf2 mRNA (Ihsan et al., 2020). Heat exposure activates Nrf2, thereby upregulating the HSP heme oxygenase-1 (HO-1), which breaks down heme to generate carbon monoxide and bilirubin (Lin and Yang, 2009; Yet et al., 2002). The downstream effect of HO-1 upregulation includes inhibition of the expression of several pro-inflammatory molecules involved in the pathophysiology of cardiovascular disease, including *E*-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 (Lin and Yang, 2009).

3.1.3. *Interleukin-6 and interleukin-10*

Inflammation is a highly conserved element of the mammalian immune response, but chronic low-grade inflammation is a fundamental driver of many chronic disease processes (Michaud et al., 2013). Maintaining the appropriate balance of pro- and anti-inflammatory factors is crucial for the development and subsequent resolution of an inflammatory response. The pathways that maintain this balance become dysregulated with age, contributing to an inflammatory bias wherein innate responses dominate, eliciting a state of chronic inflammation (Pawelec et al., 2014). Interleukin-6 (IL-6) is a pro-inflammatory cytokine that plays an important role in the regulation of central homeostatic and immunological processes (Gabay, 2006). However, IL-6 also exerts anti-inflammatory properties via its activation of interleukin-10 (IL-10), a potent anti-inflammatory cytokine (Ahmed and Ivashkiv, 2000). Whereas acute elevation of IL-6 is generally considered favorable, chronic elevation is indicative of chronic inflammation. Exercise and sauna use, which both elevate core body temperature, acutely increase IL-6 and IL-10 plasma levels and *IL-10* expression levels (Hoekstra et al., 2020; Raison, 2017; Windsor et al., 2018; Zychowska et al., 2018).

4. Sauna bathing may extend healthspan

4.1. Promotion of cardiovascular health

Heat exposure induces protective responses that promote cardiovascular health. Some of these responses recapitulate those experienced during exercise. For example, heart rate may increase up to 100 beats per minute during moderate-temperature sauna bathing sessions and up to 150 beats per minute during hotter sessions, similar to the increases observed during moderate- to vigorous-intensity physical exercise (Kukkonen-Harjula et al., 1989; Taggart et al., 1972). In a study involving 19 healthy adults in which the cardiac responses to a single 25-minute sauna session were compared to those elicited by moderate physical exercise, the cardiac loads were nearly equivalent, with participants' heart rate and blood pressure increasing immediately in both scenarios and dropping below baseline measurements taken pre-sauna or -exercise (Ketelhut and Ketelhut, 2019). Like exercise, regular sauna use generally decreases systolic and diastolic blood pressure (Gayda et al., 2012; Laukkanen et al., 2018b; Zaccardi et al., 2017); increases left ventricular ejection fraction and reduces left ventricular ejection time (Blum and Blum, 2007; Lee et al., 2018; Ohori et al., 2012); enhances arterial compliance (Lee et al., 2018; Li et al., 2020); and improves flow-mediated dilation, a measure of endothelial function (Imamura et al., 2001; Ohori et al., 2012) (Fig. 4).

4.2. Protection against cardiovascular disease

Findings from the Global Burden of Disease Study indicate that 17.9 million people died from cardiovascular diseases in 2016 (Roth et al., 2017). A growing body of evidence suggests that cardiovascular disease is largely preventable via implementation of healthy lifestyle behaviors such as exercise, healthy diet, and stress management (Buttar et al., 2005; Claas and Arnett, 2016; Yusuf et al., 2004). Sauna use has emerged as a healthy lifestyle behavior and primary prevention strategy that may reduce the risk of cardiovascular disease and related mortality.

4.2.1. Cardiovascular disease-related mortality

The KIHD studies demonstrated dose-dependent cardiovascular benefits associated with the frequency and duration of sauna use. Whereas the risk for sudden cardiac death was 22% lower for men using the sauna 2–3 times per week, the risk was 63% lower for men who used the sauna 4–7 times per week, compared to men who used the sauna 1 time per week. The risk for fatal coronary heart disease was 23% lower for men using the sauna 2–3 times per week and 48% lower for men using the sauna 4–7 times per week, compared to men using the sauna 1 time per week. The risk for fatal cardiovascular disease was 27% lower for men who used the sauna 2–3 times a week and 50% lower for men who used the sauna 4–7 times a week, compared to men who used the sauna 1 time per week. Similarly, longer duration sauna sessions were associated with a more robust effect on lowering mortality rate relative to shorter sessions. For example, the risk for sudden cardiac death among men was 7% lower among those whose sauna sessions were 11 min or less and was 52% lower among those whose sauna sessions were 19 min or more.

Additionally, aerobic exercise in combination with frequent sauna use has a synergistic effect on lowering cardiovascular-related mortality and all-cause mortality. The strongest reductions in mortality were found in people with high cardiorespiratory fitness and high frequent sauna bathing, followed by high cardiorespiratory fitness and low frequent sauna bathing, and then low cardiorespiratory fitness and high frequent sauna bathing. These reductions were more strongly associated with lower mortality outcomes compared with the separate associations for each exposure (Kunutsor et al., 2018).

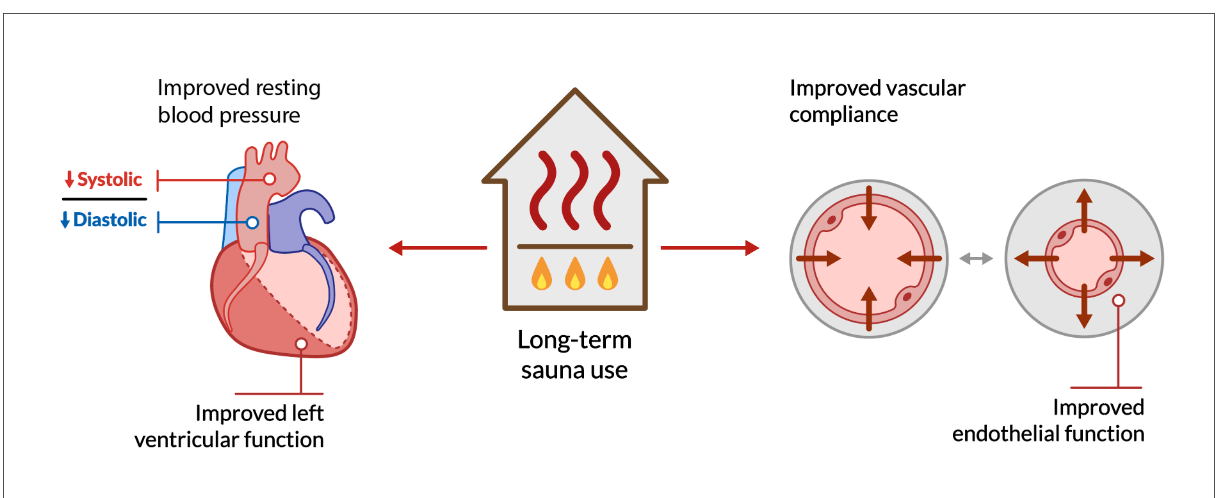

Fig. 4. Long-term sauna use protects against cardiovascular disease.
Long-term sauna use induces protective responses against the pathological processes that drive cardiovascular disease and related disability by decreasing resting systolic and diastolic blood pressure; increasing left ventricular ejection fraction and reducing left ventricular ejection time; enhancing arterial compliance; and improving flow-mediated dilation, a measure of endothelial function.

4.2.2. Congestive heart failure

Congestive heart failure (CHF) is a complex clinical syndrome that arises from structural or functional cardiac disorders that impair ventricular function (Hunt et al., 2001). The condition leads to impaired blood flow to the heart and peripheral tissues with subsequent functional losses, dyspnea, edema, and left ventricular hypertrophy. Treatment is often limited to pharmaceutical, nutritional, or palliative care. Findings from a prospective, multicentered, randomized controlled trial involving 149 patients with advanced CHF demonstrated that 2 weeks of waon therapy improved the patients' B-type natriuretic peptide levels, endurance, cardiothoracic ratio, and disease status compared to those who received standard medical care (Tei et al., 2016). In a different randomized controlled trial involving 30 CHF patients with frequent premature ventricular contractions (PVCs), 2 weeks of infrared dry sauna (waon therapy) reduced the number of PVCs the patients experienced in a 24-h period (from a baseline of 3161 ± 1104 to 848 ± 415, post-therapy). A control group that received conventional medical therapy showed no significant changes (Kihara et al., 2004).

4.2.3. Ischemic heart disease

Ischemic heart disease, the most common cause of death in most western countries, is characterized by impaired myocardial perfusion (Steenbergen and Frangogiannis, 2012). A randomized controlled trial that examined the effects of sauna use in 24 patients with ischemic heart disease with chronic total coronary artery occlusion who had not responded to non-surgical procedures and had failed or were not candidates for percutaneous coronary intervention demonstrated that 15 waon sessions given over a 3-week period improved the patients' vascular endothelial function as measured by flow-mediated dilation of the brachial artery. No significant improvements were observed in the control group that received standard medical care (Sobajima et al., 2013).

4.2.4. Peripheral artery disease

Peripheral artery disease (PAD) is characterized by arterial atherosclerotic lesions of the aorta, iliac artery, and lower extremities (Olin et al., 2016). A pilot trial involving 20 patients with PAD who received 50 waon sessions over a period of 10 weeks demonstrated improvements in pain levels, walking endurance, and lower extremity blood flow (Tei et al., 2007). A similar randomized controlled trial involving 21 patients with PAD showed comparable improvements (Shinsato et al., 2010).

4.2.5. Dyslipidemia

Dyslipidemia is a strong predictor of cardiovascular disease risk. Two small studies have demonstrated that regular sauna use modulates serum cholesterol and lipoproteins in healthy adults. Women who were exposed to seven 30-minute sauna baths over a period of 2 weeks exhibited reduced total plasma cholesterol concentrations (from 4.47 ± 0.85 mmol/L to 4.25 ± 0.93 mmol/L) and reduced plasma low-density lipoprotein (LDL) concentrations (from 2.83 ± 0.80 mmol/L to 2.69 ± 0.83 mmol/L), assessed immediately after the final sauna session (Pilch et al., 2014b). Similarly, men who were exposed to ten 45-minute sauna baths over a period of 3 weeks exhibited reduced total blood cholesterol concentrations (from 4.50 ± 0.66 mmol/L to 4.16 ± 0.54 mmol/L) and reduced blood LDL concentrations (from 2.71 ± 0.47 mmol/L to 2.43 ± 0.35 mmol/L), assessed immediately after the final session (Gryka et al., 2014).

