Systemic Cardiovascular and Carotid Baroreflex Support of Blood Pressure during Recovery from Passive Heat Stress in Young and Older Adults

by

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DISSERTATION ABSTRACT

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Title: Systemic Cardiovascular and Carotid Baroreflex Support of Blood Pressure during Recovery from Passive Heat Stress in Young and Older Adults

Much like exercise, heat stress is a profound thermoregulatory, cardiovascular, and autonomic stressor which may promote a distinct post-stress recovery period marked by altered cardiovascular support of blood pressure. For example, several studies have noted a sustained reduction in blood pressure following a single session of heat exposure or "post-heating hypotension," which is comparable to the sustained hypotension which follows a single session of exercise. While post-heating hypotension, like post-exercise hypotension, may act as a valuable "window of opportunity" in promoting blood pressure management, very little is known about the mechanisms supporting blood pressure regulation during recovery from passive heat stress. Furthermore, as advancing age increases the prevalence of hypertension and alters the thermoregulatory and cardiovascular responses to acute heat stress, it is clinically and scientifically important that investigations into the post-heating recovery period are conducted in both young and older individuals.

This dissertation aimed to characterize and compare the systemic cardiovascular and carotid baroreflex support of blood pressure during recovery from whole-body, passive heating in young and older individuals. Temperature, central, and peripheral hemodynamics were evaluated in sixteen young and nine older individuals at normothermic baseline and during 60 min of passive heating (water perfused suit) and 2 h of normothermic recovery. The neck pressure technique was additionally used to assess carotid baroreflex control of heart rate, the peripheral vasculature, and blood pressure across these time points. Contrary to our hypothesis, a single session of passive heat stress did not promote a sustained reduction in blood pressure in young or older individuals. Furthermore, the systemic cardiovascular and baroreflex responses which accompanied acute heat stress were transient and did not persist beyond 1 h of post-

heating recovery in young or older individuals despite continued elevations in core temperature. While these findings do not support the notion that the post-heating recovery period promotes robust and sustained alterations in the cardiovascular support of blood pressure, our novel characterization of the time course of thermal, systemic cardiovascular, and neurovascular recovery from whole-body, passive heat stress in young and older individuals fills important gaps in knowledge as we begin to understand the post-heating recovery profile.

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CHAPTER I
INTRODUCTION

BACKGROUND

One of the most pronounced advancements of the 20th century was the increase in life expectancy of about 30 years in much of the developed world. However, accompanying this elongated lifespan is the accumulation of physiological dysfunction due to aging, which will result in an unprecedented climb in chronic disease and disability (Christensen et al., 2009). In the United States, 20% of the population will be 65 or older by the year 2030 (Olshansky et al., 2009). Cardiovascular disease will remain the leading cause of death, accounting for 40% of deaths among this age group. The aging population will be the primary driver of increased direct cardiovascular disease associated healthcare costs, which are projected to triple over the next 10 years, reaching $818 billion by 2030 (Heidenreich et al., 2011). While these demographic shifts are inevitable, the associated development of cardiovascular disease is preventable. As high blood pressure accounts for more cardiovascular disease deaths than any other modifiable risk factor (American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, 2018), interventions aimed at the management of blood pressure in the prevention of cardiovascular disease at all ages are the lynchpin in efforts to prohibit these sobering projections from becoming reality.

Physical activity in the form of regular aerobic exercise is currently recommended as a first-line non-pharmacological treatment for the management of blood pressure in the prevention of cardiovascular disease (American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, 2018), as it promotes a widespread improvement in many cardiovascular disease risk factors (blood pressure, glucose intolerance/insulin resistance, blood lipids, obesity, etc.) (Thompson et al., 2003). However, as the chronic reductions in blood pressure are relatively modest (5-8 mmHg) and do not occur in up to 25% of individuals with high blood pressure (Hagberg et al., 2000; Wallace, 2003), many of the benefits of regular aerobic exercise on blood pressure are ascribed to the post-exercise recovery period. Specifically, a single bout of aerobic exercise promotes a sustained reduction in blood pressure, termed post-exercise hypotension. Post-exercise hypotension is characterized by a persistent drop in blood pressure compared to baseline levels between 5-10 mmHg in normotensive individuals

(Halliwill, 2001; M. J. Kenney & Seals, 1993; MacDonald, 2002) and reaching up to 20 mmHg in individuals with high blood pressure following dynamic exercise (Hagberg et al., 1987, 2000; M. J. Kenney & Seals, 1993). In normotensive individuals, post-exercise hypotension persists for ~2 h before blood pressure begins to trend toward baseline values, while blood pressure may remain depressed for up to 12 h following an exercise bout in individuals with high blood pressure (Pescatello et al., 1991). In this way, the post-exercise recovery period provides a "daily dose" of blood pressure reduction, which allows for the transient lowering of elevated blood pressure into normotensive ranges (Hagberg et al., 1987, 2000). Additionally, post-exercise hypotension may potentiate chronic blood pressure reductions as acute blood pressure responses to a single session of exercise are associated with long-term blood pressure reductions with exercise training (Hecksteden et al., 2013; Liu et al., 2012). As originally explained by Luttrell and Halliwill, the post-exercise recovery period serves as an important "window of opportunity" in this manner, capable of transiently improving cardiovascular risk factors (i.e., reduces blood pressure) and setting the stage for beneficial cardiovascular adaptation (Luttrell & Halliwill, 2015).

Unfortunately, despite the acute and chronic benefits of exercise in the prevention of cardiovascular disease, the therapeutic effectiveness of exercise is contingent on patient compliance and less than 5% of individuals meet physical activity recommendations when assessed via accelerometer (Troiano et al., 2008). This inactivity is exacerbated among older individuals who engage in less physical activity and more sedentary behavior than their younger counterparts (Interagency Forum on Aging-Related Statistics, 2016). As the beneficial reductions in blood pressure which follow an acute exercise bout are mode (Pescatello, Guidry, et al., 2004), intensity (C. L. M. Forjaz et al., 2004; Santana et al., 2013), and duration dependent (Eicher et al., 2010; C. L. Forjaz et al., 1998; MacDonald et al., 2000), older adults who do engage in exercise may still fail to utilize an appropriate modality or achieve a sufficient exercise intensity or duration to elicit clinically relevant reductions in blood pressure (Carpio-Rivera et al., 2016; C. L. M. Forjaz et al., 2000). Therefore, there is a substantial demand for alternative**,** non-pharmacological treatment options for the management of blood pressure in the prevention of cardiovascular disease at all ages.

Heat therapy, in the form of hot bath or sauna, is an ancient practice that has recently gained attention in the prevention and treatment of cardiovascular disease. Large prospective

studies suggest that regular sauna baths are associated with a reduced risk of hypertension, sudden cardiac death, coronary heart disease, cardiovascular disease, and all-cause mortality in men (Laukkanen et al., 2015; Zaccardi et al., 2017) and women (Laukkanen et al., 2018). Additionally, increased frequency and/or duration of sauna bathing is associated with progressively decreased risk of cardiovascular disease mortality (Laukkanen et al., 2015, 2018). In an intervention study, our laboratory demonstrated that chronic passive heat exposure improved endothelial function, arterial stiffness, blood pressure, and cutaneous microvascular function in healthy, young individuals (Brunt, Eymann, et al., 2016; Brunt, Howard, et al., 2016).

In the same way that the exercise recovery period is a key component in driving adaptation with exercise training (Halliwill et al., 2013; Luttrell & Halliwill, 2015), it is likely that the post-heating recovery period contributes to the cardiovascular adaptation accompanying heat therapy. Indeed, some but not all studies have demonstrated the presence of sustained hypotension following whole-body heat stress in healthy, young individuals comparable to that which follows a single session of moderate intensity aerobic exercise (post-exercise hypotension) (Francisco et al., 2021; Halliwill, 2001; M. J. Kenney & Seals, 1993; MacDonald, 2002). Post-heating hypotension has also been demonstrated among healthy older individuals and older individuals with peripheral artery disease (Neff et al., 2016; Romero, Gagnon et al., 2017; Thomas et al., 2017). Similar to post-exercise hypotension, post-heating hypotension may contribute to cardiovascular health improvement by transiently lowering elevated blood pressure into normotensive ranges and may potentiate chronic blood pressure reductions with heat therapy. As blood pressure progressively increases with age (American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, 2018) and approximately 90% of adults with normal blood pressure at age 55 or 65 will develop hypertension in their lifetime (Vasan et al., 2002), older adults may stand to gain the greatest benefit of these acute and chronic blood pressure reductions.

STATEMENT OF THE PROBLEM

Despite the promise of the post-heating recovery period as a mediator of beneficial cardiovascular adaptation, very little is known about the systemic cardiovascular and neurovascular mechanisms which underlie the post-heating *"window of opportunity"*(Luttrell & Halliwill, 2015). Furthermore, as older individuals have markedly different thermoregulatory and

cardiovascular responses to acute heat stress than young individuals and may stand to gain the greatest benefit of post-heating reductions in blood pressure, it is scientifically and clinically important that investigations into the post-heating recovery period are conducted in both young and older individuals. Therefore, the overarching purpose of this dissertation was to explore the cardiovascular support of blood pressure following whole-body, passive heat stress in young and older individuals.

SPECIFIC AIMS

We accomplished this goal by addressing the following specific aims.

1. We aimed to complete a comprehensive characterization of systemic cardiovascular hemodynamics accompanying the post-heating recovery period among young and older individuals. We hypothesized that both young and older individuals would display a sustained reduction in blood pressure following an acute bout of heat stress supported by sustained elevations in systemic vascular conductance which were not completely offset by post-heating elevations in cardiac output. In comparison with young individuals, we hypothesized that post-heating elevations in cardiac output would be attenuated among older individuals, and consequently, older individuals would display an exaggerated reduction in blood pressure during the post-heating recovery period. Lastly, we hypothesized that in both young and older individuals, the time-course of this post-heating hypotension and vasodilation would parallel the time course of sustained vasodilation seen in the calf and cutaneous vasculature.

2. We aimed to evaluate cardiac, peripheral vascular, and integrated carotid baroreflex responsiveness during the post-heating recovery period in young and older individuals. We hypothesized that cardiac carotid baroreflex responsiveness would be unaltered in the post-heating recovery period but shifted to a higher heart rate among young individuals only. We hypothesized that peripheral vascular carotid baroreflex responsiveness would be attenuated in both young and older individuals during the post-heating recovery period and shifted upward to the prevailing increase in vascular conductance in both age groups. Lastly, we hypothesized that integrated carotid baroreflex function would be shifted to lower blood pressures with no change in reflex responsiveness during the post-heating recovery period in both young and older individuals.

SIGNIFIGANCE

This research is innovative because it explores the post-stress recovery period from a new perspective: whole-body heat stress**.** The initial observation that blood pressure was lower after exercise was noted as early as 1898 (Hill, 1898). Since then, the post-exercise recovery period has emerged as a discrete physiological phenomenon which promotes clinically relevant reductions in blood pressure, is marked by alterations in central and peripheral cardiovascular control, and plays an important role in potentiating adaptation to exercise training (Luttrell & Halliwill, 2015). In stark contrast, very little is known about the post-heating recovery period. This research represents the first comprehensive evaluation of the recovery period following whole-body heat stress as a discrete physiological phenomenon. By evaluating blood pressure regulation in the post-heating recovery period, this research evaluates if whole-body heat stress is an effective means of achieving acute reductions in blood pressure in both young and older adults. The evaluation of alternative, non-pharmacological strategies to promote blood pressure management is particularly critical among our expanding aged population as older individuals have an extremely high prevalence of hypertension (American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, 2018; Vasan et al., 2002), may exhibit the greatest and most prolonged post-stress hypotensive response, and are often unable or unwilling to engage in exercise as a means of blood pressure management (Interagency Forum on Aging-Related Statistics, 2016). Additionally, in the same way that the mechanistic investigations into the exercise recovery period have improved our understanding of the adaptive role of exercise, our investigations into the post-heating recovery period improve our understanding of the adaptive role of heat stress, a promising new area of exploration for scientists and clinicians alike as heat therapy emerges as a robust means of improving cardiovascular health.

CHAPTER II
REVIEW OF THE LITERATURE

INTRODUCTION

The condition of exercise is not a mere variant of the condition of rest, it is the essence of the machine -Joseph Barcroft

Inspired by the words of Joseph Barcroft, physiologists have long leveraged various stresses encountered by humans (postural, exercise, thermal, altitude) as tools to probe the capabilities and limitations of the human machine. Within the field of cardiovascular physiology, much focus has been devoted to understanding the circulatory adjustments invoked when one transitions from a resting to a stressed state. However, lost to this stress-focused mindset is an appreciation for and understanding of the physiology of recovery. The recovery period is not merely a passive transition between the stressed and resting state, but rather a discrete physiological phenomenon and integral component of any given stress response.

Within the context of exercise, our laboratory and others have demonstrated that the exercise recovery period is marked by sustained hypotension and alterations in both neural and local vascular control which differ from both the resting and exercising state. As the recovery period alterations in cardiovascular control following exercise create both vulnerabilities and opportunities, they are an essential component of the cardiovascular response to exercise. Despite the integral nature of the recovery period to any given stress response and the demonstrated value of these investigations within the context of exercise stress, our understanding of the physiology of recovery remains in its relative infancy with respect to the various stresses encountered by humans. Much like exercise, heat stress is a profound global stressor marked by widespread thermoregulatory, cardiovascular, and autonomic adjustments and may be followed by a distinct recovery period. However, and in stark contrast to the well-studied post-exercise recovery period, little is known about the thermoregulatory, systemic cardiovascular, and neurovascular responses which accompany the post-heating recovery period.

As we embark on the study of the post-stress recovery period through the novel lens of heat stress, our knowledge of the post-exercise recovery period will provide valuable clues to guide our journey. Accordingly, this review presents a new perspective on how we might merge our collective knowledge of the thermoregulatory, cardiovascular, and autonomic adjustments

which occur *during and after exercise* and *during heat stress* to inform our current study of the post-heating recovery period. As the responses which accompany the post-stress recovery period are likely fundamentally linked to the effects of the acute stressor, each section of this review begins with a discussion and comparison of the acute responses to exercise and passive heat stress. Each section then discusses the post-exercise recovery period and recent investigations into the post-heating recovery period and concludes by proposing the shared and unique mechanisms which may contribute to thermoregulatory, systemic cardiovascular, and neurovascular control in post-exercise and post-heating recovery periods. As it is well-established that older individuals have a markedly attenuated response to acute heat stress which may modify the post-heating recovery period, the influence of age is incorporated into each level of these discussions. We conclude with a perspective on the utility of the post-heating recovery period as an alternative means of opening the "window of opportunity" posed by post-stress recovery and an exciting new area of research for both scientists and clinicians seeking alternative means of improving cardiovascular health across the lifespan.

CONSIDERATIONS IN STUDYING THE POST-STRESS RECOVERY PERIOD

Fundamental to the discussion of post-stress recovery within any population is an appreciation for the characteristics of the acute stressor and their potential influence on the observed recovery responses. For example, the key hallmark of the post-exercise recovery period is a sustained reduction in blood pressure or "post-exercise hypotension" (M. J. Kenney & Seals, 1993). While post-exercise hypotension is generally considered to be a relatively low-threshold phenomenon which can be evoked by varying exercise modalities, it is also subject to a dose-dependent phenomenon with respect to exercise duration and intensity and is most consistently observed following moderate intensity (50-60%VO_{2peak}), sustained (30-60 min), aerobic exercise (running, cycling, etc.) (Brito et al., 2014; Halliwill, 2001; Halliwill et al., 2013; M. J. Kenney & Seals, 1993; MacDonald, 2002). Therefore, the exercise component of this review will focus on discussing recovery from moderate intensity, sustained, aerobic exercise. With respect to heat stress, the most common passive heating modalities include the perfusion of a tube-lined suit with hot water, hot water immersion, and different variations of sauna. Each of these modalities impart a unique thermal (direct vs. indirect skin heating, potential for evaporative cooling) and non-thermal (influence of hydrostatic pressure/posture, tolerance to sustained bouts) profile, and

in doing so, may alter the observed recovery responses. Accordingly, as this literature review considers the recovery responses imparted by hyperthermia, the various heating modalities utilized will be specifically stated and, when available, the extent of core temperature, skin temperature, and/or mean body temperature rise will be provided as a reference reflecting the extent of thermal stress imparted.

Another key factor to consider when examining post-stress responses is the timeline and conditions of recovery assessments. For example, the mechanisms contributing to the support of blood pressure upon the immediate cessation of exercise or heat stress are distinctly different from the sustained responses observed beyond 30 min following these stressors (Amin et al., 2022; Francisco et al., 2021; Halliwill et al., 2014). With respect to the well-characterized phenomenon of post-exercise hypotension, the nadir of blood pressure following aerobic exercise generally occurs within 30 min to 1 h following exercise and blood pressure may remain depressed for up to 2 h in young healthy individuals (MacDonald, 2002). Therefore, this review will focus on exploring the sustained (>30 min recovery) alterations in the cardiovascular support of blood pressure following exercise and heat stress. Lastly, the assumed posture and environmental conditions of the recovery period may modify the observed post-stress recovery responses. Therefore, this review will principally consider evidence derived from studies utilizing a supine, thermoneutral recovery period and exceptions to this general practice will be explicitly stated.

THERMOREGULATION

The exchange of heat between the internal and external environment is modelled by the following equation.

Equation 2.1

$$S = M - (\pm W) \pm (R \pm C \pm K) - E$$

Where S is the rate of heat storage, M is the rate of metabolic heat production, W is the heat gained or lost as work, R is the rate of radiant heat exchange, C is the rate of convective heat exchange, K is the rate of conductive heat exchange, and E is the rate of evaporative heat loss. In humans, the exchange of heat between the internal and external environment primarily occurs

across the skin and directionality of this exchange is determined by the gradient between core temperature and skin temperature (Gagge & Gonzalez, 1996).

Thermoregulatory Responses to Acute Exercise and Heat Stress

Upon the initiation of exercise, metabolic heat production is dramatically increased, and heat is stored within the body as heat gain outpaces heat loss mechanisms. The subsequent increase in core temperature accompanying exercise activates heat loss responses, widens the core to skin temperature gradient, and promotes heat loss. Humans are uniquely well-equipped to dissipate heat due to a capacious cutaneous vascular bed which enables convective heat loss and a high density of eccrine glands which enables evaporative heat loss through sweating (González-alonso et al., 2008; Sawka et al., 1993). In compensable conditions, heat losses match metabolic heat production within 30-45 min of steady-state exercise and further increases in core temperature are prevented (Kenny & Jay, 2013; Kenny & Mcginn, 2017). While the extent to which core temperature rises during exercise is modified by population, environmental, and exercise characteristics, we have previously demonstrated that, among young, healthy, untrained individuals, 60 min of cycle exercise at 60% VO_{2peak} in a temperate environment (22-23°C) increases core temperature between ~1.0-1.5°C (Francisco et al., 2021; Wilkins et al., 2004). A large amount of the heat generated with exercise is stored within active skeletal muscle as skeletal muscle temperature changes generally outpace core temperature changes by 2-3°C (Kenny & Jay, 2013). Skin temperature across the body surface reflects the balance between the transfer of heat to the skin mediated by cutaneous vasodilation and evaporative cooling due to sweating, and generally remains unchanged or declines slightly from baseline values during dynamic exercise in compensable conditions. A schematic displaying whole-body heat exchange, heat storage, and tissue temperatures during exercise is presented in **Figure 2.1** adapted from Kenny et al. (Kenny & Mcginn, 2017).

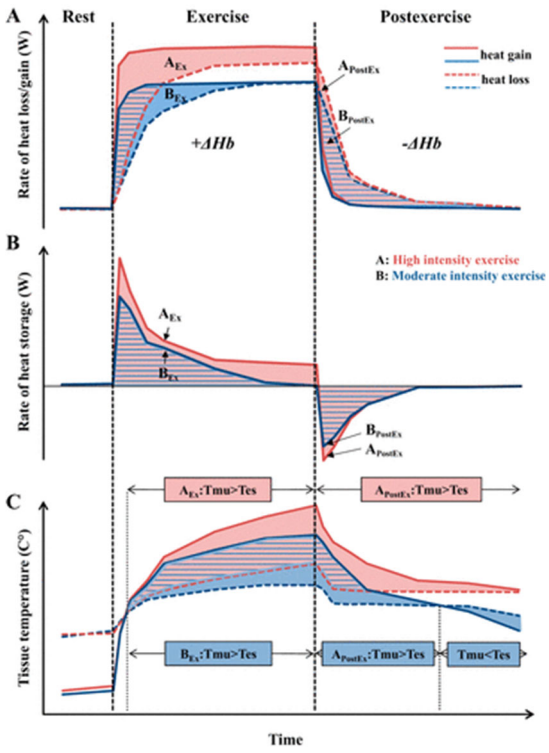

Figure 2.1 Schematic figure displaying whole-body heat exchange during and following high (A line; red) and moderate (B line; blue) exercise adapted from Kenny et al. (Kenny & Mcginn, 2017). At the beginning of exercise heat production (top panel A; solid line) outpaces heat loss (top panel A, dashed line) and the rate of heat storage increases (middle panel B) as core (bottom panel, C, dashed lines) and muscle temperature rise (bottom panel C, dashed lines). Shaded areas in panel A and B represent the amount of heat stored with striped regions denoting overlapping areas. ΔHb represents the change in body heat content.

The most common passive heating modalities include perfusion of a tube-lined suit with hot water, hot water immersion, or different variations of sauna (dry or Finnish, wet or steam rooms). Apart from infrared sauna which penetrates the surface of the skin to directly heat underlying tissue, each of these modalities applies heat to the surface of the skin, diminishes or reverses the gradient between core temperature and skin temperature, and promotes convective heat gain. Across these modalities, a typical heating session of 30-60 min completed in one or multiple bouts typically increases core temperature 0.7-1.5°C (Amin et al., 2021; Francisco et al., 2021; Larson et al., 2021; Leppaluoto, 1988; Pilch et al., 2014; Romero, Gagnon et al., 2017;

Thomas et al., 2016). Studies on Waon Therapy which combined 15 min of infrared sauna with 30 min of recovery in warm blankets to maintain elevations in body temperature, suggest that infrared sauna elicits increases in core temperature within this range (Tei et al., 1995). Like exercise, the change in muscle temperature with passive heating generally exceeds the change in core temperature by 1-3°C (Chiesa et al., 2016; Heinonen et al., 2011; Rodrigues et al., 2020; Romero, Gagnon, et al., 2017). Skin temperature is generally increased during passive heating and reflects the balance between the direct heat applied to the skin, heat delivered via locally or systemically induced cutaneous vasodilation, and the capacity for heat loss via evaporative cooling. For example, perfusing hot water (45-50°C) through a tube-lined suit directly heats the underlying skin, limits evaporative cooling, and in doing so, serves to quickly increase skin temperature within a range of 37-40°C (Rowell, Brenglemann, et al., 1969; Rowell, Murray, et al., 1969). **Figure 2.2** presents core, muscle, subcutaneous and skin temperature as measured in a single representative subject during whole-body passive heating via water perfused suit (50°C water) (Chiesa et al., 2016). Skin temperature of regions immersed in water generally mirror (within 1°C) water temperature (Romero, Gagnon, et al., 2017). When heat is not directly applied to skin and evaporative heat loss is permitted across the skin (i.e., exposed skin or skin above water level), skin temperature generally remains unchanged or is modestly elevated (+2°C) (Larson et al., 2021). Likewise, as evaporative cooling is preserved in the low humidity conditions (10-20%) of Finnish or dry sauna, extreme ambient air temperatures (80-100°C) are required to increase skin temperature within a range 40-41°C (Hannuksela & Ellahham, 2001; Heinonen & Laukkanen, 2018; Leppaluoto, 1988; Pilch et al., 2014).

