Repeated Far Infrared Sauna Bathing and Cardiometabolic Health in Individuals with an Elevated Body Mass Index

by

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DISSERTATION ABSTRACT

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Title: Repeated Far Infrared Sauna Bathing and Cardiometabolic Health in Individuals with an Elevated Body Mass Index

Increased adiposity increases the risk for cardiovascular and metabolic diseases, and there is a need for non-pharmacological lifestyle interventions to help reduce these risks. Heat therapy, such as with hot water immersion and sauna bathing, has shown improvements in both cardiovascular and metabolic outcomes in both healthy and clinical populations. One form of sauna bathing, far infrared saunas, has been investigated primarily in cardiac patients as Waon therapy. Far infrared saunas differ from traditional saunas as they emit far infrared waves from panels and elicit an additional radiant heating stimulus. However, it is unknown if these saunas can also reduce cardiovascular and metabolic disease risk in adults with an elevated body mass index (BMI). Our overall purpose was to quantify the vascular and metabolic effects of repeated far infrared sauna bathing in adults with an elevated BMI. Sixteen adults with an elevated BMI were assigned to either a heat therapy or a time control group for the 8 to 10-week intervention. The heat therapy group completed 25 to 30 far infrared sauna bathing sessions, 3 to 4 times a week. The time control group was instructed to maintain their normal lifestyle routines for the 8 to 10 week period. Vascular function testing and a skeletal muscle biopsy were completed before and after the heat therapy or time control intervention. There were no changes to measures of blood pressure, arterial stiffness, or endothelial function, but there was a reduction in fasting plasma glucose. The lack of vascular changes may have been due to the lack of body core temperature change during the far infrared sauna sessions, paired with some participants having clinically normal cardiovascular parameters (i.e., there could be limited ability to further improve on healthy vascular function). These data imply there may be some metabolic benefits with repeated far infrared sauna bathing in adults with an elevated BMI, but future research is needed to understand the mechanisms for these changes.

This dissertation includes previously published co-authored material.

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CHAPTER I

DISSERTATION PROPOSAL

INTRODUCTION

Obesity is an alarming public health concern, and it is projected that ~50% of the adult population in the United States will be classified as obese by 2030 (1). Individuals with obesity have increased adiposity marked by enlarged adipocytes. This expansion of adipocytes results in inadequate blood supply, hypoxia, and ultimately adipocyte death within the adipose tissue (2). The immune system response to adipocyte death leads to a chronic, low-grade pro-inflammatory profile. This inflammatory shift disrupts insulin signaling via serine phosphorylation of insulin-receptor-substrate-1 (IRS-1) (3). Together, the loss of glucose uptake and the suppression of free fatty acids release lead to fatty acid accumulation in non-adipose tissues such as the vasculature, liver, and skeletal muscle, also known as lipotoxicity (4-6). These physiologic changes of inflammation and lipotoxicity contribute to the elevated risk for cardiovascular (i.e., hypertension) and metabolic (i.e., insulin resistance, type 2 diabetes) conditions (7-9) in individuals with obesity. Therefore, strategies to mitigate these risks within this specific population are needed.

Regular exercise is associated with physiological responses that reduce the progression and severity of cardiovascular and metabolic diseases, independent of weight loss (10-13). However, a large portion of the population does not meet physical activity recommendations (i.e., duration, intensity) and/or have low adherence due to factors including motivation, physical limitations, tolerance, and time to reap the benefits of the adaptations (14, 15). Therefore, alternative lifestyle interventions to exercise are needed. Passive heating (i.e., hot water immersion, sauna bathing) is a physiological stressor that shares a mechanistic overlap with aerobic exercise, including increases in body temperature, peripheral blood flow, arterial compliance, and decreases in fasting glucose, insulin, and lipids (16). These mechanisms support its use as a non-exercise lifestyle intervention to target at-risk populations (17-22)

Cardiovascular Responses

Increases in body temperature, as with exercise and passive heating, increase the demands of the cardiovascular system, marked by increased heart rate and cardiac output to support the redistribution of blood flow to the periphery (i.e., skin) to dissipate heat (23, 24). With this redistribution and increase in blood flow, there is an increase in antegrade shear stress and a reduction in retrograde shear stress along the innermost endothelial lining of the blood vessels (25-

27). These shear stress patterns stimulate the release of nitric oxide, a potent vasodilator, that contributes to vascular resistance and blood pressure (28). An intact endothelium is linked with reductions in arterial blood pressure, vascular stiffness, and plaque deposition. Individuals with obesity can have reduced endothelial function, increased vascular stiffness, and a greater prevalence of high blood pressure, thus increasing the risk of cardiovascular disease (29). Previous work has shown that repeated hot water immersion (45-90 minutes for 30 sessions) improved endothelial function and reduced blood pressure in otherwise healthy but sedentary individuals and in individuals with polycystic ovarian syndrome (PCOS), independent of changes to body mass index (17, 18, 22).

In addition to the cardiovascular adjustments, both exercise and passive heating induce the expression of heat shock proteins. Heat shock proteins are associated with reducing inflammation and oxidative stress, improving nitric oxide bioavailability, and promoting angiogenesis, all of which are important for vascular health (30-33). Thus, together, these cardiovascular and circulating responses during passive heating are mechanisms for reducing cardiovascular disease risk in individuals with obesity.

Metabolic Responses

The immune response to cell death from the expansion of adipocytes with obesity results in a chronic, low-grade, pro-inflammatory state. The pro-inflammatory cytokines impair insulin signaling via serine phosphorylation of IRS-1. Disruption to this signaling cascade results in insulin resistance and increases the risk of metabolic conditions (i.e., metabolic syndrome, type 2 diabetes) (7). Exercise and passive heating stimulate both anti-inflammatory cytokines and heat shock proteins, which can both restore insulin signaling via reductions in inflammation (3, 34-37).

One of the first investigations for the therapeutic use of hot water immersion (30 minutes, 6 days a week for 3 weeks) reported reduced fasting blood glucose and glycosylated hemoglobin () in individuals with type 2 diabetes (20). Since then, repeated hot water immersion has also been shown to improve fasting glucose in individuals who are overweight and sedentary or diagnosed with polycystic ovarian syndrome (PCOS) (19, 21). It is important to note that these changes can occur independently of weight loss or changes in adiposity levels. Therefore, targeting systemic inflammation, via inflammatory cytokines and heat shock proteins, can help restore the impaired insulin signaling and reduce the progression of metabolic dysfunction in individuals with obesity.

Skeletal Muscle Responses

Skeletal muscle is a major site of insulin-mediated glucose uptake and, therefore, a target for restoring insulin impairments and metabolic dysfunction (38, 39). Acute exercise can induce improvements in insulin sensitivity due to contraction-induced GLUT4 translocation (40), increase muscle blood flow, induce glucose uptake (41), heat shock proteins (42), and improved anti-inflammatory signaling (11, 43). Further, these responses may be due to exercise-induced increases in muscle and body temperatures proportional to workload intensity (44). Local heating of the skeletal muscle, independent of whole body temperature changes, to similar temperatures seen during exercise, also shows improvements in similar biomarkers such as the upregulation of glucose transporters, reductions in inflammation, and improved mitochondrial function (36, 45, 46). Therefore, this supports the use of passive heat therapy as a means to target skeletal muscle and metabolic function in individuals with obesity.

Current Knowledge Gaps

Together, passive heating serves as a potential lifestyle intervention to target populations at risk for the development of cardiovascular and metabolic diseases. However, there are additional forms of passive heating that require further investigations for the therapeutic implementation for at risk populations, specifically in the population of individuals with obesity. Sauna bathing is an ancient practice of whole-body heating that has also been associated with beneficial cardiovascular and metabolic adaptations.

Traditional sauna bathing is a daily practice in countries such as Finland, and frequent sauna bathing has been associated with reduced risk of cardiovascular disease, all-cause mortality, dementia, and Alzheimer's disease (47, 48). Traditional saunas are between 70-100°C and sessions are typically one to three bouts of five to twenty minutes with cooling intervals (i.e., cold showers, cold baths) between bouts (49). Another form, and relatively newer form, of sauna bathing is far infrared saunas. Far infrared wavelengths (10 μm) emitted from panels within the sauna penetrate the peripheral tissue ~3-4 cm (i.e., skin, subcutaneous fat, and skeletal muscle) via thermal radiation (50, 51). Far infrared sauna sessions are between 40-60°C for 20 to 30 minutes (50).

Compared to traditional saunas, less is known about the effects of repeated far infrared sauna use on cardiovascular and metabolic health, especially in an obese population. A specific practice with far infrared sauna bathing is Waon therapy (52). This practice has been implemented

for inpatient chronic heart failure patients and has shown beneficial cardiovascular outcomes, including cardiac function, systemic vascular resistance, and flow-mediated dilation (52-54). While it is evident there are improvements within this specific clinical cardiac population, less is known about the application within an obese population and beyond an inpatient population. Further, the feasibility of sessions outside of the hospital is currently unknown (55).

Just as there are different forms of exercise, the different forms of passive heating warrant investigation as potential means to mitigate the elevated cardiovascular and metabolic risks in individuals with obesity. Individuals may have different preferences for the variety of passive heating modalities. Providing insight into the different passive heating modalities can offer an opportunity for individuals to choose a modality that meets their personal preference to increase adherence. Together, far infrared saunas may be an additional form of passive heat therapy to be utilized and target multiple avenues of health within an obese population. Therefore, the proposed project aims to investigate the effects of repeated far infrared sauna therapy as a lifestyle intervention to improve elevated cardiovascular and metabolic disease risks in an obese population.

SPECIFIC AIMS

The overall aim of the proposed project is to quantify the effects of repeated far infrared sauna bathing on cardiovascular and metabolic health in individuals with obesity. Figure 1A is a schematic for the broad, overall timeline of the project, whereas Figure 1B is the brief summary of each experimental visit.

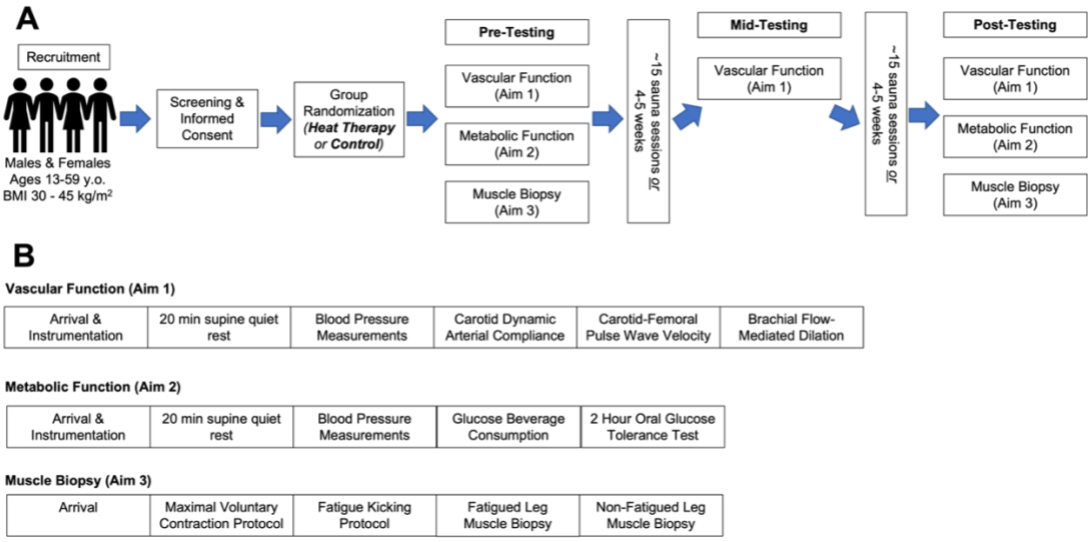

Figure 1. Schematic of overall study design and details of experimental visits

Study Design

A randomized, repeated measures, time-controlled experimental study design will be used. We will recruit men and women between the ages of 18 to 59 with a body mass index (BMI) between 30-45 kg/m^2. This BMI range was selected due to the association with increased mortality and morbidity (56). Participants will be free of diagnosed cardiovascular diseases, diabetes mellitus, or taking prescription medication that affect the blood vessels, blood coagulation, or insulin sensitivity and not participating in vigorous physical activity (> 60% age-predicted heart rate maximum, > 30 minutes/session, > 4 sessions/week). An exception is that we will include individuals with elevated blood pressure and stage 1 hypertension due to the prevalence within an obese population (57, 58). After providing written informed consent, participants will be randomized into a heat therapy group or a time-control group. For the heat therapy group, participants will complete 30 sessions of far infrared sauna bathing 3 to 4 times per week for 8 to 10 weeks. The time-control group will not participate in heat therapy sessions and will maintain their normal activities of daily living. All participants, independent of the randomization group, will complete a total of seven experimental visits (vascular function, metabolic function, and skeletal muscle biopsy) before, midway, and after the 8 to 10 weeks of participating in the protocol. The vascular function, metabolic testing, and skeletal muscle biopsy visits will be completed before and after 30 sauna sessions or 8 to 10 weeks of time control. A midway vascular visit will be completed after ~15 sauna sessions or 4 to 5 weeks of time control. The midway

vascular visit was chosen as previous work from our laboratory has shown reductions in diastolic and mean arterial blood pressure after ~15 sessions of hot water immersion in individuals with PCOS compared to a time control group (18). This provides insight into the time course of repeated far infrared sauna and repeated heat therapy that may elicit physiological changes.

Experimental Visits

Prior to each experimental visit (explained in detail below), participants will refrain from all medications and supplements other than hormonal therapy for contraception or menopause for 24 hours, alcohol and caffeine for 12 hours, food for at least 8 hours, heavy exercise for 24 hours, and heat therapy for 48 hours.

Sauna Bathing Sessions

Participants randomized to the heat therapy group completed 30 sessions of far infrared sauna bathing 3 to 4 times per week across 8 to 10 weeks. The sauna sessions will be between 30 to 45 minutes in the far infrared sauna set between 40-60°C (Sisu Sauna, Sauna 360 Inc, Cokato, MN). This time range for the sauna was selected because infrared sauna bathing sessions typically last between 15-30 min (50), our previous work using heat therapy (hot tub) showed a rise in body temperature to 38.5°C within 20 to 30 minutes (22), and our previous work with repeated hot tub therapy for at least 45 minutes improved cardiovascular and metabolic risk (i.e., blood pressure and fasting glucose) (17-19). Further, Waon therapy sessions with infrared sauna bathing are 45 min in total, consisting of 15 to 30 minutes of infrared sauna bathing (60°C) followed by 30 minutes of supine rest wrapped in blankets to raise body core temperature by 1.0-1.2°C (55). During the first five (#1-5) and the last (#30) sauna session, we will measure rectal temperature (YSI Series 400, YSI Inc., Yellow Springs, OH), skin temperature (iButtons, iButton Link, Whitewater, WI), heart rate (Polar Team Pro, Polar Electro, Kempele, Finland), thermal perceptions, and changes in nude body weight to quantify sweat loss. During the remaining sauna sessions (#6-29), we will monitor heart rate, thermal perceptions, and changes in nude body weight.

Statistical Analyses

The proposed project is a randomized, repeated measures study design with a time-control group. The data will be analyzed with repeated measures two-way (time x treatment) mixed model ANOVA for within and between group interactions.

Specific Aim 1

This aim will investigate the effects of repeated far infrared sauna bathing on blood pressure and vascular function. We hypothesize that 1) blood pressure will be reduced, 2) dynamic arterial compliance will be higher, 3) pulse wave velocity will be lower, and 4) flow-mediated dilation will be higher after 30 sessions of repeated far infrared sauna bathing. Together, these parameters represent a comprehensive overview of vascular function.

Vascular Function Visit

In the supine position, participants will rest quietly for 20 minutes before collecting resting heart rate (electrocardiogram, Cardiocap 5, Datex-Ohmeda, St. Louis, MO) and blood pressure (automated auscultation, Tango M2, Suntech Medical, Raleigh, NC) measurements. Blood pressure will be measured in triplicate in accordance with American Heart Association guidelines (59). We will then measure carotid dynamic arterial compliance (applanation tonometry, PCU-2000, Millar, Houston, TX, and linear array ultrasound, iE33, Philips, Amsterdam, Netherlands) (18), carotid-femoral artery pulse wave velocity (SphygmoCor® XCEL, ATCOR, Sydney, Australia) (60), and brachial artery flow-mediated dilation (E20, D.E. Hokanson Inc, Bellevue, WA, and linear array ultrasound, iE33, Philips, Amsterdam, Netherlands) (61).

Vascular Function Visit Analyses

For carotid artery dynamic arterial compliance, the pressure waveform will be analyzed for the trough-to-peak pressure differential (ΔP) and then analyzed relative to the change in diameter (ΔD). Dynamic arterial compliance will be calculated as: $DAC = [(\Delta D/D)/2\Delta P] \times \pi D^2$.

For pulse wave velocity, the carotid artery and femoral artery pressure waveforms will be measured simultaneously and analyzed over at least 20 cardiac cycles via the SphygmoCor® XCEL software for pulse wave velocity. Additionally, the pulse wave analysis within this system also calculates augmentation index and pulse pressure amplification, which provide further insight into vascular health (62, 63).

For flow-mediated dilation, the diameter of the brachial artery will be measured via custom software (Brachial Analyzer) at pre-occlusion baseline and during the post-occlusion recovery period (3 minutes). Dilation will be calculated as the percent change in diameter from pre-occlusion baseline to post-occlusion peak dilation. The blood velocity signal will be measured via the same custom software and analyzed for post-occlusive hyperemia. Together, these analyses will provide insight into conduit artery endothelial function and microvascular function (61).

Specific Aim 2

This aim will investigate the effects of repeated far infrared sauna bathing on metabolic function. We hypothesize that metabolic function will be improved after 30 sessions of repeated far infrared sauna bathing. We hypothesize that 1) fasting blood glucose and 2) the area under the curve for glucose and insulin will be reduced.

Metabolic Function Visit

Participants will complete a 2-hour, 75-gram oral glucose tolerance test to quantify glucose tolerance and insulin sensitivity to a glucose load (64). An intravenous catheter will be placed into an antecubital vein to obtain venous blood samples before and after (15, 30, 60, 90, and 120 minutes) consumption of a standard 75-gram glucose beverage.

Metabolic Function Visit Analyses

Plasma and serum samples collected during the study visit will be frozen and stored at -80°C for later analysis. Plasma glucose will be analyzed via enzyme electrode technology (YSI 2900, YSI Inc., Yellow Springs, OH). Plasma insulin will be analyzed via bead-based immunoassay (Luminex®, DiaSorin, Saluggia, Italy). Both of these measures will be analyzed across the time of the glucose tolerance test to calculate the area under the curve. Additionally, the homeostatic model assessment for insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI), and the Matsuda insulin sensitivity index (ISI) will be calculated (65). The fasting pre-OGTT blood samples will be used for the measurement of cholesterol, triglycerides, C-reactive protein, heat shock proteins, inflammatory cytokines (IL-1B, IL-6, TNFα), and hemoglobin A1c as these are biomarkers associated with cardiovascular and metabolic health. These additional measures will be analyzed via biochemical assays (i.e., fluorometric, colorimetric, bead-based).

Specific Aim 3

This aim will investigate the effects of repeated far infrared sauna bathing on skeletal muscle signaling pathways related to cardiovascular and metabolic health. We hypothesize that insulin signaling (i.e., phosphorylated Akt) will be improved after 30 sessions of repeated far infrared sauna bathing.

Skeletal Muscle Biopsy Visit

A bilateral, percutaneous biopsy of the vastus lateralis muscle in the thigh will be

performed. One will occur after a fatiguing kicking exercise, and the other in the non-exercising leg within the same visit. After measuring the maximal voluntary isometric torque in the dominant limb, participants will complete repeated single-knee extensions at 30% of maximal isometric torque following a metronome until task failure. Immediately after exercise, participants will be transferred to a bed for the skeletal muscle biopsy. After administration of a local anesthetic (lidocaine), a 5 mm Bergstrom biopsy needle will be inserted through a small incision made in the skin and muscle fascia to obtain the skeletal muscle tissue. The skeletal muscle tissue obtained from both legs will be analyzed for insulin signaling pathways and heat shock proteins. The skeletal muscle biomarkers and signaling pathways will be used in conjunction with each other and provide mechanistic insight into the systemic cardiovascular and metabolic responses.

Skeletal Muscle Biopsy Analyses

Muscle tissue will be flash frozen and stored at -80°C for later analyses via western blots to provide mechanistic insight for the vascular and metabolic outcomes.

This dissertation includes previously published co-authored material.

CHAPTER II
NEW INSIGHTS

The purpose of this chapter is to summarize information that was not available or known at the time of the dissertation proposal but is relevant to the work completed in the dissertation project. Of note, the historical literature on Waon therapy provided a foundation for the use of far infrared saunas (54, 66-70), but was limited to one regimen, one population group, and only one measured and reported body core temperature (pulmonary artery) during the Waon therapy session (70). More recent work has broadened the understanding and application of commercially available far-infrared saunas among the general population. Studies have now used acute heating protocols with commercially available far infrared saunas and measured body core temperature with more accessible techniques than pulmonary artery temperature, such as intestinal and rectal temperatures, and in other populations, including healthy, young adults (71) and adults with type 2 diabetes (72). Further, Fuchs et al. recently investigated the effects of repeated far infrared sauna bathing in healthy, older adults (73).