4.2.6. Hypertension

Hypertension, defined as a systolic pressure of 130 mm Hg or higher, or a diastolic pressure of 80 mm Hg or higher, is a robust predictor of future incidence of stroke, coronary heart disease, heart attack, heart failure, and cardiovascular-related death (Whelton et al., 2018). Central to the pathophysiology of hypertension is the loss of arterial compliance, which can have far-reaching effects on multiple organ systems, including the brain and kidneys. A common element among sauna users, however, is lower incidence of hypertension through improvements in arterial compliance. For example, men who reported using the sauna 2–3 sessions every week were found to have a 24% lower risk of developing hypertension, and men who reported using the sauna 4–7 times per week had a 46% lower risk for developing hypertension, compared to men who used the sauna only 1 time per week (Zaccardi et al., 2017). In fact, a single sauna session has been shown to lower blood pressure and improve arterial compliance when assessed immediately after completion of the session. These effects were sustained during a 30-minute recovery period (Lee et al., 2018). As such, sauna use may serve as a non-pharmacological means to address, or even prevent, hypertension.

4.2.7. Endothelial dysfunction

Endothelial dysfunction is characterized by decreased secretion of vasodilators and/or increased secretion of vasoconstrictors. This imbalance leads to impaired endothelium-dependent vasodilation, a common element in the pathophysiology of congestive heart failure. However, two weeks of sauna therapy in patients with congestive heart failure improved endothelial function, as evidenced by significant increases in flow-mediated dilation; and improved cardiac function, as evidenced by significant decreases in concentrations of brain natriuretic peptide (Kihara et al., 2002).

4.2.8. Left ventricular dysfunction

Dysfunction of the heart's left ventricle sets in motion a cascade of compensatory mechanisms that promote organ-level structural changes and elicit system-level hormonal adaptations. It is a common occurrence after myocardial infarction and markedly increases the risk of ischemic stroke (Hays et al., 2006). Both single-session and long-term sauna use (5 days per week for 4 weeks) improved left ventricular function in men with congestive heart failure via reduced afterload associated with thermal vasodilation. Consequently, sauna use may have therapeutic value for treating late-stage cardiovascular disease (Tei and Tanaka, 1996; Thomas et al., 2016).

4.2.9. Heart rate variability

Heart rate variability (HRV) is a measure of the variation in time between heartbeat intervals. Opposing inputs from the sympathetic and parasympathetic branches of the autonomic nervous system work in tandem to regulate heart rate and modulate HRV. Whereas increased sympathetic activity or decreased parasympathetic activity accelerates heart rate and lowers HRV, decreased sympathetic activity or increased parasympathetic activity slows heart rate and increases HRV. A higher HRV, or greater variability between heartbeats, is an indicator of autonomic nervous system health; as such, HRV is a well-established marker of cardiovascular risk (Acharya et al., 2006; Hillebrand et al., 2013). Aerobic exercise induces potent autonomic nervous system responses in the cardiovascular system and, in turn, strongly influences HRV both during and after training (Hautala et al., 2009).

Evidence suggests that sauna use elicits similar effects to exercise to increase HRV via modulation of the autonomic nervous system. Sauna use holds promise as a therapeutic strategy in the treatment of cardiac arrhythmias, a common feature of CHF (Franciosi et al., 2017; Leimbach et al., 1986). A study involving patients with CHF who experienced 200 or more premature ventricular contractions (PVCs) per 24-h period, sauna exposure (15 min per day, followed by 30 min of bedrest for 5 days per week for 2 weeks) elicited increases in HRV and markedly reduced the number of PVCs (Kihara et al., 2004). Furthermore, a single, 30-minute sauna session in 93 men with at least 1 cardiovascular risk factor elicited significant favorable effects on multiple variables associated with HRV. Specifically, the men's HRV and parasympathetic activity increased, and their resting heart rate was lower after sauna use (68/min) compared to before sauna use (77/min) (Laukkanen et al., 2019b).

4.2.10. Inflammation

Inflammation is a critical element of the body's immune response, but chronic inflammation plays a key role in the development of many chronic diseases, including cancer, cardiovascular disease, and diabetes. Markers of inflammation increase with aging. Exercise provokes an inflammatory response driven by the release of the pro-inflammatory cytokine IL-6, which in turn elicits a counter response driven via the release of anti-inflammatory cytokines IL-1ra and IL-10 (Hoekstra et al., 2020; Pedersen and Febbraio, 2008; Petersen and Pedersen, 2005; Windsor et al., 2018). This exercise-induced response is due in part to the increase in core body temperature that accompanies exertion and likely explains some of the benefits associated with regular exercise (Costello et al., 2018; Starkie et al., 2005). Passive strategies that induce increases in body temperature may similarly reduce inflammation and may be particularly well-suited for individuals who are unable to participate in regular exercise due to physical or cognitive limitations (Hoekstra et al., 2020).

C-reactive protein (CRP), an acute phase reactant, also participates in the body's inflammatory cascade. Elevated CRP is associated with the development of atherosclerosis, loss of arterial compliance, and greater incidence of cardiovascular events (Hage, 2014). Sauna use reduces blood levels of CRP, however. In a study of more than 2000 men living in Finland, CRP levels were inversely related to the frequency of sauna bathing in a dose-response fashion, with lower levels linked to greater frequency (Laukkanen and Laukkanen, 2018). As previously described, IL-10 is a potent endogenous anti-inflammatory protein. In a study involving 22 healthy male athletes and non-athletes who received two 15-minute sauna sessions at 98.2 °C (208.7 °F) separated by a 5-minute cool shower, the men's resting IL-10 levels increased, and this adaptation occurred faster in the athletes. A slight increase in some HSPs was also observed (Zychowska et al., 2018).

4.3. Cognitive and mental health

4.3.1. Enhanced neurogenesis

Heat stress and exercise increase the expression of brain-derived neurotrophic factor (BDNF) (Kojima et al., 2018), a protein that acts on neurons in the central and peripheral nervous systems, to promote the growth of new neurons. BDNF modulates neuronal plasticity and ameliorates anxiety and depression from early-life stressful events (Maniam and Morris, 2010). It is active in the hippocampus, cortex, cerebellum, and basal forebrain – areas involved in learning, long term memory, and executive function. BDNF is also produced in exercising muscle tissue, where it plays a role in muscle repair and the growth of new muscle cells (Pedersen, 2013).

Whole-body hyperthermia administered via hot water baths elicits robust increases in serum BDNF levels. An investigation of the effects of head-out immersion in hot water demonstrated that serum BDNF levels increased 66% following a 20-minute immersion in 42 °C (108 °F) water. Core body temperature increased to 39.5 °C (103.1 °F), while plasma cortisol levels dropped significantly over the immersion period. Serum BDNF remained significantly higher than before immersion for 15 minutes post-immersion (Kojima et al., 2018).

4.3.2. Neurodegenerative diseases

Findings from a large observational study of middle-aged men living in Finland demonstrated that men who used the sauna 4–7 times per week had a 65% reduced risk of developing Alzheimer's disease, compared to men who used the sauna only 1 time per week (Laukkanen et al., 2015b). There may be multiple mechanisms by which frequent sauna use may stave off neurodegenerative diseases. Normal cognitive function is dependent upon sufficient blood flow to the brain and peripheral nervous system. For this reason, cardiovascular diseases and cognitive decline are common comorbidities. For example, hypertension alters the microarchitecture of cerebral blood vessels and impairs blood flow to the brain. Poor cerebral blood flow is commonly observed in mice and humans and may contribute to impaired amyloid-beta clearance, thereby accelerating the progression of Alzheimer's disease (Iadecola, 2004). In addition, heat exposure increases the production of BDNF to promote neurogenesis. Lastly, heat shock proteins, which increase following sauna use, demonstrate critical roles in preventing Alzheimer's disease, as described previously (Leak, 2014).

4.3.3. Depression

Elevated biomarkers of inflammation are commonly observed in individuals who have depression (Dinan, 2009). Chronic activation of the body's inflammatory response system promotes the development of depressive symptoms and induces changes in brain and neuroendocrine function, suggesting that strategies that induce anti-inflammatory pathways may reduce symptoms of depression. Preclinical studies have found that exogenous administration of the anti-inflammatory cytokine IL-10 can improve depressive symptoms (Roque et al., 2009; Worthen et al., 2020).

Sauna use has been shown to reduce symptoms of depression. In a randomized controlled trial involving 28 individuals diagnosed with mild depression, participants who received 4 weeks of sauna sessions experienced reduced symptoms of depression, such as improved appetite and reduced somatic complaints and anxiety, compared to the control group, which received bedrest instead of sauna therapy (Masuda et al., 2005). In a randomized, double-blind study of 30 healthy adults diagnosed with depression, participants who were exposed to a single session of whole-body hyperthermia in which core body temperature was elevated to 38.5 °C (101.3 °F) experienced an acute antidepressant effect that was apparent within 1 week of treatment and persisted for 6 weeks after treatment (Janssen et al., 2016). Some of these benefits on mood may be due to the effects of heat stress on acutely increasing plasma levels of pro-inflammatory IL-6 and anti-inflammatory IL-10, similar to effects observed following exercise (Miller and Raison, 2016; Windsor et al., 2018; Zychowska et al., 2018). Interestingly, a small study in which individuals diagnosed with major depressive disorder received whole-body hyperthermia demonstrated that the participants' antidepressant response correlated with reductions in core body temperature in the 5 days post treatment (Hanusch et al., 2013).

4.4. Beta-endorphins and the opioid system

Beta-endorphins are endogenous opioids that are produced and stored primarily in the anterior pituitary gland of the brain. They play important roles in pain management and reward circuitry. Evidence suggests that beta-endorphins are responsible in part for the euphoric or pleasant sensations that commonly occur in response to exercise (Basso and Suzuki, 2017). The binding of beta-endorphins to mu-opioid receptors on nerve cells suppresses the release of pain-promoting substances in the brain. Sauna use promotes robust increases in beta-endorphins (Jezova et al., 1985; Kukkonen-Harjula and Kauppinen, 1988; Vescovi et al., 1992).

Dynorphin is an opioid that is generally responsible for the sensation of dysphoria, a profound sense of unease or dissatisfaction. Dynorphin may also help mediate the body's response to heat, helping the body to cool (Xin et al., 1997). Heat activates neurons in the dorsal lateral parabrachial nucleus that express dynorphin (Tan and Knight, 2018). The activation of this thermosensory pathway elicits heat-defense responses in which the binding of dynorphin to kappa-opioid receptors triggers cellular events that promote pain and distress (Nakamura and Morrison, 2010). The heat stress caused by sauna use may promote dynorphin release, which may be responsible for the general sense of discomfort experienced during heat exposure. Interestingly, in a biological feedback response that occurs after dynorphin binds to the kappa-opioid receptor, mu-opioid receptors become more sensitized to beta-endorphins (Narita et al., 2003). Thus, repeated sauna use may sensitize mu-opioid receptors to endorphins.