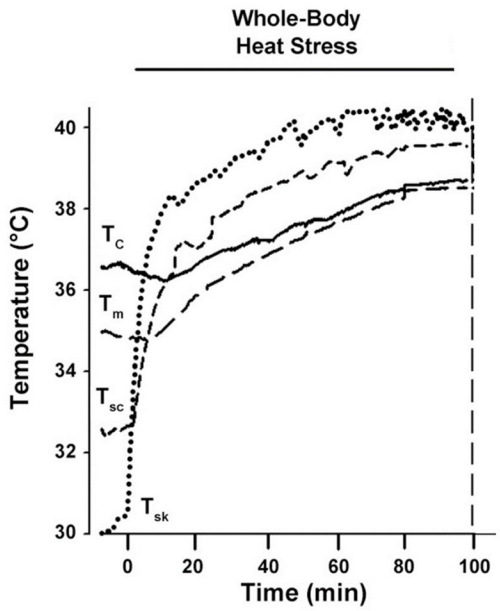

Figure 2.2 Esophageal (T_c), vastus lateralis (T_m), subcutaneous (T_{sc}), and skin temperature (T_{sk}) measured in a single representative subject during passive, whole-body heat stress via water perfused suit (50°C water). Figure and caption adapted from Chiesa et al. (Chiesa et al., 2016).

Several studies have directly compared the impact of exercise and passive heating on skin, muscle, and core temperatures. The first of these comparisons was made by Thomas and colleagues as they measured esophageal and medial gastrocnemius muscle temperature responses to a 30 min bout of treadmill running at 65-75% age-predicted maximum heart rate compared to 30 min of waist-level hot water immersion (42°C). Both core and muscle temperature increased to a greater extent with hot water immersion (Δ esophageal temperature: +1.3°C, peak muscle temperature: 38.5°C) compared to exercise (Δ esophageal temperature: +0.6°C, peak muscle temperature: 38.1°C) (Thomas et al., 2016). Similarly, Amin noted that 30 min of chest-level hot water immersion (42°C) increased rectal temperature to a larger extent (+1.3°C) than 30 min of heart rate matched semi-recumbent stepping exercise (+0.4°C) (Amin et al., 2021). Importantly, increases in core temperature are similar between passive heating and exercise when exercise duration and/or intensity is increased as Francisco noted that 60 min of chest-level hot water immersion (40°C) and 60 min of cycle exercise at 60% of VO_2 peak similarly increased rectal temperature by 1.5°C (Francisco et al., 2021). Similarly, Amin noted that 30 min of chest-level

hot water immersion (42°C), 30 min of treadmill running at an intensity equivalent to respiratory compensation point, and 5 x 4 min high intensity (85-95% of maximal heart rate) treadmill running intervals similarly increased rectal temperature by ~1.5°C. Although not measured, it is likely that skin temperature of immersed regions mirrored water temperature within 1°C and exceeded exercising skin temperatures in this study. Meanwhile, skin temperature of the forearm which was not submerged in water similarly increased in each intervention by 1.0-2.4°C (Amin et al., 2021).

Influence of Age

Compared to healthy individuals aged 20-30 years, age-related impairments in thermoregulatory function have been noted in individuals as early as 40 years of age (Larose, Boulay, et al., 2013) and the magnitude of these impairments tends to worsen with increasing age (McGinn et al., 2017). Across the literature, individuals over the age of 60 years most consistently display attenuated thermoregulatory function and this is echoed in epidemiological work noting that extreme heat events pose the greatest health risk to individuals belonging this age group (Bouchama et al., 2007; Robine et al., 2008; Semenza et al., 1999; Vandentorren et al., 2006). Therefore, the aging component of this review will principally consider individuals over the age of 60 compared to young healthy individuals (~20-30 years). It is also important to note that many factors including disease status, fitness and training status, and body morphology are all modified by age and may alter heat exchange during both exercise and passive heating. While a discussion of these factors, their influence on thermoregulation, and their interaction with aging is beyond the scope of this review, the reader is directed to an excellent review exploring these topics (Cramer et al., 2022).

It is well established that the thermoregulatory responses which support the defense of core temperature amid metabolic and environmental heat gain are markedly attenuated with increasing age. These impaired heat loss responses result from an age-related attenuation of dry heat loss via cutaneous vasodilation and evaporative cooling via sweating (Holowatz et al., 2010; W. L. Kenney, 2017; W. L. Kenney et al., 2014; Kenny et al., 2010). The age-associated reductions in evaporative cooling via sweating are thought to be mediated by a reduction of sweat output per gland (Inoue, Havenith, et al., 1999; Inoue, Shibasaki, et al., 1999; W. L. Kenney & Fowler, 1988). Attenuated dry heat loss via cutaneous vasodilation reflects age-related cutaneous microvessel remodeling, impairments in active vasodilation (Holowatz et al., 2003,

2005, 2006b, 2010), attenuated efferent skin sympathetic nerve activity during heat stress (Greaney et al., 2020; Stanhewicz et al., 2016), and attenuated central and peripheral hemodynamic adjustments to heat stress (detailed in Systemic Hemodynamics section) (Gagnon et al., 2017; Gravel, Chaseling, et al., 2021; Greaney et al., 2015; W. L. Kenney et al., 2014; Minson et al., 1998).

Sweating is the thermoregulatory response with the greatest capacity for heat loss, particularly in environments where ambient temperature exceeds skin temperature. For this reason, age-related differences in evaporative cooling often mediate differences in heat storage between young and older individuals in hot environments. With respect to exercise stress, age-related differences in sweating and heat storage increase with exercise intensity (Stapleton et al., 2015b, 2015a) and are evident in both dry and humid environmental conditions (Larose et al., 2014). With respect to passive heat stress, the influence of age-related differences in heat loss responses on heat storage is importantly influenced by heating modality. For example, water perfused suit heating limits evaporative cooling via sweating and clamps skin temperature within a desired range, effectively minimizing the effects of differences in heat loss responses between age groups. Indeed, studies often utilize this heating modality to elicit matched changes in core and skin temperature between young and older individuals (Gagnon et al., 2015, 2016; Minson et al., 1998). In contrast, hot water immersion and sauna heating modalities permit evaporative cooling across a portion of the body surface, and in doing so, may promote greater heat storage among older adults compared to young adults. This has been demonstrated in some (Engelland et al., 2020b), but not all (Inoue & Shibasaki, 1996; Romero, Gagnon, et al., 2017) studies employing hot water immersion heating modalities in young and older individuals.

In addition to altering heat loss, age-related differences in cutaneous vasodilation and sweating may also act to alter dry heat gain during exposure to hot environments or passive heating. For example, during passive heating blood flow may be lower in both directly heated and indirectly heated skin of older vs. younger individuals. This may serve to widen the environment-skin gradient among and promote greater dry heat gain among older individuals. While no study to our knowledge has demonstrated discrepancies in dry heat gain with aging in the most common recreationally used heating modalities, several studies conducted by Kenny and colleagues demonstrated that prolonged exposure to elevated ambient temperatures (3 h 44°C, 30% humidity, 2 h 36.5°C 20% humidity, 36.5°C 60% humidity) promotes greater dry

heat gain and heat storage among older vs. younger individuals (Kenny et al., 2016; Stapleton et al., 2014). As a consequence of these thermoregulatory impairments, older individuals are at higher risk for exaggerated heat storage during exercise in the heat or prolonged exposure to environmental heat stress **(Figure 2.3)** (Kenny et al., 2016; Meade et al., 2019, 2020; Stapleton et al., 2014).

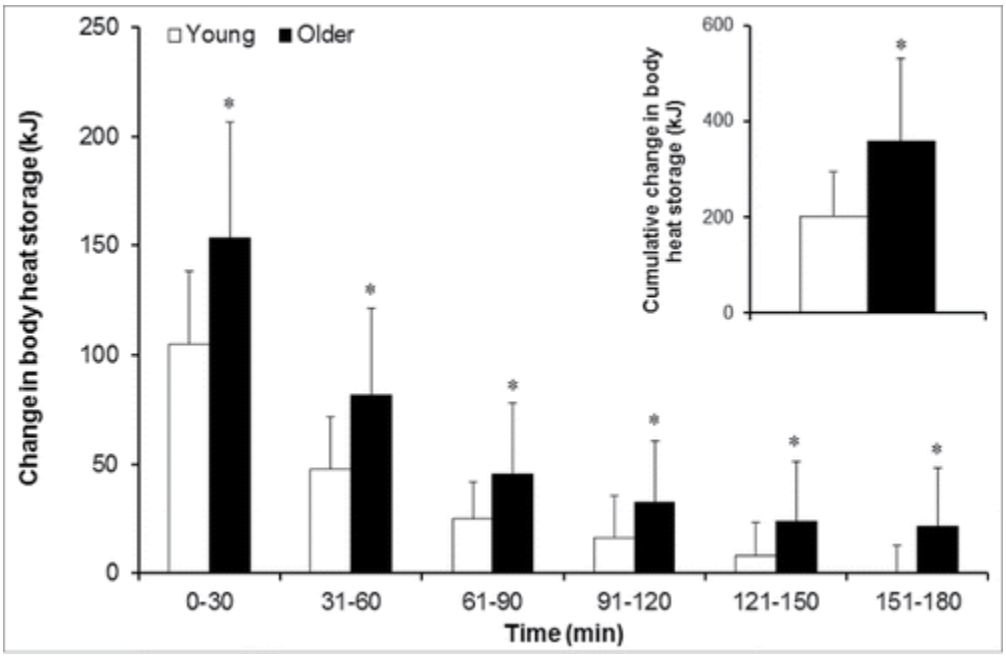

Figure 2.3 Body heat storage measured via direct calorimetry (means ± SD) during a 3 h extreme heat exposure (44°C, 30% relative humidity) in young (19-28 years; open bars) and older adults (55-73 years; closed bars). The inset figure displays that older adults stored 1.8 times more heat than young adults over the 3 h heat exposure. Figure and caption adapted from Kenney et al. (Kenny et al., 2016).

Thermoregulatory Responses during Post-Exercise and Post-Heating Recovery

Whole-body calorimetry studies have demonstrated that upon cessation of exercise, metabolic heat production returns to baseline levels within ~10 min while core and muscle temperature remain elevated (Kenny et al., 2006, 2008, 2009). Despite this maintained heat storage, skin blood flow and sweating heat loss responses are attenuated following exercise. This has been demonstrated in that the core temperature thresholds for both sweating and cutaneous vasodilation are increased above pre-exercise levels for 15-30 min of post-exercise recovery

(Kenny et al., 2000; Kenny & Journeay, 2005; Kenny & Niedre, 2002; Thoden et al., 1994). As a result of the suppression of these heat loss responses, muscle and core temperature remain elevated above baseline levels for up to 90 min following exercise (Kenny et al., 2006, 2008; Saltin & Hermansen, 1966). Kenny and colleagues utilized whole-body calorimetry to demonstrate that only 53% of heat stored during 60 min of exercise was dissipated within 60 min of post-exercise recovery and this net heat storage was reflected in sustained elevations in core (+0.2°C) and muscle temperature (+1.0°C) 60 min into the post-exercise recovery period (Kenny et al., 2008). This timeline of thermal recovery may be extended among older individuals. This is due to increased heat storage during exercise among older individuals as heat loss responses are similar following exercise among young and older individuals **(Figure 2.4)** (Larose, Wright, et al., 2013).

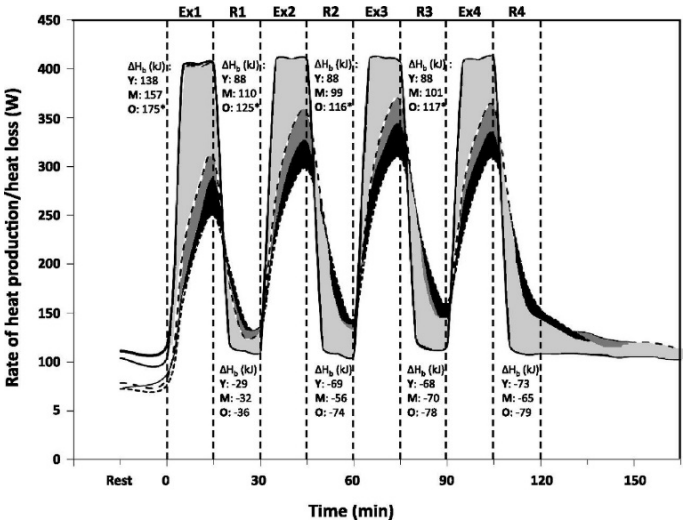

Figure 2.4 Rate of heat production and whole-body total heat loss for young (20-30 years) middle-aged (40-45 years), and older males (60-70 years) during four 15 min successive exercise (400 W) and recovery bouts in a hot, dry environment (35°C, 20% relative humidity). Changes in body heat content (ΔHb) are presented as the shaded areas and numerically for each age group within each exercise and recovery period. Light gray denotes the amount of heat stored or lost by young males, dark gray denotes the additional amount of heat stored (exercise) or lost (recovery) by middle aged males compared to young males, and black denotes the additional amount of heat stored or lost by older males compared to young and middle-aged males. *Significant differences in ΔHb compared with young males. Figure and caption adapted from Larose et al. (Larose, Wright, et al., 2013).

No studies to our knowledge have characterized post-heating alterations in thermoeffector function (sweating and cutaneous vasodilation) which may contribute to thermal recovery following passive heating. In the absence of these data, skin, muscle, and core temperature during recovery from heat stress may provide insight into thermoregulatory function during the post-heating recovery period. As presented in **Figure 2.5,** Rodrigues measured skin, muscle, and core temperature during seated thermoneutral recovery following 2 h of waist level immersion in 42°C water sufficient to raise rectal temperature by ~1.4°C, skin temperature (average of sites above and below water) by ~6°C, and deep (3.5 cm) vastus lateralis temperature by ~2.8°C. Skin temperature remained above baseline values for 15 min of recovery (~1.4°C above baseline values) and rectal temperature remained elevated above baseline levels for 35 min of recovery (~0.3°C above baseline values). Increases in muscle temperature were the most sustained as vastus lateralis temperature remained elevated above baseline values for 90 min of post-heating recovery (~0.4°C above baseline values) (Rodrigues et al., 2020). Similar studies utilizing different heating modalities among young adults have noted that skin temperature typically remains elevated 15-30 min into the post-heating recovery period, core temperature remains elevated 20 min to 2 h into the post-heating recovery period, and elevations in muscle temperature persist between 30 min to 2 h into the post-heating recovery period (Engelland et al., 2020b, 2020a; Francisco et al., 2021; Gravel, Behzadi, et al., 2021; Gravel et al., 2019; Hoekstra et al., 2021; Laukkanen et al., 2017; Neff et al., 2016; Richey et al., 2022; Romero, Gagnon, et al., 2017; Thomas et al., 2017).

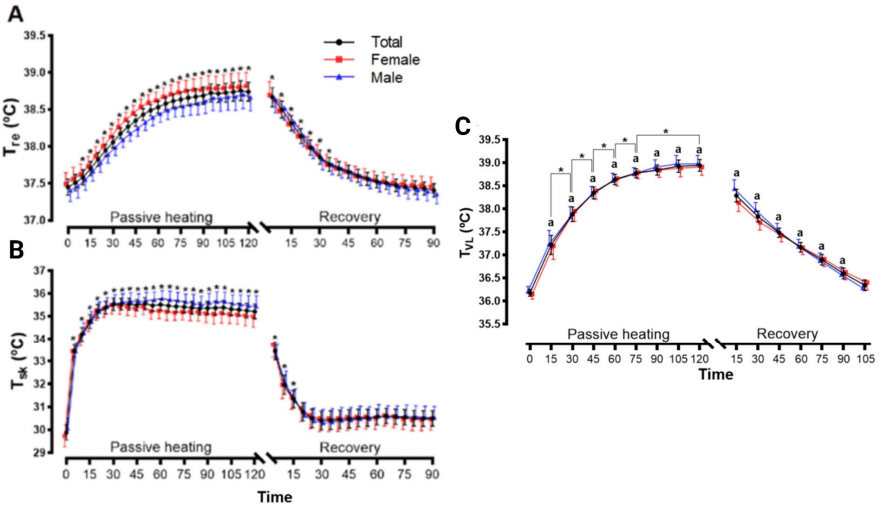

Figure 2.5 Rectal, skin, and vastus lateralis (3.5 cm deep) temperature (means ± 95% CI) measured during 2 h of waist-level hot water immersion (42°C water) and post-heating recovery in young male (blue), female (red), and total (black) participants. Panel A and B: *P<0.05 vs baseline. Panel C: *P < 0.05 between time points, ^{a}P < 0.05 vs baseline. Figures and caption adapted from Rodrigues et al. (Rodrigues et al., 2020).

Two studies have compared the recovery of intestinal, muscle, and/or skin temperature following passive heating in young and older individuals. As depicted in **Figure 2.6** Romero and colleagues demonstrated that despite a similar increase in core temperature with 45 min of lower-limb hot water immersion (Δ intestinal temperature young: +0.4°C, older: +0.5°C; Δ skin temperature immersed lower-limb: ~9°C), core temperature remained elevated only among older individuals after 30 min of post-heating recovery. This sustained increase in core temperature was perhaps the result of a greater increases in muscle temperature among older individuals during the hot water immersion intervention (Δ gastrocnemius muscle temperature young: +5.7°C, older: +6.7°C), although young and older individuals displayed similar elevations in muscle and skin temperature 30 min following hot water immersion (Romero, Gagnon, et al., 2017). Another study conducted by Engelland and Romero demonstrated that intestinal temperature remained 0.2°C and 0.4°C and above baseline values 30 min following 45 min of leg heating via water perfused suit in young and older individuals, respectively (Δ intestinal temperature during heating young: +0.4°C, older: +0.8°C; Δ skin temperature heated legs young: 6.8°C, older: 7.5°C) (Engelland et al., 2020b).

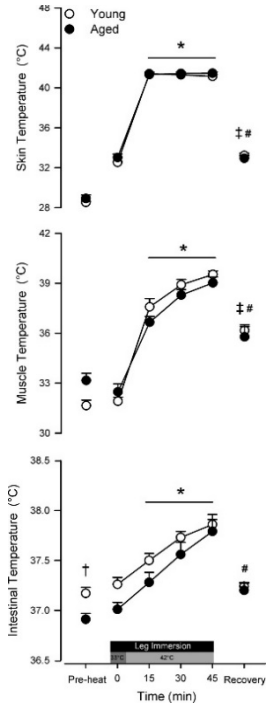

Figure 2.6 Skin, gastrocnemius muscle, and intestinal temperatures (means ± SE) in young (open circles) and older adults (filled circles) during 45 min of lower-limb hot water immersion and 30 min of post-heating recovery. *$P < 0.05$ vs. thermoneutral immersion within group; †$P < 0.05$ vs. young adults at the indicated time point; ‡$P < 0.05$ vs. preheat for young adults; #$P < 0.05$ vs. preheat for older adults. Figure and caption adapted from Romero et al. (Romero, Gagnon, et al., 2017).

Two studies have directly compared the recovery of core temperature following exercise and passive heating. Work by Francisco suggests that although 60 min of chest-level hot water immersion and cycle exercise (60% VO_2peak) elicited a similar rise in core temperature, rectal temperature was elevated above baseline values for longer (60 min vs. 40 min post-stress) and to a greater extent during the post-heating recovery period (**Figure 2.7**) (Francisco et al., 2021). This trend is supported, although not statistically, by the work of Amin and colleagues. Despite a similar rise in core temperature during 30 min of chest-level hot water immersion (42°C water; Δ rectal temperature: 1.5°C; Δ skin temperature non-immersed forearm: 2.5°C) compared to 30 min of treadmill running at an intensity equivalent to respiratory compensation point and 5 x 4 min high intensity (85-95% of maximal heart rate) treadmill running intervals, the hot water

immersion tended to elicit the greatest and most sustained elevations in core temperature during the post-heating recovery period (Amin et al., 2022).

Thermoregulation during Post-Stress Recovery: Overlapping or Alternative Mechanisms?

The recovery of core temperature following exercise is principally dependent on the amount of heat gained during the exercise bout and the amount of heat loss facilitated by cutaneous vasodilation and sweating in the recovery period. The attenuated activity of these heat-loss thermoeffectors following exercise is believed to be mediated by a host of non-thermal factors associated with the post-exercise recovery period (Kenny & Mcginn, 2017). First, the altered cardiopulmonary and/or arterial baroreceptor feedback accompanying post-exercise hypotension is believed to importantly contribute to attenuated thermoeffector function following exercise. Indeed, several studies have demonstrated that reversal of post-exercise baroreceptor unloading via head down tilt or lower body positive pressure restored post-exercise skin blood flow and sweating responses and promoted a faster post-exercise recovery of core temperature (D. N. Jackson & Kenny, 2003; Journeay et al., 2004; Kenny & Gagnon, 2010; McGinn, Paull, et al., 2014; McInnis et al., 2006). It is possible that sustained reductions in blood pressure following heating may serve to unload the baroreceptors in similar manner, and in doing so, contribute to altered thermoeffector function in the post-heating recovery period. Additionally, sweat losses during exercise promote dehydration, resulting in hypovolemia, hyperosmolality, and subsequent activation of osmoreceptors (Costill & Fink, 1974; M. N. Sawka et al., 2001). Osmoreceptor activation via hypertonic saline infusion has been demonstrated to attenuate skin blood flow and sweating responses during acute heat stress and the post-exercise recovery period (Barrera-Ramirez et al., 2014; A. G. Lynn et al., 2012; Paull et al., 2016). Dehydration induced via passive heating may act in a similar manner to promote altered thermoeffector function in the post-heating recovery period. Importantly, this mechanism may only contribute in instances of dramatic fluid loss and hyperosmolarity (Δ >12 mmol/kg) induced by prolonged or combined exercise or heat stress. Alternatively, the distinct differences between exercise and heat stress with respect to thermal loading and activation of central command, mechano- and metabo-reflexes, all of which alter thermoeffector function during the post-exercise recovery period (Carter et al., 1999, 2002; McGinn, Swift, et al., 2014; Shibasaki et al., 2004), may promote differences in post-stress thermoregulatory profiles.

Thermoregulation: Summary

While more work is needed to characterize thermoregulation and its underlying mechanisms during the post-heating recovery period, this collective discussion provides evidence that skin, core, and muscle temperature remain elevated and change dynamically throughout the post-stress recovery period. As we progress into a discussion of the systemic hemodynamic and neurovascular alterations which persist into the post-exercise and post-heating recovery period, an appreciation for the thermal backdrop against which these responses occur is critical. As the field moves forward and we learn more about the post-heating recovery period, differences in thermal profiles may facilitate comparisons across the literature using various heating modalities and, in doing so, help to unravel inconsistencies and clarify the physiology underlying the post-heating recovery period.

SYSTEMIC HEMODYNAMICS

Blood pressure is the key regulated variable of the cardiovascular system and reflects the ever-changing balance between cardiac output and systemic vascular resistance. Cardiac output, or the volume of blood pumped by the heart per min, is the product of heart rate and stroke volume or the volume of blood ejected with every beat of the heart. Systemic vascular resistance is a measure of the resistance to blood flow imparted by the entire systemic circulation and reflects the net vasoconstriction or vasodilation across all regional circulations. Vascular tone may also be expressed as systemic vascular conductance which is the reciprocal of systemic vascular resistance and reflects blood flow through the systemic circulation at a given pressure.