Acute Whole Body Heating with Far Infrared Saunas

Atencio et al. compared the thermoregulatory and cardiovascular responses to three commonly used heating modalities (hot water immersion, traditional sauna, and far infrared sauna) in healthy, young adults (71). During a 45 min far infrared sauna session, there was no change to body core temperature (intestinal and rectal), but there was an increase in skin temperature, heart rate, cardiac output, and participants did sweat (quantified by changes in body mass). Additionally, there were no changes in blood pressures (systolic and diastolic) during or after the far infrared sauna session. These changes, specifically body core temperature, were lower compared to hot water immersion (45 min at 40°C) and traditional sauna (3 x 10 min at 80°C). From this, it appears that the added radiant heating stimulus of far infrared waves at a lower overall sauna temperature did not elicit similar increases in intestinal and rectal temperatures to the traditional sauna. However, the reality of the simple assumption that by operating at a lower sauna temperature (convective and conductive heating) and increasing the radiant heating stimulus equates to similar, or greater, heat gain is much more complex than this assumption. These acute findings suggest that the lower thermal load of a far infrared sauna may

not elicit the most robust cardiovascular, thermal, or metabolic adaptations with repeated use, but more research is needed to confirm this conclusion. There are currently no longitudinal retrospective or prospective studies for the use of far infrared saunas, similar to the previous work with Finnish saunas (47, 48). While the focus of the work by Atencio et al. was primarily on cardiovascular outcomes, heat therapy has also shown merit in the context of metabolic health (19-21). Schenaarts et al. hypothesized that the "direct" effect of far infrared waves on the skeletal muscle would increase skeletal muscle blood flow and, therefore, glucose uptake in adults with type 2 diabetes (72). During a 40 min far infrared sauna session (60°C), there was an increase in tympanic (+1.5°C) and skin temperatures (+8.5°C), and heart rate (~20 bpm). It should be noted that tympanic temperature has limitations as a measure of body core temperature, especially during passive heating (74). Therefore, it is not feasible to draw direct comparisons to the body core temperature measurements with an ingestible telemetric pill and/or rectal thermistor, as directly measured by Atencio et al. There was no change to post-prandial glucose regulation with the far infrared sauna session compared to the control condition (72). However, this is not surprising as the beneficial metabolic effects of passive heating are reported more consistently with repeated passive heating, not acute passive heating (75).

Repeated Whole Body Heating with Far Infrared Saunas

Fuchs et al. investigated the effects of repeated far infrared sauna bathing at three times a week for eight weeks (45 min at 60°C) in older adults with a focus on skeletal muscle function and, more specifically, on capillarization, perfusion, and protein synthesis (73). However, they had secondary measures of resting blood pressure, glucose, and insulin levels before and during the post-prandial period after a standardized meal, and mitochondrial content and function. It is important to note that it was not an oral glucose tolerance test, but instead, a mixed meal of protein, carbohydrates, fats, and fiber. There was no measure of body core temperature during the passive heating intervention. After the heat intervention, there was an increase in skeletal muscle capillarization, lower resting systolic blood pressure (~3 mmHg), and improved post-prandial glucose handling as evidenced by a reduction in the glucose area under the curve paired with no changes to insulin concentrations. The reduction in blood pressure is below the clinically meaningful change of 5-10 mmHg for systolic blood pressure (76, 77). However, it may suggest that more prolonged use (> 8 weeks) may elicit clinically significant reductions, but this has not

been confirmed. As a mixed meal, not an oral glucose tolerance test, was used to assess post-prandial glucose handling, we cannot conclude whether the reduction was a clinically significant change. There was no change to fasting glucose levels, which are one part of the assessment for metabolic dysfunction (100 to 126 mg/dL for pre-diabetes and > 126 mg/dL for diabetes). The authors stated the metabolic improvements were not correlated to the increase in skeletal muscle capillarization, but did not clarify further mechanisms that supported these findings. There was also no change to mitochondrial content or function, despite previous findings with localized heating showing beneficial changes (46, 78, 79). The authors hypothesized that the muscle temperatures during the far infrared sauna sessions may not have increased to the temperatures shown with local heating via short-wave diathermy (39-40°C)(46, 78, 80). Again, these were all secondary outcomes to the primary research question and offer direction for future research questions to investigate the metabolic effects of repeated far infrared sauna bathing with commercially available far infrared saunas.

Overall, these recent findings provided more insight into the thermal stress and potential physiological adaptations when using commercially available far infrared saunas. Some of the findings, such as body core temperature, are conflicting with the earlier reports on Waon therapy. Despite these discrepancies, there is evidence of thermoregulation (i.e., sweating) and cardiovascular responses during the sauna sessions, thus indicating there is some level of physiological stress. It appears that repeated far infrared sauna bathing, not with Waon therapy, does have the potential to improve both cardiovascular and metabolic parameters. Future research should continue to report the temperature of the sauna and directly measure body core temperature to continue the understanding and application of this heating modality in the context of vascular and metabolic health with commercially available saunas in both healthy and clinical populations.

History and Biophysics of Far Infrared Saunas

Infrared radiation was discovered in 1800 by Sir William Herschel when he was measuring the temperature of each color of visible light emitted from a glass prism. He discovered a greater increase in temperature in the region beyond the visible red light region, where there was no visible light. Due to the lack of visible light within this area, he defined this region to have “calorific invisible light rays” (81), which later became defined as the region of

infrared radiation. This discovery provided the foundation for the use of infrared radiation within modern technology. The use of whole body heating with light, specifically the sun, dates back to the ancient Egyptians, but the more modern-day use in North America was showcased by Dr. John Harvey Kellogg at the Chicago World Fair in 1893. After meeting with a team of physicians in Europe using a similar concept, Dr. Kellogg invented the "electric light bath", which was a chamber lined with mirrors with rows of light bulbs. There were reports that these electric light baths improved kidney disease, blood pressure, and gout (82). Modern-day commercially available far infrared saunas now use carbon or a combination of both carbon and ceramic heating elements to emit far infrared waves.

Infrared radiation is one region within the electromagnetic spectrum. The infrared region is further divided into three subregions: near (short or IR-A), mid (medium or IR-B), and far (long or IR-C), with the far infrared region wavelength being between 3 and 1000 μm (83). While this wavelength range is broad, commercially available far infrared light sources are within a narrower range of 5-14 μm (84). Far infrared light waves are emitted from the panels inside a sauna. The light waves reflect, penetrate, scatter, and are absorbed by molecular bonds, specifically water, in the peripheral tissues of the body (85, 86). The absorption of this energy results in an increase in vibrations of the molecular bonds and a subsequent increase in temperature as a byproduct of the increased kinetic energy. This offers a radiant heat stimulus, which is theoretically more prominent in far infrared saunas than in traditional saunas. Due to this added radiant heating stimulus, far infrared saunas are marketed as a more "direct form of heating" or offer a "deep body heating" at lower overall temperatures. We found one review that is commonly referenced for the statement that far infrared waves penetrate up to 3 to 4 cm into the peripheral tissues of the body (87). However, we were not successful in finding the original dataset to support this claim.

Within the framework of radiation, penetration depth is defined as the depth where 63% of the radiation energy has been absorbed (88). This is dependent on the combination of the wavelength of the electromagnetic waves and the composition (i.e., thickness, water, lipids) of the target tissue. Efforts to directly quantify the penetration depth of far-infrared radiation in human tissues have been limited, especially compared with visible and near-infrared light sources (86). There are established methods for both direct and indirect quantification of reflectance, transmittance, absorption, and scattering of light waves within biological tissues

(86). Within these methods, the nature of the high absorbency of far infrared waves by water molecules in superficial tissues, such as the skin, results in minimal optical transmission to be directly quantified. Therefore, the widely cited claim for a penetration depth of up to 3 to 4 cm does not align with the inherent limitations for the quantification of optical properties of far infrared radiation. While the far infrared waves may not directly penetrate beyond a few millimeters from the surface, the temperature effects of this radiant heating at the surface may heat deeper tissues via conduction. Early investigations of this work date back to the 1940s, when researchers compared the local temperature effects of infrared radiation sources with different wavelengths (near vs. far infrared) on skin, subcutaneous adipose tissue, and muscle (89, 90). The purpose of these studies was to determine which infrared heating source penetrated deeper into the peripheral tissues of the body and thus, offered a more effective heating stimulus. Yet, their findings were not conclusive. The takeaway from their findings was that quantifying the tissue temperatures may provide some insight into the effectiveness of the far infrared waves, but it must be interpreted with caution, as we cannot omit the presence of conductive heat exchange between neighboring tissues (89, 90). These early studies have not been referenced in any recent original journal or review articles discussing far infrared radiation, but do offer a background for far infrared radiation and interactions with peripheral tissues of the human body.

The gaps in the literature for whole-body heating with a far infrared sauna led us to design a separate acute heating protocol within this dissertation project, which was executed after the original proposal was already underway, to investigate the temperature responses of the skeletal muscle during a far infrared sauna bathing session, as discussed in detail in Chapter VI. While the additional protocol was in a separate cohort from the primary heat therapy protocol, it provided us with insight to better interpret the findings of the primary protocol and information that can be applied for future research with far infrared saunas.

Classification and Terminology of Obesity

For this project, we used the World Health Organization (WHO) definition of obesity, with the anthropometric measure of body mass index (BMI) being greater than or equal to 30 kg/m^2. This was in part due to the use of this anthropometric measure (i.e., research, healthcare) and associations with increased risk for cardiovascular and metabolic diseases. BMI is correlated with fat mass (91), but the major limitation of BMI is that it does not distinguish between tissue

type (muscle vs adipose), amount, or distribution of adipose tissue. To work within this limitation, we included additional inclusion criteria, such as physical activity cutoffs, as sedentary behavior is an independent risk factor for cardiometabolic diseases (92, 93). However, we now realize our reliance on this anthropometric measure, even within our considerations, in the context of physiology research, was suboptimal. BMI classifies body size but does not directly measure physiological function, and assumptions are often made about the cardiovascular and metabolic health of individuals due to body size alone. This is also known as weight stigma (94). These assumptions are not accurate, as an elevated body mass index does not mean dysfunction, and recent findings show BMIs between 25-35 kg/m^2, defined as overweight and obese by WHO, have the lowest risk of all-cause mortality (95, 96). Six of the sixteen participants in our study had a BMI less than or equal to 35 kg/m^2.

Our primary outcomes were physiological parameters that can be altered due to increased adiposity. Yet, we relied on anthropometric measures that were limited in adequately quantifying adiposity, and we did not include a direct measure of physiological functions (i.e., glucose, triglycerides, cholesterol) that can be altered due to excess adiposity during the initial screening process. We did collect additional anthropometric measurements such as waist circumference and waist-to-hip ratio, which provide more information about fat distribution (97). However, these were used to further characterize participants instead of defining eligibility. We were hypothesizing changes in clinical parameters without an initial assessment of clinical parameters.

An additional consideration is the terminology used at the time of the research proposal and the terminology used moving forward. While our goal was to study the physiological effects of obesity, as in increased adiposity, recent findings have shown that the term “obesity” carries the greatest stigma. Alternative suggestions for terminology include “weight” or “BMI,” but it is noted that terminology is context dependent (98). Further, there is a proposal to identify obesity as a disease with a proper, adequate definition that moves away from relying solely on indirect anthropometric measures of adiposity to define a physiological condition (95).

In summary, and considering all the above, we have opted to use the terminology “elevated body mass index” instead of “individuals with obesity”. As these considerations and new insights came about after the original proposal, these adjustments will be implemented moving forward. Between 2021 and 2023, the prevalence of obesity (as defined by BMI > 30 kg/m^2) for adults in the United States was 35.5% for adults between the ages of 20-39 years and

46.4% for adults aged 40-59 years (99). Therefore, although our use of BMI as a surrogate for adiposity was flawed, the findings from this dissertation can be applied to over one-third of the adult population in the United States.

CHAPTER III

PROBLEMS ENCOUNTERED, ALTERNATIVE APPROACHES & UPDATES TO SPECIFIC AIMS

Problems Encountered & Alternative Approaches

Upon completion of the dissertation proposal presentation, a few changes were made to the protocol following discussions amongst committee members. The midpoint vascular visit, both oral glucose tolerance test visits (pre and post), and the fatiguing exercise portion of the muscle biopsy visits were removed. These visits were removed with consideration of the burden on volunteer participants and research team personnel and the forward progress of the research project. A venous blood draw was added to the vascular function visits to accommodate the removal of the oral glucose tolerance test. This allowed us to still analyze for systemic parameters such as fasting glucose and insulin, HOMA-IR, QUICKI, hemoglobin A1c, and systemic inflammatory markers. We also faced the common challenge of human research in finding participants who were interested, willing to participate, available, and met the inclusion criteria to participate. We implemented an online ad campaign to broaden the advertisement of the research study beyond Craigslist, flyers, and in-person recruitment at local community events (i.e., Lane County Farmers Market). This was successful in the number of phone screening calls, but the turnover rate was low for individuals qualifying and/or being interested in participating. The leading reasons for individuals not qualifying were being too physically active, having inadequate time to participate, and being outside of the body mass index range. Further, most individuals screened reported having normal blood pressure. We opted to include individuals with normal resting blood pressure, as some of the other parameters (i.e., pulse wave velocity, flow-mediated dilation) are independently associated with reduced cardiovascular risk, have changed with repeated heat therapy protocols, and would still allow us to answer our hypotheses for vascular function. However, due to these challenges, our sample size was smaller than the estimated sample size from the original power analysis.

As data collection continued, additional challenges and considerations came about and were addressed, as needed. During the sauna sessions, the rectal temperatures of participants did not change. This was surprising as previous reports with far infrared sauna bathing showed changes in body temperature (pulmonary artery) between 1.0-1.2°C (70). Despite the lack of change in rectal temperature, the participants reported increased feelings of warmth, thermal discomfort,

and sweating, and the presence of sweating was confirmed by changes in nude body mass. Because we did not observe a rise in body core temperature, we could not use an increased body core temperature (e.g., to 38.5-39.5°C, which is commonly used in other passive heat therapy protocols) as the target criteria for the sauna sessions, so we chose to use time as the target criteria for the sauna sessions. Our goal was to have the sauna sessions last 45 min. Some sessions were shorter, and the reasons for those exceptions are explained in detail in Chapter IV.

We used the factory-installed thermostat to set the temperature of the sauna for each sauna session. Each session started at the lower recommended temperature (45°C) and increased to the highest temperature recommended (60°C) upon the participants entering the sauna. We opted for this regimen instead of the sauna being set to 60°C to maximize the amount of time the far infrared panels were on during the sauna session, as these are the primary heating stimulus. This was established by installing an analog output box and outputting the signal into our data acquisition system. If the temperature was maintained at 60°C, the far infrared panels were on for about 58% of the sauna session, whereas starting at 45°C and increasing to 60°C had the far infrared panels on for 80% of the sauna session. Therefore, as the far infrared waves are the primary heating stimulus (radiant) in this type of sauna, we opted to have the maximal exposure to the radiant heat stimulus. We also installed a temperature probe in the opposing upper corner of the sauna to the factory-installed thermostat. The probe consistently reported a lower overall temperature than the factory thermostat by about 12°C. We were unable to increase the factory thermostat above 65°C to attempt to increase the sauna temperature further. We opted to continue with the use of the factory-installed thermostat to increase the ecological validity of our data within the context of commercially available far infrared saunas.

Second, to accommodate the schedules of participants and being able to complete the post-intervention testing within a narrow window of the last sauna session, we adjusted the total number of sauna visits from 30 to be between 25 to 30 visits. The goal was for participants to complete as many of the 30 supervised sauna sessions as possible. Previous heat therapy protocols that have investigated similar cardiovascular and metabolic outcomes have ranged from 10 to 32 sessions completed within 2 to 10 weeks (54, 73, 100-102). Therefore, we were still able to answer our research questions and make fair comparisons to previous work with the range of 25 to 30 sessions within 8 to 10 weeks. Of the nine participants in the heat therapy

group, six completed all 30 sauna sessions, one completed 28 sauna sessions, one completed 26 sauna sessions, and one completed 25 sauna sessions, for an average compliance of 95%.

Third, we were not successful in obtaining adequate amounts of skeletal muscle tissue (in milligrams) during the muscle biopsy visit and carotid dynamic arterial compliance during the vascular function visit in all participants at both pre- and post-intervention time points. During the muscle biopsy visit, various adjustments were attempted to obtain muscle tissue within the approved five passes (i.e., insertion of the Bergström needle) within our protocol, with permission of the volunteer, and based on the expertise of the research team. This may have been in part due to the depth of the skeletal muscle relative to the length of the Bergström biopsy needle. Carotid dynamic arterial compliance was not collected in all participants due to an inadequate signal for analysis, with the majority having excessive artifact in the pressure signal from the tonometer (i.e., respiration patterns, lack of pulse signal due to anatomical structures, weak pulse signal due to depth of carotid artery, and reaching the maximal pressure allowed by the tonometer). The research team would try to find a tonometer signal for 45 to 60 min before forgoing the measure during the vascular visit, with consideration for participant comfort and length of the study visit. The analysis was still completed to address the hypothesis in Specific Aim #1, within a subset of the participants.

Fourth, we used a western blot protocol for skeletal muscle samples, as established by Gupte et al. (3). With the tissue from our subset of participants, we had successful samples from one time control and three heat therapy participants, but we continued to analyze to gain some insight into the physiological responses in this small subset of participants. We ran into more troubles, including ghost bands and non-specific binding, which led to additional attempts, but we continued to run into technical difficulties. Some of the targets were successful (as shown by heat shock protein 70 in Figure 10 in Chapter V), but not all, including the two housekeeping proteins (vinculin and GAPDH). Due to the lack of success with the housekeeping proteins, we were not able to adequately quantify the levels of heat shock protein 70. Due to the time it took to troubleshoot the skeletal muscle tissue, we were not able to analyze the adipose tissue samples within the timeline of the dissertation. We plan to continue the analysis of adipose tissue beyond this dissertation project, as it is relevant in the context of passive heating and metabolic health.

Updates to Specific Aims

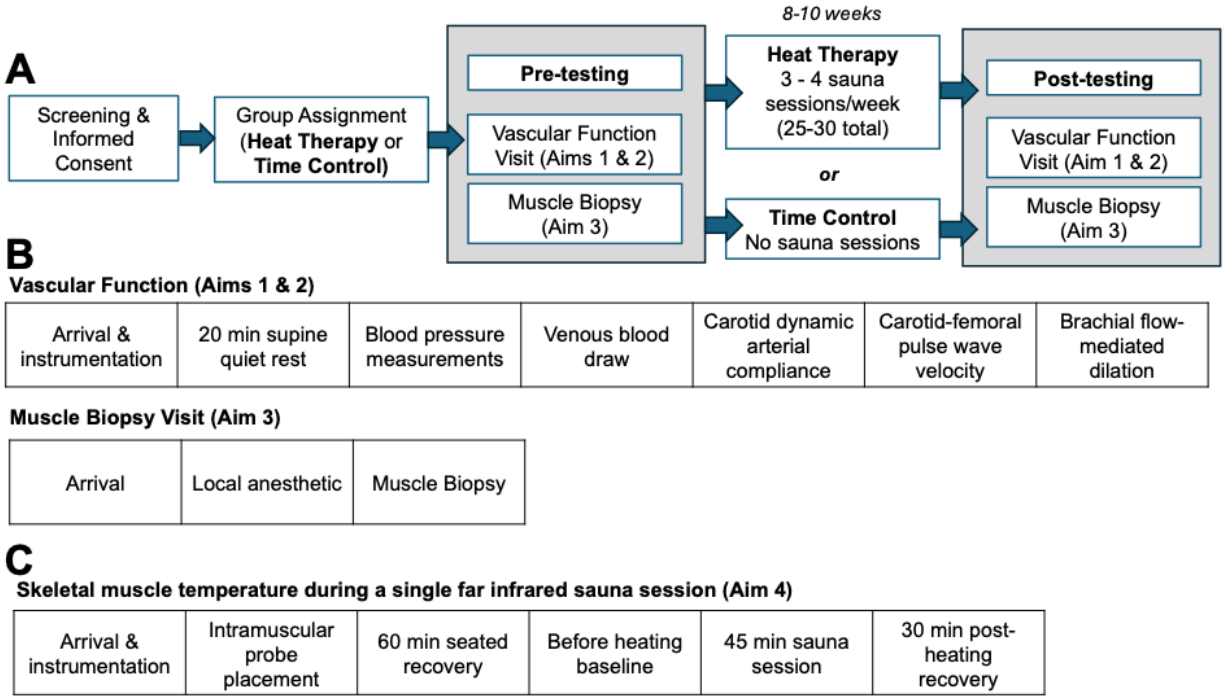

Figure 2. Schematic of the updated specific aims for the repeated heat therapy protocol in adults with an elevated BMI (A and B) and the acute heating protocol in adults without obesity for Aim 4 (C)

Below are the updates to the specific aims, taking into consideration the changes, conflicts, and alternative approaches discussed above.