4.5. Endocrine system

4.5.1. Growth hormone

Growth hormone secretion progressively declines with age and may contribute to sarcopenic obesity and frailty (Garcia et al., 2000). Sauna use promotes transient growth hormone release, which varies according to time, temperature, and frequency of exposure. For example, two 20-minute sauna sessions at 80 °C (176 °F) separated by a 30-minute cooling period elevated growth hormone levels 2-fold over baseline, but two 15-minute sauna sessions at 100 °C (212 °F) dry heat separated by a 30-minute cooling period resulted in a 5-fold increase in growth hormone (Hannuksela and Ellahham, 2001; Kukkonen-Harjula et al., 1989). Interestingly, repeated exposure to whole-body heat treatment through sauna use has an even more profound effect on boosting growth hormone immediately afterward: Seventeen men and women who were exposed to two 1-h sauna sessions at 80 °C (176 °F) dry heat (typical Finnish-style sauna) per day for 7 days exhibited a 16-fold increase in growth hormone levels by the third day (Leppaluoto et al., 1986). The growth hormone effects generally persisted for a few hours post-sauna (Hannuksela and Ellahham, 2001). It is noteworthy, however, that sauna use and exercise work synergistically to significantly elevate growth hormone when used together (Ftaiti et al., 2008).

4.6. Immune function and respiratory infection

A prominent feature of aging is impaired immune function. Evidence suggests that HSPs play critical roles in preserving immunological resilience. They serve as endogenous danger signals, facilitate the activities of antigen-presenting cells, bind pathogen-associated molecular pattern molecules, and modulate immune cell signaling, thus regulating aspects of both the innate and adaptive immune response (Osterloh and Breloer, 2008).

Sauna use is associated with reduced risk of developing certain chronic or acute respiratory illnesses, including pneumonia (Kunutsor et al., 2017). Findings from the KIHD studies indicate that among men who reported using the sauna 2–3 times per week, the risk of developing pneumonia was 27% lower than among men who reported using the sauna only 1 time per week or not at all. The risk of developing pneumonia among men who reported using the sauna 4–7 times per week was 41% lower than those who reported using the sauna only 1 time per week or not at all (Kunutsor et al., 2017).

Evidence suggests that both traditional Finnish-style sauna use and waon therapy elicit improvements in respiratory function in men with obstructive pulmonary disease (Cox et al., 1989; Umehara et al., 2008). In addition, sauna bathing demonstrates effectiveness in reducing the incidence of common colds. When 25 healthy adults used the sauna 1–2 times per week for 6 months, participants experienced fewer colds than a control group that did not use the sauna or other hyperthermic treatments. It is noteworthy that the protective effects of sauna use in this group did not manifest until the third month of treatment (Ernst et al., 1990).

The beneficial effects of sauna use on respiratory health may be related to decreases in oxidative stress and inflammation associated with hyperthermia or via direct effects on lung tissue (Sutkowy et al., 2014). For example, frequent sauna use may decrease pulmonary congestion and promote other aspects of healthy lung function, including vital capacity, tidal volume, minute ventilation, and forced expiratory volume (Laitinen et al., 1988).

Other findings point to the effects of sauna use on the immune system and heat shock proteins. A single session of Finnish-style sauna increased white blood cell, lymphocyte, neutrophil, and basophil counts in both trained and non-trained athletes (Pilch et al., 2013). Furthermore, as described above, heat stress promotes the production of heat shock proteins, such as HSP70. Maximal HSP70 protein levels in human lung epithelial cells demonstrate a linear relationship with heat exposure, increasing approximately 50% per degree Celsius at a range between 37 °C and 41 °C (98.6 °F and 105 °F) (Singh and Hasday, 2013). Increasing evidence suggests that certain HSPs play roles in both innate and adaptive immunity (Wallin et al., 2002). For example, HSPs can directly stimulate innate immune responses, such as the maturation and activation of dendritic cells and the activation of natural killer cells, suggesting there is a direct role for HSPs in regulating the innate immune response (Wallin et al., 2002). Cellular release of HSP70 can stimulate innate immune responses via feedback mechanisms involving toll-like receptors 2 and 4 (Singh and Hasday, 2013).

4.7. Physical fitness

Physical fitness is a critical component of human health and an independent predictor of mortality (Park et al., 2012). Multiple performance- and health-related measures are determinants of physical fitness, including cardiorespiratory fitness; musculoskeletal strength and endurance; flexibility; and body composition (Wilder et al., 2006), but these attributes typically decline with aging. For example, maximal oxygen consumption (VO2 max) declines approximately 10% per decade of life, regardless of activity level (Hawkins and Wiswell, 2003).

Maintaining physical fitness in older adults is associated with preserved cognitive function, reduced frailty, and overall improved quality of life (Deary et al., 2006; Jeoung and Lee, 2015; Navarrete-Villanueva et al., 2021; Park et al., 2012; Takata et al., 2010). Heat stress from sauna use may modulate improvements in physical fitness by increasing cardiorespiratory fitness and endurance and preserving muscle mass.

4.7.1. Increased endurance

A small intervention study investigated the effects of repeat sauna use on endurance and other physiological effects in 6 male distance runners. The findings showed that one 30-minute sauna session twice a week for 3 weeks post-workout increased the time that it took for the study participants to run until exhaustion by 32% compared to their baseline (Scoon et al., 2007). These endurance improvements were accompanied by a 7.1% increase in plasma volume and a 3.5% increase in erythrocytes (Scoon et al., 2007). During exercise, erythrocytes transport oxygen from the lungs to the body's tissues and deliver carbon dioxide to the lungs for expiration. Increases in erythrocyte levels may facilitate these processes and improve endurance.

4.7.2. Improved cardiovascular and thermoregulatory function

Regular sauna use improves cardiovascular and thermoregulatory mechanisms during endurance exercise via heat acclimation. During exercise, core body temperature increases, attenuating endurance and accelerating exhaustion. Heat acclimation induces complex physiological adaptations that improve thermoregulation, attenuate physiological strain, and enhance athletic performance in hot environments. These adaptations are mediated via improved cardiovascular and thermoregulatory mechanisms that reduce the deleterious effects associated with elevated core body temperature, optimizing the body for subsequent increases in core body temperature during future exercise.

In a small study involving 9 female athletes who sat for 20 min per day for 5 days in a hot environment (50 °C [122 °F], in low humidity) wearing a sauna suit to replicate sauna conditions, the women experienced thermoregulatory and cardiovascular improvements as well as reduced perceived strain compared to a control group (Mee et al., 2018). Another randomized controlled trial found that endurance training in a sauna suit led to improved performance and respiratory measures, including VO2max. The authors speculated that the improved performance time for the sauna suit group was due to improved VO2max and increased capacity for thermoregulation. For example, they noted that sweat rate during a heated 5 km time trial increased in the post-intervention group but not the control group (Van de Velde et al. 2017).

Another investigation gauged the efficacy of supplementing normal endurance training with intermittent post-exercise sauna bathing in 20 trained university athletes between the ages of 18 and 22 years. Participants completed 30-minute sauna sessions at 101°–108 °C (214°–226 °F)

3 times per week for 3 weeks, commencing within approximately 5 min of engaging in low-intensity, continuous outdoor exercise. Heat tolerance tests revealed that the sauna users' heart rate decreased 11 beats/min; skin temperature decreased 0.8 °C (1.4 °F); and peak rectal temperature decreased 0.2 °C (0.36 °F), compared to non-sauna users. Sauna users also experienced improvements in VO2max and speed. Four additional weeks of sauna exposure elicited changes in rectal temperature only (0.1 °C, 1.8 °F) (Kirby et al., 2020).

Improvements in thermoregulatory function are commonly observed following heat acclimation. Heat exposure activates the sympathetic nervous system, increasing peripheral blood flow and the sweat rate to dissipate core body heat. After acclimation, sweating occurs at a lower core temperature and the sweat rate is maintained for a longer period (Costa et al., 2014). As previously described, heat acclimation also increases plasma volume and stroke volume (Costa et al., 2014; Kukkonen-Harjula et al., 1989). This results in reduced cardiovascular strain and lowered heart rate for the same given workload (Costa et al., 2014). These cardiovascular improvements have been shown to enhance endurance in both highly trained and untrained individuals (Costa et al., 2014; Garrett et al., 2012; Kukkonen-Harjula et al., 1989).

A single exposure to heat stress from a sauna also increased blood flow to exercising muscles. One study found that a hand grip exercise performed in a sauna at 65 °C to 75 °C (149 °F to 167 °F) resulted in a 2-fold increase in blood flow in both the exercising and non-exercising forearm compared to performing the exercise at room temperature (Smolander and Louhevaara, 1992).

4.7.3. Muscle mass maintenance

Muscle loss occurs during the aging process but can also result from disease or trauma. Although exercise can help combat muscle loss, some medical conditions or physical limitations can make exercise difficult or even impossible. Whole-body hyperthermia may preserve or increase muscle mass and may also increase mitochondrial biogenesis. A small study in healthy young individuals found that two 60-minute sessions of whole-body hyperthermia at 44 °C to 50 °C (111 °F to 122 °F) and 50% humidity, separated by one week, led to increased activity of the Akt/mTOR biological pathway, a critical regulator in maintaining skeletal muscle mass. It also increased the expression of HSPs and Nrf2, indicative of mitochondrial biogenesis (Ihsan et al., 2020).

Muscular atrophy also commonly occurs with muscle immobilization or disuse following injuries. Atrophy induces substantial strength losses, especially during the first week of immobilization or disuse, due to reduced protein synthesis and increased protein degradation (Alves et al., 2013). Maintaining muscle mass requires balancing new protein synthesis with existing protein degradation. While new protein synthesis accompanies muscle use during exercise, protein degradation can occur during both muscle use and disuse. Of critical importance, therefore, is net protein synthesis. Heat acclimation, which can be achieved through sauna use, may reduce the amount of protein degradation that occurs during disuse by increasing expression of HSPs, reducing oxidative damage, and promoting release of growth hormone (Hannuksela and Ellahham, 2001; Kokura et al., 2007; Naito et al., 2000; Selsby et al., 2007). Maintaining positive net protein synthesis also has special relevance for recovery from injury since injury can tip the balance toward protein degradation and away from protein synthesis in the muscles, promoting muscle atrophy.

A small intervention study in humans found that daily heat treatments applied locally to muscle during 10 days of immobilization prevented the loss of mitochondrial function, increased HSP levels, and attenuated skeletal muscle atrophy by 37% compared to a sham treatment group (Hafen et al., 2019). These results have been replicated in animal studies. For example, when rats received whole-body hyperthermia at 41 °C (105.8 °F) for 30 min or 60 min, hindlimb muscle atrophy during disuse decreased by 20% or 32%, respectively (Naito et al., 2000; Selsby and Dodd, 2005). In another rodent study that investigated the effects of heat stress, a 30-minute intermittent hyperthermic treatment at 41 °C for 7 days induced a robust expression of HSPs (including HSP32, HSP25, and HSP72) in muscle, correlating with 30% more muscle regrowth than a control group subsequent to a week of immobilization (Naito et al., 2000; Selsby et al., 2007). This HSP induction can persist for up to 48 h after heat shock (Selsby et al., 2007). Heat acclimation causes a higher basal expression of HSPs (even when not exercising) and a more robust induction upon elevation in core body temperature (such as during exercise) (Kuennen et al., 2011; Moseley, 1997; Yamada et al., 2007). Heat shock proteins, described previously, can prevent muscle protein damage by directly scavenging reactive oxygen species and by supporting cellular antioxidant capacity through their effects on maintaining the endogenous antioxidant glutathione (Naito et al., 2000; Selsby et al., 2007). In addition, HSPs can repair misfolded, damaged proteins, thereby ensuring proteins maintain their proper structure and function (Naito et al., 2000; Selsby et al., 2007).