Systemic Hemodynamic Responses to Acute Exercise and Heat Stress

During dynamic exercise, the cardiovascular system is responsible for dramatically increasing blood flow through the skeletal muscle circulation to support the metabolic demands of active muscle. In sedentary, young individuals (~20 years) cardiac output is dramatically increased from ~5 L/min at rest up to ~20 L/min during maximal exercise. These increases in cardiac output are supported by increases in both heart rate which may approach 200 bpm and stroke volume which may increase from ~65 mL at rest to ~100 mL at maximal exercise. In addition to these central cardiovascular adjustments, blood flow can be reduced by ~75% in both the splanchnic and renal circulations during maximal exercise (Rowell et al., 1965, 1984). Blood flow through the cutaneous circulation increases linearly once core temperature exceeds a

threshold during exercise and plateaus around 50%-60% of maximal values (Simmons et al., 2011). The cardiovascular adjustments accompanying exercise culminate in a modest increase in arterial blood pressure (~93 mmHg at rest to ~100 mmHg during maximal exercise) amid the dramatic rise in in systemic vascular conductance supporting the high blood flow demands of the skeletal muscle circulation (Joyner & Casey, 2015; Rowell, 1974).

During passive heat stress the cardiovascular system is responsible for facilitating heat loss by dramatically increasing blood flow through the high capacitance cutaneous circulation. In young, healthy individuals, heating to the limits of thermal tolerance has been demonstrated to increase skin blood flow up to 7-8 L/min. This dramatic blood flow demand is met in part by an ~2-fold increase in cardiac output due to increases in heart rate which may reach ~120 bpm during severe heat stress (Rowell, Brengelmann, et al., 1969; Rowell et al., 1970). The peripheral displacement of blood volume towards the capacious cutaneous circulation in addition to a reduction in filling time accompanying heat-induced tachycardia causes both left and right sided cardiac preload to decline by 2-3 mmHg during passive heat stress (Wilson et al., 2007). Despite this reduction in preload, stroke volume either does not change or increases minimally during passive heat stress due to reductions in cardiac afterload and increases in inotropy (Brothers et al., 2009; Bundgaard-Nielsen et al., 2010; Wilson et al., 2009; Wilson & Crandall, 2011). In addition to these central cardiovascular adjustments, blood flow to the renal circulation is reduced by ~25% and splanchnic blood flow is reduced by as much as ~40% with severe heat stress (Δ internal temperature $\geq$1.8°C, Δ mean skin temperature 5°C) as a means of redistributing blood flow towards the cutaneous circulation (Minson et al., 1998; Rowell, Brengelmann, et al., 1969; Rowell et al., 1965, 1968, 1970, 1971). Skeletal muscle blood flow may increase modestly with direct, local limb heating (~ 1mL·100 g muscle^{-1}·min^{-1}), but not in response to indirect, whole-body heating (Heinonen et al., 2011; Keller et al., 2010). As a whole, the cardiovascular adjustments accompanying passive heat stress support the maintenance of arterial blood pressure amid a dramatic rise in systemic vascular conductance supporting the high blood flow demands of the capacious cutaneous circulation (Crandall & Wilson, 2015; J. M. Johnson & Proppe, 1996; Rowell, 1974, 1983).

Studies conducted by Thomas, Francisco, and Amin have directly compared the systemic hemodynamic response to chest-level hot water immersion versus a time-matched exercise bout performed at 60-85% of maximal capacity (VO_2peak, age predicted maximum heart rate, etc.)

(Amin et al., 2022; Francisco et al., 2021; Thomas et al., 2016) **(Figure 2.7)**. Collectively, these studies have demonstrated that while both interventions elevate heart rate and cardiac output, these elevations are generally greatest during exercise. The differential stroke volume response to these interventions remains unclear due to the confounding effects of hydrostatic pressure imparted during hot water immersion and the change in posture between baseline measurements and exercising/heating measurements. Francisco demonstrated that both systemic vascular conductance and brachial vascular conductance were increased to a greater extent during 60 min hot water immersion (Δ rectal temperature: 1.5°C) compared to 60 min of cycle exercise at 60% VO_2peak (Δ rectal temperature: 1.5°C). These differential responses generally support either a maintenance or increase in blood pressure with exercise, while systolic, diastolic, and mean arterial pressure generally remain unchanged or decline during heat stress.

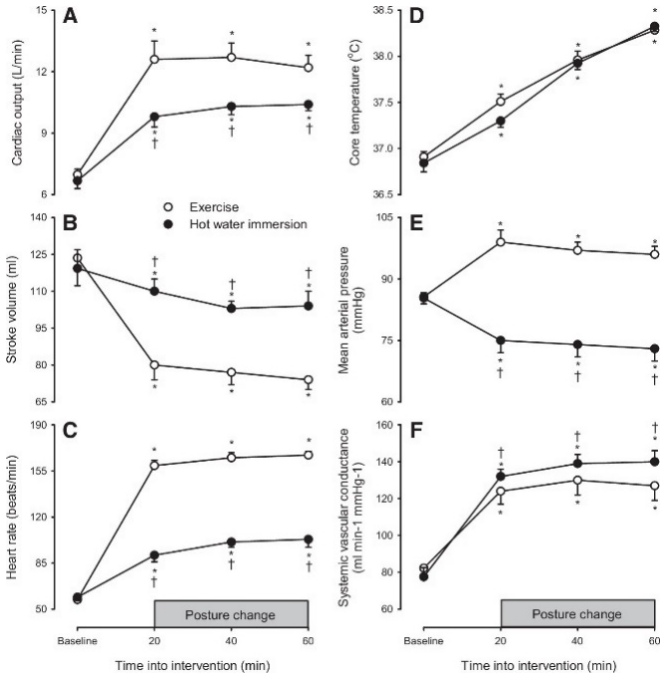

Figure 2.7 Cardiac output, stroke volume, heart rate, rectal temperature, mean arterial pressure, and systemic vascular conductance (means ± SE) at supine pre-intervention baseline and during 60 min of seated cycle exercise (open circles) or chest-level hot water immersion (closed circles). *$P < 0.05$ vs. preintervention baseline. †$P < 0.05$ vs. exercise at the same time point. Figure and caption adapted from Francisco et al. (Francisco et al., 2021).

Influence of Age

As originally demonstrated in a series of studies conducted by Minson and colleagues on young (19-28 years) and older (64-81 years) men, age importantly modifies the classical cardiovascular responses to heat stress (Minson et al., 1998, 1999). These studies were the first to demonstrate that the increase in skin blood flow was attenuated in older individuals during passive heating to the limit of thermal tolerance (Δ skin blood flow: Young: +5.8 vs Older: +2.7 L/min, Δ mean body temperature ≥ 2.0°C). This diminished skin blood flow response to heating among older individuals paralleled attenuated increases in cardiac output (Δ cardiac output Young: +4.8 vs. Older: +2.0 L/min) and a blunted redistribution of blood flow away from the splanchnic and renal circulations during heating (Δ renal and splanchnic blood flow Young: 960 vs. Older: 720 mL/min). The differences in the cardiovascular response to passive heating between young and older individuals as determined by this seminal work is summarized in **Figure 2.8**. While these attenuated cardiovascular responses limit heat dissipation among older adults, they do not appear to precipitously impair the ability of older individuals to maintain blood pressure during acute hyperthermia (Lucas et al., 2008; Minson et al., 1999; Shiraki et al., 1987).

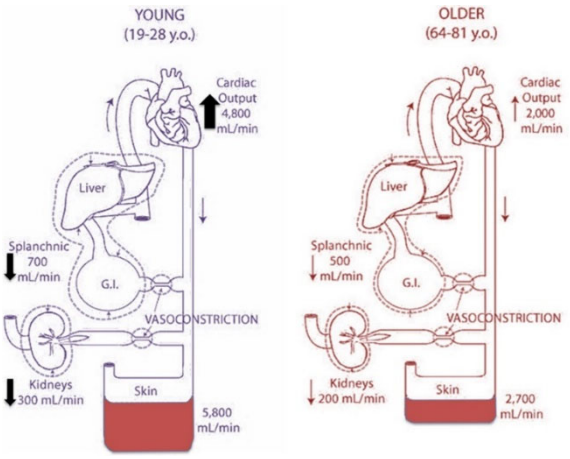

Figure 2.8 Changes in cardiac output and renal, splanchnic, and cutaneous blood flow distribution with passive heating to thermal tolerance in young and older men as determined by Minson et al. (Minson et al., 1998). Figure and caption adapted from Kenney et al. (Kenney et al., 2014).

In the 25+ years following these seminal studies, several research groups have sought to determine the mechanisms underlying the attenuated increase in cardiac output among older individuals during passive heating. Minson's early work on this topic noted that heart rate was increased and central venous pressure (measured via peripherally inserted central catheter advanced to superior vena cava) was reduced similarly during passive heating among young and older individuals. However, stroke volume was lower in older compared to younger men during the final 20 min of heating and reduced below baseline values among only older men. This observation led to the prevailing belief that the attenuated increase in cardiac output during passive heating in older individuals was due primarily to an age-related attenuation of cardiac systolic and/or diastolic function (Minson et al., 1998).

Later work conducted by Lucas and Crandall explored echocardiographic indices of systolic and diastolic function during whole-body passive heating (water perfused suit; Δ intestinal temperature: +1°C; Δ mean skin temperature: +4.6°C) in young and older men and women. Contrary to their hypothesis, the cardiac output and indices of systolic and diastolic function were not different between age groups with heating. However, this study noted that global longitudinal systolic strain increased during heating among older individuals only, while late diastolic ventricular filling increased in the young individuals only. Collectively, these findings suggest the increases in cardiac output which accompany whole-body heating may be accomplished by a greater systolic contribution among older individuals and a greater diastolic contribution among young individuals (Lucas et al., 2015). Shortly after these reports, Gagnon and Crandall used right heart catheterization to measure cardiac output (thermodilution) and assess Frank-Startling relations (pulmonary capillary wedge pressure to stroke volume relation) among young and older men and women during passive, whole-body heating (water perfused suit; Δ pulmonary artery blood temperature: +1.5°C; Δ mean skin temperature: +4.3-4.6°C). In contrast with Minson et al., the older adults displayed an attenuated rise in cardiac output during passive heating due to an attenuated chronotropic response to heating while changes in stroke volume were similar between age groups. Furthermore, the Frank-Starling relation was shifted upward and leftward such that stroke volume could be maintained amidst depressed cardiac filling pressures accompanying hyperthermia in both young and older individuals (Gagnon et al., 2016). Most recently, Fischer and Crandall examined the cardiac responsiveness to dobutamine (stimulates cardiac β1 receptors) during hyperthermia in young and older individuals. Young and

older individuals displayed similar increases in heart rate during passive, whole-body heating (Δ intestinal temperature young: +1.1°C, older: +1.3°C; Δ mean skin temperature young: +3.8°C, older: +3.3°C) and heart rate responses to dobutamine infusions were similar between groups during both normothermia and hyperthermia. While increases in peak systolic mitral annular velocity (index of left ventricular longitudinal systolic function) with dobutamine infusion were similar between age groups during normothermia, this ionotropic effect was altered during hyperthermia in an age-dependent manner. Specifically, the ionotropic effect of dobutamine was enhanced among young individuals and attenuated among older individuals during hyperthermia. These findings, along the same lines of the early work conducted by Minson et al., suggest that older individuals may have an attenuated ability to augment cardiac systolic function during hyperthermia (Fischer et al., 2022). The contrasting findings of these studies may reflect differences in the populations studied (men only vs men and women, physical fitness), the methodology used to evaluate cardiac output and cardiac function, and the degree of heat loading employed by each study. Despite these discrepancies, the majority of evidence seems to suggest that increases in cardiac output with passive heating are attenuated by about 50% among older individuals, and when core temperature is increased within the range of 0.8-1.5°C, this diminished cardiac response is primarily the result of an attenuated chronotropic response to hyperthermia among older individuals (Gagnon et al., 2016, 2017; Greaney et al., 2015; Lucas et al., 2015) .

Another important paradigm to consider when evaluating age-related differences in the systemic cardiovascular response hyperthermia is whether the markedly attenuated increase in skin blood flow during passive heating among older individuals reflects a cardiac limitation, a cutaneous vascular limitation, or an interplay between these diminished central hemodynamic and peripheral vascular responses. Greaney and Kenney explored this question by examining the cardiovascular responses to whole-body, passive heat stress (water perfused suit; Δ esophageal temperature: +0.8°C; Δ mean skin temperature: +3.8°C) after acutely correcting the peripheral vascular capacity of aged skin via sapropterin ingestion (BH_4, nitric oxide cofactor). Despite the drug-induced restoration of the skin blood flow response to passive heating in older individuals such that it was comparable to that of young individuals, the increases in cardiac output accompanying hyperthermia remained attenuated among older compared to young adults. This observation led to the conclusion that the attenuated increase in cardiac output during passive

heating in older individuals is a consequence of primary aging rather than a downstream reflection of cutaneous vascular limitations. Work conducted by Gagnon and Crandall similarly addressed this question by examining the central hemodynamic and cutaneous vascular responses to a rapid volume infusion during whole-body, passive heat stress (water perfused suit; Δ intestinal temperature: +1.5°C; Δ mean skin temperature: +5°C). In contrast with Greaney and Kenney's initial work, the saline infusion served to increase both cardiac output and skin blood flow (forearm and cutaneous vascular conductance) in both young and older adults (Gagnon et al., 2017). Unfortunately, the relative time course of these respective changes was not determined and therefore the directionality or permissive nature of the relationship between the increases in cardiac output and cutaneous vasodilation in older individuals during hyperthermia remains unknown.

Systemic Hemodynamics during Post-Exercise and Post-Heating Recovery

Blood Pressure

Records of post-exercise hypotension date back to as early as 1897 when Sir Leonard Hill, a British physiologist, noted a depression of arterial pressure following a 400-yard dash (Hill, 1898). Throughout the 1900's, post-exercise hypotension was noted by several others (Bowen, 1904; Bramwell & Ellis, 1931; Gordon, 1907; Lowsley, 1911). In 1981, the clinical utility of post-exercise hypotension was proposed when William Fitzgerald, a man in the process of writing his doctoral dissertation and frustrated by his diagnosis with labile hypertension despite his otherwise healthy lifestyle, began monitoring his own blood pressure throughout the day. An avid daily jogger, Fitzgerald noted that his blood pressure was consistently depressed for several hours following his morning runs. Fitzgerald went on to propose that jogging may be a useful blood pressure management tool for individuals with labile hypertension (Fitzgerald, 1981).

In the time since Fitzgerald's fortuitous anecdotal report, considerable investigation has been devoted to characterizing the phenomenon of post-exercise hypotension, identifying the underlying mechanisms which potentiate altered post-exercise hemodynamics, investigating the factors which influence the post-exercise hypotensive response (subject demographics, exercise type, intensity, duration, environmental conditions, etc.), and exploring the clinical relevance of post-exercise hypotension within healthy and diseased populations (Halliwill, 2001; Halliwill et al., 2013; M. J. Kenney & Seals, 1993; MacDonald, 2002). A 2016 meta-analysis of 65 studies

which explored post-exercise hypotension among various subject populations (normotensive, pre-hypertensive, and medicated and nonmedicated hypertensive) revealed that systolic blood pressure is reduced by ~6 mmHg and diastolic blood pressure is reduced by ~4 mmHg following a single bout of aerobic exercise (Carpio-Rivera et al., 2016). In normotensive individuals, a single bout of aerobic exercise serves to depress mean arterial pressure between 5-10 mmHg for up to 2 h following exercise. Post-exercise hypotension is exaggerated among hypertensive individuals as mean arterial pressure may fall by up to 20 mmHg and blood pressure may remain depressed for up to 12 h following aerobic exercise. In general, blood pressure reaches its lowest point sometime between 30 min and 1 h following exercise (MacDonald, 2002).

Table 2.1 summarizes studies completed to date which monitored blood pressure responses in the post-heating recovery period (≥ 30 min following heating). Romero and colleagues were one of the first groups to evaluate the systemic cardiovascular adjustments accompanying recovery from passive heat stress among young healthy individuals. In a 2017 study, Romero noted that blood pressure returned to baseline levels within 30 min of recovery following 45 min of lower-limb hot water immersion sufficient to increase intestinal temperature ~0.4°C and skin temperature of the immersed leg by ~9°C (Romero, Gagnon, et al., 2017). Later studies by the same group noted that blood pressure was similar to baseline values 30 min following 45 min of leg heating via water perfused suit (Δ intestinal temperature: +0.4°C; Δ skin temperature heated leg: +6.8°C) and 60 min following 60 min of lower-limb hot water immersion (Δ intestinal temperature +0.7°C; Δ skin temperature immersed leg: +7.5°C) (Engelland et al., 2020a, 2020b).

In contrast, Francisco and colleagues observed a reduction in systolic (-7 mmHg), diastolic (-8 mmHg), and mean arterial pressure (-8 mmHg) which was maintained for 60 min of recovery following 60 min of chest-level hot water immersion (Δ rectal temperature: +1.5°C). Importantly, these post-heating blood pressure reductions were similar in time course and magnitude to the post-exercise hypotension observed during recovery from 60 min of cycle exercise at 60% VO_2peak in the same participants (Francisco et al., 2021). Campbell noted a trend for reductions in blood pressure 45 min following 60 min of hot water immersion (Δ rectal temperature: +1.3°C; Δ mean skin temperature: +3°C) (Campbell et al., 2022) A recent study conducted by Amin and colleagues noted that systolic, diastolic, and mean arterial pressure were increased to a greater extent immediately following 30 min of threshold treadmill running (Δ

intestinal temperature: +1.6°C; Δ forearm skin temperature: +2.5°C) and 5 X 4 min high-intensity treadmill running (Δ intestinal temperature: +1.4°C; Δ skin temperature forearm: +1.1°C) intervals compared to 30 min of chest-level water immersion (Δ intestinal temperature: +1.5°C; Δ skin temperature forearm: +1.5°C) and generally tended to remain greater throughout 60 min of post-intervention recovery. In this study, systolic, diastolic, or mean arterial pressure returned to baseline values and were similar between interventions by 80 min of recovery (Amin et al., 2022).

Post-heating blood pressure reductions have been more consistently demonstrated among middle aged (50-60 years) and older individuals (over 60 years). Among a large cohort of middle-aged individuals with at least one cardiovascular risk factor, Laukkanen and colleagues noted that systolic blood pressure was reduced by ~7 mmHg 30 min following two 15 min sauna bouts (Δ tympanic temperature: +2°C) (Laukkanen et al., 2017). Among healthy older individuals, studies conducted by Romero and colleagues observed an ~7-8 mmHg reduction in mean arterial pressure following 45 min of lower-limb hot water immersion (Δ intestinal temperature: +0.5°C; Δ skin temperature immersed lower-limb: +9°C) and 45 min of leg heating via water perfused suit (Δ intestinal temperature: +0.8°C; Δ skin temperature immersed lower-limb: +7.5°C) (Engelland et al., 2020b; Romero, Gagnon, et al., 2017). Thomas and colleagues also noted that 30 min of waist level hot water immersion in older individuals (Δ aural temperature: +1.8°C) promoted reductions in blood pressure which were maintained for 1-4 h of post-heating ambulatory blood pressure monitoring as systolic (-14 mmHg), diastolic (-4 mmHg), and mean arterial pressure (-7 mmHg) were reduced compared to ambulatory blood pressure measured during the same time window on a control day (Thomas et al., 2017). While these studies suggest that recovery from heat stress may be accompanied by post-heating hypotension, a clear consensus across the literature has not been established. For example, studies conducted by Gravel (Gravel et al., 2019) and Richey (Richey et al., 2022) in middle aged and older adults (50-80 years) noted that blood pressure remained similar to baseline levels 40 min following two 10 min sauna bouts (Δ oral temperature: +0.9°C, Δ mean skin temperature: +8.5°C) and 90 min following 60 min of waist-level hot water immersion (Δ intestinal temperature: +1.0°C), respectively.

Post-heating blood pressure reductions have been consistently noted among middle aged and older patient populations. Early work conducted by Tei and colleagues in 1995 demonstrated

that diastolic blood pressure was reduced by ~11mmHg 30 min following either sauna or warm water bath (Δ pulmonary arterial blood temperature +1.2°C) in older individuals with congestive heart failure (Tei et al., 1995). Similarly, studies conducted by Neff (Neff et al., 2016) and Thomas (Thomas et al., 2017) demonstrated that older individuals with peripheral artery disease displayed reductions in systolic, diastolic, and mean arterial pressure following 90 min of leg heating via water perfused suit (Δ intestinal temperature: +0.5°C; Δ skin temperature heated leg: 7.1°C) and 30 min of waist level hot water immersion (Δ aural temperature: +1.8°C;), respectively. Importantly, the blood pressure reductions observed in these studies were sustained as blood pressure was lower across the 2-4 h of recovery following heating compared to a time-matched thermoneutral control condition (Neff et al., 2016; Thomas et al., 2017). Among older individuals with coronary artery disease, Gravel and colleagues noted that systolic blood pressure was reduced by ~10 mmHg at 50 min following two 10 min sauna bouts (Δ intestinal temperature: +0.7°C; Δ mean skin temperature: +1°C) (Gravel, Behzadi, et al., 2021).

Table 2.1 Summary of current studies evaluating blood pressure in the post-heating recovery period.

Study	Population	Heating Protocol	Δ Core Temperature (°C)	Recovery Characteristics	Δ Blood Pressure (mmHg)
Romero et al. 2017	Healthy young (*n*=9; 4M 28±4 yrs, 5F 28±5 yrs)	45 min lower limb hot water immersion (42°C water)	0.4 (intestinal)	30 min; supine	~ MAP
	Healthy older (*n*=9; 4M 70±2 yrs, 5F 68±4 yrs)	45 min lower limb hot water immersion (42°C water)	0.5 (intestinal)	30 min; supine	↓ MAP
Engelland et al 2020	Healthy young (*n*=13; 7M, 6F; 25±4 yrs)	45 min leg heating via water perfused suit (48°C)	0.4 (intestinal)	45 min; supine	~ MAP
	Healthy older (*n*=10; 4M, 6F 69±5 yrs)	45 min leg heating via water perfused suit (48°C)	0.8 (intestinal)	45 min; supine	↓ MAP (−7)
Engelland et al. 2020	Healthy young (*n*=10; 5M, 5F; 26±4 yrs)	60 min lower limb hot water immersion (42°C)	0.7 (intestinal)	60 min; supine	~ MAP
Francisco et al. 2021	Healthy young (*n*=12; 6M, 6F; 23±1 yrs)	60 min chest-level hot water immersion (40.5°C water)	~1.5 (rectal)	60 min; supine	↓MAP(−8) ↓SBP(−7) ↓DBP(−8)
Amin et al. 2022	Healthy young (*n*=15; 10M, 5F; 27±5 yrs)	30 min chest-level hot water immersion (42°C)	1.5 (rectal)	80 min; semirecumbent	~MAP ~SBP ~DBP
Laukkanen et al. 2017	Asymptomatic with ≥1 cardiovascular disease risk factor (*n*=102; 52M, 44F; 52±9 yrs)	2X15 min sauna 73C, 10-20% humidity	2.0 (tympanic)	30 min; supine	↓SBP(−7) ↓DBP(−7)
Thomas et al. 2017	Peripheral artery disease (*n*=8; 71±6 yrs)	30 min waist-level hot water immersion (42°C water)	1.8 (aural)	60-240 min; ambulatory	↓MAP(−6) ↓ SBP(−5) ↓DBP(−6)*
	Healthy older (*n*=9; 72±7 yrs)	30 min waist-level hot water immersion (42°C water)	1.8 (aural)	60-240 min; ambulatory	↓MAP(−7) ↓SBP(−14) ↓DBP(−4)
Gravel et al. 2019	21 healthy older (n=21; 10M, 11F; 66±6 yrs)	1X10 min sauna (80±3°C, 23% humidity)	0.5 (oral)	40 min; supine	~MAP ~SBP ~DBP
		2X10 min sauna (80±3°C, 23% humidity)	0.9 (oral)	40 min; supine	~MAP ~SBP ~DBP
Richey et al. 2022	Healthy older (*n*=8; 1 M, 7 F; 70±5 yrs)	60 min waist-level hot water immersion (40°C)	1.0 (intestinal)	90 min; supine	~ MAP
Tei et al. 1995	Congestive heart failure (n=34; 58±14 yrs)	15 min far-infrared sauna (60°C)	1.2 (pulmonary arterial blood)	30 min supine, wrapped in blankets	~SBP ↓DBP
		10 min chest-level hot water immersion (41°C water)		30 min supine, wrapped in blankets	~SBP ↓DBP
Neff et al. 2016	Peripheral artery disease (*n*=16; 14M, 2F; 63±9 yrs)	90 min leg heating via water perfused suit (48°C water)	0.5 (intestinal)	120 min; supine	↓MAP ↓SBP ↓DBP

Cardiac Output

Studies conducted in the late 1980's and early 1990's (Cléroux et al., 1992; Coats et al., 1989; Halliwill, Taylor, & Eckberg, 1996; Halliwill, Taylor, Hartwig, et al., 1996; Isea et al., 1994; Piepoli et al., 1993, 1994) largely charted the time course of the systemic cardiovascular adjustments supporting post-exercise hypotension in normotensive and hypertensive individuals. In most studies and individuals, post-exercise hypotension is mediated in large part by increases in systemic vascular conductance (or reductions in systemic vascular resistance) which persist following exercise and are not completely offset by increases in cardiac output (Halliwill, 2001; Halliwill et al., 2013; M. J. Kenney & Seals, 1993; MacDonald, 2002). Cardiac output generally remains elevated for up to 2 h following exercise. The post-exercise elevation in cardiac output is facilitated primarily by sustained elevations in heart rate as stroke volume generally returns toward baseline values following exercise (Cléroux et al., 1992; Coats et al., 1989; Halliwill, Taylor, Hartwig, et al., 1996; Isea et al., 1994; Piepoli et al., 1993, 1994). Indeed, heart rate quickly declines upon the cessation of exercise and declines more slowly thereafter such that heart rate typically remains elevated for ~1 h of post-exercise recovery (Cléroux et al., 1992; Coats et al., 1989; Halliwill, Taylor, & Eckberg, 1996; Halliwill, Taylor, Hartwig, et al., 1996; Isea et al., 1994; Piepoli et al., 1993, 1994).