Specific Aim 1: Vascular Function

We hypothesized that repeated far infrared sauna bathing in adults with an elevated BMI would improve vascular function as evidenced by 1) a decrease in resting blood pressure, 2) an increase in carotid dynamic arterial compliance, 3) a decrease in carotid-femoral pulse wave velocity, and 4) an increase in brachial artery flow-mediated dilation. This aim will be discussed in Chapter IV.

Specific Aim 2: Systemic Metabolic Health

We hypothesized that repeated far infrared sauna bathing in adults with an elevated BMI would improve metabolic health as evidenced by a reduction in fasting blood glucose. Our secondary hypothesis within this aim was that there would be reductions in systemic inflammation (i.e., IL-6, TNFα) after heat therapy. This aim will be discussed in Chapter V.

Specific Aim 3: Glucose Signaling in Skeletal Muscle

We hypothesized that repeated far infrared sauna bathing in adults with an elevated BMI would result in improved glucose signaling in the skeletal muscle, as evidenced by an increase in the phosphorylation of Akt and AS160. Our secondary hypothesis within this aim was that there would be increases in heat shock proteins after heat therapy. However, due to the limited skeletal muscle tissue and technical challenges with the analyses, we were not able to fully test this hypothesis and only gained exploratory insight. This aim will be discussed in Chapter V.

Specific Aim 4: Muscle Temperature with Far Infrared Sauna Bathing

This aim was added on after the original proposal date as we continued to develop our understanding of far infrared radiation within the context of commercially available saunas. Our purpose was to quantify skeletal muscle temperature during a single far infrared sauna bathing session. The project was exploratory by design and descriptive in nature, rather than being hypothesis driven (i.e., we did not have a specific hypothesis), but it was intended to lead to future hypothesis-driven research questions. This aim will be discussed in Chapter VI.

CHAPTER IV

NO IMPROVEMENTS TO VASCULAR FUNCTION IN ADULTS WITH AN ELEVATED BODY MASS INDEX AFTER REPEATED FAR INFRARED SAUNA BATHING

INTRODUCTION

The prevalence of obesity, as defined by the World Health Organization as a body mass index (BMI) ≥ 30 kg/m^2, continues to increase. It is projected that by the year 2030, 50% of the adult population in the United States will be classified as obese, based on BMI (1). At the cellular and tissue level, obesity is defined as an excess amount of adipose tissue, and it is well-established that excess adiposity increases the risk for other diseases, including cardiovascular, metabolic, and cancer (103). These increased risks are due in part to structural and functional changes to adipose tissue in the subcutaneous and visceral depots. This limited storage of circulating triglycerides within the adipocytes results in the deposition of triglycerides in ectopic depots, including the vasculature. The consequence is fatty acid intermediates, inflammation, and oxidative stress, and these can lead to endothelial dysfunction (i.e., reduced flow-mediated dilation), elevated arterial stiffness (i.e., elevated pulse wave velocity), and hypertension (104). These parameters and cardiovascular disease risk can be improved with lifestyle interventions such as diet, exercise, or a combination of both (105-107). Passive heat therapy (i.e., hot water immersion, sauna bathing) has also been shown to reduce cardiovascular events and disease risk (47, 108). For example, repeated passive heating increased flow-mediated dilation (17, 18, 66, 109), reduced blood pressure (17, 18, 54, 66, 110, 111), and reduced inflammation (112). These changes have occurred independent of weight loss and are due in part to the physiological responses (i.e., increased shear stress) to an increase in body core temperature as discussed in detail elsewhere (16, 29).

Despite the high prevalence of obesity as defined by an elevated BMI, only a few reports investigate the effects of passive heat therapy on vascular function in adults with an elevated BMI. It must be noted that there are reports of the effects of whole body passive heat therapy on metabolic function in adults classified as overweight (BMI of 25-29.9 kg/m^2) or with obesity (BMI of ≥ 30 kg/m^2) (21, 113), but they did not include specific measures of vascular function. The heat therapy protocols with measures of vascular function specifically recruited individuals with additional clinical conditions, including polycystic ovarian syndrome (18) and untreated

hypertension (114). While excess adiposity can increase the risk for clinical conditions, not all individuals with an elevated BMI have diagnosed tissue and organ dysfunction due to excess adiposity; this is defined as pre-clinical obesity (95). If there is tissue and organ dysfunction, this is defined as clinical obesity. It is hypothesized that individuals can either remain, as in not progress to clinical obesity, or shift between these classifications, as in from clinical to pre-clinical obesity, with proper preventative and treatment interventions (95). Thus, it may be that heat therapy offers a window of opportunity for those individuals with pre-clinical obesity to maintain, or even improve, endothelial and vascular function. This therefore reduced the risk of cardiovascular dysfunction and disease due to excess adiposity.

Just as there are different forms of exercise, understanding different forms of passive heat therapy is needed to optimize the application of this lifestyle intervention. Further, having a variety of options for heat therapy may increase adherence to this lifestyle intervention based on personal preference, as enjoyment increases adherence (115). Two types of saunas that are commercially available, traditional (or Finnish) and far infrared, have continued to increase in popularity and accessibility by the general population. Traditional saunas are between 80 and 100°C for one to three bouts of 5 to 20 min with cooling (i.e., cold showers) between each bout and elicit a primarily convective heating stimulus (49). Far infrared saunas are between 45 and 60°C for 15 to 30 min and elicit a primarily radiant heating stimulus from the emittance of far infrared waves from panels on the interior surface of the sauna (50, 51). Far infrared saunas are claimed to be a more direct form of heating at these lower overall sauna temperatures because the far infrared waves penetrate and heat the peripheral tissues of the body, including skin, subcutaneous fat, and skeletal muscle (87).

While the cardiovascular benefits of traditional sauna bathing are well documented in about 2,300 middle-aged men from Finland (47, 48), a large portion of previous research with whole body far infrared sauna bathing is limited to in-patient cardiac patients (54, 66-69, 111, 116-118). These patients underwent Waon therapy, defined as 15 min of far infrared sauna bathing at 60°C followed by 30 min of supine rest wrapped in blankets (55). This practice has been reported to elicit an increase in pulmonary artery temperature by 1.0 to 1.2°C during the 15 min sauna session (70). Overall, Waon therapy for five to seven times per week for two to three weeks reduced blood pressure (4 to 10 mmHg) and increased flow-mediated dilation (+1.3 to 1.8%), which are within the ranges of clinically meaningful changes, in adults with coronary risk

factors, chronic heart failure, or hypertension (54, 66, 76, 77, 111). Separate from a Waon therapy protocol, repeated far infrared sauna bathing for 45 min at a frequency of three times per week for eight weeks elicited reductions in systolic blood pressure (~3 mmHg) in healthy, older adults (73). Lastly, animal and cell culture models show increased endothelial nitric oxide synthase following localized heating with far infrared lamps (119-122). Together, far infrared saunas may be an additional form of whole body passive heating that can merit vascular function in adults with an elevated BMI.

The purpose of this study was to examine the effect of repeated far infrared sauna bathing on vascular function in adults with an elevated BMI in comparison to a time control group with no sauna bathing. We hypothesized that repeated far infrared sauna bathing three to four times per week for eight to ten weeks would reduce blood pressure and pulse wave velocity (as a marker of arterial stiffness) and increase flow-mediated dilation (as a marker of endothelial function).

MATERIALS AND METHODS

Participants

Volunteers were recruited from the local community and were included in the study if they were between the ages of 18 and 59 yr and had a BMI between 30 and 45 kg/m^2. Exclusion criteria included self-reported diagnosed cardiovascular and/or metabolic diseases other than elevated or stage 1 hypertension blood pressure; taking medications that affected blood pressure, blood sugar, or blood clotting; current smokers; pregnant, breastfeeding, or desiring to become pregnant in the next 6 months; participating in > 120 min of vigorous exercise a week; allergies to lidocaine, latex, and/or adhesives. Recruitment, phone screening, and enrollment after providing informed consent are shown in Figure 3.

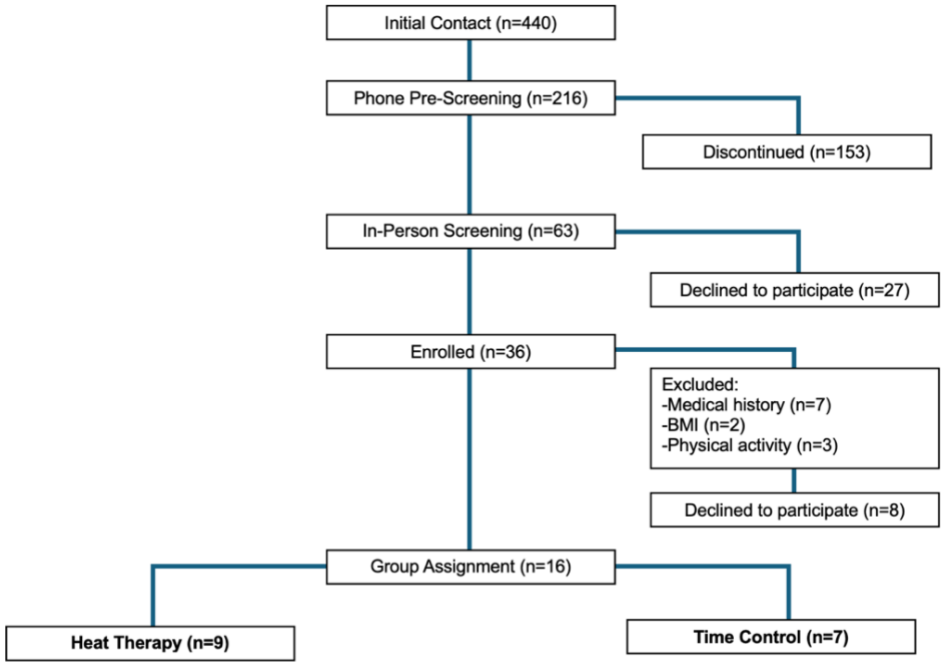

Figure 3. Diagram of the recruitment process of screening, enrollment, and group assignment.

Study Design

Participants (Table 1) were assigned to either a heat therapy or a time control group to be matched for age and BMI. Outcome variables of vascular function were measured before (PRE) and after (POST) 8 to 10 weeks of heat therapy or time control.

Table 1. Participant characteristics

Variable	Time Control (n= 7) (5 females)	Heat Therapy (n= 9) (5 females)
Age (y)	39 ± 12	41 ± 9
Body mass index ($kg \cdot m^{-2}$)	37.5 ± 3.0	37.2 ± 3.8
Waist circumference (cm)	110 ± 10	108 ± 9
Waist-to-hip ratio	0.89 ± 0.08	0.88 ± 0.07
Total Physical Activity (MET min/week)	1900 ± 2319	2072 ± 2045
HbA1c (%)	5.5 ± 0.3	5.7 ± 0.5

Data are presented as means ± standard deviations.

Heat therapy group

The goal of heat therapy was to complete thirty supervised sessions (30 to 45 min) of far infrared sauna bathing (45-60°C) in a commercially available far infrared sauna (IS 565; Finnleo,

Sauna360 Inc.; MN) within the Bowerman Sports Science Center at the University of Oregon at a frequency of 3 to 4 sessions per week within an 8 to 10 week period. The heat therapy protocol was selected to be comparable to previous investigations of heat therapy (i.e., hot water immersion) shown to elicit improvements in cardiovascular and metabolic function (18-20, 22, 123). Previous investigations, specifically with far infrared saunas (Waon therapy), showed improvements in cardiovascular function in cardiac patients. However, these heat therapy protocols were completed at a rate of 5 to 7 days for 2 to 4 weeks while the patients were in the hospital (55, 67-69, 124). We sought to mimic a regimen of only far infrared sauna bathing that may be utilized by the general population in parallel with the weekly aerobic physical activity guidelines recommended by the American College of Sports Medicine.

Upon arrival at the laboratory for each sauna session, participants voided their bladders for a urine sample used for determining euhydration status via urine specific gravity (≤ 1.020) and confirmation of a negative urine pregnancy test each once per week for participants with childbearing potential. If the urine specific gravity was > 1.020, participants were given up to 5 mL of water per kg of nude body mass. All participants were allowed to drink water ad libitum during the sauna sessions, and water bottles were weighed before and after. A nude body mass was provided in a private restroom, and participants were instructed to change into the self-selected clothes for the sauna (i.e., shorts, t-shirt or tank top, and/or bathing suit). A telemetric heart rate monitor (Polar Team Pro; Polar Electro; Kempele, Finland) was placed on the chest at the level of the heart for the continuous measurement of heart rate. For the first five and last sauna sessions, participants self-inserted a rectal thermistor (YSI Series 400; Yellow Spring Instruments; Yellow Springs, OH) at least 10 cm past the anal sphincter for the measurement of rectal temperature and instrumented 8 thermocrons (iButtons; iButtonLink Technology; Whitewater, WI) were placed on the right side of the body for the calculation of mean skin temperature:

$$= (0.21 \times forehead) + (0.06 \times forearm) + (0.12 \times upper\ arm) + (0.17 \times abdomen) + [0.21\ (chest + back)/2] + (0.15 \times thigh) + (0.08 \times calf)$$ (125).

One participant declined the 8-site and agreed to the 4-site locations:

$$= 0.3(chest + upper\ arm) + 0.2\ (thigh + calf)$$(126).

Mean body temperature was calculated as:

$$= 0.8(mean\ body\ core\ temperature) + 0.2\ (mean\ skin\ temperature)$$(127).

Before heating measurements in the seated position were recorded in a temperature-controlled room (22-25°C), and participants entered the sauna where they remained seated for between 30 and 45 min. During the sauna sessions, participants could self-select to sit quietly, read, and/or use their personal electronic devices. Upon completion of the heating, participants remained seated for 5 min in the laboratory, after heating measurements were recorded, and participants were deinstrumented. A second nude body mass was obtained and used with the change in water bottle mass to calculate body mass changes and estimate the whole body sweat rate.

Before each visit, the sauna thermostat was set to 45°C. Upon participant entry, the thermostat was increased to 60°C to maximize the "on" cycle for the far infrared emitters for the duration of the sauna session. We recorded the on/off cycle in a data acquisition system (WinDaq; DATAQ Instruments; Akron, OH), and the far infrared emitters were on for 81% (~36 min) during the sauna sessions. During pilot testing, we found that starting the sauna at the highest temperature setting (60°C) allowed per the factor limits kept the infrared panels on for ~58% (~26 min) of a simulated sauna session. Lastly, we used the factory-installed thermostat to set the sauna within the recommended temperature range (45 to 60°C), but also installed a temperature probe (Vaisala HUMICAP; Vantaa, Finland) in the opposing, upper corner of the sauna. We note a temperature difference between the two, with the additional probe (42.7°C [40.7, 44.8]) being lower than the factory thermostat (54.7°C [51.8, 57.5]). However, we were unable to increase the sauna thermostat beyond 65°C due to factory limits, so we sought to mimic what users of the commercially available far infrared sauna would be utilizing.

Time control group

Participants in the time control group did not participate in the sauna sessions and were instructed to maintain their lifestyle habits for the duration of the protocol. We did not employ a sham sauna group as part of the time control group. This was initially because a well-matched sham group would be sitting in the sauna at a temperature of 22-24°C, but we were already limited to scheduling with one sauna for the heat therapy sessions. An alternative would be for the participants to sit in a room at a controlled temperature (22-24°C). In the end, we decided against this with consideration for the participants' time and schedules. However, it may have served as a stronger comparison due to the heat therapy group having up to 3 hours in a given

week away from their normal lifestyle responsibilities and also having engagement with the research team.

Vascular function visit

Before the experimental testing days, participants were instructed to abstain from medications and supplements (except for hormonal contraception) and heavy exercise for ≥ 24 hours, alcohol and caffeine for ≥12 hours, and food for ≥ 8 hours. Participants completed a food and beverage log for the 24 hours before the pre-testing day and were provided with a copy to match for the 24 hours prior to the post-testing visit. All post-testing visits were completed at a minimum of 36 h and a maximum of 1 week after the last sauna session. The start time of the visits was held constant within 1 hour of pre-testing to minimize confounding measures of circadian rhythm (128). Participants with childbearing potential provided the start date of their last menstrual cycle at the start of each visit, but the visits were not scheduled to control for menstrual cycle phase. Upon arrival at the laboratory, all participants provided a urine sample to test for euhydration status via urine specific gravity (≤1.020) and confirmation of a negative urine pregnancy test for each participant with childbearing potential. If the urine specific gravity was > 1.020, participants were given up to 5 mL of water per kg of nude body mass. Anthropometric measures of minimally clothed body mass (shorts and t-shirt), waist circumference, and hip circumference were measured for additional measures of body composition to characterize the participants. All participants were instructed to rest quietly, supine in the laboratory maintained at temperatures between 22-24°C for the duration of the visit.

Blood pressure and heart rate

Participants were instrumented with a 3-lead electrocardiogram (Cardiocap 5; Datex-Ohmeda, St. Louis, MO) and a blood pressure cuff on the left upper arm. After 20 min of quiet rest, resting heart rate and blood pressure via automated auscultation of the brachial artery (Tango M2; Suntech Medical; Morrisville, NC) were measured in triplicate with 1 min between each measurement to obtain ≥ 3 values within ≤ 10 mmHg. Mean arterial pressure was calculated as DBP + 1/3 (SBP-DBP).

Dynamic Arterial Compliance and Beta-Stiffness Index

Simultaneous measurements of linear array Doppler ultrasound (11.0MHz; iE33; Philips; Amsterdam, Netherlands) of the left common carotid artery and applanation tonometry (PCU-2000; Millar; Houston, TX) of the right common carotid artery were obtained for the calculation of dynamic arterial compliance (DAC) and ß-stiffness index (ß-SI). Ultrasound recordings were collected at 32 Hz and analyzed offline for the change in diameter (ΔD) for each cardiac cycle (Brachial Analyzer for Research; Medical Imaging Applications, LLC; Coralville, IA). The pulse pressure waveform obtained from applanation tonometry was recorded and analyzed in the data acquisition system for the trough-to-peak pressure differential (ΔP). The ΔP was analyzed relative to the ΔD for a minimum of 15 cardiac cycles.

DAC was calculated as:

$$DAC = (\Delta D/D_{mean})/2\Delta P] \times \pi {D_{mean}}^2$$

ß-SI as:

$$ß\text{-}SI = Ln\ (systolic\ blood\ pressure/diastolic\ blood\ pressure) \times D_{mean}/\Delta D$$

These measurements were obtained in a subset of participants (total *n*= 11; control *n*=6 and heat *n*=5) due to technical difficulty in acquiring signals adequate for analysis.

Arterial stiffness

Carotid-femoral pulse wave velocity was obtained for the assessment of arterial stiffness with applanation tonometry of the right common carotid artery and pulse analysis with an inflated cuff of the right femoral artery (SphygmoCor® EXCEL; AtCor Medical; Naperville, IL). Two pulse wave velocity measurements were made. If the difference between the two measurements was >0.3 m/s, a third measurement was collected. Measurements of distance between anatomical landmarks as defined by the software were obtained by two investigators after each pulse wave velocity measurement.

Endothelial and microvascular function

Flow-mediated dilation (FMD) and post-occlusive reactive hyperemia (PORH) of the brachial artery were measured for the assessment of endothelial and microvascular function in accordance with established guidelines (129). The right arm was abducted to 80-90 deg at heart

level in a supported arm res. A Doppler ultrasound (11.0MHz; iE33; Philips; Amsterdam, Netherlands) recording of the right brachial artery on the distal third of the upper arm was obtained before occlusion (baseline; 1 min) and after occlusion (post-occlusion; 3 min). An occlusion cuff (E20 Rapid Cuff Inflater, Hokanson, Bellevue, WA) placed distal to the antecubital fossa was rapidly inflated to 250 mmHg for 5 min. The diameter and blood velocity were recorded continuously via a screen capture software (Vascular Imager, Medical Imaging Applications, LLC; Coralville, IA) and analyzed offline for each cardiac cycle for the baseline (mean diameter) and post-occlusion (peak diameter) periods. Absolute FMD (mm) was calculated as: [post-occlusion peak diameter – baseline diameter]/baseline diameter. This was further multiplied by 100 for relative FMD (%). The relevant shear rate stimulus was calculated as the area under the curve (AUC) above baseline shear rate to peak dilation during the post-occlusion period.

For PORH, blood flow was calculated for each cardiac cycle as: π (diameter/2)^2 X (mean velocity/2) X 60. Peak PORH was determined as the peak blood flow in the post-occlusion period, total PORH was calculated as the mean blood flow during the post-occlusion period, and PORH AUC was calculated as the blood flow AUC above baseline blood flow during the post-occlusion period.

Statistical Analyses

The original grant proposal for this project calculated effect sizes for systolic and diastolic blood pressures as the primary outcomes were d=0.96-1.23 based on SD=5 mmHg for differences between previous pre- and post-heat therapy interventions and pilot testing(17, 22, 123). These were the smallest effect sizes out of other variables of interest, including arterial compliance (d=1.70), β-stiffness (d=1.43), flow-mediated dilation (d=2.55), and fasting glucose (d=2.89). With a power of 90% and α set at 0.05, the targeted sample size was 30 participants (15 per group). Due to recruitment challenges, the final sample size was 9 in the heat therapy group and 7 in the time control group. Therefore, we ended up with less statistical power than originally planned.