Furthermore, exposing mouse myoblasts to 42 °C (106 °F) for 30 min enhanced the activity of transcription factors involved in myogenesis (Obi et al., 2019). This may have special relevance for slowing age-related sarcopenia, a progressive condition characterized by loss of skeletal muscle mass and strength and a leading cause of functional decline and loss of independence in older adults.

5. Sauna bathing concerns

5.1. Male fertility

Heat exposure has notable, but reversible, effects on male sperm and fertility measures. In a study involving 10 healthy men who underwent two 15-minute sauna sessions at 80 °C to 90 °C (176 °F to 194 °F) every week for 3 months, the men experienced reduced sperm counts and motility. These measures returned to normal, however, within 6 months of sauna use cessation (Garolla et al., 2013).

5.2. Special populations

5.2.1. Pregnant women

Some central nervous system birth defects, such as anencephaly and spina bifida, are linked with exposure to extreme heat during pregnancy. However, in Finland, where the majority of women practice sauna bathing at least once a week throughout their pregnancies, the incidence of anencephaly is the lowest in the world (Rapola et al., 1978). Similarly, observational studies conducted in Finland and the United States showed no links between sauna use and higher incidence of cardiovascular malformations, the most common form of birth defects (Kukkonen-Harjula and Kauppinen, 2006).

The suggested teratogenic threshold for core body temperature in pregnant women is 39.0 °C (102.2 °F) (Graham et al., 1998). A systematic review of 12 studies investigated the effects of heat stress from exercise (land-based or water immersion) or passive modalities (hot water bathing or sauna use) among 347 pregnant women. Among those engaging in land-based or water immersion exercise, the highest mean core body temperatures were 38.3 °C (100.9 °F) and 37.5 °C (99.5 °F), respectively. Among women engaging in hot water bathing or sauna use, the highest mean core body temperatures were 36.9 °C (98.4 °F) and 37.6 °C (99.7 °F), respectively. The investigators concluded that exercise and passive heat modalities did not increase core body temperatures to teratogenic levels if performed within the following parameters: land-based exercise for up to 35 min at 80% to 90% of maximum heart rate in 25 °C (77 °F) and 45% relative humidity (RH); water immersion exercise at temperatures less than or equal to 33.4 °C (92.1 °F) for up to 45 min; or sitting in hot baths (40 °C; 104 °F) or hot, low humidity saunas (70 °C; 158 °F; 15% RH) for up to 20 min (Ravanelli et al., 2019). Evidence indicates that pregnant women with toxemia exhibit increased resistance to blood flow in the uterine artery, potentially compromising fetal health, and should exercise caution when using the sauna (Kukkonen-Harjula and Kauppinen, 2006). Women should consult with their physician during pregnancy regarding sauna use.

5.2.2. Children

Children have less efficient thermoregulatory mechanisms than adults due to critical differences in their anatomy and physiology. In particular, they have lower sweat rates than adults, which can compromise their ability to dissipate body heat through evaporation (Gomes et al., 2013). Whether healthy children are more vulnerable to hyperthermia has been called into question, however (Rowland, 2008; Smith, 2019). Conversely, children with sinoatrial node disorders may be at greater risk of fainting during the cool-down phase after sauna bathing due to the sudden drop in blood pressure that often accompanies cooling (Jokinen and Valimaki, 1991).

5.3. Other factors and contraindications

The sauna is generally well-tolerated and safe for most healthy individuals as well as for those with stable heart disease. Several studies have shown that individuals with certain types of cardiovascular disease may experience improvements in their symptoms and disease status with sauna use (Hussain and Cohen, 2018). Because many of the physiological responses to heat stress from sauna bathing are similar to moderate aerobic activity, using the sauna may be especially beneficial for individuals with various injuries and disabilities such as sports injury, osteoarthritis, spinal cord injury (in the absence of sweat impairment), or aging, or those who cannot participate in regular physical activity for extended periods. Sauna poses little risk of cardiovascular complications in healthy adults, however (Vuori, 1988).

Some contraindications for sauna use have been identified, including alcohol use, hypotension (especially in older adults), recent myocardial infarction, unstable angina pectoris, severe aortic stenosis (Eisalo and Luurila, 1988; Luurila, 1992), and among individuals with altered or reduced sweat function, which can occur with autoimmune disorders, spinal cord injury, neurological disorders, and in young children (Saari et al., 2009; Shibasaki et al., 1997; Swinn et al., 2003; Trbovich et al., 2020). Decompensated heart failure and cardiac arrhythmia are relative contraindications. Sauna use in patients with a history of stroke or transient ischemic attacks has not been studied, so it should be avoided until the condition stabilizes (Hannuksela and Ellahham, 2001). Individuals with acute illness accompanied by fever or those with inflammatory skin conditions should avoid sauna use (Kukkonen-Harjula and Kauppinen, 2006). Individuals taking any kind of medication, whether prescribed or over-the-counter, should consult a physician before sauna use (Kukkonen-Harjula and Kauppinen, 2006).

5.4. Hydration and electrolytes

Proper hydration and electrolyte balance are critical to maintain the body's fluid balance and to promote normal muscle contractility and nerve function. As described above, approximately 0.5 kg of fluid is lost as sweat during a single sauna session. Sweat loss rates may vary according to body composition, with higher body mass correlating with greater losses (Podstawski et al., 2014). Accompanying the loss in fluid is loss of electrolytes, especially sodium, chloride, potassium, magnesium, and calcium (Sawka and Montain, 2000). Skeletal muscle cramps and fatigue are associated with dehydration and electrolyte deficits. Sauna users should take care to drink sufficient fluids prior to and after sauna sessions and should consume electrolyte-rich foods post-sauna use, such as cooked spinach, avocado, tomatoes, fish, nuts, and seeds (Rodriguez et al., 2009). Individuals who limit their caloric intake, eliminate 1 or more food groups from their diet, adhere to severe weight-loss practices, or eat unbalanced diets that are low in micronutrients may require supplements (Rodriguez et al., 2009). Alcohol consumption before or during sauna use can cause severe dehydration, hypotension, arrhythmia, and possibly embolic stroke and should be avoided (Hannuksela and Ellahham, 2001).

6. Other heat stress modalities

Other strategies for elevating core body temperature such as the use of hot-water blankets, hyperthermic baths, heating coils, or specialized lamps that emit infrared-A radiation in a confined area or chamber may also have favorable effects on the cardiovascular and central nervous systems. Hot water immersion, in particular, elicits beneficial effects on several markers of cardiac health (Tei et al., 1995). For example, hot water bathing more than 5 times per week was associated with lower biomarkers of atherosclerosis and lower markers of cardiac loading, a measure of cardiac function. The temperature and frequency of hot water baths had dose-dependent effects on improving biomarkers of cardiac health (Kohara et al., 2018). Hot baths have been shown to increase heat shock proteins, a biomarker for heat stress. One study demonstrated that waist-down immersion in a 40 °C (104 °F) hot bath for 1 h increased HSP70 (Faulkner et al., 2017). Hot baths also elicit favorable effects on the brain, including increased cerebral blood flow, particularly in the frontal lobe (Watanabe and Yorizumi, 1997). Furthermore, a randomized controlled trial found that hot water baths for 8 weeks had a moderate but significant effect on improving depressive symptoms in participants with depressive disorder compared to placebo treatment (Naumann et al., 2017). Taken together, these data suggest that hot water baths may have positive effects on health.

7. Conclusions

Sauna bathing is associated with many health benefits, from cardiovascular and cognitive health to physical fitness and muscle maintenance. It is generally considered safe for healthy adults and may be safe for special populations with appropriate medical supervision. Heat stress via sauna use elicits hormetic responses driven by molecular mechanisms that protect the body from damage, similar to those elicited by moderate- to vigorous-intensity exercise, and may offer a means to forestall the effects of aging and extend healthspan.

CRediT authorship contribution statement

Rhonda P. Patrick, Ph.D.: Conceptualization, Investigation, Writing - Original draft preparation; Writing - Reviewing and editing, Resources, Supervision; Teresa L. Johnson: Investigation, Writing - Original draft preparation; Writing - Reviewing and editing.

Declaration of competing interest

Rhonda Patrick, Ph.D., is cofounder of FoundMyFitness, LLC, and frequently lectures on the science of sauna as a potentially healthful modality through podcasts, videos, and articles published on foundmyfitness.com. Teresa L. Johnson, M.S.P.H., M.A., R.D., is the founder and president of TLJ Communications, LLC, a provider of science writing and health communications. Neither Dr. Patrick nor Ms. Johnson profit from the sale of saunas nor do they retain any ownership stake or other formal relationship with any businesses involved in or affiliated with sauna manufacture or commercialization.

Acknowledgements

The authors wish to acknowledge Daniel Patrick for his comments on the manuscript and Alison Guidry Gates and Dagmar Bouwer for their assistance on the figures presented in this publication.

Funding

Rhonda P. Patrick, Ph.D. and Teresa L. Johnson receive funding from FoundMyFitness.com, a science journalism website.

References

Acharya, U.R., Joseph, K.P., Kannathal, N., Lim, C.M., Suri, J.S., 2006. Heart rate variability: a review. Med. Biol. Eng. Comput. 44, 1031–1051.

Ahmed, S.T., Ivashkiv, L.B., 2000. Inhibition of IL-6 and IL-10 signaling and stat activation by inflammatory and stress pathways. J. Immunol. 165, 5227–5237.

Alves, J., Leal-Cardoso, J., Santos-Junior, F., Carlos, P., Silva, R., Lucci, C., Báo, S., Ceccatto, V., Barbosa, R., 2013. Limb immobilization alters functional electrophysiological parameters of sciatic nerve. Braz. J. Med. Biol. Res. 46, 715–721.

Amorim, F.T., Fonseca, I.T., Machado-Moreira, C.A., Magalhaes Fde, C., 2015. Insights into the role of heat shock protein 72 to whole-body heat acclimation in humans. Temperature (Austin) 2, 499–505.

Basso, J.C., Suzuki, W.A., 2017. The effects of acute exercise on mood, cognition, neurophysiology, and neurochemical pathways: a review. Brain Plast 2, 127–152.