Very few studies have characterized cardiac output during the post-heating recovery period. Among young individuals, Romero and colleagues estimated cardiac output using the Modelflow method and demonstrated that cardiac output (+0.5 L/min) and heart rate (+4-5 bpm) were elevated after 30 min of recovery following 45 min of lower-limb hot water immersion (Δ intestinal temperature: +0.4°C; Δ immersed leg skin temperature: +9°C). This increase in cardiac output offset post-heating increases in vascular conductance and blood pressure was similar to baseline values following heating (Romero, Gagnon, et al., 2017).

The most comprehensive comparison of post-heating and post-exercise central hemodynamics among young individuals completed to date was conducted by Francisco and colleagues **(Figure 2.9)**. Using the open circuit acetylene washin method, this group observed that cardiac output was comparably increased (~1.8 L/min) 20 min following 60 min of chest-level hot water immersion and 60 min of cycle exercise at 60% VO_2peak (Δ rectal temperature: +1.5°C). This post-intervention increase in cardiac output was maintained for 40 min following exercise versus only 20 min following heating. Post-intervention elevations in cardiac output

were supported by elevations in heart rate as stroke volume did not change from baseline values during post-heating recovery and was reduced below baseline values during post-exercise recovery (-15-20 mL/beat 20-60 min following exercise). Post-intervention elevations in heart rate were approximately two-fold greater and most sustained following exercise compared to heating. Blood pressure was comparably reduced following both heating and exercise in this study as these temporary increases in cardiac output did not offset systemic vascular conductance which remained similarly elevated throughout the 60 min post-intervention recovery periods (Francisco et al., 2021). Similarly, a recent study conducted by Amin and colleagues demonstrated that heart rate was elevated to a greater extent throughout 80 min of recovery following 30 min of threshold treadmill running (Δ intestinal temperature: +1.6°C; Δ skin temperature forearm: +1.5°C) and 5 X 4 min high-intensity treadmill running (Δ intestinal temperature: +1.4°C; Δ skin temperature forearm: +1.1°C) intervals compared to 30 min of chest-level water immersion (Δ intestinal temperature: 1.5°C; Δ skin temperature forearm: +2.5°C) (Amin et al., 2022).

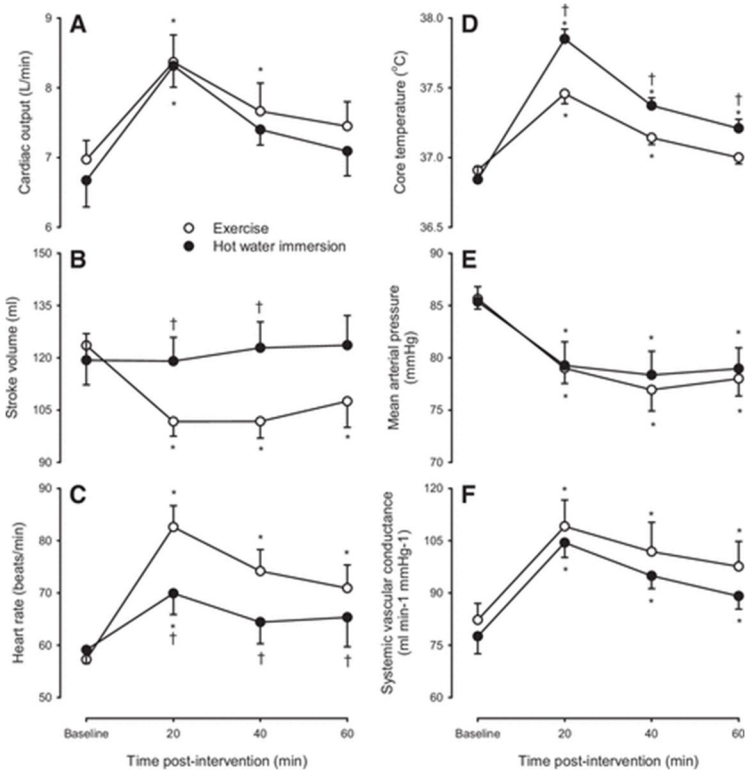

Figure 2.9 Cardiac output, stroke volume, heart rate, rectal temperature, mean arterial pressure, and systemic vascular conductance (means ± SE) at supine pre-intervention baseline and throughout 60 min of supine recovery following seated cycle exercise (open circles) or chest-level hot water immersion (closed circles). *$P < 0.05$ vs. preintervention baseline. †$P < 0.05$ vs. exercise at the same time point. Figure and caption adapted from Francisco et al. (Francisco et al., 2021).

Not all studies have demonstrated elevations in cardiac output and heart rate during the post-heating recovery period among young individuals. Studies conducted by Engelland and Romero noted that cardiac output and heart rate were similar to baseline values 30 min following 45 min of leg heating via water perfused suit (Δ intestinal temperature: +0.4°C; Δ skin temperature heated leg: +6.8°C) and 60 min following 60 min of lower-limb hot water immersion in young individuals (Δ intestinal temperature: +0.7°C; Δ skin temperature immersed leg: +7.5°C). Importantly, post-heating blood pressure and presumably systemic vascular resistance also remained similar to baseline values in these studies (Engelland et al., 2020a, 2020b). Furthermore, Brunt and colleagues noted that heart rate was reduced below baseline

values 60 and 100 min following hot water immersion, although this study also noted abnormally high baseline heart rate values (~80 bpm) (Brunt, Jeckell, et al., 2016).

Post-heating elevations in cardiac output may not occur among older individuals. Work conducted by Romero and colleagues demonstrated that cardiac output and heart rate remained similar to baseline values 30 min following 45 min of lower-limb hot water immersion (Δ intestinal temperature: +0.5°C; Δ skin temperature immersed leg: +9°C) **(Figure 2.10)** and 45 min of leg heating via water perfused suit (Δ intestinal temperature: +0.8°C; skin temperature heated leg: +7.5°C). Importantly, the absence of an elevation in cardiac output among older individuals in these studies contributed to a post-heating reduction in blood pressure as systemic vascular resistance remained elevated during post heating recovery (Engelland et al., 2020b; Romero, Gagnon, et al., 2017). Post-heating elevations in heart rate seem to occur inconsistently among middle-aged and older individuals in both health and disease. For example, some studies have noted that heart rate remains elevated by 3-4 bpm 30-40 min into the post-heating recovery period among older individuals (Engelland et al., 2020b; Gravel et al., 2019), while others have noted that heart rate returns to baseline values (Gravel, Behzadi, et al., 2021; Laukkanen et al., 2017; Richey et al., 2022; Romero, Gagnon, et al., 2017) or is depressed below baseline values following heating (Laukkanen et al., 2019).

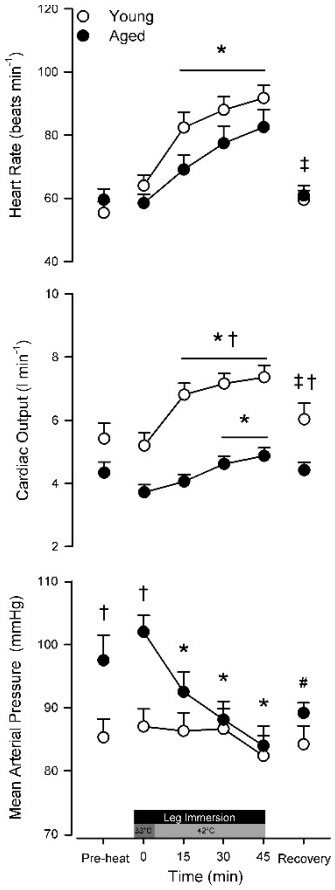

Figure 2.10 Heart rate, cardiac output, mean arterial pressure (means ± SE) pre-heating, throughout 45 min of lower limb heating, and 30 min into post-heating recovery in young (open circles) and older adults (closed circles). *$P < 0.05$ vs. thermoneutral (33°C) immersion within group; †$P < 0.05$ vs. young adults at the indicated time point; ‡$P < 0.05$ vs. preheat for young adults; #$P < 0.05$ vs. preheat for older adults. Figure and caption adapted from Romero et al. (Romero, Gagnon, et al., 2017).

Blood Flow Distribution

The skeletal muscle, splanchnic, renal, and cutaneous regional circulations play the largest role in blood flow and pressure regulation during and following exercise and passive heating. The maintained increases in systemic vascular conductance following exercise are mediated largely by sustained post-exercise vasodilation of skeletal muscle. Sustained post-exercise vasodilation is believed to occur within both previously active skeletal muscle and inactive muscle (Halliwill et al., 2000). Indeed, calf and forearm vascular resistance have been

demonstrated to decline by ~36% and ~47%, respectively, following 60 min of cycle exercise at 60% VO_2peak (Halliwill et al., 2000). In contrast, vascular conductance within the splanchnic and renal circulations is unchanged following exercise (Pricher et al., 2004). Wilkins et al. examined the contribution of cutaneous circulation to post-exercise increases in systemic vascular conductance and hypotension. In this study, post-exercise hypotension persisted for 60 min following cycle exercise, despite the return of cutaneous vascular conductance to pre-exercise values within 20 (forearm and leg), 30 (chest), and 50 (thigh) min post-exercise. The discrepancy in the observed time course of post-exercise hypotension and changes in cutaneous vascular conductance suggests that cutaneous vasodilation may contribute, but is not obligatory, to increases in vascular conductance and hypotension following exercise (Wilkins et al., 2004).

As previously outlined, studies conducted by Romero and Francisco have demonstrated that systemic vascular conductance remains elevated for 30-60 min following recovery from passive heat stress in both young and older individuals (Francisco et al., 2021; Romero, Gagnon, et al., 2017). Importantly, Francisco demonstrated that these post-heating elevations in systemic vascular conductance were similar in time course and magnitude to those observed during recovery from 60 min of cycle exercise at 60% VO_2peak in the same participants **(Figure 2.9)** (Francisco et al., 2021). This sustained peripheral vasodilation is likely localized within the muscle and/or skin circulations. Among both young and older adults many, but not all (Engelland et al., 2020a; Gravel et al., 2019), studies have demonstrated elevations in blood flow and vascular conductance within both directly heated and indirectly heated limbs which is maintained for 20-80 min following hot water immersion, sauna, and water perfused suit heating (Amin et al., 2022; Engelland et al., 2020b; Francisco et al., 2021; Gravel, Behzadi, et al., 2021; Romero, Gagnon, et al., 2017; Thomas et al., 2017). Furthermore, studies in both young and older adults have demonstrated improved macrovascular endothelial function (flow-mediated dilation; (Coombs et al., 2021; Didier et al., 2022; Tinken et al., 2009), improved microvascular function (reactive hyperemia response; (Cheng et al., 2019, 2021; Romero, Gagnon, et al., 2017)), and increased protection against ischemia reperfusion following acute heat exposure (Brunt, Jeckell, et al., 2016; Engelland et al., 2020a; Hemingway, Richey, Moore, Olivencia-Yurvati, et al., 2022; Hemingway, Richey, Moore, Shokraeifard, et al., 2022).

Francisco demonstrated that 60 min of chest-level hot water immersion and 60 min of cycle exercise at 60% VO_2peak (Δ rectal temperature: +1.5°C) promoted similar elevations in

brachial vascular conductance (173-209% above baseline values) which were maintained for 20 min into the post-stress recovery period and returned to baseline values thereafter. Femoral vascular conductance was also similarly elevated 20 min following these heating and exercise interventions (69-112% above baseline values), but this leg vasodilation was sustained longer following exercise (40 min post-exercise vs 20 min post-heating) (Francisco et al., 2021). In contrast, Amin demonstrated that compared to both 30 min of treadmill running at an intensity equivalent to respiratory compensation point and 5 x 4 min high intensity running intervals (85-95% of maximal heart rate), 30 min of chest-level hot water immersion (Δ intestinal temperature: +1.5°C across interventions) promoted the most dramatic increases in femoral vascular conductance immediately post-intervention. This leg vasodilation was sustained similarly between interventions 20, 60, and 80 min into the post-stress recovery period **(Figure 2.11)** (Amin et al., 2022).

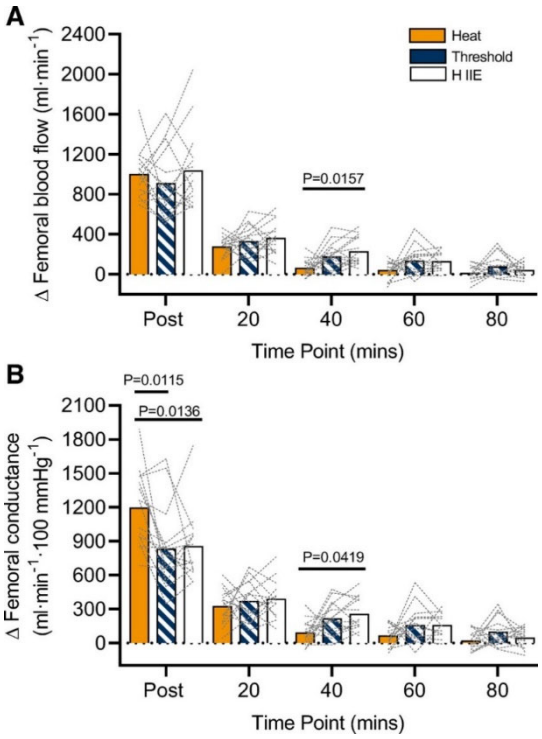

Figure 2.11 Change in femoral blood flow (Panel A) and vascular conductance (Panel B) from baseline during recovery from hot water immersion (orange bars), threshold running (stripe bars), and high intensity running intervals (open bars). Figure and caption adapted from Amin et al. (Amin et al., 2022).

As both renal and splanchnic vascular conductance is attenuated during passive heat stress, it is unlikely that elevations in renal and splanchnic vascular conductance contribute importantly to increased systemic vascular conductance during the post-heating recovery period. Along these lines, Chapman et al. recently used Doppler ultrasound to demonstrate that renal and segmental artery blood velocity returned to baseline levels immediately upon active skin cooling following whole-body heat stress via water perfused suit (Δ intestinal temperature: +1.2°C; Δ mean skin temperature: +4.1°C) (Chapman et al., 2019). No studies to our knowledge have characterized splanchnic blood flow during recovery from heat stress.

Systemic Hemodynamics during Post-Stress Recovery: Overlapping or Alternative Mechanisms?

Autonomic and Thermal Influences Supporting Heart Rate

When present, post-exercise and post-heating elevations in cardiac output are primarily supported by sustained elevations in heart rate. Post-stress elevations in heart rate may stem from the direct effects of increased temperature on cardiac pacemaker cells and/or altered autonomic modulation of heart rate (Gorman & Proppe, 1984). In humans, it is generally accepted that heart rate increases by about 30 beats per min per 1.0°C increase in internal temperature (J. M. Johnson & Proppe, 1996). This heat-induced tachycardia results from the direct effects of temperature to reduce action potential duration at the sinoatrial and atrioventricular nodes (Thibault et al., 1998; Yamagishi & Sano, 1967) and to increase action potential conduction from these pacemaker cells to cardiac myocytes (Y. hua Chen & DeHaan, 1993). Therefore, if core temperature is increased 1.0-1.5°C with exercise or passive heating and remains elevated by 0.3-0.6°C 30 min following exercise or heating (Francisco et al., 2021; Hoekstra et al., 2021; Kenny & Mcginn, 2017; Rodrigues et al., 2020), heart rate may be expected to be elevated by ~3-6 bpm in the post-stress recovery period due to the direct effects of temperature alone. This is reasonably consistent with the 3-9 bpm increase in heart rate which has been demonstrated 20-55 min into the post-heating recovery period (Campbell et al., 2022; Engelland et al., 2020b; Francisco et al., 2021; Gravel et al., 2019; Rodrigues et al., 2020; Romero, Gagnon, et al., 2017).

With respect to the autonomic modulation of the heart, exercise elicits increases in heart rate through withdrawal of cardiac parasympathetic activity and increased sympathetic activation. Studies using both pharmacological blockade and heart rate variability analyses to assess autonomic control of the heart following exercise have determined that the fall in heart rate within the first few min of exercise cessation is mediated by parasympathetic reactivation.

Beyond this immediate recovery window, post-exercise heart rate is determined by a balance of parasympathetic re-activation and sympathetic withdrawal (Borresen & Lambert, 2008; Imai et al., 1994; Kannankeril et al., 2004; Savin et al., 1982). Similarly, acute heat stress decreases vagal and increases sympathetic modulation of heart rate (Crandall et al., 2000; Gorman & Proppe, 1984). If these autonomic changes persist following heating, they may contribute to sustained elevations in heart rate in the post-heating recovery period. It is important to note, however, that the sustained post-exercise elevations in cardiac sympathetic activity are likely largely influenced by the extent of the initial stress-induced sympathoexcitation (Pierpont et al., 2000). It is possible that heat stress, which elicits a comparably modest elevation in heart rate compared to exercise, does not promote sustained alterations in cardiac sympatho-vagal balance which support post-heating elevations in heart rate.

Two studies conducted to date have used heart rate variability derived indices to assess autonomic control of the heart following a single bout of heat stress. Among patients with untreated hypertension, Gayda noted that sauna alone (two 8 min sessions separated by a 2 min cold shower and 10 min of rest) and combined exercise and sauna (30 min cycle ergometry at 75% of maximal heart rate followed by the sauna protocol outlined above) comparably increased low frequency power (index of sympathetic activity) and decreased high frequency power (index of parasympathetic tone) 15 min into the post-stress recovery period compared to a time control group. These alterations in cardiac autonomic tone were not sustained and all heart rate variability indices returned to baseline values after 120 min of recovery (Gayda et al., 2012). In contrast, among a cohort of middle-aged individuals with at least once cardiovascular disease risk factor, Laukkanen noted that heart rate variability indices of sympathetic activity were decreased while indicines of parasympathetic activity were increased 30 min following two 15 min dry sauna bouts separated by a 2-min warm shower (Δ tympanic temperature: +2.0°C). Interestingly, this study also noted that heart rate was reduced 9 bpm below baseline values during post-heating recovery which is in contrast with the majority of studies reporting tachycardia in the post-heating recovery period (Laukkanen et al., 2019). These inconsistencies may reflect the different populations studied, heart rate variability methods and analyses utilized, or heating protocols employed. The autonomic control of heart rate during recovery from passive heating remains an interesting area for future research.

Autonomic and Thermal Influences Supporting Stroke Volume

Stroke volume generally returns toward baseline values following exercise and is determined by the complex interplay between preload, afterload, and cardiac inotropy (Cléroux et al., 1992; Coats et al., 1989; Halliwill, Taylor, Hartwig, et al., 1996; Isea et al., 1994; Piepoli et al., 1993, 1994). Following 60 min of upright cycle exercise, Halliwill and colleagues demonstrated that central venous pressure is typically reduced by ~2 mmHg. This reduction in cardiac preload likely stems from the peripheral displacement of blood volume towards the skeletal muscle circulation upon the cessation of the muscle pump and a reduction in filling time accompanying post-exercise tachycardia (Halliwill et al., 2000). Cardiac afterload, or the pressure a ventricle must generate to eject blood into circulation, typically declines following exercise as sustained post-stress vasodilation promotes reductions in systemic vascular resistance and post-exercise hypotension. The post-heating recovery period, which is likely accompanied by peripheral displacement of blood volume, tachycardia, and sustained vasodilation and hypotension, may be similarly accompanied by reductions in cardiac preload and afterload. Post-exercise and post-heating recovery are also likely both accompanied by increased cardiac inotropy secondary to increases in cardiac sympathetic nerve activity. Along these lines, it is well-established acute heat stress is accompanied by reductions in cardiac preload and afterload and increased inotropic function (Brothers et al., 2009; Bundgaard-Nielsen et al., 2010; Wilson et al., 2007, 2009).

Importantly, the interplay between post-stress preload, afterload, cardiac inotropy and downstream stroke volume and cardiac output responses is likely influenced by both protocol characteristics (fluid loss, recovery posture, exercise/heating characteristics) and subject population (heathy untrained, trained, sex, patient populations). While the influence of these factors on the post-exercise recovery period has been thoroughly demonstrated (Brito et al., 2014; B. M. Lynn et al., 2007, 2009; Raine et al., 2001; Senitko et al., 2002), the extent to which these factors may similarly alter the post-heating recovery period remains largely unknown.

The only study to date characterizing cardiac function in the post-heating recovery period was conducted by Tei and colleagues. This study measured intracardiac pressures (Swan-Ganz catheter), cardiac output (thermodilution method) and ejection fraction (M-mode echocardiograms) at baseline and after 30 min following either a 10 min hot water immersion bout and 15 min far infrared sauna bout (Δ pulmonary artery blood temperature +1.2°C). Both

hot water immersion and sauna promoted post-heating reductions in right atrial and pulmonary capillary wedge pressures (indices of right and left cardiac preload) and systemic and pulmonary vascular resistance (indices of right and left cardiac afterload). Furthermore, ejection fraction, stroke volume, and cardiac output were all increased above baseline values in the post-heating recovery period (Tei et al., 1995). While these results are impressive, participants were wrapped in blankets during this post-heating recovery period (Waon therapy) which may have promoted exaggerated or extended post-heating responses compared to what may be expected during a thermoneutral recovery period. Furthermore, the extent to which the post-heating recovery period alters cardiac function and stroke volume in healthy young and older individuals remains unknown.