Data were analyzed in GraphPad Prism (v.10.6.0) with α set at 0.05 and presented as means [95% confidence intervals], unless otherwise noted. For the outcome variables, statistical inferences were drawn from a two-way mixed effects model with main effects for time (PRE and

POST) and groups (Control and Heat), and a time x group interaction term with pre-planned comparisons. Inferences regarding the differences between groups were drawn from Sidak's Multiple Comparisons Test, restricted to comparisons within the same time point (PRE or POST). Inferences regarding the differences within groups were drawn from Sidak's Multiple Comparisons Test, restricted to comparisons between timepoints (POST versus PRE). If any data were missing at PRE or POST, we excluded the unpaired data (i.e., we only analyzed paired data at both PRE and POST timepoints).

RESULTS

Heat therapy

Upon completion of the heat therapy protocol, there was a 95% adherence rate to completing all 30 sauna sessions. The average length of the sauna sessions was 44 min, with 88% of the sauna sessions being 45 min. Reasons for the sauna sessions lasting between 30 and 40 min were due to participants' requests (n=8 visits), due to scheduling, and based on the participants' comfort during the first five to eight sauna sessions. For five participants, the first sauna visit was 30 min and increased to 45 min by the fifth sauna visit (n=4) and the eighth visit (n=1). All participants tolerated the heat therapy well, and we report no adverse events.

Table 2 shows the comparisons of variables between the first and last sauna visits, which were made at the same corresponding time points (i.e., at 30 min for the first and last sauna visit), even if the participants remained in the sauna longer for the last sauna visit. The one exception is that we did not control for this within the percent change in body mass, but we were able to account for this in the calculation of whole-body sweat rate. There was an increase in mean body temperature during the first (+1.5 [1.3, 1.7]°C) and last sauna (+1.8 [1.4, 2.1]°C) visits, but the increase did not differ between visits. The increase in mean body temperature was due to an increase in mean skin temperature during both the first (+7.8 [7.2, 8.4]°C) and last sauna (+9.2 [7.8, 10.5]°C) visits, as there was no change in rectal temperature during or between sauna visits. The increase in heart rate during the first (+16 [12, 19] bpm) sauna visit was greater than the increase in heart rate during the last sauna visit (+9 [5, 13] bpm). There was no difference between sauna visits for the percent change in body mass or whole body sweat rate. During both the first and last sauna visits, participants reported higher thermal sensation, greater thermal discomfort, and greater perception of sweating. The mixed effects model showed a main

effect of visit for thermal comfort, but the multiple comparisons did not reveal significance specifically before the sauna, between the first and last sauna visit.

Table 2. Physiological and perceptual values before and after the first and last sauna session in the heat therapy group

Variable	Time Point	First Sauna Session	Last Sauna Session	Visit	Time	Visit x Time
Rectal temperature (°C)	Before sauna	37.4 [37.2, 37.6]	37.3 [37.2, 37.4]	0.38	0.13	0.84
	End sauna	37.3 [37.0, 37.7]	37.2 [37.0, 37.4]			
Skin temperature (°C)	Before sauna	29.7 [29.0, 30.3]	28.1 [26.6, 29.7]	0.08	< 0.01	0.08
	End sauna	37.5* [37.2, 37.8]	37.3* [36.7, 37.9]			
Mean body temperature (°C)	Before sauna	35.9 [35.7, 36.1]	35.5 [35.1, 35.9]	0.14	< 0.01	0.16
	End sauna	37.4* [37.1, 37.7]	37.2* [37.0, 37.5]			
Heart rate (bpm)	Before sauna	81 [74, 88]	82 [76, 88]	0.39	< 0.01	0.02
	End sauna	97* [88, 106]	92* [87, 97]			
Δ Body mass (%)		-0.21 [-0.31, -0.11]	-0.28 [-0.40, -0.15]	0.35	-	-
Whole body sweat rate (L/h)		0.35 [0.18, 0.53]	0.40 [0.22, 0.58]	0.68	-	-
Thermal sensation (a.u.)	Before sauna	4 [2, 5]	4 [3, 5]	0.73	< 0.01	0.54
	End sauna	6* [6, 7]	6* [6, 7]			
Thermal comfort (a.u.)	Before sauna	2 [1, 3]	1 [1, 1]	0.04	< 0.01	0.43
	End sauna	3* [2, 3]	2* [2, 3]			
Sweating sensation (a.u.)	Before sauna	0 [0, 1]	0 [0,1]	0.37	< 0.01	0.72
	End sauna	6* [4, 8]	5* [3, 7]			

Data are presented as means [95% CI]. * P < 0.05 compared to before sauna

Hemodynamics

Figure 4 shows measures of systolic and diastolic blood pressures at both time points in both groups. At PRE, systolic (P = 0.95, Fig. 4A) and diastolic (P = 0.72, Fig. 4B) blood

pressures were similar between Control and Heat groups. These measures did not change from PRE to POST in either group.

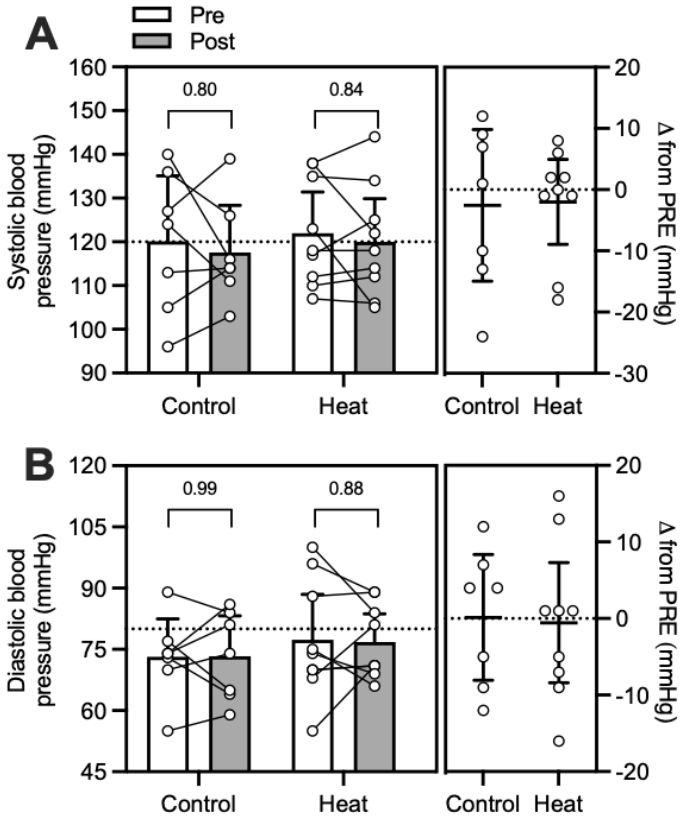

Figure 4. Resting systolic (A) and diastolic (B) blood pressures measured before (PRE; open bars) and after (POST; gray bars) 8 to 10 weeks of time control (n=7) or heat therapy (n=9). Data are presented as means [95% CI] with individual responses for absolute values (left panel) and change (Δ) from PRE (right panel). P-values shown are from pre-planned comparisons of Sidak's multiple comparisons test within groups between timepoints from the mixed-effects model (Group effect $P \geq 0.46$, Time effect $P \geq 0.42$, Interaction effect $P \geq 0.87$).

Vascular function

Figure 5 shows measures of arterial stiffness via pulse wave velocity between the carotid and femoral arteries at both time points in both groups. At PRE, carotid-femoral pulse wave velocity was similar between the Control and Heat groups ($P = 0.94$, Fig. 5). This did not change from PRE to POST in either group. Figure 6 shows measures of endothelial function in the brachial artery at both time points in both groups. Diameter, shear rate stimulus, and reactive hyperemia measures are shown in Table 3. At PRE, the absolute ($P = 0.61$; Fig. 6A) and relative ($P = 0.88$, Fig. 6B) measures of flow-mediated dilation were similar between the Control and

Heat groups. These measures did not change from PRE to POST in either group. Figure 7 shows measures of dynamic arterial compliance and ß-stiffness index of the carotid artery at both time points in a subset of both groups. At PRE, dynamic arterial compliance was similar between the Control and Heat groups (P= 0.88, Fig. 7A). This did not change from PRE to POST in either group. At PRE, the B-stiffness index of the carotid artery was similar between the Control and Heat groups (P= 0.24, Fig. 7B). This did not change from PRE to POST in either group. The diameter measures are shown in Table 4.

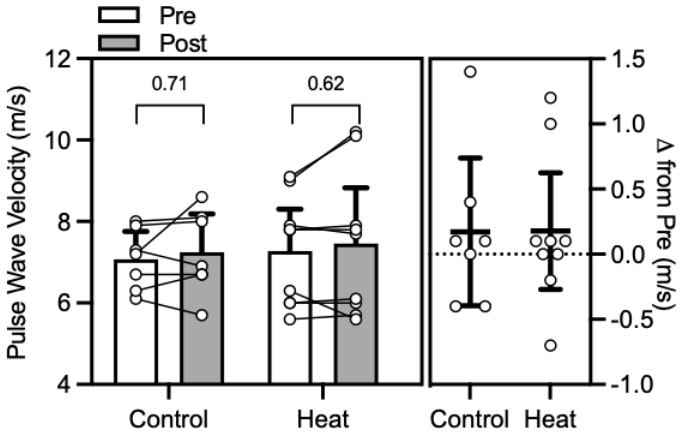

Figure 5. Carotid-femoral pulse wave velocity measured before (PRE; open bars) and after (POST; gray bars) 8 to 10 weeks of time control (*n*=7) or heat therapy (*n*=9). Data are presented as means [95% CI] and individual responses for absolute values (left panel) and change (Δ) from PRE (right panel). P-values shown are from pre-planned comparisons of Sidak's multiple comparisons test within groups between timepoints from the mixed-effects model (Group effect P = 0.75, Time effect P = 0.26, Interaction effect P = 0.98).

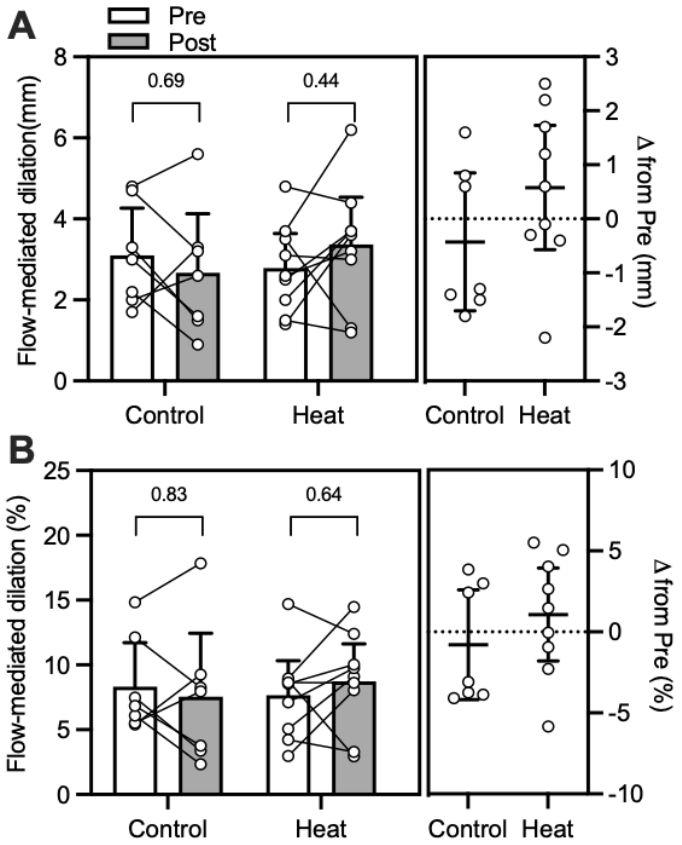

Figure 6. Endothelial function in the brachial artery represented by absolute (A) and relative (B) flow-mediated dilation measured before (PRE; open bars) and after (POST; gray bars) 8 to 10 weeks of time control (*n*=7) or heat therapy (*n*=9). Data are presented as means [95% CI] and individual responses for absolute values (left panel) and change (Δ) from PRE (right panel). P-values shown are from pre-planned comparisons of Sidak's multiple comparisons test within groups between timepoints from the mixed-effects model (Group effect $P \geq 0.74$, Time effect $P \geq 0.83$, Interaction effect $P \geq 0.18$).

Table 3. Diameters and endothelial function variables of the brachial artery

Variable	Group	Pre	Post	Group	Time	Group x Time
Baseline Diameter (mm)	Control	3.77 [3.32, 4.22]	3.73 [3.26, 4.19]	0.97	0.19	0.92
	Heat	3.87 [3.42, 4.13]	3.83 [3.50, 4.16]			
Peak Diameter (mm)	Control	4.08 [3.61, 4.54]	4.08 [3.75, 4.42]	0.95	0.18	0.22
	Heat	4.02 [3.69, 4.35]	4.16 [3.79, 4.53]			
Flow-mediated dilation (mm)	Control	3.10 [1.94, 4.26]	2.67 [1.21, 4.13]	0.75	0.84	0.19
	Heat	2.44 [1.33, 3.56]	3.29 [2.02, 4.56]			
Flow-mediated dilation (%)	Control	8.33 [4.92, 11.72]	7.54 [2.65, 12.43]	0.88	0.88	0.34
	Heat	7.67 [5.02, 10.32]	8.74 [5.85, 11.63]			
Relevant shear (AUC)	Control	17091 [8144, 26037]	19524 [8283, 20765]	0.24	0.50	0.82
	Heat	23795 [12888, 34702]	25323 [16596, 34049]			
Reactive hyperemia (peak flow; ml/min)	Control	300 [208, 391]	327 [284, 370]	0.14	0.38	0.38
	Heat	384 [296, 473]	384 [307, 459]			
Reactive hyperemia (average flow; ml/min)	Control	93 [62, 125]	94 [65, 122]	0.08	0.73	0.74
	Heat	123 [91, 155]	128 [101, 155]			
Reactive hyperemia (AUC above baseline; ml)	Control	160 [85, 236]	167 [96, 238]	0.21	0.68	0.97
	Heat	207 [137, 276]	214 [167, 262]			

Data are presented as means [95% CI].

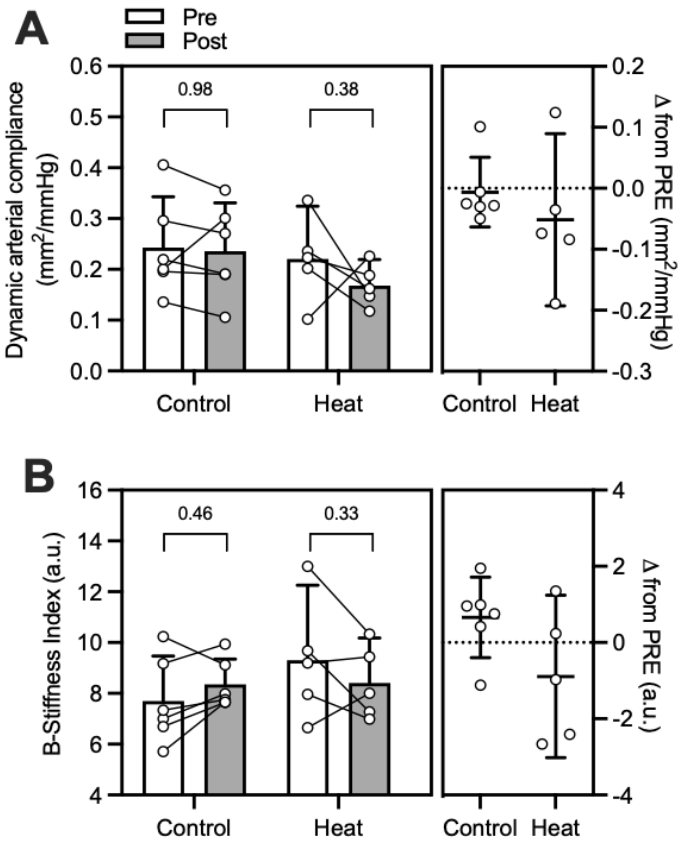

Figure 7. Dynamic arterial compliance (A) and β-stiffness index (B) of the carotid artery measured before (PRE; open bars) and after (POST; gray bars) 8 to 10 weeks of time control (n=6) or heat therapy (n=5). Data are presented as means [95% CI] and individual responses for absolute values (left panel) and change (Δ) from PRE (right panel). P-values shown are from pre-planned comparisons of Sidak's multiple comparisons test within groups between timepoints from the mixed-effects model (Group effect $P \geq 0.33$, Time effect $P \geq 0.30$, Interaction effect $P \geq 0.10$).

Table 4. Diameters, compliance, and stiffness variables of the carotid artery.

Variable	Group	Pre	Post	Group	Time	Group x Time
Systolic Diameter (mm)	Control	7.31 [6.69, 7.92]	7.26 [6.74, 7.78]	0.78	0.51	0.89
	Heat	7.25 [6.83, 7.66]	7.20 [6.80, 7.59]			
Diastolic Diameter (mm)	Control	6.87 [6.34, 7.837	6.91 [6.38, 7.44]	0.50	0.18	0.09
	Heat	6.89 [6.51, 7.27]	6.56 [6.04, 7.08]			
Mean Diameter (mm)	Control	7.07 [6.53, 7.60]	7.12 [6.51, 7.72]	0.80	0.38	0.87
	Heat	6.96 [6.34, 7.57]	7.06 [6.62, 7.49]			
$\Delta D/D_{mean}$ (%)	Control	7.29 [5.49, 9.09]	6.46 [4.97, 8.00]	0.42	0.17	0.15
	Heat	6.21 [4.38, 8.03]	6.23 [5.00, 6.23]			
Dynamic Arterial Compliance (mm^2/mmHg)	Control	0.24 [0.14, 0.34]	0.24 [0.14, 0.33]	0.32	0.29	0.41
	Heat	0.22 [0.12, 0.32]	0.17 [0.22, 0.17]			
ß-Stiffness Index (a.u)	Control	7.69 [5.92, 9.46]	8.35 [7.34, 9.35]	0.39	0.79	0.09
	Heat	9.30 [6.35, 12.20]	8.40 [6.63, 10.18]			

Data are presented as means [95% CI]. ΔD = systolic diameter – diastolic diameter.

DISCUSSION

The purpose of the present study was to investigate the effects of repeated far infrared sauna bathing for eight to ten weeks on vascular function in adults with an elevated BMI. Our main finding was that repeated far infrared sauna bathing did not affect vascular function in adults with an elevated BMI, as there were no changes to blood pressure, arterial stiffness, or endothelial function. This was potentially due to a low thermal load, as evidenced by the lack of change in rectal temperature during the sauna visits and a low overall cardiovascular risk in our participants. Together, these data would suggest that repeated far infrared sauna bathing with a commercially available sauna for eight to ten weeks did not change metrics of cardiovascular health.

Thermal load of the far infrared sauna

The improvements in vascular function that have been observed with heat therapy are typically associated with increases in body core temperature by 1.0-1.5°C to about 38-39°C, with some vascular improvements noted at lower temperatures (25, 26, 29, 70). In our participants, there was no increase in rectal temperature during the sauna visits. This was surprising as the far infrared sauna exposure time was two to three times longer for each session compared to the Waon therapy protocols that report an increase in pulmonary artery temperature by 1.0-1.5°C during the 15 min sauna period (70). We also recently reported no increase in intestinal temperature in adults without an elevated BMI (18.5 to 24.9 kg/m^2) with a single bout of far infrared sauna bathing (71, 130). While we had a greater exposure time to the far infrared waves, the temperature of the sauna sessions during the Waon therapy protocols was higher (~60°C) compared to ours. Additionally, the Waon therapy protocols were in a custom-made far infrared sauna versus our commercially available one (70). As discussed in our methods, we used the factory-installed thermostat to heat the sauna for each session. We found the average temperature of the sauna to be lower (~43°C), as measured by a separate temperature probe, than what was reported on the factory thermostat (~55°C). Despite the lower temperature, at least 15 min of the sauna sessions were within the recommended temperature range (45-60°C) as measured by the temperature probe. We opted to maintain the ecological validity by following the factory thermostat of a commercially available far infrared sauna, but this may explain the discrepancies in our findings compared to previous reports for body core temperature.

Of note, the premise of far infrared saunas is that the far infrared waves provide a more direct heating stimulus at a lower overall sauna temperature (87). Our interpretation of this was that there would be similar increases in body core temperature as other heating modalities. Recent data from our laboratory do not fully support this claim, as 45 min in a far infrared sauna elicited no increase in intestinal temperature, whereas a 3 x 10 min session in a traditional sauna at 80°C elicited a +0.4°C increase in esophageal temperature in adults without an elevated BMI (18.5 to 24.9 kg/m^2) (71). In a different subset of adults without an elevated BMI, we reported a ~1°C increase in muscle temperature at a depth of 3.4 cm below the skin during a 45 min far infrared sauna session without changes in intestinal temperature (130). Additionally, the more superficial tissues (1.4 to 2.4 cm deep) had larger temperature increases (~2 to 3°C) compared to the deep muscle temperature. We did not have a direct comparison to a traditional sauna, but

Leach et al. reported an increase of 1.9°C at 3.5 cm below the skin surface after 2 x 20 min in an 80°C sauna with a 1.5°C increase in esophageal temperature (131). Therefore, it does not appear that far infrared saunas provide a more direct form of heating at lower sauna temperatures. We are limited in that the current and recent data (71, 130) are from only one kind of commercially available far infrared sauna, but show similar results in individuals with and without an elevated BMI. It could be that the temperature recommended for far infrared saunas should be 60°C instead of between 45-60°C. However, the lower temperatures may be more appealing based on personal preference or individual thermal tolerance. Simply increasing the sauna temperature to greater than 60°C would begin to encroach on the temperatures typically used with traditional saunas (starting at about 80°C) and consequently negate the novelty of the premise behind far infrared saunas operating at lower temperatures. However, there needs to be a better quantification of the contribution of radiant heating stimulus during a far infrared sauna session. Reporting of only air temperature may not adequately characterize the physiological stimulus.