Beever, R., 2009. Far-infrared saunas for treatment of cardiovascular risk factors: summary of published evidence. Can. Fam. Physician 55, 691–696.

Blum, N., Blum, A., 2007. Beneficial effects of sauna bathing for heart failure patients. Exp. Clin. Cardiol. 12, 29–32.

Brunt, V.E., Minson, C.T., 2021. Heat therapy: mechanistic underpinnings and applications to cardiovascular health. J. Appl. Physiol. 1985 (130), 1684–1704.

Buttar, H.S., Li, T., Ravi, N., 2005. Prevention of cardiovascular diseases: role of exercise, dietary interventions, obesity and smoking cessation. Exp. Clin. Cardiol. 10, 229–249.

Cheng, Y., LeGall, T., Oldfield, C.J., Dunker, A.K., Uversky, V.N., 2006. Abundance of intrinsic disorder in protein associated with cardiovascular disease. Biochemistry 45, 10448–10460.

Claas, S.A., Arnett, D.K., 2016. The role of healthy lifestyle in the primordial prevention of cardiovascular disease. Curr. Cardiol. Rep. 18, 56.

Costa, R.J., Crockford, M.J., Moore, J.P., Walsh, N.P., 2014. Heat acclimation responses of an ultra-endurance running group preparing for hot desert-based competition. Eur. J. Sport Sci. 14 (Suppl. 1), S131–S141.

Costello, J.T., Rendell, R.A., Furber, M., Massey, H.C., Tipton, M.J., Young, J.S., Corbett, J., 2018. Effects of acute or chronic heat exposure, exercise and dehydration on plasma cortisol, IL-6 and CRP levels in trained males. Cytokine 110, 277–283.

Cox, N.J., Oostendorp, G.M., Folgering, H.T., van Herwaarden, C.L., 1989. Sauna to transiently improve pulmonary function in patients with obstructive lung disease. Arch. Phys. Med. Rehabil. 70, 911–913.

Deary, I.J., Whalley, L.J., Batty, G.D., Starr, J.M., 2006. Physical fitness and lifetime cognitive change. Neurology 67, 1195–1200.

Dinan, T.G., 2009. Inflammatory markers in depression. Current opinion in psychiatry 22, 32–36.

Ehrenfried, J.A., Evers, B.M., Chu, K.U., Townsend Jr., C.M., Thompson, J.C., 1996. Caloric restriction increases the expression of heat shock protein in the gut. Ann. Surg. 223, 592–597.

Eisalo, A., Luurila, O.J., 1988. The finnish sauna and cardiovascular diseases. Ann. Clin. Res. 20, 267–270.

Ely, B.R., Clayton, Z.S., McCurdy, C.E., Pfeiffer, J., Minson, C.T., 2018. Meta-inflammation and cardiometabolic disease in obesity: can heat therapy help? Temperature (Austin) 5, 9–21.

Ernst, E., Pecho, E., Wirz, P., Saradeth, T., 1990. Regular sauna bathing and the incidence of common colds. Ann. Med. 22, 225–227.

Faulkner, S.H., Jackson, S., Fatania, G., Leicht, C.A., 2017. The effect of passive heating on heat shock protein 70 and interleukin-6: a possible treatment tool for metabolic diseases? Temperature (Austin) 4, 292–304.

Fortney, S.M., Miescher, E., 1994. Changes in Plasma Volume During Heat Exposure in Young and Older Men. Fluid Replacement and Heat Stress. National Academies Press, US. https://www. ncbi. nlm. nih. gov/books/NBK231117.

Franciosi, S., Perry, F.K., Roston, T.M., Armstrong, K.R., Claydon, V.E., Sanatani, S., 2017. The role of the autonomic nervous system in arrhythmias and sudden cardiac death. Auton. Neurosci. 205, 1–11.

Ftaiti, F., Jemni, M., Kacem, A., Zaouali, M.A., Tabka, Z., Zbidi, A., Grelot, L., 2008. Effect of hyperthermia and physical activity on circulating growth hormone. Appl Physiol Nutr Metab 33, 880–887.

Gabay, C., 2006. Interleukin-6 and chronic inflammation. Arthritis Res. Ther. 8 (Suppl. 2), S3.

Garcia, J.M., Merriam, G.R., Kargi, A.Y., 2000. In: Feingold, K.R., Anawalt, B., Boyce, A., Chrousos, G., de Herder, W.W., Dungan, K., Grossman, A., Hershman, J.M., Hofland, J., Kaltsas, G., Koch, C., Kopp, P., Korbonits, M., McLachlan, R., Morley, J. E., New, M., Purnell, J., Singer, F., Stratakis, C.A., Trence, D.L., Wilson, D.P. (Eds.), Growth Hormone in Aging. Endotext, South Dartmouth (MA).

Garolla, A., Torino, M., Sartini, B., Cosci, I., Patassini, C., Carraro, U., Foresta, C., 2013. Seminal and molecular evidence that sauna exposure affects human spermatogenesis. Hum. Reprod. 28, 877–885.

Garrett, A.T., Creasy, R., Rehrer, N.J., Patterson, M.J., Cotter, J.D., 2012. Effectiveness of short-term heat acclimation for highly trained athletes. Eur. J. Appl. Physiol. 112, 1827–1837.

Gayda, M., Paillard, F., Sosner, P., Juneau, M., Garzon, M., Gonzalez, M., Belanger, M., Nigam, A., 2012. Effects of sauna alone and postexercise sauna baths on blood pressure and hemodynamic variables in patients with untreated hypertension. J. Clin. Hypertens. 14, 553–560.

Genuis, S.J., Birkholz, D., Rodushkin, I., Beesoon, S., 2011. Blood, urine, and sweat (BUS) study: monitoring and elimination of bioaccumulated toxic elements. Arch. Environ. Contam. Toxicol. 61, 344–357.

Gomes, L.H.L., Carneiro-Júnior, M.A., Marins, J.C.B., 2013. Thermoregulatory responses of children exercising in a hot environment. Rev. Paul. Pediatr. 31, 104–110.

Goto, S., Radak, Z., 2009. Hormetic effects of reactive oxygen species by exercise: a view from animal studies for successful aging in human. Dose Response 8, 68–72.

Graham Jr., J.M., Edwards, M.J., Edwards, M.J., 1998. Teratogen update: gestational effects of maternal hyperthermia due to febrile illnesses and resultant patterns of defects in humans. Teratology 58, 209–221.

Gravel, H., Behzadi, P., Cardinal, S., Barry, H., Neagoe, P.E., Juneau, M., Nigam, A., Sirois, M.G., Gagnon, D., 2021. Acute vascular benefits of finnish sauna bathing in patients with stable coronary artery disease. The Canadian journal of cardiology 37, 493–499.

Gryka, D., Pilch, W., Szarek, M., Szygula, Z., Tota, L., 2014. The effect of sauna bathing on lipid profile in young, physically active, male subjects. Int. J. Occup. Med. Environ. Health 27, 608–618.

Hafen, P.S., Preece, C.N., Sorensen, J.R., Hancock, C.R., Hyldahl, R.D., 2018. Repeated exposure to heat stress induces mitochondrial adaptation in human skeletal muscle. J. Appl. Physiol. 1985 (125), 1447–1455.

Hafen, P.S., Abbott, K., Bowden, J., Lopiano, R., Hancock, C.R., Hyldahl, R.D., 2019. Daily heat treatment maintains mitochondrial function and attenuates atrophy in human skeletal muscle subjected to immobilization. J. Appl. Physiol. 1985 (127), 47–57.

Hage, F.G., 2014. C-reactive protein and hypertension. J. Hum. Hypertens. 28, 410–415.

Hannuksela, M.L., Ellahham, S., 2001. Benefits and risks of sauna bathing. Am. J. Med. 110, 118–126.

Hanusch, K.U., Janssen, C.H., Billheimer, D., Jenkins, I., Spurgeon, E., Lowry, C.A., Raison, C.L., 2013. Whole-body hyperthermia for the treatment of major depression: associations with thermoregulatory cooling. Am. J. Psychiatry 170, 802–804.

Hasan, J., Karvonen, M.J., Piironen, P., 1966. Special review. I. Physiological effects of extreme heat as studied in the finnish "sauna" bath. Am. J. Phys. Med. 45, 296–314 contd.

Hautala, A.J., Kiviniemi, A.M., Tulppo, M.P., 2009. Individual responses to aerobic exercise: the role of the autonomic nervous system. Neurosci. Biobehav. Rev. 33, 107–115.

Hawkins, S., Wiswell, R., 2003. Rate and mechanism of maximal oxygen consumption decline with aging: implications for exercise training. Sports Med. 33, 877–888.

Hays, A.G., Sacco, R.L., Rundek, T., Sciacca, R.R., Jin, Z., Liu, R., Homma, S., Di Tullio, M.R., 2006. Left ventricular systolic dysfunction and the risk of ischemic stroke in a multiethnic population. Stroke 37, 1715–1719.

Heydari, A.R., Wu, B., Takahashi, R., Strong, R., Richardson, A., 1993. Expression of heat shock protein 70 is altered by age and diet at the level of transcription. Mol. Cell. Biol. 13, 2909–2918.

Hillebrand, S., Gast, K.B., de Mutsert, R., Swenne, C.A., Jukema, J.W., Middeldorp, S., Rosendaal, F.R., Dekkers, O.M., 2013. Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: meta-analysis and dose–response meta-regression. EP Europace 15, 742–749.

Hoekstra, S.P., Bishop, N.C., Leicht, C.A., 2020. Elevating body termperature to reduce low-grade inflammation: a welcome strategy for those unable to exercise? Exerc. Immunol. Rev. 26, 42–55.

Hoffmann, G., Hartel, M., Mercer, J.B., 2016. Heat for wounds - water-filtered infrared-A (wIRA) for wound healing - a review. Ger. Med. Sci. 14, Doc08.

Hunt, A.P., Minett, G.M., Gibson, O.R., Kerr, G.K., Stewart, I.B., 2019. Could heat therapy be an effective treatment for Alzheimer's and Parkinson's diseases? A narrative review. Front. Physiol. 10, 1556.

Hunt, S.A., Baker, D.W., Chin, M.H., Cinquegrani, M.P., Feldman, A.M., Francis, G.S., Ganiats, T.G., Goldstein, S., Gregoratos, G., Jessup, M.L., Noble, R.J., Packer, M., Silver, M.A., Stevenson, L.W., Gibbons, R.J., Antman, E.M., Alpert, J.S., Faxon, D.P., Fuster, V., Gregoratos, G., Jacobs, A.K., Hiratzka, L.F., Russell, R.O., Smith Jr., S.C., American College of Cardiology/American Heart Association Task Force on Practice, G., International Society for, H., Lung, T., Heart Failure Society of, A, 2001. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. Circulation 104, 2996–3007.