Sustained Vasodilation

The sustained elevations of systemic vascular conductance and limb blood flow following both exercise and heat stress suggest that the post-exercise and post-heating recovery period may similarly promote sustained post-stress vasodilation. This sustained vasodilation is primarily localized to skeletal muscle following exercise. However, as studies to date have utilized vascular ultrasound to assess limb blood flow, the distribution of blood flow between the skin and muscle circulations during the post-heating recovery period remains unknown. Furthermore, it is possible that increased vascular conductance within the splanchnic and renal circulations contribute to elevations in systemic vascular conductance following heating. The following section will discuss these possibilities as we highlight both the shared and unique avenues by which passive heating might promote sustained post-stress vasodilation.

Sustained vasodilation of skeletal muscle is a hallmark of the post-exercise recovery period. Accordingly, several investigations have focused on systematically searching for the local vasodilator which may mediate sustained post-exercise vasodilation in skeletal muscle. While these investigations considered many likely local vasodilators including nitric oxide (Halliwill et al., 2000) and prostanoids (Lockwood, Pricher, et al., 2005), identification of the local vasodilator mediating sustained post-exercise vasodilation and hypotension remained elusive. In 2005, Lockwood and colleagues demonstrated that the early stage (~30-60 min) of the post-exercise vasodilatory response is mediated by H_1 receptor mediated vasodilation as systemic blockade of histamine H_1 receptors via a high dose of a H_1 receptor antagonist (540 mg oral fexofenadine hydrochloride) blunted the increase in femoral vascular conductance 30 min

following a 60 min bout of moderate intensity cycle exercise (Lockwood, Wilkins, et al., 2005). McCord and colleges additionally demonstrated that systemic blockade of histamine H_2 receptors via a high dose of a H_2 receptor antagonist (300 mg ranitidine hydrochloride) blunted the increase in femoral vascular conductance 60 min following a 60 min bout of moderate intensity cycle exercise (J. L. McCord et al., 2006). Finally, McCord and Halliwill demonstrated that the combined blockade of H_1 and H_2 (540 mg fexofenadine and 300 mg ranitidine) reduced post-exercise vasodilation by ~80% following 60 min of moderate-intensity cycle exercise (J. L. McCord & Halliwill, 2006). Continued work by this group revealed that increases in intramuscular histamine accompanying exercise are mediated by mast cell degranulation and *de novo* formation via histamine decarboxylase (Romero, McCord, et al., 2017). Collectively this work established histamine release and receptor activation as a putative mediator of sustained post-exercise vasodilation of skeletal muscle.

Like post-exercise recovery, it is possible that elevations in systemic vascular conductance following heating are localized to the skeletal muscle circulation. In support of this concept, recent studies utilizing ^{133}Xenon clearance and positron emission tomography have revealed that muscle blood flow modestly increases with direct whole body or local limb heating (~ 1mL·100 g muscle^{-1}·min^{-1}) (Heinonen et al., 2011; Keller et al., 2010). Furthermore, Amin and colleagues demonstrated that femoral blood flow remained above baseline values up to 80 min following 30 min of chest level water immersion (Δ rectal temperature: +1.5°C; Δ skin temperature forearm: +2.5°C) despite the use of a fan and application of wet towels to attenuate sustained increases in skin temperature and blood flow (Amin et al., 2022). Along these lines, Richey and colleagues used skeletal muscle microdialysis to assess skeletal muscle blood flow and microvascular function during recovery from heat stress in older individuals. While local blood flow (ethanol washout technique) in the vastus lateralis was similar 90 min following hot water immersion (Δ intestinal temperature: +1°C) and thermoneutral water immersion, the hyperemic response to graded infusions of acetylcholine and sodium nitroprusside was increased following hot water immersion **(Figure 2.12)**. This finding suggests that microvascular function in skeletal muscle is improved during the post-heating recovery period among older individuals (Richey et al., 2022). Importantly, as this study was conducted only in older adults, the degree to which skeletal muscle microvascular function may be altered in young individuals during the post-heating recovery period remains unknown.

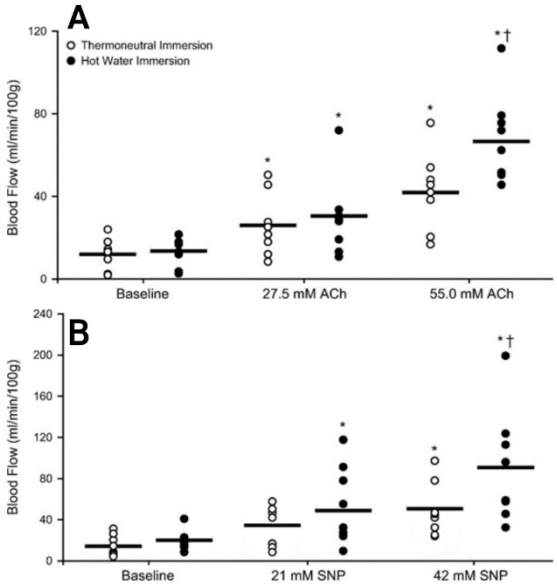

Figure 2.12 Local skeletal muscle blood flow at baseline and during graded infusion of acetylcholine (Panel A) or sodium nitroprusside (Panel B) 90 min following 60 min of thermoneutral (open circles) or hot water immersion (closed circles). *$P < 0.01$ vs. baseline within thermal condition; †$P < 0.01$ vs. thermoneutral water immersion at the indicated dose of acetylcholine or nitroprusside (Richey et al., 2022).

If increases in systemic vascular conductance are indeed localized to the skeletal muscle, it is possible that they are similarly mediated by histaminergic signaling mechanisms. In support of this notion, Mangum et al. recently demonstrated that 60 min of local heating via pulsed short-wave diathermy (vastus lateralis temperature reached 38.9°C, Δ +6.3°C from pre-heating baseline) promoted a 41% increase in intramuscular histamine concentration which likely reflected increased *de novo* histamine formation via histidine decarboxylase **(Figure 2.13)**. Although these heating induced increases in intramuscular histamine were only one third of the ~150% increase in intramuscular histamine seen with aerobic exercise, this work suggests a potential role for histamine release in the skeletal muscle vasodilation which accompanies or persists following acute heat stress (Mangum et al., 2022). The extent to which intramuscular histamine release accompanies recovery from whole-body heating and contributes to post-heating vasodilation of skeletal muscle remains unknown.

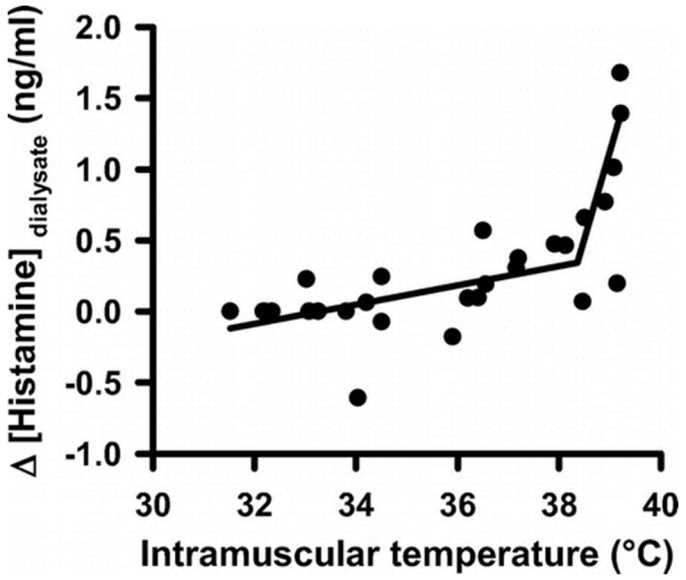

Figure 2.13 Inflection point analysis relating intramuscular temperature and histamine concentrations in vastus lateralis muscle dialysate during 60 min of heating by pulsed short-wave diathermy. Lines show best fit for piecewise linear regression to identify the inflection point for the rise in histamine concentration versus intramuscular temperature. Figure and caption adapted from Mangum et al. (Mangum et al., 2022).

While histaminergic signaling may be a shared mediator of sustained post-stress vasodilation, it is also possible that sustained vasodilation within skeletal muscle following passive heating is supported by a distinct local vasodilator. Indeed, potential mechanisms underlying the increases in muscle blood flow with direct heating may include the direct effect of the rise in muscle temperature on skeletal muscle microvasculature or increased metabolic activity of the heated muscle due to the Q^{10} effect (Crandall & Wilson, 2015; van't Hoff, 1884). Changes in muscle temperature, vascular shear stress (Thomas et al., 2016, 2017), or heat shock protein expression (Cheng et al., 2021; Faulkner et al., 2017; Hafen et al., 2018, 2019; Neff et al., 2016) with direct heating may also serve to modify the release or action of vasodilating substances which may in turn contribute to heat-induced hyperemia of skeletal muscle. Promising vasodilators in this role include ATP (Kalsi & González-Alonso, 2012; Pearson et al., 2011) and nitric oxide (Harris et al., 2003; Ives et al., 2012), but other vasoactive substances including adenosine, potassium, hydrogen ions, prostanoids, or endothelium-derived hyperpolarizing factors may also contribute (Clifford & Hellsten, 2004).

On the other hand, elevations in systemic vascular conductance following heating could be localized to the cutaneous circulation. At rest, the cutaneous circulation receives relatively little blood flow (250 mL/min, 5% of cardiac output) and promotes heat dissipation roughly equivalent to basal metabolic heat production, ~80-90 kcal/h. Under conditions of heat stress skin blood flow is markedly increased, reaching 7-8 L/min and comprising 60% of cardiac output (Charkoudian, 2003; J. M. Johnson, Brengelmann, et al., 1986; J. M. Johnson & Proppe, 1996; Rowell, 1974, 1983). The initial 10% of the reflexive increase in skin blood flow with whole-body heating is thought to reflect the withdrawal of tonic sympathetic vasomotor tone, while the remaining 90% is facilitated by sympathetically mediated active vasodilation (Wong & Hollowed, 2017). Furthermore, the increase in local skin temperature directly promotes vasodilation of underlying cutaneous blood vessels which is influenced by both the degree and speed of local warming (Barcroft & Edholm, 1943; Hodges et al., 2009; Minson et al., 2001) such that a maintained skin temperature of 42°C will elicit maximal cutaneous vasodilation (J. M. Johnson, O'Leary, et al., 1986; W. F. Taylor et al., 1984). It is possible that dramatic cutaneous vasodilation persists into the post-heating recovery period amid sustained post-heating elevations in core and/or skin temperature.

Work by Amin and colleagues provides the only assessment of skin blood flow in the post-heating recovery period to our knowledge. In this study, 30 min of chest-level hot water immersion, 30 min of treadmill running at an intensity equivalent to respiratory compensation point, and 5 x 4 min high intensity (85-95% of maximal heart rate) promoted comparable increases in forearm skin blood flux which remained similarly elevated above baseline values for 80 min of post-stress recovery (Amin et al., 2022).

Systemic Hemodynamics: Summary

This collective work suggests that exercise and passive heat stress may act through shared and divergent mechanisms to promote sustained post-stress reductions in blood pressure supported by sustained elevations in systemic vascular conductance which are incompletely offset by post-stress elevations in cardiac output. Increasing age may importantly modify the balance between post-heating systemic vascular conductance and cardiac output as post-heating hypotension is most consistently noted among older individuals. While it is well established that the sustained increases in systemic vascular conductance which persist following exercise are

mediated by sustained vasodilation of skeletal muscle, the circulations which mediate increases in vascular conductance following heating remain unknown.

NEUROVASCULAR CONTROL

Arterial blood pressure is regulated in the short term by baroreflex modulation of the sympathetic and parasympathetic branches of the autonomic nervous system. Within this negative feedback baroreflex arc, mechanosensitive baroreceptors in the carotid sinus and aortic arch sense blood pressure as absolute stretch and changes in stretch and relay this afferent feedback to the cardiovascular control centers in the medulla where it is compared against the regulated blood pressure level or "operating point." If blood pressure is below the operating point, a reflexive reduction in parasympathetic and increase in sympathetic efferent activity will elicit increases in heart rate, contractility, and vascular resistance as a means of raising blood pressure.

Because the baroreflex tightly regulates blood pressure in the short term through modulation of sympathetic and parasympathetic outflow, the sustained nature of the post-stress hemodynamic shifts outlined in the previous section are suggestive of altered post-stress neurovascular support of blood pressure. The following section will review our current understanding of the neurovascular adjustments which support the acute and recovery responses to exercise and passive heating.

Neurovascular Responses to Acute Exercise and Heat Stress

During dynamic exercise, feedforward motor command signals and afferent feedback arising originating from mechano- and metabo-sensitive receptors within active skeletal muscle are relayed to the cardiovascular control centers in the medulla oblongata and serve to "reset" the baroreflex to operate around a higher blood pressure. This baroreflex resetting causes the previously prevailing resting blood pressure to be sensed as lower than intended during exercise and promotes a withdrawal of parasympathetic outflow and an increase in sympathetic outflow. Progressive parasympathetic withdrawal mediates the cardiovascular response to exercise up to heart rates of ~100 bpm. Sympathetic nerve activity increases in proportion with exercise intensity during dynamic, aerobic exercise above 20% of VO_{2peak} and continues to increase with extended exercise duration (Katayama & Saito, 2019; Saito et al., 1993, 1997; White & Raven, 2014).

Similarly, the thermoregulatory and cardiovascular responses which accompany heat stress are mediated by a profound sympathoexcitation. Rowell originally characterized heat stress as a "hyperadrenergic state" noting the pronounced rise in circulating norepinephrine which accompanied hyperthermia (Rowell, 1990). Subsequent studies have demonstrated that muscle sympathetic nerve activity increases 40-90% with hyperthermia in young individuals (Cui et al., 2002a, 2006; Greaney et al., 2016; Low et al., 2011; Niimi et al., 1997a). The change in core temperature accompanying heat stress directly influences the degree of this sympathoexcitation as progressive increases in muscle sympathetic nerve activity have been demonstrated with mild (Δ tympanic temperature: +0.3°C; Δ mean skin temperature: +3.9°C) (Niimi et al., 1997b), moderate (Δ intestinal temperature: +0.6°C; Δ mean skin temperature: +4.1°C), and more intense heating (Δ intestinal temperature: +1.3°C; Δ mean skin temperature: +4.7°C) (Low et al., 2011). Skin sympathetic nerve activity also increases dramatically with passive hyperthermia and mediates increased sweating and cutaneous active vasodilation (Bini et al., 1980; Cui et al., 2006; Low et al., 2011; Wilson et al., 2001). While our knowledge of heat-induced sympathoexcitation is limited to the muscle and skin circulations in humans, increases in sympathetic nerve activity accompanying hyperthermia are believed to be systemic, as increases in renal, lumbar, splenic, and splanchnic sympathetic activity with heating have been noted in rats (M. J. Kenney et al., 1995, 1998).

Influence of Age

It is well-established that sympathetic activity increases with advancing age such that muscle sympathetic nerve activity is essentially doubled between 25 and 65 years of age in healthy individuals (Ng et al., 1993; Seals & Esler, 2000). Interestingly, work by Gagnon and colleagues demonstrated that despite the attenuated systemic cardiovascular response to heat stress with aging, young and older individuals display comparable increases in muscle sympathetic nerve activity during both moderate (Δ intestinal temperature young: +0.6°C, older: +0.6°C; Δ mean skin temperature young: +3.9°C older: +4.2°C) and more intense (Δ intestinal temperature young: +1.2°C, older: +1.2°C; Δ mean skin temperature young: +3.9°C, older: +4.1°C) passive heating via water perfused suit **(Figure 2.14)**. Furthermore, young and older individuals displayed similar sympathetic activation in response to sympathoexcitatory stimuli (cold pressor test or lower body negative pressure) superimposed on hyperthermia (Gagnon et al., 2015). As muscle sympathetic nerve activity is assumed to reflect sympathetic outflow to

cardiac, renal, and splanchnic circulations (Wallin et al., 1992, 1996), this suggests that the attenuated cardiac, renal, and splanchnic responses to heat stress among older individuals may reflect age-related changes in the intrinsic properties or adrenergic responsiveness of these organs.

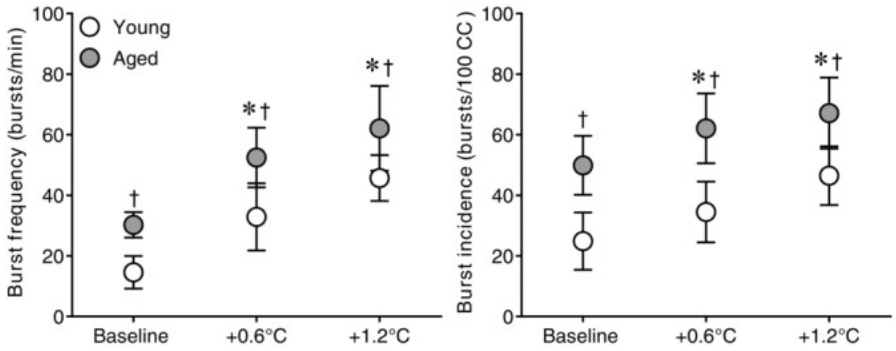

Figure 2.14 Muscle sympathetic nerve activity burst frequency and burst incidence (means ± 95% CI) in healthy young and older individuals during whole-body, passive heat stress via water perfused suit. *$P < 0.05$ vs baseline; †$P < 0.05$ between young and older adults. Figure and caption adapted from Gagnon et al. (Gagnon et al., 2015).

In the cutaneous circulation, Stanhewicz and colleagues demonstrated that although skin sympathetic nerve activity was comparable between young and older individuals at baseline, older individuals displayed attenuated increases in skin sympathetic nerve activity during whole body passive heating via water perfused suit (Δ esophageal temperature: +1.0°C) **(Figure 2.15)** (Stanhewicz et al., 2016). A follow-up retrospective analysis conducted by Greaney demonstrated that the attenuated increase in skin sympathetic nerve activity among older adults during hyperthermia was due to both an increased body temperature activation threshold and attenuated response sensitivity (Greaney et al., 2020). These impaired skin sympathetic responses to hyperthermia likely contribute to impaired cutaneous vasodilation during passive heating among older individuals.

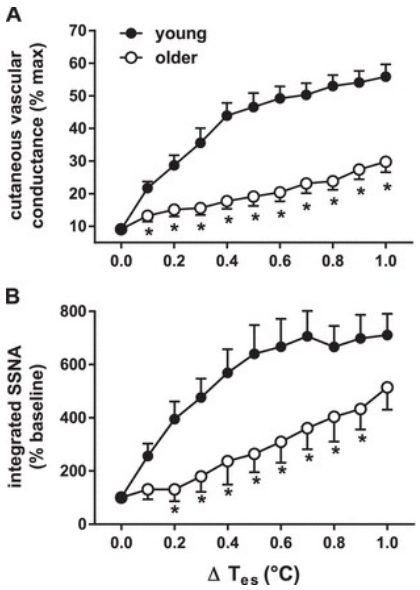

Figure 2.15 Cutaneous vascular conductance and integrated skin sympathetic nerve activity (means ± SE) during whole-body, passive heating via water perfused suit in young (filled circles) and older (blank circles) adults. *$P < 0.05$ vs young. Figure and caption adapted from Stanhewicz et al. (Stanhewicz et al., 2016).

Neurovascular Control during Post-Exercise and Post-Heating Recovery

The absence of a baroreflex mediated response to the post-stress sustained reduction in blood pressure suggests a post-stress alteration of baroreflex regulation of blood pressure. This may be mediated centrally by a resetting of the baroreflex to operate around a lower sympathetic nerve activity or blood pressure or a diminished sensitivity or gain of the baroreflex to changes in blood pressure or peripherally by a blunting of the transduction of sympathetic outflow into vascular resistance. These alterations, depicted in **Figure 2.16**, may act in isolation or in combination following exercise and passive heating to alter the neurovascular support of blood pressure.

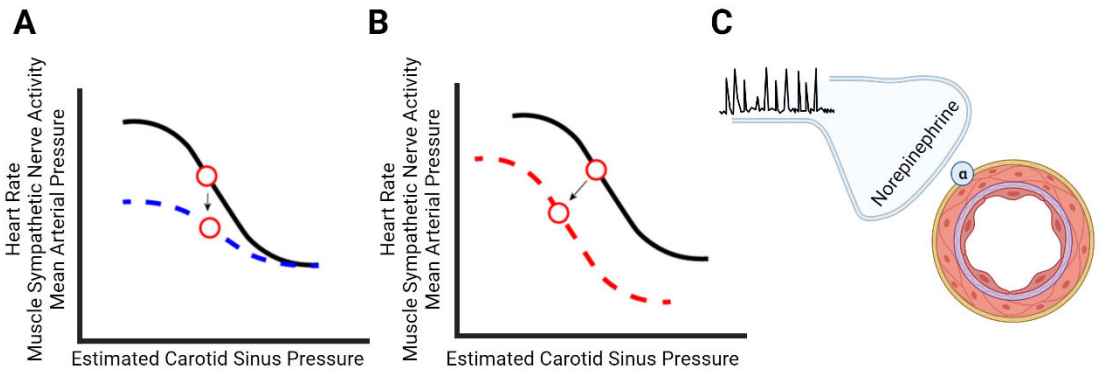

Figure 2.16 Schematic model of central and peripheral neurovascular regulation at rest (solid lines) and potential alterations supporting post-heating hypotension following whole-body, passive heat stress (dashed lines). (A) The sensitivity or gain of the baroreflex may be diminished such that the effector response is attenuated for a given change in blood pressure. (B) The baroreflex may be reset to defend a lower blood pressure (leftward shift) or to lower tonic effector activity at a given blood pressure level (downward shift). (C) Sympathetic vascular transduction may be attenuated so that a given amount of sympathetic activity elicits an attenuated increase in vascular resistance. Image created by Emily Larson using Biorender.com.

With respect to post-exercise recovery, work conducted Floras and colleges in borderline hypertensive men was the first to demonstrate altered neural control of blood pressure following exercise as they observed that sympathetic nerve activity was reduced by 36% following a single 45 min treadmill running bout despite a simultaneous reduction in blood pressure (Floras et al., 1989). In 1996, Halliwill built on these observations by examining blood pressure, muscle sympathetic nerve activity, and arterial baroreflex sensitivity following a single bout of aerobic exercise (60 min of cycle exercise at 60% of VO_2peak) or a sham period of seated upright rest in healthy, normotensive individuals (Halliwill, Taylor, & Eckberg, 1996). Arterial baroreflex sensitivity was assessed using the modified Oxford protocol in which muscle sympathetic nerve activity was recorded over a range of arterial pressure changes induced by the sequential infusion of sodium nitroprusside and phenylephrine. Compared to the post-sham condition, sympathetic nerve activity was reduced by ~30% following exercise despite a simultaneous reduction of

mean arterial pressure by 7 mmHg. This attenuation of sympathetic nerve activity was mediated by a resetting of the baroreflex to defend lower blood pressures as sympathetic nerve activity was lower across all diastolic blood pressures induced by the drug infusions following exercise. Importantly, there were no differences in the slope of the relationship between diastolic blood pressure and sympathetic nerve activity post-exercise compared to the post-sham intervention, indicating that this post-exercise baroreflex resetting occurred in the absence of any changes in baroreflex sensitivity to changes in blood pressure. As reflexive increases in sympathetic nerve activity contribute to raising hypotensive blood pressures back up towards the prevailing blood pressure operating or set point, the post-exercise attenuation of sympathetic nerve activity and baroreflex resetting, even in the absence of alterations in baroreflex sensitivity, is believed to play a key role in the sustained hypotension and vasodilation which follows a single bout of exercise.