Despite the lack of increase in rectal temperature, there was still a modest thermal load during the sauna sessions as evidenced by the increase in skin temperature, heart rate, and loss of body mass due to sweating. The heart rate response in our participants was slightly less compared to others (70, 72), but this may have been due to the lower overall sauna temperature. The skin temperatures and change in body mass were similar with a single far infrared sauna session in adults with type 2 diabetes (72). The heart rate and sweating responses were likely driven by the increase in mean body temperature due to an increase in skin temperature, and therefore, peripheral thermoreceptor afferent signaling and thermoeffector output (132, 133). It could be that the sweating was sufficient to offset increases in rectal temperature, whereas during the supine rest in Waon therapy, it may hinder evaporative cooling. Additionally, participants reported perceptions of feeling warmer, more thermally uncomfortable, and sweatier during the sauna sessions compared to before the sauna session. This may be a more tolerable and therefore more enjoyable form of passive heating for some individuals. While not directly investigated in this study, individuals may use far infrared saunas for reasons beyond cardiovascular adaptations, such as for stress, pain management, and fatigue (134-137). These may result in improved quality of life for some individuals; these benefits should not be dismissed and should continue to be investigated.

Blood Pressure

Recent meta-analyses reported that heat therapy has the potential to reduce blood pressure by 1-5 mmHg (138-140). The majority of the investigations, with one exception (69), with repeated far infrared sauna bathing show reductions in systolic blood pressure between 3 and 10 mmHg (54, 66, 73, 111), which are almost all within the clinically meaningful change of 5-10 mmHg for systolic blood pressure (76, 77). Our data did not show a reduction in blood pressure with repeated far infrared sauna bathing. Despite the longer time in the sauna during each session compared to Waon therapy protocols, we did have a lower weekly frequency of three to four times per week, whereas the Waon therapy protocols had daily sessions five to seven times per week (54, 66, 69). Therefore, it could be that far infrared sauna bathing may be more effective with more frequent sessions on a weekly basis. However, recent work by Fuchs et al. with far infrared sauna bathing three times per week (45 min each) for 8 weeks did report a reduction (~3 mmHg) in blood pressure in older adults (73). Fuchs et al. did not directly measure body core temperature, but it does support the frequency of three times a week at a higher sauna temperature (60°C) is sufficient to elicit potential hemodynamic improvements with far infrared sauna bathing in an older but otherwise healthy population.

We recruited individuals with elevated BMI (>30 kg/m^2) without diagnosed cardiovascular and metabolic diseases, except for elevated or stage 1 hypertension. Before the intervention and regardless of group, 50% of our participants presented with elevated or high blood pressure, with the majority due to systolic blood pressure numbers. Therefore, 50% of our participants had normal blood pressure and thus a potentially lesser capacity for a beneficial effect. Brunt et al. reported reductions in blood pressure in normotensive but sedentary individuals with repeated hot water immersion with a much higher thermal load (17). This supports the notion that improvements can be made to already healthy cardiovascular parameters with repeated heat therapy. However, it does not appear that a higher blood pressure (66, 73, 111, 114) before a heat therapy protocol consistently results in a greater reduction in blood pressure compared to those with normal blood pressure (54, 69, 111, 141). This could be due to the complex interaction of blood pressure regulation and the passive heating modality. Reductions in blood pressure following heat therapy may be due to changes in peripheral (i.e., arterial stiffness) and/or central (i.e., sympathetic activity) mechanisms (18, 142). Previous reports with a single session of far infrared sauna bathing (~60°C) showed a reduction in blood

pressure, and this was sustained between 30 and 120 min after heating in heart failure patients and adults with type 2 diabetes (70, 72). On the contrary, in healthy adults and compared to hot water immersion, our laboratory recently found that a single bout of far infrared sauna did not reduce blood pressure during or after heating (71, 130). Again, this could be due to differences in the temperature of the sauna sessions. We did not obtain blood pressure measurements during or after the sauna sessions in our participants. This would have provided more insight into the timing of hemodynamic responses during and after the sauna sessions, as post-heating hypotension shows similarities with post-exercise hypotension (143). The repeated reductions in blood pressure after exercise, and potentially heat therapy, may contribute to lower resting blood pressure and reduced risk of cardiovascular disease (144).

While we report no improvements in resting blood pressure, it remains unknown if prolonged use (i.e., years) of far infrared sauna bathing, similar to the retrospective findings with traditional Finnish sauna (47), is sufficient to reduce the risk of established hypertension and other chronic conditions in adults with an elevated BMI. Some of our participants were likely in the classification of pre-clinical obesity, rather than clinical obesity (95). It has been recently suggested that the diagnoses of clinical obesity should be determined by anthropometric measures beyond just BMI, and with clinical measures confirming organ dysfunction (i.e., glucose, cholesterol, liver enzymes). In our participants, all but one had an at-risk waist circumference (> 88 cm for females and > 102 cm for males). For the waist-to-hip ratio, only one male participant was classified as moderate risk (0.96-1.0), whereas four females were moderate risk (0.81-0.85) and three were high risk (> 0.85). Further, all but one individual had a fasting blood glucose (<100 mg/dL), 50% of our participants had a HbA1c (< 5.7%), 50% had an optimal to normal age-adjusted pulse wave velocity (145), and 50% had normal blood pressures (<120/ < 80 mmHg). This, in combination with the lower thermal load, raises the question of whether far infrared sauna bathing may be a better fit as a preventative lifestyle intervention to slow the progression of cardiovascular or metabolic diseases (146) in adults with pre-clinical obesity, sedentary lifestyles, and/or family history of cardiometabolic diseases than reverse (or treat) established cardiometabolic dysfunction and disease associated with clinical obesity (95), as shown with more robust forms of heat therapy (18, 19).

Vascular and Endothelial Function

Arterial stiffness and endothelial function have been independently associated with cardiovascular disease risk (147-149). Changes in these vascular parameters may precede changes to blood pressure and/or offer merit independent of reductions in blood pressure (150, 151). Obesity, as defined by an excess adiposity, can impair these vascular parameters through mechanisms of functional (i.e., nitric oxide, inflammation) and/or structural (i.e., collagen, elastin, vascular smooth muscle) components (152, 153). We report no changes to arterial stiffness, arterial compliance, or endothelial function in our participants. To our knowledge, there are no reports of repeated whole-body far infrared sauna bathing on arterial stiffness or compliance to draw direct comparisons to. While not a direct measure of arterial stiffness, the ankle-brachial pressure index (ABI) is used in the assessment and diagnosis of peripheral artery disease. A lower number of ABI indicates greater impairment due to atherosclerotic buildup, which can increase arterial stiffness (154). In patients with peripheral artery disease, ten weeks of Waon therapy improved ABI and increased the formation of collateral blood vessels (quantified by angiograms) (118). The mean increase in ABI was below 0.15, which is the change associated with clinical outcomes (155). However, it appears there is a trend for improvement of clinical vascular parameters, but this did not occur in our participants for arterial stiffness or compliance.

We did not report a change in endothelial function as there was no change in flow-mediated dilation in our participants. Waon therapy improved endothelium function as evidenced by a mean increase of 1.7% in flow-mediated dilation in cardiac patients (54, 66, 69), which meets the clinically relevant change in flow-mediated dilation of 1% (156). Further, animal models with far infrared sauna therapy also report increased endothelial nitric oxide synthase (120-122), which is vasoprotective. We did not have a measure of blood flow and shear stress during the sauna sessions to determine if there was an increase in shear stress, the primary modulator for improved vascular function with heat therapy (25, 27). Mild whole body heating with water-perfused suits did elicit increased shear stress in the femoral arteries with similar increases in skin temperature (+6.4°C) and heart rate (+12 bpm) as our participants (+8.5°C and +13 bpm), but there was still an increase in esophageal temperature (+0.4°C) (157). However, it is unknown if those increases in shear were a sufficient stimulus to improve endothelial function with repeated exposures of the mild whole body heating stimulus. Our data imply there was not a sufficient shear stress stimulus to elicit functional (i.e., flow-mediated dilation) and/or structural

(i.e., diameter) changes to the peripheral vasculature, both of which are part of the biphasic pattern of vascular adaptations (25, 26, 158, 159). As others have concluded, 8 to 10 weeks may not be sufficient to elicit structural changes, even with a more robust thermal stimulus (as evidenced by an increase in core temperature) with a traditional sauna (141). Although not a primary outcome, we also report no change to post-occlusive hyperemia of the brachial artery, as a marker of microvascular function. The function of the microvasculature is relevant in the context of passive heating with obesity and associated metabolic diseases as there are reductions in skin blood flow responses in this clinical population (160). Future work may investigate the skin blood flow and microvasculature responses with far infrared sauna bathing, as far infrared radiation promoted angiogenesis in microvascular endothelial cells (161) and increased cutaneous microcirculation in rats (162).

Altogether, the commercially available sauna used in this protocol did not elicit increases in rectal temperature, and it is unknown if there were increases in shear stress sufficient to elicit vascular adaptations in adults with an elevated BMI. Having a measure of shear stress during the sauna sessions would have provided more insight into the thermoregulatory and subsequent cardiovascular responses associated with the primary increase in skin temperature with the far infrared sauna.

Localized heating and cell cultures with far infrared emitters

In addition to the investigations with whole-body far infrared sauna bathing, there are multiple reports with far infrared emitter lamps as a form of localized heating across cellular, animal, and human models, as discussed in detail elsewhere (84). Without the whole body systemic responses, such as shear stress, these localized heating models reveal additional mechanisms that far infrared radiation may warrant beneficial vascular adaptations. For example, far infrared exposure stimulated the phosphorylation of endothelial nitric oxide synthase via calcium/calmodulin-dependent protein kinase-II in bovine aortic endothelial cells (119) and inhibited adhesion molecules through the anti-inflammatory effect of the induction of heme oxygenase-1 (163). In the context of our participants, due to the depth (~2.1 cm below the surface of the skin) and location of the carotid artery relative to the far infrared panels in the sauna (~15 to 60 cm), it could be that the above cellular responses may be relevant in reducing arterial stiffness or increasing arterial compliance through endothelial cell signaling. The cell

culture models report culture temperatures increasing from 28.0-34.5°C (119) to 36.6-39.7°C (161, 163) with 30 to 40 min of far infrared radiation. Based on the findings of the muscle temperature, the temperature of the tissue surrounding the carotid artery likely reached ~ 36.7°C. This is only a speculation, as tissue type and thickness are important considerations for the biophysics of heating with far infrared saunas. Therefore, our thermal load may not have reached a similar temperature threshold, and it could be that the local emitters offer a more targeted radiant heating stimulus than the whole body far infrared sauna. Qin et al. have suggested parameters for which the local emitters should be used, but such guidelines for far infrared saunas do not exist to our knowledge (84).

Conclusions

In summary, repeated far infrared sauna bathing in a commercially available sauna for 8 to 10 weeks did not improve markers of vascular function in adults with an elevated BMI. This is likely due to the lower thermal load, marked by a lack of increase in rectal temperature and the baseline cardiovascular health of our participants. We opted to start the sauna at the lower recommended temperature of 45°C to maintain the presence of the far infrared panels. However, this may explain the lack of rectal temperature change and may imply that a higher temperature is needed. Our participants still experienced some level of thermal stress as evidenced by increases in skin temperature, perceptions of warmth, thermal discomfort, and sweating, but an additional measure of shear stress would have provided more insight into the cardiovascular stress from this heating modality. A more prolonged use over time (> 10 weeks) of a commercially available far infrared sauna may be required to elicit vascular adaptations if the sauna is at the lower end (45°C) of the recommended temperature range. Further, a higher temperature within the recommended range (60°C) may be warranted for beneficial adaptations, as shown with previous Waon therapy protocols. However, these need to be confirmed with future research. It should be noted that the Waon therapy protocols at 60°C were only 15 min compared to the 45 min in our protocol at the lower temperatures. Nonetheless, the use of a commercially available far infrared sauna may still warrant benefits over a sedentary lifestyle, especially for individuals with an elevated BMI, and be more appealing to those with a lower thermal tolerance or naïve to heat therapy, or serve as a "stepping stone" to other more robust forms of passive heating or exercise.

CHAPTER V

REDUCTIONS IN BLOOD GLUCOSE WITHOUT CHANGES TO INFLAMMATION IN ADULTS WITH AN ELEVATED BODY MASS INDEX AFTER REPEATED FAR INFRARED SAUNA BATHING

INTRODUCTION

Individuals with increased adiposity are at risk for metabolic diseases due, in part, to the structural and functional changes of adipose tissue with excess adiposity (164, 165). Adipose tissue stores excess nutrients in the form of triglycerides, and the storage capacity of adipose tissue can increase by size (hypertrophy) and/or number (hyperplasia). However, adipocytes can be limited in their storage capacity due to structural components (i.e., collagen) and the ability to increase in number (i.e., adipogenesis). Further, hyperplastic adipose tissue expansion increases the number of small adipocytes, which have limited storage capacity compared to larger adipocytes. Prolonged energy excess, one of the multifactorial causes of excess adiposity, can result in enlarged adipocytes, reduced blood supply, and ectopic adipose accumulation in the vasculature, liver, and skeletal muscle (6). This results in elevated levels of free fatty acids, adipokines, reactive oxygen species, and pro-inflammatory immune cells and cytokines in tissues and systemically (7, 166-170). This leads to a disruption of the insulin signaling cascade, particularly in the skeletal muscle, which is the primary location of insulin-mediated glucose uptake (171, 172). Pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), and stress kinases (i.e., JNK, IKKB), impair skeletal muscle insulin signaling by phosphorylating IRS-1 on a serine residue instead of a tyrosine residue (167, 173, 174). The translocation of GLUT4 for insulin-mediated glucose uptake is then reduced due to a reduction in the phosphorylation of AS160 and Akt. This signaling disruption results in insulin resistance and increased risk for metabolic diseases, such as type 2 diabetes.

The use of lifestyle interventions to reduce this disruption due to inflammation can reduce the risk of metabolic diseases. The use of heat therapy as a lifestyle intervention to target metabolic function in humans, independent of weight loss, has been researched for over 25 years (20). The primary mechanism proposed is a reduction in stress kinases and pro-inflammatory cytokines via the induction of heat shock proteins elicited by increases in body temperature, as discussed in detail elsewhere (175, 176), which restores the insulin signaling cascade.

Heat therapy protocols that have shown improvements in fasting glucose and/or glucose handling have been with hot water immersion (~38 to 42°C), which increased body temperature by 0.8 to 1.6°C to 38.5-38.7°C (18, 20, 21). Other forms of passive heating, including sauna bathing, have shown increases in body temperature of 0.5 to 1.6°C to 37.8 to 38.6°C with the Finnish sauna (131, 141, 177) and 1.2°C to 38.1°C after 15 min of far infrared sauna bathing with Waon therapy (15 min of far infrared sauna followed by 30 min of supine rest in blankets) (53). This would imply the potential for similar metabolic improvements with far infrared sauna bathing. Metabolic outcomes are relatively less investigated compared to cardiovascular outcomes in the context of sauna bathing. Regular Finnish sauna bathing has been associated with reduced systemic inflammation (112) and some improvements in lipid profiles (177, 178). Repeated Waon therapy reduced fasting glucose in in-patient cardiac patients, but this was secondary outcome (66). Further, repeated far infrared sauna bathing did improve postprandial glucose handling in older adults (73). Despite the improved postprandial glucose handling after a mixed meal, there were no differences in fasting glucose or insulin levels (73), which are clinically relevant parameters.

Far infrared saunas differ from traditional saunas as there is a radiant heating stimulus, and due to this added radiant heating, far infrared saunas are recommended to operate at lower overall temperatures. The far infrared waves are claimed to penetrate up to 3 to 4 cm below the surface of the skin (87). By increasing the vibrations of the molecular bonds, there is an increase in the temperature of the peripheral tissues of the body. This would imply that skeletal muscle temperatures may increase due to the far infrared exposure and offer a mechanism for improving insulin-mediated glucose uptake. Additionally, heating of tissues such as subcutaneous adipose tissue and/or intermuscular adipose tissue may also result in improved metabolic function of the skeletal muscle (179). Acute heating with a far infrared sauna did not improve postprandial glucose handling in adults with type 2 diabetes (72), but other passive heating modalities do not report improvements in glucose handling with acute heating (101, 180) but do with repeated heating (19-21, 181). This is due to the differences in physiological mechanisms between acute and repeated heat therapy (75).

Therefore, the repeated use of far infrared saunas may be a lifestyle intervention to target metabolic health, but this has not been directly investigated or applied in a cohort of individuals with an elevated BMI. Our purpose was to investigate the effects of repeated far infrared sauna

bathing on metabolic health in adults with an elevated BMI. We hypothesized that repeated far infrared sauna bathing in adults would reduce fasting glucose and systemic inflammation (IL-6 and TNFα). The secondary hypothesis was that these improvements in metabolic health would be due to improved glucose handling and heat shock proteins within the skeletal muscle.

MATERIALS AND METHODS

Participants

Volunteers were recruited from the local community and were included in the study if they were between the ages of 18 and 59 years and had a BMI between 30 and 45 kg/m^2. Exclusion criteria included diagnosed cardiovascular and/or metabolic diseases other than elevated or stage 1 hypertension; taking medications that affected blood pressure, blood sugar, or blood clotting; current smokers; pregnant, breastfeeding, or desiring to become pregnant in the next 6 months; participating in > 120 min of vigorous exercise a week; allergies to lidocaine, latex, and/or adhesives.

Study Design

Participants were assigned to either a heat therapy or a time control group to be matched for age and BMI. A blood draw and muscle biopsy (described in detail below) were collected before (PRE) and after (POST) 8 to 10 weeks of heat therapy or time control. Table 1 in Chapter IV shows the characteristics of participants.

Heat therapy

The heat therapy protocol is described in detail above (see Chapter IV). In short, participants completed 25 to 30 sessions in a commercially available sauna 3 to 4 times per week for 8 to 10 weeks. The sauna sessions were between 30 and 45 min at temperatures between 45-60°C.

Experimental visit procedures

Before the experimental testing days, participants were instructed to abstain from medications and supplements (except for hormonal contraception) and heavy exercise for ≥ 24 hours, alcohol and caffeine for ≥ 12 hours, and food for ≥ 8 hours. Further, before the muscle

biopsy visit, participants were instructed to refrain from taking non-steroidal anti-inflammatory drugs (NSAIDs) for the 4 days before the visit. Participants completed a food and beverage log for the 24 hours before the pre-testing day with the blood draw and were provided with a copy to match for the 24 hours before post-testing. All post-testing visits were completed at a minimum of 36 h and a maximum of 1 week after the last sauna session. The start time of the visits is held constant within 1 hour of pre-testing to minimize confounding measures of circadian rhythm (128). Participants with childbearing potential provided the start date of their last menstrual cycle at the start of each visit, but the visits were not scheduled to control for menstrual cycle phase. Upon arrival at the laboratory, participants with childbearing potential provided a urine sample for confirmation of negative urine pregnancy tests. All participants were instructed to rest quietly, supine for the duration of the visit.

Phlebotomy

A venous blood draw from the antecubital space of the arm was obtained during the Vascular Function Testing day (as discussed in Chapter IV) in the supine position after 20 min of quiet rest. The Vascular Function testing day occurred within 2-6 days of the muscle biopsy visit. We were unable to obtain an adequate blood draw in one participant at pre-testing. A sodium citrate-treated plasma vacutainer was centrifuged immediately at 4°C, 1,300 relative centrifugal force (RCF) for 10 min, aliquoted, and stored at -80°C until further analysis. A serum separating clot activator-treated serum vacutainer clotted upright at room temperature for 30 min, centrifuged at 4°C, 1,300 relative centrifugal force (RCF) for 10 min, aliquoted, and stored at -80°C until further analysis.

Percutaneous biopsy procedures

The biopsy was completed in the same leg at both time points, and participants selected the side on which the biopsy occurred. The percutaneous biopsy was completed under sterile technique as described elsewhere (182). The biopsy area was sterilized, and a local anesthetic was injected. A small incision was made in the skin and the muscle fascia for the passage of a Bergström biopsy needle. Our original goal was to obtain skeletal muscle samples from the vastus lateralis muscle. We obtained adequate muscle tissue in 7 out of 16 (43%) of our participants, in addition to obtaining adipose tissue in 12 out of 16 (75%) of our participants at

both time points (pre and post). Muscle and adipose tissue were removed from the biopsy needle and immediately flash frozen in liquid nitrogen and stored at -80°C for later analyses.