Hussain, J., Cohen, M., 2018. Clinical effects of regular dry sauna bathing: a systematic review. Evid. Based Complement. Alternat. Med. 2018, 1857413.

Iadecola, C., 2004. Neurovascular regulation in the normal brain and in Alzheimer's disease. Nat Rev Neurosci 5, 347–360.

Iguchi, M., Littmann, A.E., Chang, S.H., Wester, L.A., Knipper, J.S., Shields, R.K., 2012. Heat stress and cardiovascular, hormonal, and heat shock proteins in humans. J. Athl. Train. 47, 184–190.

Ihsan, M., Deldicque, L., Molphy, J., Britto, F., Cherif, A., Racinais, S., 2020. Skeletal muscle signaling following whole-body and localized heat exposure in humans. Front. Physiol. 11.

Imamura, M., Biro, S., Kihara, T., Yoshifuku, S., Takasaki, K., Otsuji, Y., Minagoe, S., Toyama, Y., Tei, C., 2001. Repeated thermal therapy improves impaired vascular endothelial function in patients with coronary risk factors. J. Am. Coll. Cardiol. 38, 1083–1088.

Janssen, C.W., Lowry, C.A., Mehl, M.R., Allen, J.J., Kelly, K.L., Gartner, D.E., Medrano, A., Begay, T.K., Rentscher, K., White, J.J., Fridman, A., Roberts, L.J., Robbins, M.L., Hanusch, K.U., Cole, S.P., Raison, C.L., 2016. Whole-body hyperthermia for the treatment of major depressive disorder: a randomized clinical trial. JAMA Psychiatry 73, 789–795.

Jeoung, B.J., Lee, Y.C., 2015. A study of relationship between frailty and physical performance in elderly women. J Exerc Rehabil 11, 215–219.
Jezova, D., Vigas, M., Tatar, P., Jurcovicova, J., Palat, M., 1985. Rise in plasma beta-endorphin and ACTH in response to hyperthermia in sauna. Horm. Metab. Res. 17, 693–694.
Ji, L.L., Dickman, J.R., Kang, C., Koenig, R., 2010. Exercise-induced hormesis may help healthy aging. Dose Response 8, 73–79.
Jia, D., Liu, J., 2010. Current devices for high-performance whole-body hyperthermia therapy. Expert Rev. Med. Devices 7, 407–423.
Jokinen, E., Valimaki, I., 1991. Children in sauna: electrocardiographic abnormalities. Acta Paediatr. Scand. 80, 370–374.
Kaeberlein, M., 2018. How healthy is the healthspan concept? Geroscience 40, 361–364.
Kauppinen, K., 1989. Sauna, shower, and ice water immersion. Physiological responses to brief exposures to heat, cool, and cold. Part II. Circulation. Arctic Med. Res. 48, 64–74.
Ketelhut, S., Ketelhut, R.G., 2019. The blood pressure and heart rate during sauna bath correspond to cardiac responses during submaximal dynamic exercise. Complement. Ther. Med. 44, 218–222.
Kihara, T., Biro, S., Imamura, M., Yoshifuku, S., Takasaki, K., Ikeda, Y., Otuji, Y., Minagoe, S., Toyama, Y., Tei, C., 2002. Repeated sauna treatment improves vascular endothelial and cardiac function in patients with chronic heart failure. J. Am. Coll. Cardiol. 39, 754–759.
Kihara, T., Biro, S., Ikeda, Y., Fukudome, T., Shinsato, T., Masuda, A., Miyata, M., Hamasaki, S., Otsuji, Y., Minagoe, S., 2004. Effects of repeated sauna treatment on ventricular arrhythmias in patients with chronic heart failure. Circ. J. 68, 1146–1151.
Kirby, N.V., Lucas, S.J.E., Armstrong, O.J., Weaver, S.R., Lucas, R.A.I., 2020. Intermittent post-exercise sauna bathing improves markers of exercise capacity in hot and temperate conditions in trained middle-distance runners. Eur. J. Appl. Physiol. 121, 621–635.
Kivimaki, M., Virtanen, M., Ferrie, J.E., 2015. The link between sauna bathing and mortality may be noncausal. JAMA Intern. Med. 175, 1718.
Kohara, K., Tabara, Y., Ochi, M., Okada, Y., Ohara, M., Nagai, T., Ohyagi, Y., Igase, M., 2018. Habitual hot water bathing protects cardiovascular function in middle-aged to elderly Japanese subjects. Sci. Rep. 8, 1–8.
Kojima, D., Nakamura, T., Banno, M., Umemoto, Y., Kinoshita, T., Ishida, Y., Tajima, F., 2018. Head-out immersion in hot water increases serum BDNF in healthy males. Int. J. Hyperth. 34, 834–839.
Kokura, S., Adachi, S., Manabe, E., Mizushima, K., Hattori, T., Okuda, T., Nakabe, N., Handa, O., Takagi, T., Naito, Y., Yoshida, N., Yoshikawa, T., 2007. Whole body hyperthermia improves obesity-induced insulin resistance in diabetic mice. Int. J. Hyperth. 23, 259–265.
Kuennen, M., Gillum, T., Dokladny, K., Bedrick, E., Schneider, S., Moseley, P., 2011. Thermotolerance and heat acclimation may share a common mechanism in humans. Am. J. Physiol. Regul. Integr. Comp. Physiol. 301, R524–R533.
Kukkonen-Harjula, K., Kauppinen, K., 1988. How the sauna affects the endocrine system. Ann. Clin. Res. 20, 262–266.
Kukkonen-Harjula, K., Kauppinen, K., 2006. Health effects and risks of sauna bathing. Int. J. Circumpolar Health 65, 195–205.
Kukkonen-Harjula, K., Oja, P., Laustiola, K., Vuori, I., Jolkkonen, J., Siitonen, S., Vapaatalo, H., 1989. Haemodynamic and hormonal responses to heat exposure in a Finnish sauna bath. Eur. J. Appl. Physiol. Occup. Physiol. 58, 543–550.
Kunutsor, S.K., Laukkanen, T., Laukkanen, J.A., 2017. Sauna bathing reduces the risk of respiratory diseases: a long-term prospective cohort study. Eur. J. Epidemiol. 32, 1107–1111.
Kunutsor, S.K., Khan, H., Laukkanen, T., Laukkanen, J.A., 2018. Joint associations of sauna bathing and cardiorespiratory fitness on cardiovascular and all-cause mortality risk: a long-term prospective cohort study. Ann. Med. 50, 139–146.
Kunutsor, S.K., Lavie, C.J., Laukkanen, J., 2021. Finnish sauna and COVID-19. Infez. Med. 29, 160–162.
Laitinen, L.A., Lindqvist, A., Heino, M., 1988. Lungs and ventilation in sauna. Ann. Clin. Res. 20, 244–248.
Laukkanen, J.A., Laukkanen, T., 2018. Sauna bathing and systemic inflammation. Eur. J. Epidemiol. 33, 351–353.
Laukkanen, J.A., Laukkanen, T., Kunutsor, S.K., 2018a. Cardiovascular and other health benefits of sauna bathing: a review of the evidence. Mayo Clin. Proc. 93, 1111–1121.
Laukkanen, J.A., Laukkanen, T., Kunutsor, S., 2019a. In reply-sauna bathing and healthy sweating. Mayo Clin. Proc. 94, 727–728.
Laukkanen, T., Khan, H., Zaccardi, F., 2015a. The link between sauna bathing and mortality may be noncausal-reply. JAMA Intern. Med. 175, 1719–1720.
Laukkanen, T., Khan, H., Zaccardi, F., Laukkanen, J.A., 2015b. Association between sauna bathing and fatal cardiovascular and all-cause mortality events. JAMA Intern. Med. 175, 542–548.
Laukkanen, T., Kunutsor, S., Kauhanen, J., Laukkanen, J.A., 2017. Sauna bathing is inversely associated with dementia and Alzheimer's disease in middle-aged Finnish men. Age Ageing 46, 245–249.
Laukkanen, T., Kunutsor, S.K., Zaccardi, F., Lee, E., Willeit, P., Khan, H., Laukkanen, J.A., 2018b. Acute effects of sauna bathing on cardiovascular function. J. Hum. Hypertens. 32, 129–138.
Laukkanen, T., Laukkanen, J.A., Kunutsor, S.K., 2018c. Sauna bathing and risk of psychotic disorders: a prospective cohort study. Med. Princ. Pract. 27, 562–569.
Laukkanen, T., Lipponen, J., Kunutsor, S.K., Zaccardi, F., Araújo, C.G.S., Mäkikallio, T. H., Khan, H., Willeit, P., Lee, E., Poikonen, S., 2019b. Recovery from sauna bathing favorably modulates cardiac autonomic nervous system. Complement. Ther. Med. 45, 190–197.
Leak, R.K., 2014. Heat shock proteins in neurodegenerative disorders and aging. J. Cell. Commun. Signal. 8, 293–310.
Lee, E., Laukkanen, T., Kunutsor, S.K., Khan, H., Willeit, P., Zaccardi, F., Laukkanen, J.A., 2018. Sauna exposure leads to improved arterial compliance: findings from a non-randomised experimental study. Eur. J. Prev. Cardiol. 25, 130–138.
Leimbach Jr., W.N., Wallin, B.G., Victor, R.G., Aylward, P.E., Sundlöf, G., Mark, A.L., 1986. Direct evidence from intraneural recordings for increased central sympathetic outflow in patients with heart failure. Circulation 73, 913–919.
Leppaluoto, J., Huttunen, P., Hirvonen, J., Vaananen, A., Tuominen, M., Vuori, J., 1986. Endocrine effects of repeated sauna bathing. Acta Physiol. Scand. 128, 467–470.
Li, Z., Jiang, W., Chen, Y., Wang, G., Yan, F., Zeng, T., Fan, H., 2020. Acute and short-term efficacy of sauna treatment on cardiovascular function: a meta-analysis. Eur. J. Cardiovasc. Nurs. 20, 96–105.
Lin, C.C., Yang, W.C., 2009. Prognostic factors influencing the patency of hemodialysis vascular access: literature review and novel therapeutic modality by far infrared therapy. J. Chin. Med. Assoc. 72, 109–116.
Lopez-Otin, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153, 1194–1217.
Luurila, O.J., 1992. The sauna and the heart. J. Intern. Med. 231, 319–320.
Lyon, M.S., Milligan, C., 2019. Extracellular heat shock proteins in neurodegenerative diseases: new perspectives. Neurosci. Lett. 711, 134462.
Maniam, J., Morris, M.J., 2010. Voluntary exercise and palatable high-fat diet both improve behavioural profile and stress responses in male rats exposed to early life stress: role of hippocampus. Psychoneuroendocrinology 35, 1553–1564.
Masuda, A., Nakazato, M., Kihara, T., Minagoe, S., Tei, C., 2005. Repeated thermal therapy diminishes appetite loss and subjective complaints in mildly depressed patients. Psychosom. Med. 67, 643–647.
Mattson, M.P., 2008. Hormesis defined. Ageing Res. Rev. 7, 1–7.
McCarty, M.F., Barroso-Aranda, J., Contreras, F., 2009. Regular thermal therapy may promote insulin sensitivity while boosting expression of endothelial nitric oxide synthase–effects comparable to those of exercise training. Med. Hypotheses 73, 103–105.
Mee, J.A., Peters, S., Doust, J.H., Maxwell, N.S., 2018. Sauna exposure immediately prior to short-term heat acclimation accelerates phenotypic adaptation in females. J. Sci. Med. Sport 21, 190–195.
Michaud, M., Balardy, L., Moulis, G., Gaudin, C., Peyrot, C., Vellas, B., Cesari, M., Nourhashemi, F., 2013. Proinflammatory cytokines, aging, and age-related diseases. J. Am. Med. Dir. Assoc. 14, 877–882.
Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16, 22–34.
Milligan, A.J., 1984. Whole-body hyperthermia induction techniques. Cancer Res. 44, 4869s–4872s.
Miyata, M., Tei, C., 2010. Waon therapy for cardiovascular disease: innovative therapy for the 21st century. Circ. J. 74, 617–621.
Mori, Y., Deguchi, A., Miwa, C., Shimasaki, H., Nakamura, T., Hamaguchi, M., Isshiki, H., 2017. Changes in core and skin temperatures, skin blood flow, and subjective responses during sauna at a radioactive spring. J. Jpn. Soc. Balneology Climatol. Phys. Med. 2311.
Moseley, P.L., 1997. Heat shock proteins and heat adaptation of the whole organism. J. Appl. Physiol. 1985 (83), 1413–1417.
Moura, C.S., Lollo, P.C.B., Morato, P.N., Amaya-Farfan, J., 2018. Dietary nutrients and bioactive substances modulate heat shock protein (HSP) expression: a review. Nutrients 10.
Naito, H., Powers, S.K., Demirel, H.A., Sugiura, T., Dodd, S.L., Aoki, J., 2000. Heat stress attenuates skeletal muscle atrophy in hindlimb-unweighted rats. J. Appl. Physiol. 1985 (88), 359–363.
Nakamura, K., Morrison, S.F., 2010. A thermosensory pathway mediating heat-defense responses. Proc. Natl. Acad. Sci. 107, 8848–8853.
Narita, M., Khotib, J., Suzuki, M., Ozaki, S., Yajima, Y., Suzuki, T., 2003. Heterologous mu-opioid receptor adaptation by repeated stimulation of kappa-opioid receptor: up-regulation of G-protein activation and antinociception. J. Neurochem. 85, 1171–1179.
Naumann, J., Grebe, J., Kaifel, S., Weinert, T., Sadaghiani, C., Huber, R., 2017. Effects of hyperthermic baths on depression, sleep and heart rate variability in patients with depressive disorder: a randomized clinical pilot trial. BMC Complement. Altern. Med. 17, 172.
Navarrete-Villanueva, D., Gomez-Cabello, A., Marin-Puyalto, J., Moreno, L.A., Vicente-Rodriguez, G., Casajus, J.A., 2021. Frailty and physical fitness in elderly people: a systematic review and meta-analysis. Sports Med. 51, 143–160.
Obi, S., Nakajima, T., Hasegawa, T., Nakamura, F., Sakuma, M., Toyoda, S., Tei, C., Inoue, T., 2019. Heat induces myogenic transcription factors of myoblast cells via transient receptor potential vanilloid 1 (Trpv1). FEBS Open Bio 9, 101–113.
Ohori, T., Nozawa, T., Ihori, H., Shida, T., Sobajima, M., Matsuki, A., Yasumura, S., Inoue, H., 2012. Effect of repeated sauna treatment on exercise tolerance and endothelial function in patients with chronic heart failure. Am. J. Cardiol. 109, 100–104.
Olin, J.W., White, C.J., Armstrong, E.J., Kadian-Dodov, D., Hiatt, W.R., 2016. Peripheral artery disease: evolving role of exercise, medical therapy, and endovascular options. J. Am. Coll. Cardiol. 67, 1338–1357.
Osterloh, A., Breloer, M., 2008. Heat shock proteins: linking danger and pathogen recognition. Med. Microbiol. Immunol. 197, 1–8.