In addition to assessing arterial baroreflex function following exercise, Halliwill and colleagues also evaluated the transduction of sympathetic nerve activity into vasoconstriction following exercise. Sympathetic vascular transduction was quantified as the slope of the relationship between calf vascular resistance and muscle sympathetic nerve activity during sympathoexcitatory isometric handgrip exercise. This investigation revealed an attenuated capacity to transduce sympathetic nerve activity into vasoconstriction following exercise such that for the same increase in sympathetic nerve activity there was a blunted increase in vascular resistance following exercise (Halliwill, Taylor, & Eckberg, 1996). The attenuation of sympathetic vascular transduction which follows exercise may be due to pre- or post-synaptic alteration of the α-adrenergic pathway or competing vasodilating influences at the level of the vascular smooth muscle (Halliwill, 2001).

Engelland and colleagues were the first to investigate the neurovascular support of blood pressure following heat stress **(Figure 2.17)** (Engelland et al., 2020a). In this study, muscle sympathetic nerve activity was measured before and 30 min following 45 min of leg heating via water perfused suit (Δ intestinal temperature young: +0.4°C, older: +0.8°C; Δ skin temperature heated leg young: +6.8°C, older: +7.5°C). Among young individuals, blood pressure remained similar to baseline values following heating and was accompanied by an increased sympathetic nerve activity. In contrast, blood pressure was reduced from baseline values following heating in older individuals while sympathetic nerve activity remained unchanged from baseline values.

Engelland also assessed the transduction of sympathetic nerve activity into vasoconstriction during the post-heating recovery period. Using an approach similar to Halliwill's early studies on the post-exercise recovery period, sympathetic vascular transduction was assessed by relating changes in muscle sympathetic nerve activity to femoral vascular conductance during isometric handgrip exercise. In contrast with Halliwill's work on the post-exercise recovery period, sympathetic vascular transduction did not differ pre- to post-heating in young or older individuals. Collectively these findings suggest that, in the absence of alterations in sympathetic vascular transduction, acute heat stress promotes sympathoinhibition and sustained hypotension during post-heating recovery period in older, but not young individuals.

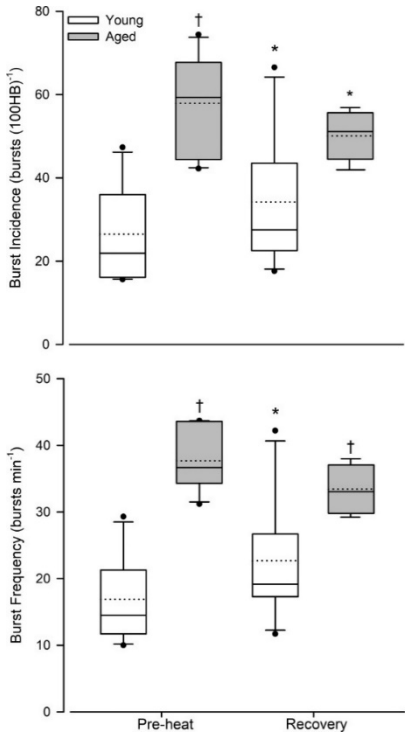

Figure 2.17 Muscle sympathetic nerve activity burst incidence (top) and frequency (bottom) before (pre-heat) and 30 min after (recovery) 45 min of leg heating via water perfused suit in young (open bars) and older (grey bars) adults. Data are presented in box and whisker plots where each box denotes the 25th, median, and 75th percentiles and whiskers denote the 10th and 90th percentiles. The mean is represented with a dotted line in the middle of each plot. *P < 0.01 vs. preheat; †P < 0.01 vs. young adults at the indicated time point (Engelland et al., 2020a).

While this investigation provides valuable insight into the neurovascular alterations which accompany the post-heating recovery period, it had several important limitations. First, this investigation utilized only mild thermal stress (Δ intestinal temperature: +0.4-0.8°C) and thus may not adequately describe the recovery responses which accompany more aggressive heating modalities used to elicit chronic cardiovascular adaptation (Brunt, Eymann, et al., 2016; Brunt, Howard, et al., 2016). Second, although Engelland did not statistically compare the change in intestinal temperature with heating between age groups, the mild heating method resulted in an approximately 2x greater increase in intestinal temperature among older compared to young adults. Differences in core temperature response to water perfused suit heating are not typically seen between age groups and could reflect the fact that only the legs, and not the upper body, were covered by the suit in this study. It is possible that younger individuals were able to dissipate heat more effectively across the uncovered upper body (sweating and cutaneous vasodilation) compared to older individuals and therefore experienced an attenuated rise in core temperature with passive heating. Due to this discrepancy, the age-related blood pressure and neurovascular differences may reflect thermal loading inconsistencies and not physiological differences due to aging. Lastly, this study assessed recovery responses 30 min following heating. This timeline allowed for the confounding influence of differentially elevated skin (young: +1°C, older: +1.5°C) and core temperature (young: +0.2°C, older: +0.4°C) on neurovascular assessments and is shorter than the 2 h period recommended for the full characterization of post-stress recovery responses (De Brito et al., 2019).

Following up on Engelland's finding that neurovascular support of blood pressure is altered in the post-heating recovery period, Hemingway and colleagues recently conducted a study to investigate if prior heat exposure altered the pressor response to voluntary hypoxic apnea (Hemingway et al., 2023). In this study, young individuals completed voluntary hypoxic apneas after breathing gas mixtures of varying inspired oxygen percentages (21%, 16%, 12%; randomized) at baseline and ~90 min following whole-body, passive heating via water perfused suit (Δ intestinal temperature: +1.2°C). While mean arterial pressure was elevated relative to baseline levels following heating, the increase in blood pressure in response to voluntary apneas was attenuated during post-heating recovery across all three gas mixtures utilized. The change in forearm vascular resistance in response to voluntary apnea did not differ from baseline to post-heating recovery. While, these findings suggest that the post-heating recovery period attenuates

the pressor response to voluntary hypoxic apnea, it remains unknown if this cross-stressor effect is mediated by alterations in chemoreflex sensitivity, sympathoexcitation, or attenuated transduction of sympathetic outflow into vascular resistance.

Neurovascular Control during Post-Stress Recovery: Overlapping or Alternative Mechanisms?

Centrally Mediated Sympathoinhibition

Research efforts conducted in the decade that followed Halliwill's observations of downward baroreflex resetting following exercise revealed that the central signaling mechanisms responsible for upward baroreflex resetting *during* exercise mediate the downward baroreflex resetting *following* exercise. During exercise, polymodal group III (myelinated) and group IV (unmyelinated) muscle afferents, which are sensitive to mechanical (Kaufman et al., 2002), chemical (Light et al., 2008), and thermal stimuli (Hertel et al., 1976), are activated (Adreani et al., 1997; Pickar et al., 1994). Through a series of steps these muscle afferents serve to inhibit barosensitive neurons within the nucleus tractus solitarius of the medulla and, in doing so, promote sympathoexcitation during exercise (Potts, 2006). Specifically, muscle afferents project to the caudal nucleus tractus solitarri in the medulla and serve to increase the release of the neurotransmitter substance P onto neurokinin 1 receptors on γ-aminobutyric acid (GABA) inhibitory interneurons. Increased activity of these inhibitory interneurons reduces the firing of second order barosensitive neurons which project to the caudal ventrolateral medulla. This, in turn, decreases inhibition of sympathetic neurons in the rostral ventrolateral medulla and promotes the increase in sympathetic activity and upward and rightward baroreflex resetting which accompanies exercise. Building on this foundational work, Chen and colleagues demonstrated that sustained muscle afferent stimulation during exercise causes internalization of neurokinin 1 receptors on the inhibitory in interneuron within the caudal nucleus tractus solitarius of the medulla. Following exercise, this serves to reduce the inhibition of second order barosensitive neurons and promotes post-exercise sympathoinhibtion and downward and leftward baroreflex resetting (C. Y. Chen et al., 2009; C. Y. Chen & Bonham, 2010). **Figure 2.18**, taken from a review by Halliwill et al (Halliwill et al., 2013), summarizes of the neural pathways responsible for baroreflex resetting in the post-exercise recovery period.

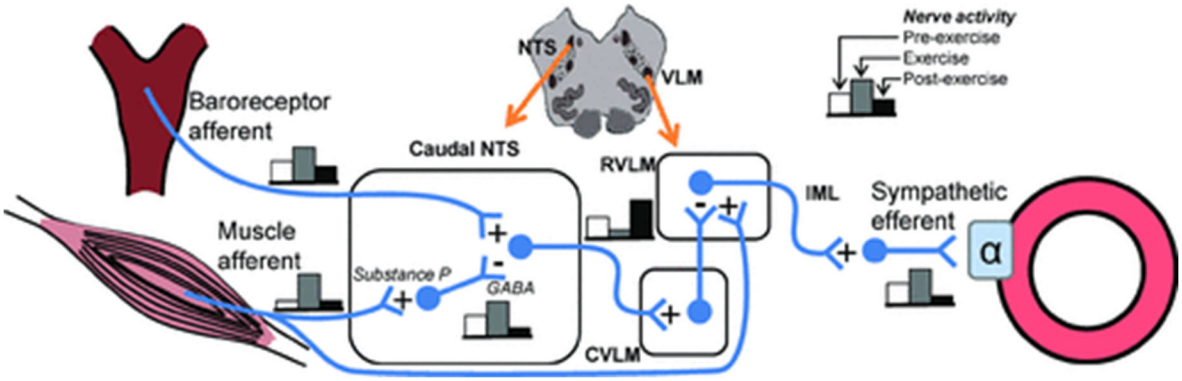

Figure 2.18 Neural pathways which mediate baroreflex resetting during and following exercise, taken from Halliwill et al. (Halliwill et al., 2013). During exercise, muscle afferents alter signaling within the cardiovascular control centers in the medulla to increase sympathetic outflow and promote an upward and rightward baroreflex resetting. Following exercise, this sustained muscle afferent signaling ceases and promotes sympathoinhibition and downward and leftward baroreflex resetting.

Similarly, acute heat stress may serve to promote sustained firing of thermosensitive polymodal group III and IV muscle afferents. During the post-heating recovery period, this sustained afferent signaling could promote receptor internalization on inhibitory interneurons signaling within the caudal nucleus tractus solitarri, reduce inhibition of second order barosensitive neurons, and promote post-heating sympathoinhibition and hypotension (i.e., downward and leftward baroreflex resetting). Consistent with this notion, studies conducted in several animal models have demonstrated that warming of muscle tissue within a physiological range elicits progressive increases in group III and IV muscle afferent firing (Hertel et al., 1976; Kumazawa & Mizumura, 1977; Mense & Meyer, 1985). Furthermore, local heating of the forearm (Δ intramuscular temperature: 4.5°C), in the absence of tympanic temperature changes, augments the sympathetic response to submaximal isometric handgrip exercise but not post-exercise muscle ischemia, suggesting a role for heat stress in activating or sensitizing skeletal muscle afferents (Ray & Gracey, 1997).

Alternatively, altered neurovascular control in the post-heating recovery period could be mediated more directly by altered central nervous system control of sympathetic outflow. The

preoptic area of the hypothalamus is a primary site of central temperature sensation and is sensitive to both direct heating (Andersson et al., 1956; Carlisle & Laudenslager, 1979; Magoun et al., 1938) and afferent feedback from the peripheral thermosensitive sites (Boulant & Hardy, 1974; Wit & Wang, 1968). During acute heat stress, increased warm sensation at the level of the preoptic area of the hypothalamus is transmitted down various neural pathways and then proceeds to activate peripheral sympathetic, parasympathetic, or somatic motor neurons and initiate heat loss thermoeffector responses (Tan & Knight, 2018). Specifically, work conducted by Kenney and colleagues in rodent models strongly suggests that altered regulation of sympathetic neural circuits within the rostral ventrolateral medulla plays a key role in mediating that the widespread sympathoexcitation accompanying heat stress. (Hosking et al., 2009; M. J. Kenney et al., 2000, 2011; M. J. Kenney & Fels, 2003). Like exercise, it is possible that the sustained alterations in signaling along these central sympathoexcitatory pathways which accompany acute heating serve to potentiate sympathoinhibition in the post-heating recovery period.

Altered Baroreflex Sensitivity

Neurovascular support of blood pressure could by altered in the post-stress recovery period due to a blunted sensitivity of the baroreflex to changes in blood pressure. With the exception of spontaneous baroreflex assessments, baroreflex sensitivity is most commonly assessed by measuring the baroreflex-initiated end organ response (heart rate, muscle sympathetic nerve activity, blood pressure) to a change in baroreceptor feedback (pharmacologically, reflexively, or mechanically induced changes in baroreceptor stretch). As this dissertation will assess changes in carotid baroreflex responsiveness during heating and post-heating recovery, this discussion will primarily focus on studies exploring carotid baroreflex function through the use of the variable neck pressure technique.

As attenuated baroreflex sensitivity would be expected to promote lower blood pressures and compromise the maintenance of blood pressure amid postural or hemorrhagic stressors, the sustained hypotension and common reports of syncope following exercise might be assumed to reflect a reduction in baroreflex sensitivity during the post-exercise recovery period. On the contrary, several studies utilizing both variable neck pressure (Hart et al., 2010; Kanda et al., 2020) and drug infusion-based baroreflex assessment approaches (Halliwill, Taylor, & Eckberg, 1996; Hart et al., 2010) have noted that baroreflex control of blood pressure appears to be

preserved following exercise albeit shifted to a lower prevailing level. Halliwill previously demonstrated that although sympathetic activity is reduced following exercise, baroreflex control of sympathetic activity is preserved. Similarly, carotid baroreflex control is heart rate is typically preserved or enhanced following exercise (Convertino & Adams, 1991; Halliwill, Taylor, Hartwig, et al., 1996; Kanda et al., 2020; Piepoli et al., 1993; Somers et al., 1985).

No studies to our knowledge have assessed baroreflex function during the post-heating recovery period. In the absence of these data, our understanding of changes in baroreflex function during acute heat stress may be informative as these alterations may persist into or modify baroreflex control during the post-heating recovery period. Early work conducted by Crandall and colleagues noted that integrated carotid baroreflex support of blood pressure was attenuated during heat stress while cardiac carotid baroreflex sensitivity was preserved (Crandall, 2000). Importantly, this study utilized a "stair-step" variable neck pressure protocol in which neck pressure/suction was applied across four cardiac cycles before being "stepped" to the next prescribed stimulus level. As heat stress increases heart rate, the attenuated integrated carotid baroreflex sensitivity noted could simply reflect a reduced stimulus duration imparted to the carotid baroreceptors. Krnjacic and colleagues highlighted this limitation and evaluated carotid baroreflex responses to 5 sec trials of various levels of neck pressure and suction. In contrast with Crandall, Krnjajic demonstrated that carotid baroreflex control of heart rate was enhanced (particularly in response to simulated hypertension) while integrated carotid baroreflex support of blood pressure was preserved (Krnjajic et al., 2016). Studies utilizing sequential drug infusion to assess baroreflex function have demonstrated that baroreflex control of sympathetic nerve activity is generally preserved during hyperthermia and shifted to a higher prevailing level (Cui et al., 2002a, 2002b). Utilizing a lower body negative pressure to simulate the more real-world experiences of orthostasis or hemorrhage, Cui demonstrated that muscle sympathetic nerve activity response to increasing levels of lower body negative pressure and reductions in central blood volume was enhanced during hyperthermia (Cui et al., 2004; Keller, Cui, et al., 2006) (**Figure 2.19**). From this collective research, it is generally accepted that despite a heat-induced shift in the prevailing heart rate, sympathetic nerve activity, and blood pressure, baroreflex control of heart rate and muscle sympathetic nerve activity is preserved or augmented during hyperthermia. In the absence of clear attenuations in baroreflex sensitivity, impaired orthostatic tolerance during acute heat stress likely results from attenuated adrenergic responsiveness. In

light of these collective investigations preserved or enhanced carotid baroreflex sensitivity during the post-exercise recovery period and acute heat stress, it seems unlikely that attenuated baroreflex control of heart rate or sympathetic outflow mediates sustained hypotension in the post-heating recovery period.

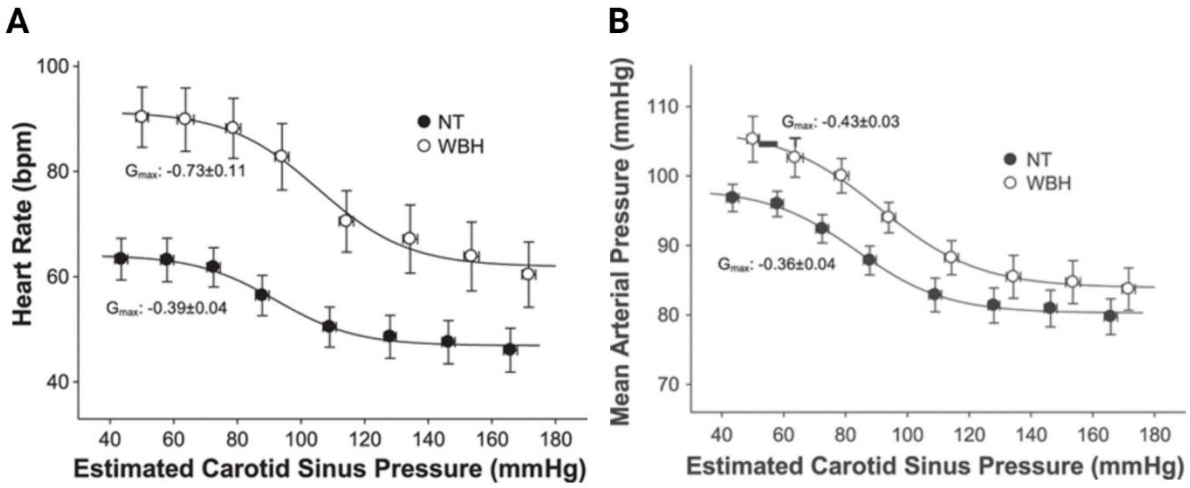

Figure 2.19 Cardiac and integrated carotid baroreflex stimulus response relationships during normothermia (NT; filled circles) and passive, whole-body heating (WBH; open circles) in young men. Cardiac carotid baroreflex function was shifted to the prevailing elevated heart rate and maximal gain (G_{max}) was enhanced during passive, whole-body heating. Integrated carotid baroreflex function (operating point and maximal gain) did not differ between normothermia and passive, whole-body heating (Krnjajic et al., 2016).

Attenuated Adrenergic Responsiveness

Lastly, neurovascular support of blood pressure may be altered in the post-stress recovery period due to an attenuated action of the efferent arm of the baroreflex in which increased sympathetic outflow promotes vasoconstriction. Indeed, the post-exercise recovery period is accompanied by attenuated sympathetic vascular transduction which may be supported by pre- or post-synaptic alteration of the α-adrenergic pathway or competing vasodilating influences at the level of the vascular smooth muscle. Post-synaptic inhibition is not a likely culprit for the attenuation of sympathetic vascular transduction following exercise as it has previously been demonstrated that vasoconstriction accompanying intra-arterial infusions of phenylephrine (α_1

agonist) and clonidine (α_2 agonist) is preserved during recovery from cycle exercise (Halliwill et al., 2003).

In contrast with the post-exercise recovery period, Engelland noted that sympathetic vascular transduction was preserved in both young and older individuals during the post-heating recovery period (Engelland et al., 2020b). However, because this observation was made in a limited number of participants (6 young, 6 aged), the possibility that the sympathetic vascular transduction is altered in the post-heating recovery period warrants further consideration. Indeed, it is well appreciated that systemic vascular responses to adrenergic stimulation are attenuated during acute heat stress (Cui et al., 2002b, 2010) and it is possible that this attenuated vasoconstrictor responsiveness persists into the post-heating recovery period. If present, attenuated vascular responsiveness in the post-heating recovery period would likely be localized within the cutaneous circulation as whole-body heating attenuates cutaneous vasoconstrictor responsiveness to exogenous norepinephrine infusion (Wilson et al., 2002a) and lower body negative pressure (Pearson et al., 2013). The renal circulation may also play a role in altered post-heating vasoconstrictor responsiveness as hyperthermia attenuates increases in renal and segmental artery resistance (calculated as blood flow velocity divided by mean arterial pressure) during the cold pressor test (Chapman et al., 2019; Freemas et al., 2022). The effect of hyperthermia on skeletal muscle vascular responsiveness is unclear. While a series of studies conducted by Ives, Gifford, and Richardson demonstrated that heating isolated human skeletal muscle feed arteries to 39°C (+2°C) attenuated α_1 adrenergic vasoconstriction by ~40% (Ives et al., 2011), *in vivo* pharmacological studies in humans have demonstrated that α_1 and α_2 adrenergic responsiveness is preserved during leg heating (Δ muscle temperature ~4°C). Furthermore, Cui and colleagues demonstrated that the pressor response accompanying the cold pressor test, a sympathoexcitatory maneuver which increases muscle but not skin sympathetic nerve activity, was attenuated during hyperthermia (Cui et al., 2010). Across these vascular beds, attenuated vasoconstrictor responsiveness during hyperthermia may result from the increases in local temperature, vascular shear stress (Thomas et al., 2016, 2017), or heat shock protein (Cheng et al., 2021; Faulkner et al., 2017; Hafen et al., 2018, 2019; Neff et al., 2016) expression which accompany acute heat stress or the downstream promotion of vasodilators. Indeed, nitric oxide, which plays a role in mediating cutaneous vasodilation during both local and whole-body heat stress (Kellogg et al., 1998, 1999; Minson et al., 2001; Shastry et al., 1998), contributes to

attenuated cutaneous adrenergic responsiveness during hyperthermia (Shibasaki et al., 2007, 2008). Similarly, increases in nitric oxide bioavailability contribute to heat induced sympatholysis within isolated human skeletal muscle feed arteries (Gifford et al., 2014; Ives et al., 2012).

Neurovascular Control: Summary

This collective work suggests that exercise and heat stress are both profound autonomic stressors which may potentiate altered neural, baroreflex, and sympathetic vascular control in the post-stress recovery period. While considerable work has evaluated neurovascular function during these acute stressors and the post-exercise recovery period, our understanding neurovascular support of blood pressure in the post-heating recovery period is very limited.

POST-STRESS REOCVERY: OPENING THE WINDOW OF OPPORTUNITY

Since Fitzgerald's early observation that his daily jogs lowered his own labile hypertension (Fitzgerald, 1981), decades of continued research have established that the post-exercise recovery period is a discrete physiological phenomenon which promotes clinically relevant reductions in blood pressure, is marked by alterations in central and peripheral cardiovascular control, and plays an important role in potentiating adaptation to exercise training. As highlighted by Luttrell and Halliwill, these investigations have demonstrated that the post-exercise recovery period presents a valuable "window of opportunity" during which risk factors in many disease states can be attenuated and beneficial cardiovascular adaptation may be mediated (Luttrell & Halliwill, 2015).