Blood sample analysis

Whole blood was analyzed for HbA1c with a point-of-care assay (Afinion™ HbA1c, Abbott, Abbott Park, IL). Plasma glucose and serum insulin were analyzed by the Oregon Clinical and Translational Research Institute via an oxidase assay and enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden). We calculated the homeostasis model assessment of insulin resistance (HOMA-IR):

$$HOMA - IR = [glucose\ (mg/dL) \times\ insulin\ (\mu U/mL)]/405$$

and the quantitative insulin sensitivity check index (QUICKI):

$$QUICKI = 1/[Log\ (glucose) + Log\ (insulin)]$$

Systemic inflammation was quantified in the serum samples with commercially available high-sensitivity ELISA kits for IL-6 (Cat. No. HS600C, R&D Systems, Minneapolis, MN) and TNFα (Cat. No. HSTA00E, R&D Systems, Minneapolis, MN).

Muscle tissue analysis

Frozen skeletal muscle samples were homogenized at a 12:1 ratio (volume/weight) of cold buffer with 10 ul/1 ml protease inhibitor cocktail. The homogenized samples remained on ice for 90 min and were then centrifuged for 5 min at 3,000 rpm at 4°C. Protein quantification of the supernatant was quantified. Samples were prepared in buffer with 2 mM dithiothreitol and heated at 70°C for 10 min. Samples were loaded at 30 ug protein and subjected to SDS-PAGE (4-12%) followed by a wet transfer to a PVDF membrane for 60 min (200V). Membranes were blocked for 1 hour, followed by an overnight incubation with primary antibodies at a concentration of 1:1000 for p-AS160, total AS160, p-Akt, total Akt, GLUT4, and HSP70. Following 3 x 5 min rinses in TBST, secondary antibodies were applied at concentrations of 1:15,000 for 1 hour at room temperature, 3 x 10 min rinses in TBST, and bands were quantified via LI-COR Odyssey infrared imaging system.

Statistical Analyses

Data were analyzed in GraphPad Prism (v.10.6.0) with a set at 0.05 and presented as means [95% confidence intervals], unless otherwise noted. For the outcome variables, statistical inferences were drawn from a two-way mixed effects model with main effects for time (PRE and POST) and groups (Control and Heat), and a time x group interaction term with pre-planned comparisons. Inferences regarding the differences between groups were drawn from Sidak's Multiple Comparisons Test, restricted to comparisons within the same time point (PRE or POST). Inferences regarding the differences within groups were drawn from Sidak's Multiple Comparisons Test, restricted to comparisons between timepoints (POST versus PRE).

RESULTS

Plasma glucose and serum insulin

Figure 8 shows measures of systemic fasting parameters. At PRE, fasting glucose was similar between the Control and Heat groups ($P = 0.07$, Fig 8A). Fasting glucose decreased from PRE to POST in the Heat group ($P < 0.01$) but not in the Control Group ($P = 0.47$). At PRE, fasting insulin was similar between the Control and Heat groups ($P = 0.82$, Fig. 8B). This did not change from PRE to POST in either group. At PRE, HOMA-IR was similar between the Heat and Control groups ($P = 0.43$, Fig. 8C). HOMA-IR did decrease from PRE to POST in the Heat group ($P = 0.04$) but not the Control Group ($P = 0.94$). At PRE, QUICKI was similar between the Control and Heat groups ($P = 0.73$, Fig. 8D). This did not change from PRE to POST in either group. At PRE, HbA1c was similar between the Control and Heat groups ($P = 0.86$, Table 1). This did not change from PRE to POST in either group.

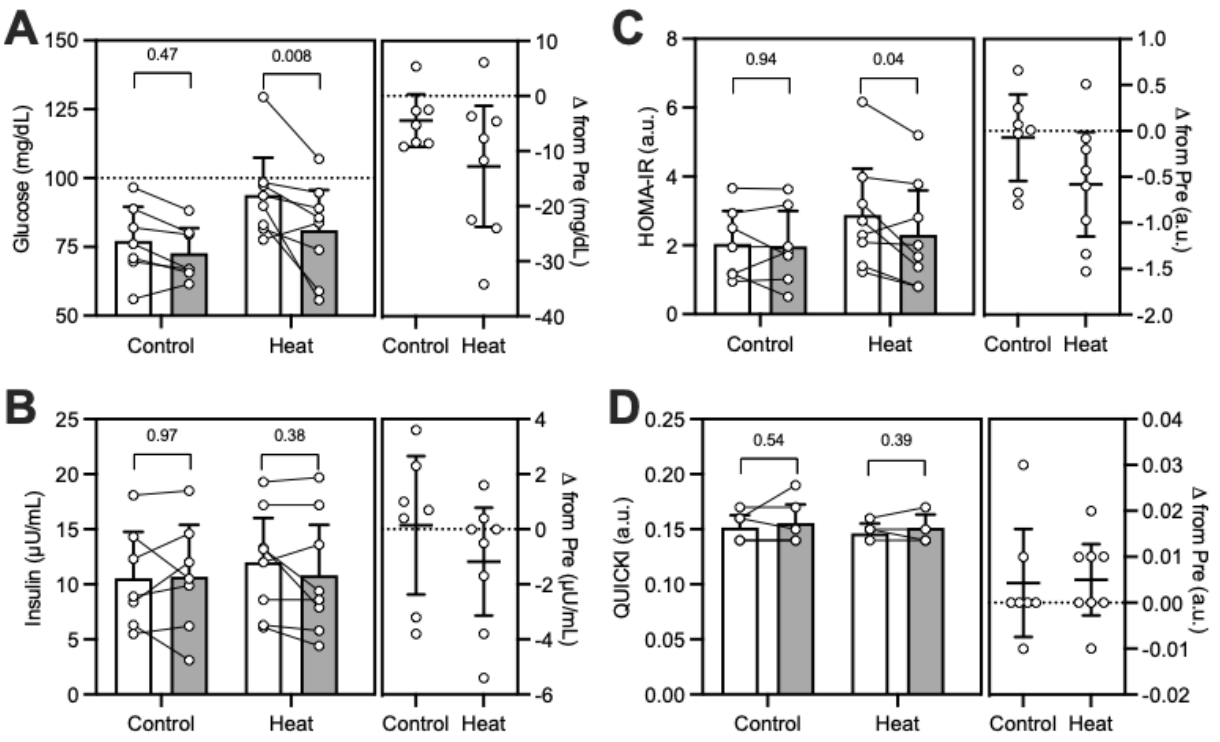

Figure 8. Systemic fasting parameters of plasma glucose (A), serum insulin (B), and calculated homeostatic model assessment for insulin resistance (HOMA-IR)(C) and calculated quantitative insulin sensitivity check (QUICKI)(D) measured before (PRE; open bars) and after (POST; gray bars) 8 to 10 weeks of time control (n=7) or heat therapy (n=8). Data are presented as means [95% CI] and individual responses for absolute values (left panel) and change (Δ) from PRE (right panel). P-values shown are from pre-planned comparisons of Sidak's multiple comparisons test within groups between timepoints from the mixed-effects model (Group effect $P \geq 0.10$, Time effect $P \geq 0.01$, Interaction effect $P \geq 0.13$).

Systemic inflammation

Figure 9 shows measures of systemic inflammation (IL-6 and TNFα) at both time points in both groups. At PRE, IL-6 was similar between the Control and Heat groups (P = 0.28, Fig. 9A). This did not change from PRE to POST in either group. At PRE, TNFα was similar between the Control and Heat groups (P = 0.78, Fig. 9B). This did not change from PRE to POST in either group.

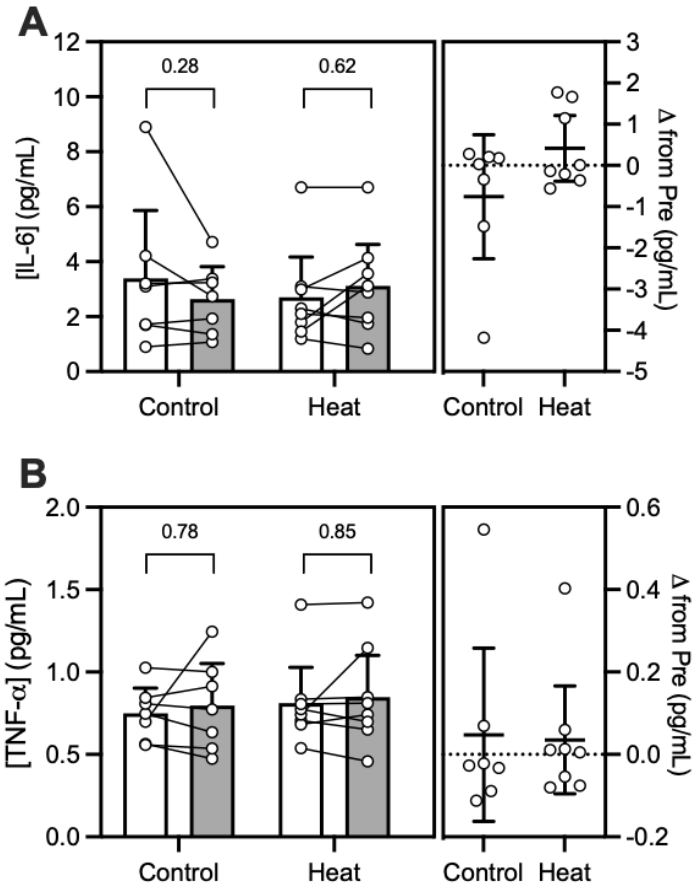

Figure 9. Systemic inflammation of IL-6 (A) and TNFα (B) measured before (PRE; open bars) and after (POST; gray bars) 8 to 10 weeks of time control (n=7) or heat therapy (n=8). Data are presented as means [95% CI] and individual responses for absolute values (left panel) and change (Δ) from PRE (right panel). P-values shown are from pre-planned comparisons of Sidak's multiple comparisons test within groups between timepoints from the mixed-effects model (Group effect $P \geq 0.65$, Time effect $P \geq 0.42$, Interaction effect $P \geq 0.11$).

Skeletal muscle biopsy

Figure 10 shows the representative figure of the western blot analysis for HSP70, although we were unable to adequately quantify the skeletal muscle targets, as described in Chapter III.

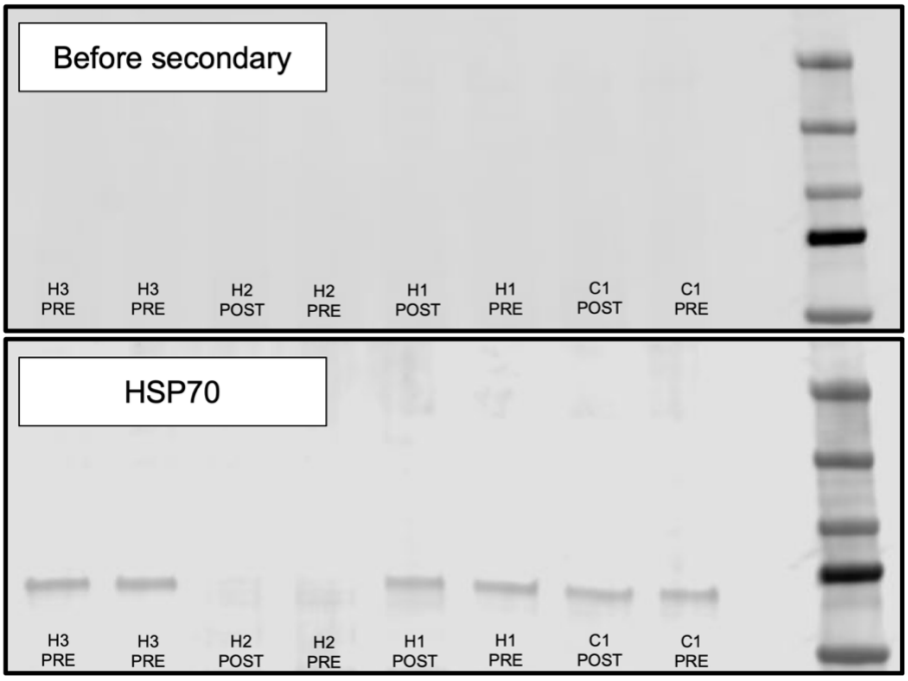

Figure 10. Representative image of western blot analyses from skeletal muscle in one control (C1) and three heat therapy (H1-H3) participants at PRE and POST.

DISCUSSION

The purpose of the present study was to investigate the effects of repeated far infrared sauna bathing for 8 to 10 weeks on metabolic health parameters in adults with an elevated BMI. Our main findings were that repeated far infrared sauna bathing reduced fasting glucose, but there were no changes to serum insulin and systemic inflammation. These findings imply there may be metabolic benefits with repeated far infrared sauna bathing, but more research is needed to understand the mechanisms (such as in the skeletal muscle) for this reduction in glucose, independent of inflammatory status, in adults with an elevated BMI.

Fasting Glucose and Insulin

Our findings of a reduction in fasting glucose and no change to insulin match some but not all previous investigations with repeated far infrared sauna bathing (66, 73). In these previous studies, the blood glucose and insulin parameters were secondary outcomes. These investigations included individuals with a primarily healthy metabolic profile, and yet still saw improvements. All but one of our participants had normal fasting blood glucose levels (< 100 mg/dL) at pre-testing, and nine of the sixteen participants had a normal HbA1c (< 5.7%). Therefore, although

most of our participants did not have insulin resistance, our findings still suggest an improvement in their insulin sensitivity. We recognize a limitation of our findings is that we only measured fasting parameters of glucose and insulin. The addition of an oral glucose tolerance test or hyperinsulinemia-euglycemic clamp would have better supported the conclusion of an improvement in insulin sensitivity. For example, while there were no changes to fasting parameters, Fuchs et al. reported an improvement in post-prandial glucose handling in adults after 24 sessions of far infrared sauna bathing (45 min each) (73). The authors noted the largest improvement occurred in the individuals with more dysfunction (i.e., higher pre-intervention fasting glucose), although they were otherwise healthy. While we did not have these dynamic measures of glucose handling, we originally included the analyses of the skeletal muscle to provide mechanistic insight into these fasting parameters.

Inflammation & heat shock proteins

A consequence of adipose tissue expansion is the chronic low-grade inflammation that is a primary culprit for insulin resistance and the negative metabolic consequences of excess adiposity (7, 104, 183). Further, heat shock proteins (HSP) are reduced in individuals with obesity, insulin resistance, and type 2 diabetes (184), but an overexpression of HSP72 improved skeletal muscle glucose uptake (185). We hypothesized that metabolic improvements would be due to reductions in inflammation via the induction of HSPs (3, 176, 186). Contrary to our hypothesis, there were no changes to systemic markers of inflammation, IL-6, or TNFα, with repeated far infrared sauna bathing. There are limited reports for inflammation and heat shock proteins in humans with far infrared saunas. Some animal and cell models have shown reductions in inflammation, although the literature is quite limited (163, 187). A single bout of far infrared whole body exposure increased HSP70 (188), and this increase is consistent with other acute heating modalities (36, 189, 190) but not all (191). We were unsuccessful in our attempts to quantify HSP70 in the skeletal muscle tissue. We suspect there was no change, due to the lack of increase in rectal temperature during the sauna visits, but this must be confirmed with future research. With repeated heat therapy protocols, some but not all (181) report increases in HSP, but this may be due to either the thermal stimulus and/or the quantification of intracellular versus extracellular HSP. There are no reports of the quantification of HSP with repeated far infrared sauna bathing, except for an increase in cardiac muscle from hamsters (67).

Skeletal muscle temperature is relevant to consider, especially in the context of the radiant heating stimulus from the far infrared waves. Local heating of skeletal muscle with short-wave diathermy increased skeletal muscle temperature to about 39-40°C and increased heat shock proteins, mitochondrial adaptations, and prevented atrophy during immobilization (46, 78). We did not have a measure of skeletal muscle temperature during the sauna sessions in our cohort of individuals, and this prompted the acute investigation discussed in detail in Chapter VI. Additionally, there may be additional metabolic benefits to heating the subcutaneous and potentially intramuscular adipose tissues, which would provide further insight into metabolic mechanisms with passive heating.

Insulin-mediated glucose handling

As originally hypothesized, we sought to first investigate the insulin-mediated glucose uptake cascade (i.e., phosphorylated AS160 and AKT) in the skeletal muscle to offer mechanistic insight into changes, if any, in fasting plasma glucose. Heat therapy has been shown to improve insulin-mediated glucose uptake in skeletal muscle in rats (3) and insulin signaling in adipose tissue in humans (19). One consideration is that we only had basal, non-stimulated biopsy tissues, and stimulation with insulin could have provided even more insight. As stated previously, we were unable to adequately quantify these targets within the skeletal muscle, but we encourage future research to address these important outcomes. Due to the lack of change in the systemic inflammation paired with the normal fasting glucose levels, it was unlikely that stress kinases (i.e., JNK, IKKB) and inflammation within the skeletal muscle were also elevated in our participants. This may be supported by the fact that we recruited individuals who did not have diagnosed metabolic diseases. For comparison, the levels of IL-6 were almost double those of adults without an elevated BMI (71, 192) but may not have been elevated to levels that cause dysfunction. However, these need to be confirmed with these more detailed measures within the skeletal muscle, which may precede systemic changes and warrant future investigation with far infrared sauna bathing.

Additional mechanisms for improvements in fasting blood glucose

Other mechanisms for increases in glucose uptake, independent of the hypothesized mechanism, include increased endothelial nitric oxide synthase and nitric oxide, skeletal muscle

capillarization and blood flow, changes in adipokines (i.e., leptin, adiponectin), and reductions in systemic fatty acids (193-197). These have been mechanisms proposed and measured for improvements in glucose uptake in previous heat therapy protocols (113, 195). The vascular responses are likely driven by increases in shear stress with the redistribution of blood flow during passive heating (29). More recently, local passive heating can increase skeletal muscle blood flow and may further support the mechanism for vascular adaptations (i.e., angiogenesis) within the skeletal muscle (198, 199). Elevated systemic free fatty acids can impair insulin signaling and glucose endogenous production (200, 201). Heat therapy has been shown to reduce free fatty acid levels in mice (202) and humans (19, 113), but there are no reports for far infrared sauna bathing. Lastly, Morera et al. used a far infrared heat lamp over the cage of mice and reported improvements in insulin signaling due to changes to adipokines in adipose, muscle, and liver (196). This may support future investigations to directly quantify changes within adipose tissue, particularly subcutaneous or intermuscular depots, due to the potential interaction with the far infrared waves.

Specific to whole body far infrared sauna bathing, Fuchs et al. reported an increase in skeletal muscle capillarization, but interestingly concluded it did not correlate with the improvements in post-prandial glucose handling (73). Again, they did not have a measure of body core temperature, but did report a higher temperature during their sauna sessions, which makes it challenging to draw comparisons to. Nonetheless, this research group and others have suggested that at lower skeletal muscle temperatures, vascular adaptations may support some improvements to metabolic function and precede the mitochondrial adaptations with larger increases in skeletal muscle temperature (46, 78, 79, 195). Based on the lower temperature profile of the sauna and lack of rectal temperature change in our individuals, we would speculate vascular adaptations within the skeletal muscle, and potentially adipose tissue, to be a mechanism supporting the improvements in fasting glucose.

Conclusion

In summary, repeated far infrared sauna bathing in a commercially available sauna for 8 to 10 weeks reduced fasting plasma glucose in adults with an elevated BMI. Contrary to our hypothesis, there was no reduction in inflammation to support this reduction in fasting plasma glucose, and we unfortunately could not use the skeletal muscle markers of the insulin signaling

cascade to offer further mechanistic insight. Our data imply that repeated far infrared sauna bathing may be a lifestyle intervention to target metabolic health in adults with an elevated BMI, but the mechanisms behind this warrant further investigation with more dynamic and detailed measures (i.e., oral glucose tolerance test, skeletal muscle or adipose tissue signaling).

CHAPTER VI

MUSCLE TEMPERATURE INCREASES DURING A SINGLE FAR INFRARED SAUNA SESSION WITHOUT CHANGES IN INTESTINAL TEMPERATURE

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INTRODUCTION

Skeletal muscle contributes to multiple functions, including postural support, physical movement ranging from activities of daily living to elite performance, and metabolism. The maintenance of skeletal muscle mass and function is important for overall health, as a reduced skeletal muscle mass is associated with a greater mortality (203-205). While regular physical activity is protective of muscle mass and function, only about 30% of the adult population meets the recommended guidelines for both aerobic and strength physical activities (206). The use of passive heating, for example, with hot tubs and saunas, has been proposed as another lifestyle means to reduce the risk of cardiovascular and metabolic disease, improve performance or recovery, and maintain skeletal muscle function (29, 51, 207, 208). This may be in part due to the similar increases in skeletal muscle temperature during passive heating as observed during exercise.