Park, Y.-I., Lee, K.-Y., Kim, T.-I., Jeon, M.-H., Kim, D.-O., Kim, J.-H., 2012. The effects of exercise in the frail elderly. J. Korean Acad. Commun. Health Nurs. 23, 91–101.
Pawelec, G., Goldeck, D., Derhovanessian, E., 2014. Inflammation, ageing and chronic disease. Curr. Opin. Immunol. 29, 23–28.
Pedersen, B.K., 2013. Muscle as a secretory organ. Compr. Physiol. 3, 1337–1362.
Pedersen, B.K., Febbraio, M.A., 2008. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol. Rev. 88, 1379–1406.
Petersen, A.M., Pedersen, B.K., 2005. The anti-inflammatory effect of exercise. J. Appl. Physiol. 1985 (98), 1154–1162.
Pilch, W., Pokora, I., Szygula, Z., Palka, T., Pilch, P., Cison, T., Malik, L., Wiecha, S., 2013. Effect of a single finnish sauna session on white blood cell profile and cortisol levels in athletes and non-athletes. J Hum Kinet 39, 127–135.
Pilch, W., Szygula, Z., Palka, T., Pilch, P., Cison, T., Wiecha, S., Tota, L., 2014a. Comparison of physiological reactions and physiological strain in healthy men under heat stress in dry and steam heat saunas. Biol Sport 31, 145–149.
Pilch, W., Szygula, Z., Tyka, A., Palka, T., Lech, G., Cison, T., Kita, B., 2014b. Effect of 30-minute sauna sessions on lipid profile in young women. Med. Sportiva 18.
Pizzey, F.K., Smith, E.C., Ruediger, S.L., Keating, S.E., Askew, C.D., Coombes, J.S., Bailey, T.G., 2021. The effect of heat therapy on blood pressure and peripheral vascular function: a systematic review and meta-analysis. Exp. Physiol. 106, 1317–1334.
Podstawski, R., Boraczynski, T., Boraczynski, M., Choszcz, D., Mankowski, S., Markowski, P., 2014. Sauna-induced body mass loss in young sedentary women and men. Sci. World J. 2014, 307421.
Radak, Z., Chung, H.Y., Goto, S., 2005. Exercise and hormesis: oxidative stress-related adaptation for successful aging. Biogerontology 6, 71–75.
Radak, Z., Chung, H.Y., Koltai, E., Taylor, A.W., Goto, S., 2008b. Exercise, oxidative stress and hormesis. Ageing Res. Rev. 7, 34–42.
Radak, Z., Chung, H.Y., Goto, S., 2008a. Systemic adaptation to oxidative challenge induced by regular exercise. Free Radic. Biol. Med. 44, 153–159.
Radak, Z., Ishihara, K., Tekus, E., Varga, C., Posa, A., Balogh, L., Boldogh, I., Koltai, E., 2017. Exercise, oxidants, and antioxidants change the shape of the bell-shaped hormesis curve. Redox Biol. 12, 285–290.
Raison, C., 2017. 419. inflammation in treatment resistant depression: challenges and opportunities. Biol. Psychiatry 81, S171.
Rapola, J., Saxen, L., Granroth, G., 1978. Anencephaly and the sauna. Lancet 311, 1162.
Ravanelli, N., Casasola, W., English, T., Edwards, K.M., Jay, O., 2019. Heat stress and fetal risk. environmental limits for exercise and passive heat stress during pregnancy: a systematic review with best evidence synthesis. Br. J. Sports Med. 53, 799–805.
Raynes, R., Leckey Jr., B.D., Nguyen, K., Westerheide, S.D., 2012. Heat shock and caloric restriction have a synergistic effect on the heat shock response in a sir2.1-dependent manner in Caenorhabditis elegans. J. Biol. Chem. 287, 29045–29053.
Robins, H.I., Woods, J.P., Schmitt, C.L., Cohen, J.D., 1994. A new technological approach to radiant heat whole body hyperthermia. Cancer Lett. 79, 137–145.
Rodriguez, N.R., DiMarco, N.M., Langley, S., 2009. Position of the American Dietetic Association, Dietitians of Canada, and the American College of Sports Medicine: nutrition and athletic performance. J. Am. Diet. Assoc. 109, 509–527.
Romeyke, T., Scheuer, H.C., Stummer, H., 2015. Fibromyalgia with severe forms of progression in a multidisciplinary therapy setting with emphasis on hyperthermia therapy–a prospective controlled study. Clin. Interv. Aging 10, 69–79.
Roque, S., Correia-Neves, M., Mesquita, A.R., Palha, J.A., Sousa, N., 2009. Interleukin-10: a key cytokine in depression? Cardiovasc. Psychiatry Neurol. 2009, 187894.
Roth, G.A., Johnson, C., Abajobir, A., Abd-Allah, F., Abera, S.F., Abyu, G., Ahmed, M., Aksut, B., Alam, T., Alam, K., 2017. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J. Am. Coll. Cardiol. 70, 1–25.
Rowland, T., 2008. Thermoregulation during exercise in the heat in children: old concepts revisited. J. Appl. Physiol. 1985 (105), 718–724.
Saari, A., Tolonen, U., Paakko, E., Suominen, K., Jauhiainen, J., Sotaniemi, K.A., Myllyla, V.V., 2009. Sweating impairment in patients with multiple sclerosis. Acta Neurol. Scand. 120, 358–363.
Sandstrom, M.E., Madden, L.A., Taylor, L., Siegler, J.C., Lovell, R.J., Midgley, A., McNaughton, L., 2009. Variation in basal heat shock protein 70 is correlated to core temperature in human subjects. Amino Acids 37, 279–284.
Sawka, M.N., Montain, S.J., 2000. Fluid and electrolyte supplementation for exercise heat stress. Am. J. Clin. Nutr. 72, 564S–572S.
Scoon, G.S., Hopkins, W.G., Mayhew, S., Cotter, J.D., 2007. Effect of post-exercise sauna bathing on the endurance performance of competitive male runners. J. Sci. Med. Sport 10, 259–262.
Selsby, J.T., Dodd, S.L., 2005. Heat treatment reduces oxidative stress and protects muscle mass during immobilization. Am. J. Physiol. Regul. Integr. Comp. Physiol. 289, R134–R139.
Selsby, J.T., Rother, S., Tsuda, S., Pracash, O., Quindry, J., Dodd, S.L., 2007. Intermittent hyperthermia enhances skeletal muscle regrowth and attenuates oxidative damage following reloading. J. Appl. Physiol. 1985 (102), 1702–1707.
Senf, S.M., Dodd, S.L., McClung, J.M., Judge, A.R., 2008. Hsp70 overexpression inhibits NF-kappaB and Foxo3a transcriptional activities and prevents skeletal muscle atrophy. FASEB J. 22, 3836–3845.
Shibasaki, M., Inoue, Y., Kondo, N., Iwata, A., 1997. Thermoregulatory responses of prepubertal boys and young men during moderate exercise. Eur. J. Appl. Physiol. Occup. Physiol. 75, 212–218.
Shinsato, T., Miyata, M., Kubozono, T., Ikeda, Y., Fujita, S., Kuwahata, S., Akasaki, Y., Hamasaki, S., Fujiwara, H., Tei, C., 2010. Waon therapy mobilizes CD34+ cells and improves peripheral arterial disease. J. Cardiol. 56, 361–366.
Singh, I.S., Hasday, J.D., 2013. Fever, hyperthermia and the heat shock response. Int. J. Hyperth. 29, 423–435.
Singh, R., Kolvraa, S., Bross, P., Christensen, K., Bathum, L., Gregersen, N., Tan, Q., Rattan, S.I., 2010. Anti-inflammatory heat shock protein 70 genes are positively associated with human survival. Curr. Pharm. Des. 16, 796–801.
Smith, C.J., 2019. Pediatric thermoregulation: considerations in the face of global climate change. Nutrients 11.
Smolander, J., Kolari, P., 1985. Laser-doppler and plethysmographic skin blood flow during exercise and during acute heat stress in the sauna. Eur. J. Appl. Physiol. Occup. Physiol. 54, 371–377.
Smolander, J., Louhevaara, V., 1992. Effect of heat stress on muscle blood flow during dynamic handgrip exercise. Eur. J. Appl. Physiol. Occup. Physiol. 65, 215–220.
Sobajima, M., Nozawa, T., Ihori, H., Shida, T., Ohori, T., Suzuki, T., Matsuki, A., Yasumura, S., Inoue, H., 2013. Repeated sauna therapy improves myocardial perfusion in patients with chronically occluded coronary artery-related ischemia. Int. J. Cardiol. 167, 237–243.
Sobajima, M., Nozawa, T., Fukui, Y., Ihori, H., Ohori, T., Fujii, N., Inoue, H., 2015. Waon therapy improves quality of life as well as cardiac function and exercise capacity in patients with chronic heart failure. Int. Heart J. 56, 203–208.
Sohar, E., Shoenfeld, Y., Shapiro, Y., Ohry, A., Cabili, S., 1976. Effects of exposure to finnish sauna. Isr. J. Med. Sci. 12, 1275–1282.
Staib, J.L., Quindry, J.C., French, J.P., Criswell, D.S., Powers, S.K., 2007. Increased temperature, not cardiac load, activates heat shock transcription factor 1 and heat shock protein 72 expression in the heart. Am. J. Physiol. Regul. Integr. Comp. Physiol. 292, R432–R439.
Starkie, R.L., Hargreaves, M., Rolland, J., Febbraio, M.A., 2005. Heat stress, cytokines, and the immune response to exercise. Brain Behav. Immun. 19, 404–412.
Steenbergen, C., Frangogiannis, N.G., 2012. In: Ischemic Heart Disease, Muscle. Elsevier Inc, pp. 495–521.
Sutkowy, P., Wozniak, A., Boraczynski, T., Mila-Kierzenkowska, C., Boraczynski, M., 2014. The effect of a single Finnish sauna bath after aerobic exercise on the oxidative status in healthy men. Scand. J. Clin. Lab. Invest. 74, 89–94.
Swinn, L., Schrag, A., Viswanathan, R., Bloem, B.R., Lees, A., Quinn, N., 2003. Sweating dysfunction in Parkinson's disease. Mov. Disord. 18, 1459–1463.
Taggart, P., Parkinson, P., Carruthers, M., 1972. Cardiac responses to thermal, physical, and emotional stress. Br. Med. J. 3, 71–76.
Takata, Y., Ansai, T., Soh, I., Awano, S., Yoshitake, Y., Kimura, Y., Sonoki, K., Kagiyama, S., Yoshida, A., Nakamichi, I., Hamasaki, T., Torisu, T., Toyoshima, K., Takehara, T., 2010. Quality of life and physical fitness in an 85-year-old population. Arch. Gerontol. Geriatr. 50, 272–276.
Tan, C.L., Knight, Z.A., 2018. Regulation of body temperature by the nervous system. Neuron 98, 31–48.
Tei, C., Tanaka, N., 1996. Thermal vasodilation as a treatment of congestive heart failure: a novel approach. J. Cardiol. 27, 29–30.
Tei, C., Horikiri, Y., Park, J.-C., Jeong, J.-W., Chang, K.-S., Toyama, Y., Tanaka, N., 1995. Acute hemodynamic improvement by thermal vasodilation in congestive heart failure. Circulation 91, 2582–2590.
Tei, C., Shinsato, T., Miyata, M., Kihara, T., Hamasaki, S., 2007. Waon therapy improves peripheral arterial disease. J. Am. Coll. Cardiol. 50, 2169–2171.
Tei, C., Imamura, T., Kinugawa, K., Inoue, T., Masuyama, T., Inoue, H., Noike, H., Muramatsu, T., Takeishi, Y., Saku, K., Harada, K., Daida, H., Kobayashi, Y., Hagiwara, N., Nagayama, M., Momomura, S., Yonezawa, K., Ito, H., Gojo, S., Akaishi, M., Miyata, M., Ohishi, M., Investigators, W.-C.S., 2016. Waon therapy for managing chronic heart failure- results from a multicenter prospective randomized WAON-CHF study. Circ. J. 80, 827–834.
Thomas, K.N., van Rij, A.M., Lucas, S.J., Gray, A.R., Cotter, J.D., 2016. Substantive hemodynamic and thermal strain upon completing lower-limb hot-water immersion; comparisons with treadmill running. Temperature 3, 286–297.
Trbovich, M., Ford, A., Wu, Y., Koek, W., Wecht, J., Kellogg Jr., D., 2020. Correlation of neurological level and sweating level of injury in persons with spinal cord injury. J. Spinal Cord Med. 1–8.
Umehara, M., Yamaguchi, A., Itakura, S., Suenaga, M., Sakaki, Y., Nakashiki, K., Miyata, M., Tei, C., 2008. Repeated waon therapy improves pulmonary hypertension during exercise in patients with severe chronic obstructive pulmonary disease. J. Cardiol. 51, 106–113.
Vescovi, P., Casti, A., Michelini, M., Maninetti, L., Pedrazzoni, M., Passeri, M., 1992. Plasma ACTH, beta-endorphin, prolactin, growth hormone and luteinizing hormone levels after thermal stress, heat and cold. Stress Med. 8, 187–191.
Vomund, S., Schafer, A., Parnham, M.J., Brune, B., von Knethen, A., 2017. Nrf2, the master regulator of anti-oxidative responses. Int. J. Mol. Sci. 18.
Vuori, I., 1988. Sauna bather's circulation. Ann. Clin. Res. 20, 249–256.
Wallin, R.P., Lundqvist, A., Moré, S.H., von Bonin, A., Kiessling, R., Ljunggren, H.-G., 2002. Heat-shock proteins as activators of the innate immune system. Trends Immunol. 23, 130–135.
Watanabe, H., Yorizumi, K., 1997. Effects of bathing on cerebral blood flow in healthy volunteers. Using Patlak plot method with technetium-99m ethyl cysteinate dimer. Nippon Onsen Kiko Butsuri Igakkai Zasshi 60, 96–100.
Whelton, P.K., Carey, R.M., Aronow, W.S., Casey Jr., D.E., Collins, K.J., Dennison Himmelfarb, C., DePalma, S.M., Gidding, S., Jamerson, K.A., Jones, D.W., MacLaughlin, E.J., Muntner, P., Ovbiagele, B., Smith Jr., S.C., Spencer, C.C., Stafford, R.S., Taler, S.J., Thomas, R.J., Williams Sr., K.A., Williamson, J.D., Wright Jr., J.T., 2018. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J. Am. Coll. Cardiol. 71, e127–e248.