With respect to hypertension, a recent meta-analysis conducted among medicated and unmedicated hypertensive individuals demonstrated that a single bout of aerobic exercise reduced 24-h ambulatory (systolic: -2.7 mmHg, diastolic: -1.3 mmHg), daytime (systolic: -4.0 mmHg, diastolic: -2.3 mmHg), and nighttime blood pressure (systolic: -3.2, diastolic: 2.3 mmHg) (Saco-Ledo et al., 2021). The immediate blood pressure lowering effect of exercise may be clinically meaningful as reductions in systolic and diastolic blood pressure of 1 mmHg (S. T. Hardy et al., 2015) and 2 mmHg (Cook et al., 1995), respectively, have been demonstrated to reduce risk of coronary heart disease and stroke. Notably, 5 mmHg reductions systolic blood pressure have been demonstrated to reduce the risk of major cardiovascular events by 10% (Ettehad et al., 2016). In this way, a single bout of exercise may be thought of as a "daily dose"

of blood pressure reduction. Furthermore, this beneficial post-exercise profile may play a fundamental role in mediating the widespread cardiovascular benefits which accompany exercise training. For example, as originally proposed by Nobrega and further discussed by Brito (Brito et al., 2018; da Nobrega, 2005), when exercise is repeated consistently, these acute reductions in blood pressure may progressively superimpose on one another and culminate in the chronic reductions in blood pressure seen with exercise training. Consistent with this notion, several studies conducted in both healthy and patient populations have demonstrated that the acute blood pressure lowering effects of exercise are associated with the chronic reductions in blood pressure seen with exercise training (Hecksteden et al., 2013; Kiviniemi et al., 2015; Liu et al., 2012; Wegmann et al., 2018). Furthermore, a recent study in individuals with severe osteoarthritis demonstrated that the systolic and diastolic blood pressure reductions which persisted in the 20 min following an acute bout of heat exposure (20-30 min hot water immersion followed by ~15 min light resistance exercise) were moderately correlated with the reductions in blood pressure which accompanied the larger 12 week heat therapy intervention in which participants completed 3 sessions of this acute regimen per week (Roxburgh et al., 2023).

As we present in this review, the emerging body of research on the post-heating recovery period suggests that, with respect to altered post-stress cardiovascular support of blood pressure, there may be more than one way to open this "window of opportunity." Much like exercise, acute heat stress is a profound thermoregulatory, cardiovascular, and autonomic stressor which may act through shared and unique mechanisms to potentiate a similarly distinct and valuable recovery period. However, despite the clinical relevance and scientific promise of this post-heating "window of opportunity" and the demonstrated value of these investigations with respect to exercise stress, our understanding of recovery from heat stress is remarkably limited. Specifically, preliminary work in this area suggests that the cardiovascular support of blood pressure may be altered following a single bout of heat stress but the systemic hemodynamic and neurovascular mechanisms which contribute to these alterations remain largely unknown.

Importantly, the questions posed by this dissertation are just the beginning of an emerging area of research in which there are more questions than answers. In the same way that study of the post-exercise recovery period plays a critical role in mediating adaptations to exercise training across multiple organ systems, the post-heating recovery period may prove to be an important contributor to heat acclimation responses and the improvements in

cardiovascular and metabolic health which accompany heat therapy. Continued study of the post-heating recovery period in this manner will not only enhance our specific knowledge relevant to recovery from passive heating, but also serve to broaden our view of the physiology of recovery and illustrate its relevance to the various stresses encountered by humans. Ultimately, this expanded perspective may illuminate new avenues by which lifestyle or pharmacological interventions may act to open the "window of opportunity" posed by post-stress recovery.

CHAPTER III
METHODS

OVERVIEW OF PROJECT

The overarching goal of this dissertation was to explore the cardiovascular support of blood pressure in young and older individuals during recovery from whole-body, passive heat stress. Towards this end, we designed a repeated measures study in which we assessed blood pressure, systemic cardiovascular hemodynamics, and cardiac, peripheral vascular, and integrated carotid baroreflex function in young and older humans during a normothermic baseline period, at the end of whole-body, passive heat stress, and throughout 2 h of normothermic post-heating recovery. All study days were conducted on the University of Oregon Campus within the Bowerman Sports Science Center.

PARTICIPANTS

The Institutional Review Board at the University of Oregon approved this study (Protocol #08102020.012). Prior to participation, all participants provided oral and written informed consent as set forth by the *Declaration of Helsinki*.

Participant characteristics are presented in Table 4.1. Sixteen young (8 women, 8 men) and nine older (6 women, 3 men) volunteers participated in this study. Participant inclusion criteria included individuals aged 18-35 (young) and 60-75 (older). All individuals were healthy with no history of cardiovascular disease and not taking prescription medications other than hormonal contraceptives. Seated resting blood pressure was assessed during the initial screening visit in accordance with clinical guidelines (American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, 2018) and individuals with Stage 2 hypertension (≥140 mmHg systolic blood pressure and/or ≥90 mmHg diastolic blood pressure) were excluded from the study. Height and weight were assessed during the initial screening visit and individuals with a body mass index below 18.5 or above 35 kg/m^2 were excluded from the study. Individuals who were endurance training (vigorous aerobic exercise > 60 min/session on ≥5 days per week), training for non-recreational athletic competition, or regularly engaging in a heat therapy regimen (whole-body heating ≥30 min/session and ≥3 sessions per week) were

excluded from participating in the study. Physical activity habits were assessed using the International Physical Activity Questionnaire (IPAQ) short form (Craig et al., 2003).

Upon study enrollment, skin and adipose tissue thickness at various anatomical landmarks was assessed (men: chest, abdomen, thigh; women: triceps, suprailiac, thigh) and the Jackson-Pollock 3 site algorithm was used to estimate body density and body fat percentage in all participants (A. S. Jackson et al., 1980; A. S. Jackson & Pollock, 1978) . To ensure that individuals were good candidates for the neck pressure technique utilized in the study, an investigator used Doppler ultrasound to determine the location of both carotid artery bifurcations. If the carotid artery bifurcations were located too close to the jawline and not accessible by the neck collar, the participant was excluded from the study at this time. Additionally, an investigator used a stethoscope to listen to both carotid arteries for "bruits" or vascular sounds suggestive or reduced or turbulent carotid arterial blood flow. If carotid bruits were indicated, the individual was excluded from participating in the study.

FAMILIARIZATION VISIT

Individuals who chose to enroll in the study and satisfied all inclusion criteria and no exclusion criteria were asked to participate in an initial familiarization visit before participation in the experimental study day. During this visit, participants were fitted with the brace-like neck collar and coached to breathe with an audio cue at 0.25 Hz for 1 min. Participants were asked to perform an end-expiratory breath hold at the end of this min of paced breathing, during which time an investigator applied 50 mmHg of pressure for 5 sec across the neck using the neck collar. After each neck pressure application, participants were coached to resume paced breathing at 0.25 Hz for 1 min. These neck pressure applications and paced breathing intervals were repeated 5-7 times. Throughout this carotid baroreflex assessment, heart rate (lead II electrocardiograph; Cardiocap 5, Datex-Ohmeda, St. Louis, MO) and beat-by-beat blood pressure were measured (Nexfin, BMEYE, Amsterdam, Netherlands). If investigators were unable to obtain a good fit of the neck collar participants were excluded from the study at this time.

EXPERIMENTAL SESSION

To avoid the confounding influence of circadian rhythms on cardiovascular and thermoregulatory measures, experimental sessions were conducted at the same time of day and

began between 0700 and 1000. For the experimental session, individuals were studied having refrained from all over-the-counter medications (including vitamins, supplements, recreational drugs, etc.) for 24 h, alcohol and caffeine for 12 h, food for 2 h, and heavy exercise or heat stress for 24 h. Participants on a daily aspirin regimen were additionally asked to refrain from aspirin for one week prior to participation in the experimental session. Female participants were studied under low hormone conditions: during the early follicular phase of the menstrual cycle, placebo phase of oral contraceptive use (B. M. Lynn et al., 2007; Minson et al., 2000; Senitko et al., 2002), and/or in the absence of hormone replacement therapy (Brooks et al., 1997; Dunbar & Kenney, 2000; Tankersley et al., 1992). Euhydration was evaluated in all participants prior to each experimental session by a first morning urine specific gravity of less than 1.024. If urine specific gravity was greater than 1.024, participants drank 3 ml/kg of body weight before beginning the protocol. This urine sample was also used to conduct a pregnancy test on all participants of child-bearing potential before the experimental study visit.

EXPERIMENTAL SESSION PROTOCOL

Figure 3.1 shows an overview of the timeline for the experimental session. The experimental session was held in a 23.7±0.4°C thermoneutral laboratory environment. During the experimental session participants were instrumented with a sterile rectal thermistor probe, six skin temperature loggers, electrocardiograph leads to monitor heart rate and respiration, an automated auscultatory blood pressure cuff on their arm, a beat-by-beat finger blood pressure monitor, 4 laser Doppler flowmetry probes placed on the surface of one calf, and the equipment needed for venous occlusion plethysmography of the contralateral calf (see *Calf Blood Flow* section for detailed description). Participants periodically breathed on a mouthpiece which allowed for the non-invasive assessment of cardiac output using the open circuit acetylene washin method. Throughout each experimental session, participants rated their perceived exertion, thermal comfort, and how wet their skin felt using standardized perceptual scales. Thermoregulatory, hemodynamic, and perceptual data was collected at baseline (following at least 20 min of supine rest) and throughout the 60 min whole-body, passive heating intervention and 2 h normothermic recovery period. Cardiac, peripheral vascular, and integrated carotid baroreflex responsiveness were assessed at baseline, at the end of the heating intervention, and every 30 min throughout the 2 h normothermic recovery period.

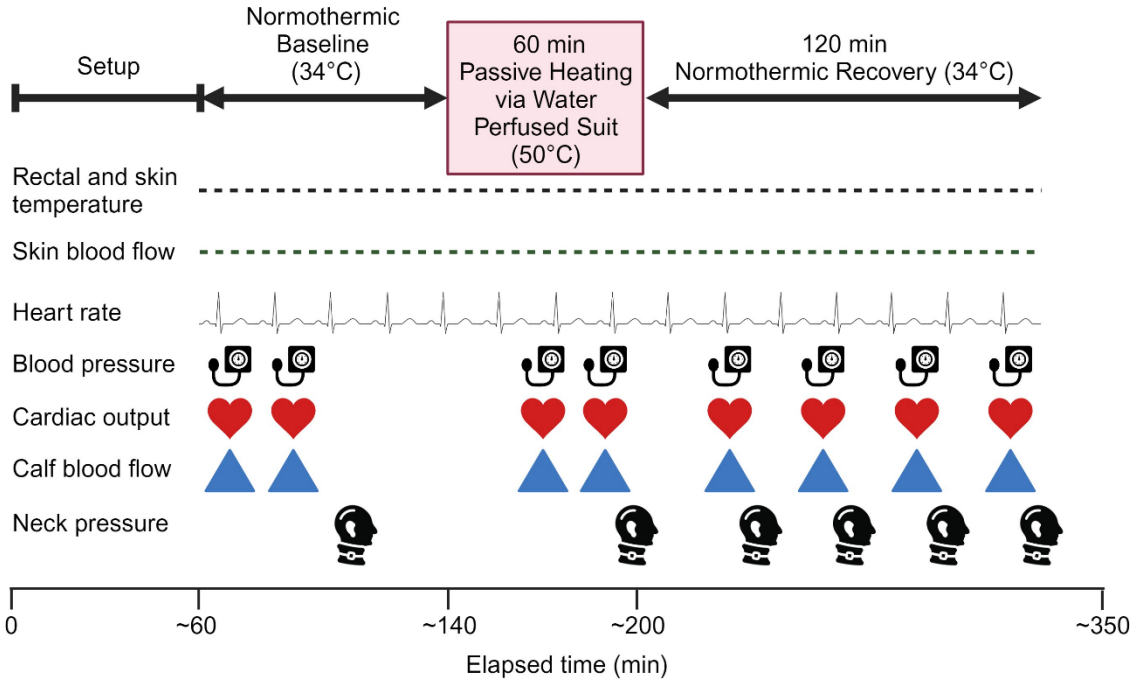

Figure 3.1 Study design investigating systemic cardiovascular and carotid baroreflex support of blood pressure during recovery from passive heat stress in young and older individuals. Neck pressure was used in combination with continuous measures of heart rate, brachial blood flow, and beat-by-beat arterial pressure to evaluate cardiac, peripheral vascular, and integrated carotid baroreflex responsiveness. Nude body weight was measured at the beginning and end of the experimental session. Image created by Emily Larson using BioRender.com.

THERMOREGULATORY METHODS AND MEASURES

Water Perfused Suit

In this experiment, participants donned a two-piece nylon suit that had small tubes sewn into the inside of the suit (Med-Eng Systems, Ottowa, Canada). The suit covered the entire body except for the head, hands, feet, and calves (used for calf and skin blood flow measurements). During baseline and the normothermic recovery period, a water circulating bath (HT CIRC 7L AD, Polyscience, Niles, Illinois) was used to circulate 34°C water through the suit. During the heat stress intervention, participants donned a mylar thermal blanket, thick cotton blankets, and a hat while 50°C water was perfused through the suit. If rectal temperature increased by 1°C, the

temperature of the water was decreased to 45°C to prevent further increases in core temperature. In all participants, the blankets and hat were removed at the conclusion of the final measurements during passive heating and before the neck pressure measurements during the passive heating intervention. At the conclusion of the neck pressure measurements during heating, 34°C water was circulated through the suit for a 2 h period of normothermic recovery.

The primary advantage of the water perfused suit heating method is that it eliminates evaporative heat loss and allows for modification of the temperature of the water perfusing the suit to effectively "clamp" core and skin temperature within a desired range. Previous work in our laboratory has demonstrated that this heating modality quickly elicits increases in skin temperature within a range of 37-40°C and subsequently increases oral temperature by 0.8-1°C within 60 min (Brunt et al., 2013; Wong & Minson, 2006). Furthermore, this heating method has been successfully employed to elicit matched changes in core temperature of at least 1°C in young and older individuals (Gagnon et al., 2015; Minson et al., 1998). Other advantages of this heating modality include its compatibility with a broad range of physiological measurements and the absence of confounding effects of increased hydrostatic pressure on the body surface, which are inherent to other heating modalities (e.g., hot water immersion). The primary disadvantage of this technique is that, between the direct application of heat to the skin and elimination of effective evaporative cooling and resulting high skin temperature, water perfused suit heating does not perfectly replicate heat stress which may be encountered in a hot environment or during exercise. Despite this limitation, the experimental advantages of water perfused suit heating have made it a classical experimental model.

Other Methods

Compared with other models of passive heat stress, immersion in hot water (40-42°C) is generally the fastest way to increase core body temperature. Previous studies involving varying depths (lower limb, waist-level, nipple-level, neck level) of immersion for 30-60 min have noted increases in rectal temperature ranging from 0.7-1.5°C (Amin et al., 2021; Francisco et al., 2021; Larson et al., 2021; Romero, Gagnon, et al., 2017; Thomas et al., 2016). Skin temperature of immersed regions generally mirrors (within 1°C) water temperature (Romero, Gagnon, et al., 2017), whereas skin temperature above water level remains unchanged or is modestly elevated (+2°C) (Larson et al., 2021) and reflects the balance between the heat delivered via cutaneous vasodilation and the heat lost via sweating. Muscle temperature of partially immersed limbs has

been noted to increase by 3-7°C (Rodrigues et al., 2020; Romero, Gagnon, et al., 2017). While hot water immersion promotes rapid heat gain by taking advantage of the high thermal conductivity of water and limiting evaporative heat loss across immersed regions, it also introduces the confounding influence of increased hydrostatic pressure. Increased hydrostatic pressure serves to aid venous return to the heart and can therefore independently alter central blood volume, cardiac filling pressures, and baroreflex loading, each of which can have downstream effects on central and peripheral hemodynamics and the neuroendocrine regulation of blood pressure and blood volume (Campbell et al., 2022; Gabrielsen et al., 2000; Löllgen et al., 1981). The magnitude of these confounding influences is likely proportional to the degree of water immersion (lower limb vs. whole-body water immersion). Furthermore, like water perfused suit heating, hot water immersion involves the direct application of heat to the skin and can result in high skin temperatures and widespread cutaneous vasodilation secondary to the effects of local skin heating.

Sauna is another commonly employed passive heating modality. There are various iterations of sauna including Finnish or dry sauna, wet sauna or steam rooms, and infrared sauna. Sauna baths are often completed as several 5-20 min sessions interspersed with brief periods of recovery in cooler environments. Finnish or dry sauna bathing utilizes extreme ambient air temperatures (80-100°C) and very low humidity levels (10-20% relative humidity). Typical Finnish sauna sessions held at 80°C increase skin temperature to values between 40-41°C and increase rectal temperature by ~1°C (Hannuksela & Ellahham, 2001; Heinonen & Laukkanen, 2018; Leppaluoto, 1988; Pilch et al., 2014). Unlike water perfused suit heating and hot water immersion, dry sauna allows for the preservation of heat loss via sweating across the entire body surface. Wet sauna or steam rooms typically utilize more modest ambient air temperatures (40-70°C) and elevated humidity levels (50-100%). The high water vapor pressure of wet sauna or steam rooms limits effective evaporative cooling and leads to more exaggerated increases in core and skin temperature. Prolonged bouts of wet sauna are typically not tolerated as well as dry or Finnish sauna baths (Pilch et al., 2014). Far infrared sauna emits thermal radiation which directly heats tissue underlying the skin and therefore utilizes more modest ambient temperatures (~50-60°C). A 15 min bout of Waon therapy, a variation of heating that utilizes infrared sauna and is followed by recovery in warm blankets, typically increases core temperature by 1.0-1.2°C (Miyata & Tei, 2010). Interestingly, no study to our knowledge has measured muscle

temperature during sauna use and this remains an interesting area for future research. While sauna is perhaps the most widely employed passive heating modality used recreationally across cultures, disadvantages to its use in the research setting include a reduced ability to tightly control core and skin temperature changes, reduced tolerance to sustained bouts (particularly in humid conditions) (Campbell et al., 2022), and postural influences as sauna sessions and post-sauna recovery are often completed in a seated posture.

Core Temperature

Rectal temperature was monitored continuously at baseline and throughout whole-body, passive heating and normothermic recovery using a thermistor inserted ~10 cm past the anal sphincter. Rectal temperature measurement allowed for a consistent and minimally invasive, albeit slower responding, measurement of core temperature changes which was appropriate for the protracted research protocol utilized.

Other Methods

Pulmonary artery temperature is the "gold standard" approach for the measurement of core temperature as it represents the temperature of the mixed venous blood which is returning to the heart from all regions of the body and responds rapidly to changes in temperature (Robinson et al., 1998). However, this measurement method requires the placement of a pulmonary artery catheter, a procedure which is invasive and carries substantial risk. As such, measurement of pulmonary artery temperature is typically reserved for patient populations with an existing pulmonary artery catheterization or studies in which pulmonary artery catheterization is a requisite component of a larger research question. Esophageal temperature is another preferred method of assessing core temperature due to proximity of temperature measurement to the left ventricle, aorta, and blood flow to the hypothalamus and, as a result, its rapid response to temperature changes. Along these lines, esophageal temperature is in closer agreement with pulmonary artery temperature compared to other temperature measurement locations (tympanic, axillary, rectal, bladder) (Robinson et al., 1998) and responds to core temperature changes more quickly than rectal temperature and intestinal temperature (Lee et al., 2000; G. R. McCord et al., 2006). This technique requires that local anesthetic is given to the participant and a temperature probe is inserted into the nasal passage as an individual continually swallows, allowing the probe to pass from the nasopharynx to the oropharynx and into the esophagus. Once in the esophagus, the probe is inserted to the level of the left atrium. Disadvantages of this technique include

discomfort and difficulty associated with thermistor insertion and impact of oral fluid ingestion on the measurement (Pasquier et al., 2020). Lastly, the use of telemetric pills to measure intestinal temperature is an increasingly popular method of measuring core temperature within thermoregulatory research. While this method is perhaps the most convenient and minimally invasive of all methods discussed, the location of temperature measurement may vary with gastrointestinal motility (both within and between individuals) and, therefore, may promote confounded or missing data.

Skin and Mean Body Temperature.

Skin temperature was monitored continuously at baseline and throughout whole-body, passive heating and normothermic recovery using 6 thermochron temperature loggers (DS1922L, OnSolution Pty Ltd, NSW, AU) placed at standard locations on the chest, upper back, lower back, abdomen, thigh, and calf. Skin temperature (T_{sk}) was calculated as the weighted average of these six assessment sites (chest 22%, upper back 19%, lower back 19%, abdomen 14%, thigh 14%, calf 11%) as previously described (Gagnon et al., 2015, 2016; W. F. Taylor et al., 1989). Various approaches for calculating average skin temperature have been proposed which include varying numbers of measurement sites (Burton, 1935; J. D. Hardy et al., 1938; Nadel et al., 1973; Ramanathan, 1964). The skin temperature weighting system utilized in this research was selected to be consistent with previous research studies investigating thermoregulatory, cardiovascular, and autonomic differences between young and older individuals during passive heat stress (Robinson et al., 1998). Mean body temperature was calculated as the weighted average of core temperature (90%) and mean skin temperature (10%) which is consisted with similar studies investigating human thermoregulatory responses within a hot environment (Jay et al., 2007).

Sweat Losses

Participant fluid consumption was restricted to the heating period of the experimental session, during which time participants consumed 3 mL/kg of water. Fluid consumption was additionally recorded by measuring fluid weight before and after the heating intervention period. Urine losses were collected and measured during each experimental session. Fluid loss during each experimental session was obtained by measuring dry nude body weight at baseline and at the end of the recovery period. The overall sweat loss during the experimental session (from

before baseline measurements to after the recovery period) was calculated using the following equation.

Equation 3.1

$$\text{Sweat loss (kg)} = \Delta \text{ Body weight (kg)} + \text{Fluid consumption (kg)} - \text{Urine Loss}$$

HEMODYNAMIC MEASURES

Heart rate

Heart rate was monitored continuously at baseline and throughout whole-body, passive heating and normothermic recovery using a three-lead (Lead II) electrocardiograph (Cardiocap 5, Datex-Ohmeda, St. Louis, MO). Additionally, heart rate measures were completed during cardiac output measures and used to calculate stroke volume.

Blood Pressure

Arterial blood pressure was measured in the arm using an automated sphygmomanometer (Tango M2, SunTech Medical, Morrisville, NC). Arterial blood pressure was measured in duplicate at baseline, every 10 min throughout whole-body, passive heating, and every 30 min throughout normothermic recovery. Additionally, arterial pressure measurements were completed prior to each cardiac output assessment and subsequently used in calculations of systemic vascular conductance. Mean arterial pressure was calculated using the following equation.

Equation 3.2

$$\text{Mean arterial pressure (mmHg)} = (1/3 \text{ Systolic arterial pressure (mmHg)}) + (2/3 \text{ Diastolic arterial pressure (mmHg)})$$

Cardiac Output

Cardiac output was assessed in duplicate at baseline and every 30 min throughout whole-body, passive heating and normothermic recovery. Cardiac output was assessed using the open circuit acetylene washin method. This method was developed by Stout (Stout et al., 1975) in anesthetized dogs and further developed in humans by Gan (Gan et al., 1993), Nielsen (Nielsen

et al., 1994), and Johnson (B. D. Johnson et al., 2000). This method of determining cardiac output is based on the Fick Principle in which blood flow can be calculated using the uptake of a marker substance if the following are known: 1) the rate at which a substance is consumed by an organ, 2) the concentration of the substance in arterial blood, and 3) the concentration of the substance in venous blood (Fick, 1870). In the direct Fick approach, the systemic circulation is the organ of interest, the rate of oxygen consumption is measured, and blood flow through the left heart (cardiac output) is determined. In the open circuit acetylene washin method, the pulmonary circulation is the organ of interest, the rate of acetylene uptake across the pulmonary capillaries is measured, and blood flow/cardiac output of the right heart is determined. This technique offers the primary advantage of providing a non-invasive measurement of cardiac output which has been validated against the direct Fick method both at rest and during exercise. Furthermore, compared to non-invasive inert gas rebreathing techniques, the open circuit approach allows individuals to be exposed to stable levels of oxygen and carbon dioxide throughout cardiac output measurement. Importantly, in measuring pulmonary blood flow, the open circuit acetylene washin method models the lung as including a single well-mixed gas exchanging compartment and a single dead space compartment. In cases where this assumption is violated (ventilation-perfusion mismatch, right to left shunts) the open circuit acetylene washin method may underestimate cardiac output (B. D. Johnson et al., 2000).