Skeletal muscle temperature increases during exercise, as a byproduct of skeletal muscle contraction, are directly related to the workload and can be further altered by the environmental conditions (44, 209). The skeletal muscle temperatures during different modalities, intensities, and durations of exercise range between 37.8-40.2ºC (80, 189, 209-213). Changes in skeletal muscle temperatures during passive heating are due to the heat exchange with the external environment, adjacent tissues, and blood flow (214-216). The muscle temperatures during passive heating with localized short-wave diathermy (~39-40ºC) (46, 78, 80, 217), hot water immersion (39ºC) (218), and traditional sauna (37.5ºC) (131) are similar to exercise. The increase in skeletal muscle temperature is associated with increased endothelial nitric oxide synthase (195, 219), angiogenesis and capillary growth (189, 195, 198, 220), mitochondrial function (46, 78), insulin signaling (197, 221), and heat shock proteins (46, 78, 219, 222). These

responses are associated with improvements in cardiovascular, metabolic, and musculoskeletal outcomes with repeated exposures and offer support for the use of passive heating as a lifestyle intervention.

Far infrared saunas have panels on the interior of the sauna that emit far infrared waves, a radiant heat stimulus, and are claimed to penetrate 3 to 4 cm into the peripheral tissues (51, 87). The full far infrared range within the electromagnetic spectrum is between 3 and 1000 mm (83) but commercially available sources are within a more narrow range of 5 to 14 mm (84). These saunas are continuing to increase in popularity and accessibility by the general public. A typical far infrared sauna session is between 15 to 30 min at temperatures between 45-60ºC (50). The sauna session can then be followed up by a 30 min period wrapped in blankets, known as Waon therapy (52). Some cardiovascular improvements have been observed with repeated use of Waon therapy with a custom-made sauna in patients with cardiac conditions (55, 68). These improvements were likely due to increases (1.0-1.5ºC) in pulmonary artery temperature. Others have reported tympanic temperature increased during a single far infrared session (40 min) in adults with type 2 diabetes (72). In addition, repeated far infrared sauna bathing (45 min) in older adults increased skeletal muscle capillarization (73). However, Atencio et al. reported minimal or no change to core temperature (rectal and intestinal) during a 45 min far infrared sauna session in young, healthy adults (71). These participants felt warmer and sweat appreciably (as marked by changes in body mass of about -0.3%). However, the skeletal muscle temperature responses during far infrared sauna bathing are currently unknown. Quantifying the skeletal muscle temperatures may offer further insight for the thermoregulatory responses, mechanistic understanding, and application of these saunas as a passive heating modality used by recreational, athletic, and clinical populations to optimize targeted outcomes. Therefore, the purpose of this exploratory study was to quantify the skeletal muscle temperature response during a single far infrared sauna visit.

MATERIALS AND METHODS

The protocol was approved by the Institutional Review Board at the University of Oregon and conformed to the principles of the Declaration of Helsinki, except for registration in a database.

Participants

Ten young, healthy individuals (6 women, 4 men) volunteered to participate in the protocol, and the characteristics of the participants are shown in Table 5. Inclusion criteria included being between the ages of 18-40 years, a body mass index between 18-28 kg/m^2, and classification of Tier 0 or Tier 1 for physical activity levels according to McKay et al. (223). Exclusion criteria included self-reported medical conditions impacting cardiovascular, respiratory, metabolic, neurologic, gastrointestinal systems, or blood clotting or anemia disorders, use of prescription medications other than hormonal contraceptives, and any hypersensitivities or allergies to drugs, local anesthetics, skin disinfectants, adhesives, or latex. Participants were excluded if systolic blood pressure was > 120 mmHg or diastolic blood pressure > 80 mmHg (Tango M2, Suntech Medical, North Carolina, USA). Ultrasonography (iE33, Philips, Amsterdam, Netherlands) was used to quantify tissue thickness of the thigh (subcutaneous adipose and muscle) at half the distance between the anterior superior iliac spine and superior aspect of the patella, with the target tissue being the vastus lateralis quadriceps muscle. This was to ensure sufficient tissue for the placement of the intramuscular temperature probe while avoiding large veins, arteries, and the iliotibial band. Participants were excluded if the tissue thickness was < 4.0 cm.

Table 5. Participant characteristics

Variable	
Age (y)	24 ± 4
Height (cm)	168 ± 10
Weight (kg)	68.3 ± 11.7
Body mass index (kg m^{-2})	23.8 ± 1.9
Body fat (%)	19.8 ± 6.8
Thigh volume (cm^3)	9612 ± 2009
Subcutaneous fat thickness (cm)	0.72 ± 0.33
Vastus lateralis muscle thickness (cm)	2.05 ± 0.48
Vastus intermedius muscle thickness (cm)	1.44 ± 0.33
n	10

Values are means ± standard deviations.

Study design

Participants were instructed to refrain from eating food for 2 h, caffeine for 10 h, and nutritional supplements, alcohol, drugs, and moderate to vigorous exercise for 24 h prior to the start of the study visit. Participants were provided with the ingestible telemetry pill (e-Celsius Performance, BodyCap Medical, Hérouville Saint-Clair, France) for the measurement of core temperature and instructed to ingest the telemetry pill at least 4 h prior to the start of the study visit (mean time of ingestion was 7.5 [5.6, 9.4] h). After instrumentation (described below), participants were seated for 60 min in an ambient temperature room (23 [23, 24]°C; 49 [46, 52]% relative humidity) then the "before heating" data were recorded. Next, participants entered the far infrared sauna and remained seated in the sauna for 45 min at which the "end of heating" data were recorded. Lastly, after exiting the sauna, participants remained seated for 30 min in the ambient temperature room then de-instrumented.

Far infrared sauna

The sauna thermostat was set to 45°C until the participant entered, then was immediately increased to 65°C to maximize the "on" cycle of the far infrared emitters throughout the duration of heating (IS 565, Finnleo, Sauna360 Inc., Minnesota, USA). According to vendor websites, the emitters for this sauna emit with the 8.4 to 9.4 mm range. We directly tracked the on/off cycle by linking the signal to the emitters to a data acquisition system (WinDaq, DATAQ Instruments, Akron, Ohio, USA). Far infrared emitters were on for 93% (42 [40, 44] min) of the 45 min that participants were in the sauna. While we used the factory-installed thermostat and recommended temperature settings (45-65°C) of the sauna, we also recorded temperature and humidity with a probe (Vaisala HUMICAP®, Vantaa, Finland) located at the same height as the thermostat but at the opposing upper corner of the sauna. We note that this additional probe recorded a lower average temperature of 43 [42, 44]°C) compared to the factory-installed thermostat sensor which averaged 57 [52, 62]°C.

Instrumentation and measurements

Upon arrival to the laboratory, a urine sample was obtained to quantify hydration status via urine specific gravity (<1.020) and a urine pregnancy test for those participants of childbearing potential to confirm they were not pregnant. A nude body weight was measured in a

private room to the nearest 10 g (Sartorius Midrics 2, Goettingen, Germany). Participants changed into the self-selected clothes for the sauna – shorts and a t-shirt, tank top, or sports bra.

A telemetry heart rate monitor (Polar Team Pro, Polar Electro, Kempele, Finland) was placed at the level of the heart. A blood pressure cuff was placed on the upper arm. Mean arterial blood pressure was calculated as: 0.3(systolic blood pressure-diastolic blood pressure) + diastolic blood pressure. Skin temperature was measured with temperature thermocrons (iButtons, iButton Link Technology, Wisconsin, USA) secured on the skin via adhesive tape to the chest, upper arm (triceps), thigh, and calf. Mean skin temperature was calculated as: *0.3(chest + upper arm) + 0.2(thigh + calf)* (126). Mean body temperature was calculated as: *0.8(core temperature) + 0.2(mean skin temperature)*(127). To quantify body fat percentage, skin fold thickness was measured via skinfold thickness at three locations: for women - the triceps, hip, and thigh; for men - the chest, abdomen, and thigh (224, 225). The measurement of thigh volume was calculated by measuring the total thigh length (L), the circumferences at midway (C_1) and 10 cm above (C_2) and 10 cm below (C_3) the midline, and accounting for skinfold thickness at the thigh (S) (226):

$$Thigh\ volume\ (cm^3) = L \times (12\pi)^{-1} \times (C_1^2 + C_2^2 + C_3^2)$$

$$-(S - 0.4) \times 2^{-1} \times L \times (C_1 + C_2 + C_3) \times 3^{-1}$$

A multi-sensor intramuscular temperature probe (Physitemp Instruments, LLC, New Jersey, USA) was inserted into the lateral thigh with the participant in the supine position. The probe had three thermocouples including one at the tip (deep), 10 mm from the tip (middle), and 20 mm from the tip (superficial). The location for the placement was scouted via ultrasonography half the distance between the anterior superior iliac spine and the superior border of the patella. Images were obtained with the ultrasound probe both parallel and perpendicular to the vastus lateralis while avoiding compression of the tissues (227, 228). The images were analyzed for the thickness of subcutaneous fat and quadricep muscles (vastus lateralis and vastus intermedius). This allowed us to define the tissue localization for the three thermocouples following the protocol. The surface of the thigh was sterilized with 2% chlorhexidine gluconate/70% isopropyl alcohol followed by the placement of a fenestrated drape. The skin was anesthetized with prilocaine hydrochloride (4%) followed by lidocaine

(2%)/epinephrine. A 17-gauge introducer needle was inserted perpendicular to the muscle tissue and the intramuscular probe inserted so the tip of the probe would be at ~4 cm deep. This depth was selected as it has been reported that far infrared penetrates 3 to 4 cm into peripheral tissues (51, 87). We opted for an absolute depth across participants in order to determine the depth of heating of peripheral tissues, rather than attempting to control the placement of probes relative to subcutaneous fat and/or muscle thickness as suggested by others (229). This was to increase the ecological validity of our results for users of commercially available saunas. We do recognize that tissue types, thickness, and depths can alter temperature profiles and should be considered for future research (189, 218, 229-232). The probe was secured with steri-strips and covered with a Tegaderm dressing.

After the probe was placed, participants rested in the seated position for 60 min for muscle temperature to stabilize post-insertion. At the end of 60 min, "before heating" data were obtained in the seated position. Then, participants were carefully moved into the sauna while research team members offered physical support to avoid the participants putting weight on the leg with the temperature probe secured in position with the Tegaderm dressing.

Heart rate, muscle temperature, core temperature, skin temperature, and sauna conditions (temperature and humidity) were recorded continuously during the sauna session. Perceptions of thermal sensation (233), thermal comfort (233), and perceived sweating (234) were reported by participants every 10 mins. At the end of 45 min, "end of heating" data were obtained prior to participants exiting the sauna.

At the end of the protocol, the probe was marked where it exited the skin so that when it was removed, the length that had resided in tissue could be directly measured. A second nude body weight was measured. Whole body sweat loss was calculated as the change in nude body weight corrected for *ad libitum* fluid intake and urine loss, if applicable.

Statistical analyses

Data were analyzed in GraphPad Prism (Version 10.4.0) with α set at 0.05 for all statistical inferences including familywise error rates. Inferences regarding the change in absolute muscle temperatures were drawn from a two-way mixed-effects model (tissue depth and before heating vs. end of heating) with pre-planned comparisons (Šidák's multiple comparisons

test, restricted to comparisons at the same timepoint between depths or same depth but between timepoints). Inferences regarding the change in muscle temperatures at each tissue depth (from before heating to end of heating) were drawn from a one-way mixed effects model (Šidák's test between each tissue depth). A simple linear regression between the tissue depth and change in temperatures (from before heating to end of heating) was completed with thigh skin temperature representing 0 cm and all other depths were from the multi-sensor intramuscular temperature probe. From this regression, we calculated the effective thermal penetration as the depth at which the thermic effect was reduced by 63%, a concept derived from analysis standards for radiant energy (235). Inferences regarding the changes in core temperature, mean body temperature, skin temperatures, perceptions, and heart rate were drawn from paired two-tailed t-tests (before heating vs. end of heating). Values represent means [95% confidence intervals], unless otherwise noted.

RESULTS

Skeletal muscle temperature

The skeletal muscle temperatures at each depth are shown in Figure 11 and Supplemental Table 2. The depths of the thermocouples within the single intramuscular temperature probe were 1.4 cm (superficial), 2.4 cm (middle), and 3.4 cm (deep) below the surface of the skin. Further, the superficial thermocouple was in the vastus lateralis muscle (n=8) and subcutaneous fat (n=2), the middle thermocouple was in the vastus lateralis (n=8) and vastus intermedius (n=2) muscles, and the deep thermocouple was in the vastus lateralis (n=1) and vastus intermedius (n=9) muscles. All three depths increased in temperature from before heating to end of heating (all $P<0.04$). At before heating, superficial (34.2 [33.3, 35.1] °C) was lower than middle (34.8 [33.9, 35.7] °C) and deep (35.4 [34.6, 36.3] °C), and middle was lower than deep (all $P<0.01$). At end of heating, superficial (37.2 [36.5, 37.8] °C) was greater than middle (36.7 [36.2, 37.3] °C) and deep (36.5 [36.1, 37.0] °C) (both $P<0.01$) but middle was not different from deep ($P=0.35$). The change in temperature from before heating to end of heating was greater in superficial (+3.0 [1.8, 4.1] °C) compared to middle (+1.9 [1.0, 2.9] °C) and deep (+1.1 [0.3, 1.9] °C) (both $P<0.01$) and in middle compared to deep ($P=0.01$). The results from a simple linear regression analysis between depth and change in temperature are shown in Figure 12. The

overall regression was significant (R^2=0.720, F(1, 38)=[97.92], P<0.01). The fitted regression model was y= -1.57x + 5.97, which has an x-intercept of 3.79 cm (indicating no change in temperature at that depth). The effective thermal penetration (the depth at which the thermic effect was reduced by 63%) was 2.39 cm.

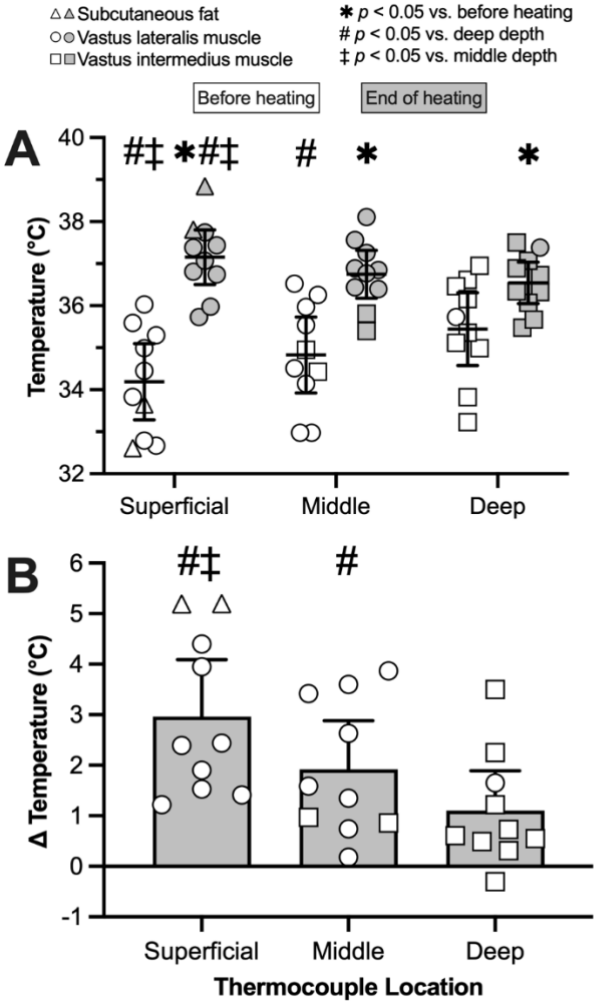

Figure 11. Individual muscle temperatures at before heating and end of heating (A). The means and 95% confidence intervals are represented by the black lines. Data were analyzed with a two-way mixed effects model for depth x time with Sidak's multiple comparisons test. The change in muscle temperatures from before heating and end of heating (B). The data show means (gray bars) and 95% confidence intervals (black lines) with individual data (white symbols). Data were analyzed with a one-way mixed effects model with Sidak's multiple comparisons test. The depths of the thermocouples were superficial (1.4 cm), middle (2.4 cm), and deep (3.4 cm).

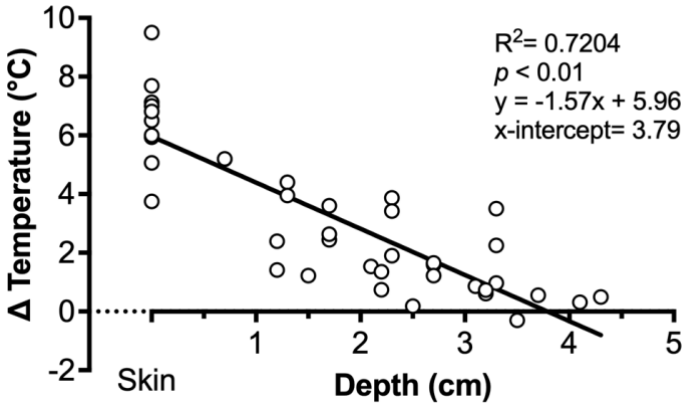

Figure 12. Simple linear regression analysis between the depth and change in temperature (from before heating to end of heating) where thigh skin temperature is represented by 0 cm and all other depths are from the multi-sensor intramuscular temperature probe.

Core temperature, skin temperatures, heart rate, and blood pressures

The core and skin temperature responses are shown in Figure 13. There was no change in intestinal core temperature from before heating to end of heating ($P=0.94$). There was an increase in mean body temperature from before heating to end of heating ($P<0.01$). This was driven by increases in mean skin temperature ($P<0.01$). There was an increase in skin temperature for all the skin temperature locations (chest, upper arm, thigh, and calf) (all $P<0.01$). There was an increase in heart rate from before heating (67 [64, 71] bpm) to end of heating (101 [89, 112] bpm) ($P<0.01$). There were no changes from before heating to end of heating for systolic, diastolic, or mean arterial blood pressures (Supplemental Table 3).

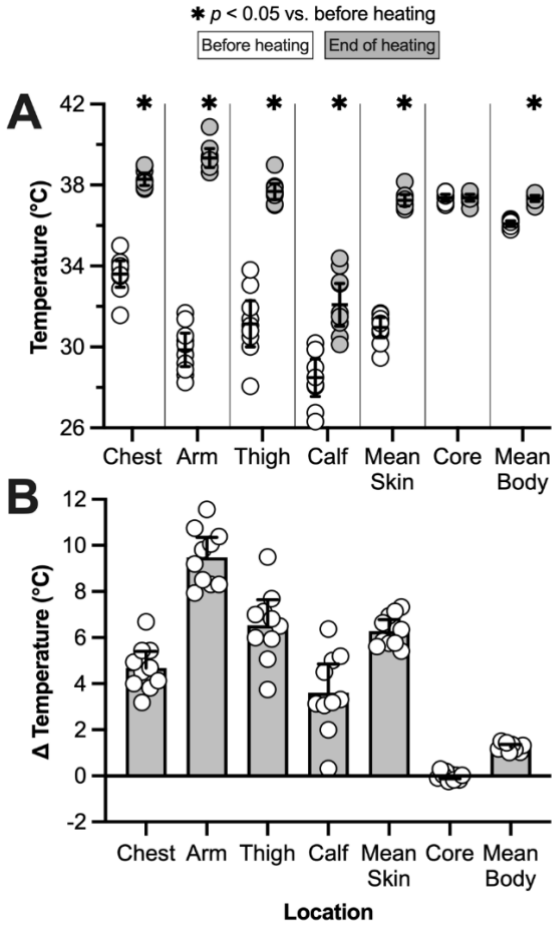

Figure 13. Individual core and skin temperatures at before heating and end of heating (A). The means and 95% confidence intervals are represented by the black lines. Data were analyzed with paired two-tailed *t*-test between pre and end of heating. The change of core and skin temperatures from before heating to end of heating (B) are shown as means (gray bars) and 95% confidence intervals (black bars) with individual data (white symbols).

Perceptions and whole body sweat rate

The perceptual responses are shown in Figure 14 and Supplemental Table 4. Thermal sensation, thermal comfort, and sweating perception all increased from before heating to min 40 of the sauna (all P<0.01). Participants lost 0.48 [0.37, 0.60] % of their body mass during the study visit and whole body sweat rate was calculated to be 0.46 [0.31, 0.61] L/h.

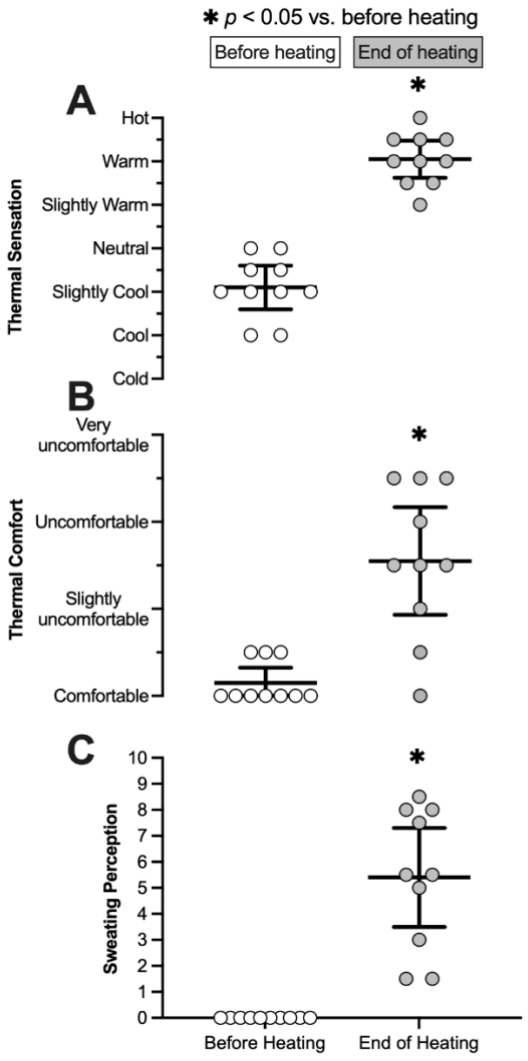

Figure 14. Individual perceptual responses at before heating and end of heating for thermal sensation (A), thermal comfort (B), and sweating (C). The means and 95% confidence intervals are represented by the black lines. Data were analyzed with paired two-tailed *t*-test between before heating and end of heating.