Wilder, R.P., Greene, J.A., Winters, K.L., Long 3rd, W.B., Gubler, K., Edlich, R.F., 2006. Physical fitness assessment: an update. J. Long-Term Eff. Med. Implants 16, 193–204.

Windsor, M.T., Bailey, T.G., Perissiou, M., Meital, L., Golledge, J., Russell, F.D., Askew, C.D., 2018. Cytokine responses to acute exercise in healthy older adults: the effect of cardiorespiratory fitness. Front. Physiol. 9, 203.

Worthen, R.J., Garzon Zighelboim, S.S., Torres Jaramillo, C.S., Beurel, E., 2020. Anti-inflammatory IL-10 administration rescues depression-associated learning and memory deficits in mice. J. Neuroinflammation 17, 246.

Xin, L., Geller, E.B., Adler, M.W., 1997. Body temperature and analgesic effects of selective mu and kappa opioid receptor agonists microdialyzed into rat brain. J. Pharmacol. Exp. Ther. 281, 499–507.

Yamada, P.M., Amorim, F.T., Moseley, P., Robergs, R., Schneider, S.M., 2007. Effect of heat acclimation on heat shock protein 72 and interleukin-10 in humans. J. Appl. Physiol. 1985 (103), 1196–1204.

Yet, S.-F., Melo, L.G., Layne, M.D., Perrella, M.A., 2002. Heme oxygenase 1 in regulation of inflammation and oxidative damage. In: Methods in Enzymology. Elsevier, pp. 163–176.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J., Lisheng, L., Investigators, I.S., 2004. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 364, 937–952.

Zaccardi, F., Laukkanen, T., Willeit, P., Kunutsor, S.K., Kauhanen, J., Laukkanen, J.A., 2017. Sauna bathing and incident hypertension: a prospective cohort study. Am. J. Hypertens. 30, 1120–1125.

Van de Velde, SS., Byrd, B.R., Fargo, J.S., Buchanan, C.A., Dalleck, L.C., 2017. The Performance Benefits of Training With a Sauna Suit: A Randomized, Controlled Trial. Int J Appl Exerc Physiol 13, 1–11.

van der Zee, J., 2002. Heating the patient: a promising approach? Ann. Oncol. 13, 1173–1184.

Zhong, N., Zhang, Y., Fang, Q.Z., Zhou, Z.N., 2000. Intermittent hypoxia exposure-induced heat-shock protein 70 expression increases resistance of rat heart to ischemic injury. Acta Pharmacol. Sin. 21, 467–472.

Zychowska, M., Nowak-Zaleska, A., Chruscinski, G., Zaleski, R., Mieszkowski, J., Niespodzinski, B., Tymanski, R., Kochanowicz, A., 2018. Association of high cardiovascular fitness and the rate of adaptation to heat stress. Biomed. Res. Int. 2018, 1685368.