DISCUSSION

The overall purpose of the present study was to quantify the skeletal muscle temperature responses during a single far infrared sauna session with a commercially available sauna in young, healthy adults. The main finding was that skeletal muscle temperature increased during the sauna session with the magnitude of the increase being dependent on the depth of the skeletal muscle relative to the skin surface. The increase in skeletal muscle temperature coincided with increases in skin and mean body temperatures, heart rate, perceptions of warmth, thermal discomfort, and sweating. Interestingly, these all occurred without changes to core temperature

measured via ingestible pill due to the increase in whole-body sweating. Together, this would imply that the commercially available far infrared sauna used in this current protocol increased the temperature of superficial tissues to a greater extent than deep muscles, heating is negligible by 3.8 cm below the skin surface, and the effective thermal penetration is about 2.4 cm (or a little less than an inch) in young, healthy adults.

Pattern of muscle heating

Before heating, the deep muscle (3.4 cm) had the highest before-heating temperature (35.4°C), and the superficial muscle (1.4 cm) had the lowest before-heating temperature (34.2°C). This temperature gradient before heating was expected as the superficial thermocouple was the furthest away from the core and closest to the external environment. The deep muscle had the smallest change in temperature during heating (+1.1°C). The superficial muscle had the greatest temperature response (+3.0°C), even when excluding the two individuals with the superficial probe in the subcutaneous fat (+2.4°C). The pattern was a depth dependent temperature gradient before heating and a more homogenous temperature profile at the end of heating, as shown in Figure 15. This is similar to previous findings of multi-depth muscle temperatures with hot water immersion, localized heating, and exercise (89, 90, 211, 218). While the patterns are similar, the muscle temperatures at the end of the far infrared sauna session (36.5-37.2°C) were lower compared to previously observed muscle temperatures with exercise (37.8-40.2°C)(80, 189, 209-213) and passive heating (37.5-40°C)(46, 78, 80, 131, 217, 218).

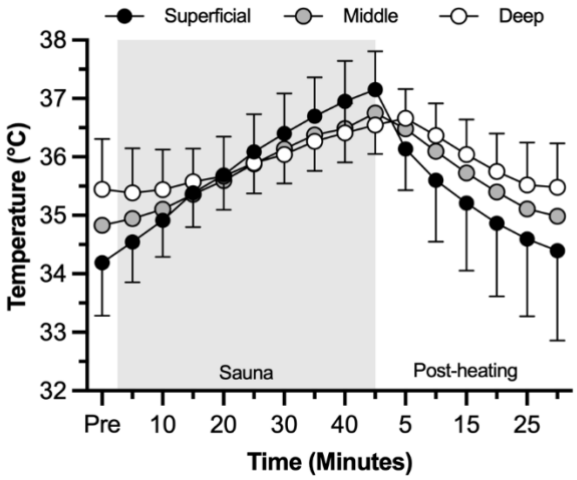

Figure 15. The muscle temperatures at each depth at 5 min intervals during the 45 min sauna session and the 30 min post-heating period. The means and 95% confidence intervals are shown for deep (white), middle (gray), and superficial (black) muscle temperatures.

Effective thermal penetration

The claim of far infrared waves penetrating up to 3 to 4 cm (1.5 inches) below the surface is cited across scientific and media platforms (51, 87). To our knowledge, there is a lack of data supporting this statement and it appears that there is heavy reliance on its mention in one review (87). Penetration depth is defined as the depth at which the radiant energy is at 37% of the original intensity (235) and absorption is the increase in energy within a target matter originating from a source. The penetration depth and absorption of electromagnetic waves are dependent on the wavelength and the composition (type and thickness) of the target tissue. Water has a high absorption capacity within the far infrared range due to the oxygen-hydrogen bonds and is essential for the use of far infrared waves as a heating stimulus. Far infrared waves penetrate the tissue and are absorbed by the molecular bonds of water, resulting in an increase in vibration, stretching, rotation, and bending of the molecular bonds with, and thus, an increase in temperature. It has been discussed that far infrared energy is absorbed more by the superficial tissues due to high water content, thus, penetration depth is more shallow than other bands of electromagnetic radiation (236). There is also reflection and scattering of the infrared waves which may further reduce penetration depth. To adequately quantify penetration depth and absorption, *ex vivo* work with specialized equipment such as a far infrared emitter source, a target tissue of known depth, and a detector (i.e., Fourier Transform Infrared spectroscopy) is

needed. While this would be the ideal way to quantify the depth to which far infrared waves penetrate human tissue, we employed an alternative and more practical or applied approach, one that intends to capture the penetration of not only the primary infrared waves but also the potentially conductive conveyance of thermal energy (that is absorbed by more superficial tissue) toward deeper tissue. Hence, we determined the effective thermal penetration of far infrared as it is deployed in our commercially available sauna to be 2.4 cm, or a little less than an inch.

Our findings are from only one anatomical region (lateral thigh) from a small cohort of individuals (young, healthy). Regions with less subcutaneous fat and/or more superficial structures may have greater increases in regional muscle temperatures. On the contrary, individuals with more subcutaneous fat may have lesser increases in muscle temperatures due to more of the far infrared energy being absorbed in a thicker superficial layer and less reaching the underlying muscle. In our cohort, subcutaneous fat thickness (0.72 cm) comprised ~30% of the effective thermal penetration whereas the subcutaneous fat thickness in a cohort of individuals with obesity (2.3 cm) (237) would have comprised ~96% of the effective thermal penetration. Furthermore, subcutaneous fat is a thermal insulator (low thermal conductivity) (232, 238), so we speculate that heating of subcutaneous fat may lead to less conductive heating of underlying muscle, but this assumption is untested. We do not know if heating subcutaneous fat will have health benefits, but perhaps fat inflammation or metabolic function would be improved, if the tissue temperature remains elevated (19, 239). It is also possible that heated subcutaneous fat would help maintain muscle temperature for longer following heating. Rodrigues et al. reported longer temperature recovery of the vastus lateralis temperature following hot water immersion (42°C for 120 min) with greater subcutaneous fat thickness (218). Therefore, anatomical regions and/or populations with differences in subcutaneous fat thicknesses should be considered in the application of our findings and future research, especially in the context of utilizing far infrared saunas to target cardiovascular, metabolic, and musculoskeletal function and health.

Infrared penetration versus thermal conduction

It is important to note that a temperature increase at a depth may not necessarily equate to the far infrared waves penetrating to that depth, as introduced above. Early work comparing localized heating of muscle with a near infrared lamp (1 mm) versus a far infrared carborundum rod (4-5 mm) showed similar increases in muscle temperatures despite different wavelengths

(89, 90). These early reports concluded that conductive heat exchange between adjacent tissues cannot be ignored and may explain the similar temperature profiles. The contribution of conductive heat exchange with a commercially available far infrared sauna may be overlooked as marketing emphasizes the radiant heat thermal stimulus, often characterized as more "directly" or "efficiently" heating the body, at lower sauna temperatures (240). However, comparing other passive heating modalities suggest that ambient temperature may be more important than electromagnetic wavelength. Specifically, muscle temperature increased more (by ~2°C at 3.5 cm depth) with a traditional "Finnish" sauna at 80°C (131) compared to the current far infrared investigation (by ~1°C at 3.4 cm depth).

Whole body thermic effects of far infrared sauna

Similar to the prior report by Atencio et al., there was no change in core temperature via an ingestible telemetry pill after 45 min in the far infrared sauna (71). One prior report, which relied on pulmonary artery temperature, found a 1.0-1.2°C increase core temperature in cardiac patients with far infrared sauna (70). Pulmonary artery and intestinal temperatures are thought to compare favorably during whole-body passive heating (241). Another report, using tympanic temperature, found a ~1.8°C increase in adults with type 2 diabetes during far infrared sauna (72). However, tympanic temperature is considered a limited estimate of core temperature in a warm environment (74). Thus, far infrared sauna does not typically elevate core temperature when measured by best methods in healthy individuals, but results have varied based on methodology and population. Other sources of variation across studies include variation in temperature throughout the sauna, the size of the sauna, distance from the far infrared panels, and duration of exposure. We opted for 45 min of sauna time to match the overall heating time with Waon therapy (15 min sauna, 30 min blankets). However, there was ~50% more exposure to far infrared radiation in our protocol compared to the typical Waon therapy sessions and yet no changes to core temperature. During Waon therapy, the post-sauna 30-min period that is spent wrapped in blankets may prevent effective convective and evaporative heat loss, thus generating a more sustained elevation in body temperature during this phase. In our protocol, the rate of evaporative heat loss via sweating was sufficient to achieve thermal balance throughout the passive heating.

Even though we found no change in core temperature, our participants reported increased thermal sensation (feeling warmer), thermal comfort (more uncomfortable), and perceived sweating (sweatier). The perception of sweating was corroborated by measured sweat losses. These observations are consistent with Atencio et al. (71). Clearly, far infrared saunas elicit whole body thermal responses. In this case, thermal sensation and responses may be dictated more by skin and peripheral tissue temperatures (possibly including the spinal cord) whereas with other passive heating modalities they may be dictated by skin, peripheral tissue, and core temperatures (233, 242-246).

Thermoregulation pathways

Body temperature of humans is regulated at neural circuits in the preoptic anterior hypothalamus that receive inputs from peripheral (skin) and central (brain, spinal cord, visceral organs, and great veins) thermoreceptors (247). Additionally, the skeletal muscle may also have thermosensitive afferent signals or non-thermosensitive afferent signals that elicit thermoregulatory responses with small increases in temperature, but this is not well documented in humans (248). Early work determined the importance of peripheral afferents for the onset threshold and sensitivity of thermoeffector output (132, 133) which supports the use of a calculated mean body temperature, weighted for both skin and core temperature, for quantifying thermoeffector output (102, 249). In the present study, the rise in calculated mean body temperature was driven solely by the elevation in skin temperature, which would evoke sweating (and although not measured, cutaneous vasodilation) to offset increases in core temperature (132, 250).

It is unknown if central thermoreceptors within the spinal cord or brain would be sensitive to far infrared heating. While the preoptic anterior hypothalamus is likely too deep to be impacted, it remains plausible that far infrared radiation could warm the spinal cord and some thermosensitive brain regions at depths comparable to what was observed for muscle. Overall, it would appear that peripheral thermoreceptors in the skin are the primary drivers of thermoeffector responses, and additional contributions from deeper tissues would likely be less due to smaller changes in tissue temperature.

What do we expect from routine far infrared sauna use?

It is tempting to believe that far infrared sauna may offer a more tolerable form of passive heating due to the minimal changes to core temperature and the sensation of being warm but not overly so. However, it is unclear if the passive heat stress pattern of elevated skin and superficial peripheral tissue (e.g., muscle) temperatures in the absence of core temperature elevation is a sufficient stimulus for adaptations to the cardiovascular, metabolic, and muscular systems that are often touted for heat therapy and heat acclimation. Passive heating, including with far infrared saunas, has also been proposed as a means to reduce cardiovascular strain during heat waves (251) but this has not been directly investigated. Additionally, far infrared emitters have been used locally and shown improvements in lymphedema and neuropathy (252-254) but the parameters (wavelength, distance) appear to be more regulated and controlled than with commercially available saunas.

Local elevations in skeletal muscle temperatures between 39-40°C have previously shown to elicit muscle mitochondrial adaptations (i.e., content and function) and heat shock proteins (46, 78, 79) whereas lower skeletal muscle temperatures of ~37°C were still sufficient to result in vascular adaptations (i.e., endothelial nitric oxide synthase, capillarization) within the skeletal muscle (73, 195, 198, 219). The local vascular adaptations could be due to the increased blood flow and shear stress patterns in the femoral arteries (common, superficial, and profunda) with isolated thigh heating that were similar to moderate whole body heat stress (157). While *in vitro* and *in vivo* glucose uptake increased with increasing muscle temperature in rats (38-42°C) (197), prolonged passive heating without an increase in core temperature, and likely lower skeletal muscle temperatures, did not change glucose transporter type 4 (GLUT4) expression in human skeletal muscle (195). Therefore, one would predict that the modest increases in muscle temperature may elicit local adaptations (i.e., vascular) whereas cellular adaptations (i.e., heat shock protein, mitochondrial function or content, glucose transporters) may be absent, limited, or more superficially located and not broadly expressed in skeletal muscle with the commercially available far infrared sauna used in this protocol.

In the present study and recent report by Atencio et al, the whole body response to far infrared sauna, evidenced by increases in heart rate and sweating, was modest when compared to hot water immersion (i.e., conventional hot tubs) and traditional sauna (71). The heart rate response to far infrared sauna was similar to what was reported with Waon therapy (70, 72). As

passive heating can be promoted as an exercise mimetic (29, 175), a commercially available far infrared sauna may offer a starting point for individuals with a lower thermal tolerance and/or cardiovascular fitness before progressing to other heating modalities or exercise. While the modest thermal and cardiovascular stimuli may hold merit over a sedentary lifestyle, some commercially available saunas may not offer the most robust adaptations given the large differences in the heart rate, cardiac output, and core temperature responses between passive heating modalities reported recently (71). It is unknown whether there is an increase in shear stress with our temperature patterns, or if the increase is sufficient for subsequent endothelial adaptations (255, 256), as shown with other passive heating modalities (26). Recent findings reported lower systolic blood pressure after repeated far infrared sauna bathing in older adults (73). However, there were no measures of core or muscle temperatures to compare temperature patterns with their model of a far infrared sauna (73). Lastly, mild increases in muscle temperature are associated with increased contractile function (257). Far infrared saunas may be appealing as a pre-exercise warm-up modality as the peripheral tissues are warm but do not hinder performance due to thermoregulatory and cardiovascular adjustments that can come with higher core temperatures (258, 259).

Conclusions

We conclude that skeletal muscle temperature increases during a single far infrared sauna session and these increases are depth dependent up until 3.8 cm below the skin surface. While this would align with the claim that far infrared penetrates 3 to 4 cm below the skin surface, the increase in temperature is likely due to a combination of both radiant and conductive heating and the effective thermal penetration is much less (2.4 cm, or less than an inch). Despite these muscle temperature increases and due to the lack of core temperature changes, far infrared saunas may offer a more tolerable form of passive heating for individuals naïve to or with a lower thermal tolerance for heat while targeting the more superficial levels of skeletal muscle. While more tolerable, we speculate that the cardiovascular, metabolic, and musculoskeletal adaptations or heat acclimation adaptations may be limited with repeated use in healthy and clinical populations compared to other forms of passive heating. We intend for the results from this exploratory

protocol to be considered to further the understanding and application of commercially available far infrared saunas to optimize targeted outcomes.

CHAPTER VII

PERSPECTIVES

The primary objective of this project was to investigate the potential means of a far infrared sauna to improve parameters related to cardiovascular and metabolic health in individuals with an elevated BMI. The application and takeaways of our findings are to be considered if and when individuals choose to use a commercially available far infrared sauna. For example, a 45 min session in a far infrared sauna starting at 45°C and then increasing to 60°C may not be fit for individuals seeking a large, robust thermal stimulus, whereas it may be ideal for an individual who is naïve to heat therapy. Individuals may choose to sauna bathe beyond targeting their cardiovascular and metabolic health for reasons such as pain management, stress release, post-exercise recovery, or to feel a sense of community, and these should not be dismissed in the application of far infrared saunas. We must continue to investigate the physiological effects of far infrared sauna bathing, with adequate quantification of the conditions of the sauna, when using a commercially available sauna. As stated at the beginning, just as there are different forms of exercise, there are different forms of passive heating available, and understanding these different heating modalities can help optimize the application of it as a meaningful lifestyle habit to those who choose to use a far infrared sauna.

Far infrared regimen

The majority of the far infrared sauna research stems from the use of Waon therapy in cardiac patients in hospitals in Japan in the late 1990s through early 2010s (67-70, 124). We applaud the researchers for implementing a non-pharmacological intervention within a hospital setting and clinical population, as their findings have provided a foundation for research with far infrared sauna bathing. It does not appear that current far infrared sauna bathing practices, particularly in North America, have continued with the inclusion of the practice of Waon therapy. The translation of Waon therapy is “soothing and warm” in a 60°C custom-made sauna, whereas present-day commercially available far infrared saunas are marketed as a more “direct” form of heating at lower sauna temperatures (45-60°C) for 15 to 30 min sessions (50). The custom-made sauna may offer better control over the temperature, distance, and distribution of the far infrared panels than the commercially available sauna. This is evidenced by the temperatures in our commercially available sauna being almost 20°C lower than the custom-

made sauna, but we could not increase the temperature further. Some panels were only a few centimeters from the participants, whereas others were two to three feet away, as our sauna is fit for multiple individuals. Additionally, during the post-sauna bathing period, being wrapped in blankets may prevent evaporative cooling and sustain elevations in pulmonary artery temperature, whereas during our protocols, participants were able to sweat effectively to prevent an increase in rectal temperature. Therefore, while the sauna type is the same (far infrared), it appears the magnitude of the thermal and, therefore, physiological stimulus is not.

Temperature of the sauna

Far infrared saunas are promoted to operate at lower temperatures, compared to a traditional sauna, between 45-60°C (50). This is due to the concept that the added radiant heating stimulus of the far infrared waves elicits a more "direct" form of heating, so the sauna does not need to be as warm. Further, some marketing claims state that users can enter the sauna immediately as it is turned on to be exposed to the far infrared waves, whereas others recognize it might be preferred to pre-heat the sauna prior to entry. In our protocol, we opted to have the greater exposure to the far infrared waves with the sauna starting at 45°C and then increasing to 60°C, versus having the sauna maintained at 60°C. Others have used steady state protocols (20-45 min) at set temperatures between 50-63°C (73, 135). These varying practices have not been directly compared nor supported by data for the thermal stimulus provided via radiation and subsequent physiological responses.

Quantification of far infrared radiation

While the temperature guidelines are important to consider, there is a greater need to monitor, quantify, and report the contribution of radiant heat during far infrared sauna sessions. It appears some assumptions have been made about this radiant heating modality, but we must not act on assumptions moving forward. We must gain a stronger understanding of whether the primary stimulus is the far infrared radiation, the temperature of the sauna, or the combination of both. While we installed the analog output box to monitor the duty cycle of the sauna, this does not fully provide insight into the actual contribution and interaction of the far infrared waves within the sauna and to the sauna bather. A relatively affordable and accessible option would be to place a black globe thermometer for all sauna sessions to calculate mean radiation and

operative temperatures. This would allow better quantification of the biophysics of heat exchange and physiological differences between different types of heating modalities. To our knowledge, there has not been a direct quantification (or comparison) of heat balance between traditional and far infrared saunas to support the claims that far infrared saunas do elicit a more "direct" form of heating. The framework of "directly" heating the peripheral tissues or "targeting" the skeletal muscle is not an accurate description of the biophysics of heat exchange. Between traditional and far infrared saunas, the relative contribution of conductive, convective, and radiant heat exchange differs. Further, some of the variables that determine the rates of heat gain and loss mechanisms via conductive (i.e., thermal conductivity of materials), convective (i.e., heat transfer coefficient), and radiant (i.e., emissivity) heat exchange also differ (260). From this, we cannot assume, or confirm, that the lower temperatures paired with a greater radiant heating equate to a similar, or even greater, thermal stimulus without better measurements. There is also a need for more quantification of how far infrared waves interact with the skin, subcutaneous and intramuscular adipose tissue, and skeletal muscle. These tissue types have different properties (i.e., water, lipids) as well as vary in thickness and distribution within and between individuals, all of which are relevant to thermal load and thermoregulation.

Conclusion

Our findings indicate that there are limited changes to markers of cardiometabolic health, except for fasting glucose, in adults with an elevated BMI after completing a heat therapy protocol in a commercially available far infrared sauna. Further, skeletal muscle temperature increased without increases in body core temperature, but the more superficial tissues had the largest increase in temperature. With these findings, it must be considered that we only used one type of commercially available sauna, the temperature of the sauna was on the lower end of the recommended temperature range, we only had a measure of metabolic health from a single time point, and our participants did not all have cardiovascular or metabolic dysfunction at baseline. We opted for a more ecologically valid model within our study design, but more mechanistic findings may have come about from a different heat therapy protocol (i.e., consistent temperature of the sauna sessions), quantification of the infrared radiation, and a population with clinical dysfunction of cardiovascular and/or metabolic parameters, independent of an elevated BMI. Nonetheless, all the participants in the heat therapy group reported that they enjoyed the sauna

bathing sessions. This further confirms that the modality is feasible and has the potential to be adopted into daily routines. However, much more work is needed to further our understanding of this passive heating modality, as the current evidence is far from complete.

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