In this experiment, participants were asked to breathe a gas mixture containing 0.6% acetylene, 9.0% and helium, 20.9% oxygen, and balance nitrogen. Over the course of 8 breaths, breath-by-breath measurements of inspired and expired gases were completed using a respiratory mass spectrometer (acetylene and helium concentration) and a pneumotach (volume). Both acetylene and helium are inert gases. Because acetylene is readily absorbed across the pulmonary capillaries, analysis of inspired and expired acetylene allowed for the estimation of acetylene uptake and arteriovenous acetylene difference. In contrast, helium is insoluble in blood. Therefore, analysis of inspired and expired helium allowed for estimation of changes in lung volume and alveolar dead space. The calculation approach for the open circuit acetylene washin method has been described previously (B. D. Johnson et al., 2000). Stroke volume, in mL, was calculated as cardiac output divided by heart rate. Systemic vascular conductance, expressed as mL/min/mmHg, was calculated as cardiac output divided by mean arterial pressure.

Other Methods

The Fick approach is the gold standard method of determining cardiac output and relies on direct measurement of the variables in the Fick equation including arterial oxygen concentration, mixed venous oxygen concentration, and total oxygen consumption as presented below (Fick, 1870).

Equation 3.3

$$\text{Cardiac Output (L/min)} = \text{Oxygen Consumption } \left(\frac{mL}{min}\right) \div \text{Arteriovenous Oxygen Consumption } \left(\frac{mL\ oxygen}{L\ blood}\right)$$

To obtain these measures directly, individuals must be instrumented with a catheter placed in either the pulmonary artery or right ventricle (mixed venous blood) and an arterial catheter (radial or femoral artery). Additionally, total oxygen consumption must be measured. While this method avoids the various assumptions of other techniques, it requires that cardiac output values be obtained in a stable hemodynamic and metabolic state and its invasive and labor-intensive nature restricts its use in many settings (Ehlers et al., 1986).

Stewart and Hamilton were the first to propose that blood flow through the circulation could be determined by introduction of a tracer substance into the circulation and measurement of the diluted tracer substance at a downstream point in the circulation. In this scheme, cardiac output is inversely related to the downstream concentration of the tracer substance over time (Kinsman et al., 1929; Stewart, 1897). Building on this idea, Felger developed the thermodilution method in anesthetized dogs which utilized temperature (the presence or absence of heat) as the tracer substance (Fegler, 1954). This method was popularized for use in humans in the 1970s following the development of a specialized pulmonary artery catheter with an infusion port located in the right atrium and a thermistor port located in the pulmonary artery. In this method, a known volume of cold saline is injected into the right atrium and the downstream rate of change in temperature at the pulmonary artery is measured (Forrester et al., 1972; Ganz et al., 1971; Ganz & Swan, 1972). The thermodilution method is commonly used in clinical settings (particularly among patients with existing pulmonary artery catheterizations) as it does not require arterial blood gas sampling, can be repeated quickly and easily, and is in good agreement

with the direct Fick approach (Branthwaite & Bradley, 1968). The primary disadvantage of the thermodilution method is the invasiveness of the technique and the importance of operator technique to measurement quality. Additionally, the thermodilution method assumes unidirectional blood flow through the heart such that the presence of valvular regurgitation or intracardiac shunts may lead to underestimation of cardiac output (Argueta & Paniagua, 2019; Ehlers et al., 1986).

Calf Blood Flow

Venous occlusion plethysmography was used to measure calf blood flow in duplicate at baseline and every 30 min throughout whole-body, passive heating and normothermic recovery. Venous occlusion plethysmography was first used in 1905 by Brodie and Russel (Brodie & Russel, 1905) and is based on the underlying rationale that when venous outflow from an anatomical compartment, such as the calf, is occluded, rate of increase in limb volume which occurs in the early phase of this occlusion is proportional to the arterial inflow at that time (Joyner et al., 2001).

Instrumentation for venous occlusion plethysmography included a venous occlusion cuff placed around the thigh (A.T.S. Disposable Cuffs, Zimmer Biomet, Warsaw IN), an arterial occlusion cuff placed around the ankle (A.T.S. Disposable Cuffs, Zimmer Biomet, Warsaw IN), and a mercury-in-Silastic strain gauge (Hokanson Inc., Bellevue, WA) placed around the widest girth of the calf and connected to a plethysmograph (EC6 Plethysmograph, Hokanson Inc., Bellevue, WA). This instrumentation is depicted in **Figure 3.2**. The mercury-in-Silastic strain gauge measured changes in calf volume as the venous occlusion cuff was transiently inflated to 60 mmHg for 7.5 sec out of every 15 sec. This instrumentation and protocol provided one measurement of calf blood flow every 15 sec. To ensure that measurements reflected blood flow through the calf and not the arteriovenous anastomoses of the foot, the arterial occlusion cuff around the ankle was inflated to supra-systolic pressures (250 mmHg) 1 min prior to calf blood flow measures. Calf blood flow was averaged over a 5 (baseline) or 2 min period (heating intervention and normothermic recovery) and presented as mL/min/dL tissue. Calf vascular conductance (mL/min/dL tissue/mmHg) was calculated as calf blood flow divided by mean arterial pressure. Venous occlusion plethysmography offers the advantage of being a non-invasive, easily repeatable, and inexpensive means of measuring absolute changes in limb blood flow. The primary disadvantage of using venous occlusion plethysmography is that the

measurement is highly susceptible to movement artifacts, and therefore, its use is restricted to studying blood flow in stationary limbs (Gliemann et al., 2018; Rådegran, 1997).

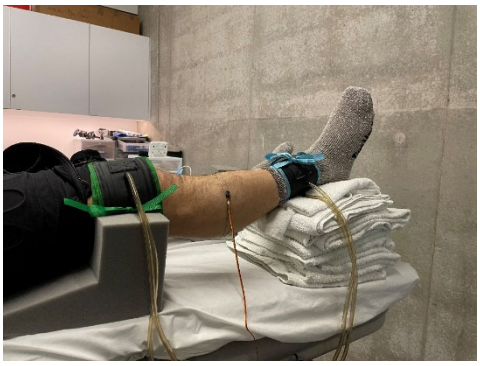

Figure 3.2 Measurement of calf blood flow via venous occlusion plethysmography. The venous occlusion cuff is placed around the thigh above the knee, the arterial occlusion cuff is placed around the ankle, and the mercury in-Silastic strain gauge is placed around the widest circumference of the calf. Transient inflation of the venous occlusion cuff elicits an increase in calf circumference proportional to calf blood flow. Elevation of ankle (above knee) and knee (above hip) supports venous drainage upon venous cuff deflation. Photo by Emily Larson.

Other Methods

In addition to venous occlusion plethysmography, indicator dilution techniques are a classical approach to determining limb blood flow. Like the indicator dilution methods of determining cardiac output, limb blood flow can be determined by infusing a known concentration of tracer substance into the circulation, allowing complete mixing of the tracer in circulation, and measurement of the diluted tracer substance at a point downstream of the circulation of interest. In this scheme, blood flow through a particular circulation (i.e., leg blood flow) is inversely related to the downstream concentration of the tracer substance over time (Kinsman et al., 1929; Stewart, 1897). Commonly used tracers include indocyanine green (Jorfeldt & Wahren, 1971) and cold saline (thermodilution) (Wahren & Jorfeldt, 1973). The primary advantage of indicator dilution techniques over other methods is that they do not require a stationary participant or limb and can be conducted in exercising participants. However, because indicator dilution techniques are invasive (arterial and/or multiple venous catheters required) and can be expensive depending on the selected tracer substance, their use is typically

reserved for studies focused on blood flow during exercise or passive movement (Gliemann et al., 2018; Rådegran, 1997).

In the 1980s ultrasound emerged as a promising means of determining limb blood flow both at rest and during exercise. In vascular ultrasound, a probe containing piezoelectric crystals is placed on the surface of the skin and used to emit sound waves which travel into a conductive gel medium and underlying tissues. A portion of these sound waves are reflected to the transducer and the principles of sound wave reflection and Doppler shift are applied to this reflected signal to generate a two-dimensional image of the underlying tissue (which permits measurement of vessel diameter) and Doppler derived measurements of blood flow velocity. (Thrush et al., 2010). Blood flow through an imaged vessel is calculated from these measures as the product of vessel cross sectional area and blood flow velocity. Doppler ultrasound derived measurements of blood flow are well correlated with those obtained by venous occlusion plethysmography at rest, during exercise (Byström et al., 1998; Green et al., 2011; Tschakovsky et al., 1995), during thermal stress, and during baroreceptor loading/unloading (Brothers et al., 2010). Additionally, ultrasound measurements can be obtained non-invasively, continuously, have the highest temporal resolution of all blood flow measurement methods, and yield additional information on blood vessel diameter which can be used to subsequently calculate indices of vascular shear stress (Rådegran, 1999). Importantly, a highly trained ultrasound technician is needed to obtain accurate and reproducible ultrasound derived measures (Gill, 1985; Mikkonen et al., 1996).

Skin Blood Flow

Skin blood flow was assessed on the calf and monitored continuously at baseline and throughout whole-body, passive heating and normothermic recovery using laser Doppler flowmetry (Leahy et al., 1999). In this technique, laser Doppler probes are placed perpendicular to the surface of the skin. Each probe emits laser light of a known wavelength into the underlying tissue. While the majority of this light was absorbed or reflected to the probe without a change in this known wavelength, a portion of this laser light is reflected by moving red blood cells within the cutaneous microvasculature. Due to the Doppler shift, this light is reflected to the probe at an altered wavelength. The proportion of light received at this Doppler shifted wavelength is used to estimate the concentration of red blood cells in the underlying cutaneous tissue. The magnitude of the change in wavelength observed in the reflected light is used to estimate the velocity of the

red blood cells traveling though the cutaneous microvasculature. Red blood cell flux, an index of the blood flow through the cutaneous microvasculature, is calculated as the product of red blood cell concentration and velocity.

In this experiment, two single-point (MP12; Moor Instruments, Axminster, UK) and two integrated laser Doppler probes (MP1/7-V2; Moor Instruments, Axminster, UK) were placed flush against and perpendicular to the surface of the skin of the lateral calf. The single point probes were seated within local heating units (SH02 Skin Heater/Temperature Monitor; Moor Instruments, Axminster, UK) **(Figure 3.3)**. These laser Doppler probes were connected to a server unit with three satellite units which allowed for continuous monitoring at the four locations throughout the experiment. Skin blood flow at baseline was determined as the average flux over two 5 min periods of baseline rest. Skin blood flow was determined every 10 min during heating and every 30 min during normothermic recovery as the average flux over a 2 min period. During these skin blood flow recording periods, participants were coached to remain still, breathe normally, and refrain from talking. Importantly, changes in skin blood flow/flux can be driven by changes in blood pressure or vasomotor tone. In this experiment cutaneous vascular conductance (flux units/mmHg) values reflect changes in cutaneous vasomotor tone independent of changes in blood pressure and were calculated by dividing laser Doppler flowmetry derived red blood cell flux values by mean arterial pressure.

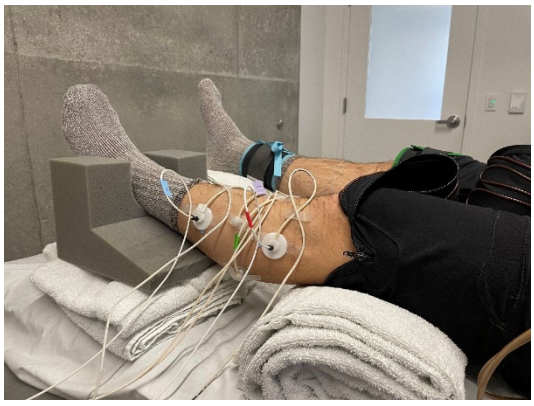

Figure 3.3 Four laser Doppler probes positioned on the skin surface of the lateral calf. The two single point probes were seated within a local heating unit. Photo by Emily Larson.

The primary advantage the laser Doppler flowmetry technique for the assessment of skin blood flow is that, because commercially available laser Doppler probes penetrate underlying tissue at a maximum depth of 0.73 mm (Fredriksson et al., 2009), the derived changes in blood flow are believed to reflect only changes in blood flow through the skin microcirculation and not underlying tissues. Additional advantages of laser Doppler flowmetry include that it is non-invasive and permits continuous monitoring of skin blood flow with high temporal resolution. The greatest limitation to laser Doppler assessment of skin blood flow is that each probe assesses a small and unknown cutaneous sample volume. As cutaneous microvascular anatomy and, consequently, skin blood flow vary widely within a limb and across the body surface, this limitation serves to introduce substantial spatial heterogeneity into laser Doppler derived assessments of skin blood flow (Braverman et al., 1990; Braverman & Schechner, 1991). Furthermore, the unknown nature of this sample volume relative to the total cutaneous microvasculature prevents extrapolation of qualitative red blood cell flux values to quantitative changes in cutaneous blood flow.

In this experiment, we took several steps to allow for valid intra- and inter-individual comparisons amidst the substantial spatial heterogeneity and qualitative nature of our laser Doppler derived assessments of skin blood flow (Chaseling et al., 2020). First, to minimize the spatial heterogeneity of our assessments within an individual, Doppler probes were not relocated within a given study day. Second, two of the four laser Doppler probes used were integrated or multi-site probes which sampled blood flow across a larger area (7 mm in diameter) than that of single-site probes in which one emitting and receiving component permit assessment across a smaller area (1 mm in diameter) (Brothers et al., 2010). Third, to allow for intra- and inter-individual comparisons, red blood cell flux and cutaneous vascular conductance values obtained using the single-point probes were normalized to a site-specific maximal value. Typically, maximal flux is attained by locally heating the skin to >42°C or by local infusion of the nitric oxide donor sodium nitroprusside (J. M. Johnson & Kellogg, 2010). In this experiment, local heating to 43.5°C at a rate of 0.1°C/sec was performed on two of the four skin blood flow sites 90 min into the 2 h normothermic recovery period to obtain maximal flux (Lorenzo & Minson, 2010; G. R. McCord et al., 2006). For these two sites, flux and conductance values are presented as a percentage of maximum cutaneous vascular conductance.

Other Methods

Venous occlusion plethysmography and Doppler ultrasound have been commonly employed to investigate changes in skin blood flow during thermal challenges (Chaseling et al., 2020). The primary disadvantage of these methods is that they are based on the assumption that changes in limb blood flow are isolated to the cutaneous circulation. Importantly, this assumption may not be valid in all cases as previous studies have demonstrated increased muscle blood flow with whole-body heating in which direct heat is applied to the skin (Heinonen et al., 2011). The primary advantage of these techniques is that the quantitative nature and more broad assessment area of the obtained measurements negates some of the spatial heterogeneity and qualitative nature of laser Doppler derived assessments of skin blood flow. Importantly, despite these tradeoffs, Brothers noted similar changes in skin blood flow between these three measurement methods during heat stress and baroreflex perturbations (Brothers et al., 2010).

SUBJECTIVE EXPERIENCE MEASURES

Participants were asked to rate their perceived exertion (6-20 scale) (Borg, 1982), thermal sensation (7 point scale; 1 = cold, 7 = hot) (Gagge et al., 1967, 1969), and skin wettedness (7 point scale: +3 = very wet, 0 = neutral, -3 = very dry) (Filingeri et al., 2015; Vargas et al., 2018) at baseline, every 10 min throughout whole-body, passive heating, and every 30 min throughout normothermic recovery. These scales have been previously utilized to assess perceptual responses to passive heat stress via pater perfused suit in young and older individuals (Schlader et al., 2015).

NEUROVASCULAR MEASURES

Cardiac, Peripheral Vascular, and Integrated Baroreflex Function. Cardiac, peripheral vascular, and integrated carotid baroreflex responsiveness were assessed by measuring the heart rate, brachial vascular conductance, and blood pressure response to neck pressure applied via external neck collar. The technique of altering neck pressure to assess carotid baroreflex function was first described in 1957 by Ernsting and Parry (Ernsting & Parry, 1957). The neck collar device used today is a modification of the design developed in 1957 by Eckberg and colleagues (Eckberg et al., 1975). In this technique, the neck collar device is used to increase (neck pressure) or decrease (neck suction) pressure over the carotid sinus. The application of neck

pressure serves to reduce carotid transmural pressure and results in the contraction and reduced firing of the carotid baroreceptors. To counter this hypotensive stimulus, the cardiovascular control centers in the medulla initiate a reflexive reduction in parasympathetic tone and an increase in sympathetic tone. This altered autonomic control serves to elicit increases heart rate, vascular tone, and blood pressure. In contrast, the application of neck suction serves to increase carotid transmural pressure and results in distention and increased firing of the carotid baroreceptors. To combat this hypertensive stimulus the cardiovascular control centers in the medulla increase parasympathetic tone and reduce sympathetic tone. These autonomic responses facilitate a reduction in heart rate, vascular tone, and blood pressure. In this scheme, the heart rate, blood pressure, and vascular tone responses to the applied hypo- or hypertensive stimulus can be used to assess cardiac, vascular, and integrated carotid baroreflex responsiveness, respectively. Additionally, variable pressure may be applied in a stepwise manner (simulate multiple levels of hypotension and hypertension) to characterize these carotid baroreflex responses over the entire operating range of the reflex (Cooper & Hainsworth, 2009; Fadel et al., 2003; La Rovere et al., 2008; Wehrwein & Joyner, 2013).

In this experiment, neck pressure was applied to assess carotid baroreflex responsiveness at baseline, at the end of the heating intervention, and every 30 min throughout the 2 h post-heating recovery period. Neck pressure of 50 mmHg was administered using an external neck collar that enclosed the anterior two-thirds of the neck and was sealed against the mandible, collarbones, and sternum. The neck collar was connected to a bellows pressure controller (PPC-1000, Engineering Development Laboratory, Inc., Newport News, VA) and interfaced with custom software to deliver R-wave activated 5 sec bouts of neck pressure. To minimize the influence of respiratory-induced changes in heart rate and blood pressure, each neck pressure stimulus was administered during a voluntary end expiration apnea (Eckberg et al., 1980). This apnea was maintained for 3 sec prior to neck pressure application, 5 sec during the neck pressure application, and the subsequent 7 sec after neck pressure application. This process was repeated 5-7 times to obtain high quality neck pressure applications at each time point. Each round of neck pressure applications was preceded by 1 min of paced breathing at 0.25 Hz and consecutive neck pressure trials were separated by at least 1 min of paced breathing at 0.25 Hz (Buck et al., 2015; Pellinger & Halliwill, 2007). Brachial blood pressure was measured prior to each round of

neck pressure application and carotid sinus pressure was estimated as the difference between brachial mean arterial pressure and neck collar pressure.

During each neck pressure application, heart rate (lead II ECG, Cardiocap 5, Datex-Ohmeda, St. Louis, MO) and beat-by-beat arterial blood pressure (Nexfin, BMEYE, Amsterdam, Netherlands) were continuously monitored at 250 Hz (Windaq, Dataq Instruments, Akron, OH). Brachial artery blood flow was measured via duplex ultrasonography with an insonation angle of 60° (Phillips iE33 ultrasound with 9 MHz linear-array vascular probe, Andover, MA, USA). To ensure that brachial blood flow was reflective of arm blood flow and not flow through the arteriovenous anastomoses of the hand, a pressure cuff was placed around the wrist and inflated to 250 mmHg for 1 min prior to ultrasound measurements. Measurements were made in the distal third of the upper arm and placement locations were marked following baseline measurements to ensure that the same area was imaged for repeated measurements. A 5 sec B-mode recording was completed before each set of neck pressure trials and automated wall tracking software (Vascular Research Tools 5; Medical Imaging Applications LLC, Coralville, IA) was used to determine brachial artery diameter (cm) along the highest quality portion of this image. The retrograde and anterograde audio signal output from the Doppler ultrasound was Fourier transformed to generate a continuous analog signal of mean blood velocity (cm/s). Brachial blood flow velocities were multiplied by artery cross-sectional area to determine beat-by-beat brachial blood flow (mL/min). Brachial vascular conductance (mL/min/mmHg) was calculated by dividing brachial blood flow by mean arterial pressure measured via finger plethysmography.

Cardiac baroreflex responsiveness was estimated as the peak heart rate response observed 1-7 sec after the onset of neck pressure, integrated carotid baroreflex responsiveness was estimated as the peak mean arterial pressure response observed 2-9 sec after the onset of neck pressure, and peripheral vascular carotid baroreflex responsiveness was estimated as the nadir of the brachial vascular conductance response 3-12 sec after the onset of neck pressure. Based on prior work conducted in both young and older individuals, these selected time windows likely encapsulated the peak responses to neck pressure application in both age groups (Fisher et al., 2009; Pellinger & Halliwill, 2007). Because changes in brachial vascular conductance with applied neck pressure were used as an index of peripheral vascular responsiveness, these values are presented as a percentage change from pre-neck pressure values. This presentation is

consistent with prior work evaluating carotid baroreflex control of the vasculature (Buckwalter & Clifford, 2001; Keller et al., 2003, 2004). **Figure 3.4** below displays a representative tracing of data obtained during a single neck pressure trial in a single participant.

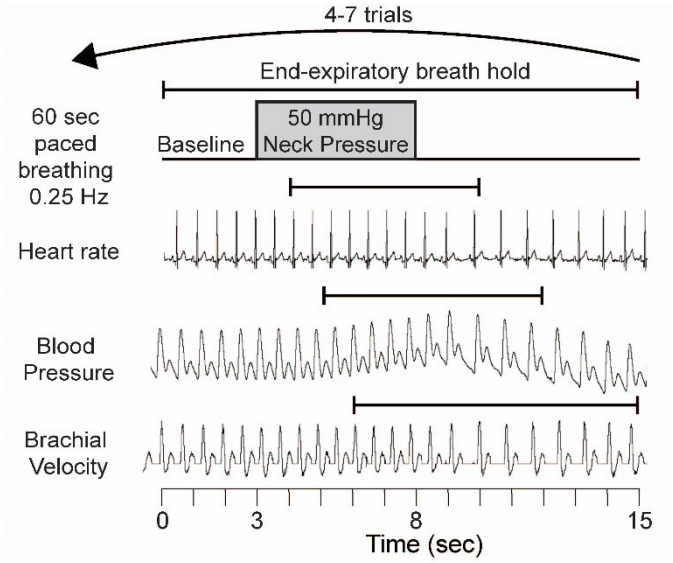

Figure 3.4 Representative tracing of neck pressure protocol. Heart rate, beat-by-beat blood, brachial blood flow velocity, and beat-by-beat blood data have been synchronized such that each R-R interval corresponds with the appropriate arterial pressure and blood flow velocity envelope. Brackets seen above heart rate, brachial blood flow velocity, and beat-by-beat blood pressure data represent time windows used in analysis of peak responses to neck pressure.

The neck collar approach offers several advantages including that it delivers a non-invasive, non-pharmacological, easily repeatable, and precisely controlled stimulus which can be performed at rest or during various stresses including exercise. Additionally, when neck pressure and suction are employed in a stepwise manner, the neck collar technique can generate complete stimulus response curves over a wide range of carotid sinus pressures. The primary disadvantage to the neck chamber method is that it only alters pressure sensed by the carotid baroreceptors and therefore, conflicting feedback of the aortic baroreceptors may act to attenuate the observed reflexive responses. Another concern in the neck pressure technique is inadequate transmission of pressure from the neck collar device to the carotid sinus and resulting inaccurate carotid sinus pressure (Cooper & Hainsworth, 2009; Fadel et al., 2003; La Rovere et al., 2008; Wehrwein &

Joyner, 2013). Importantly, however, this limitation can be considerably reduced and nearly complete pressure transmission can be achieved when anatomical variation of the carotid sinus is well matched to the neck collar (Ludbrook et al., 1976; Querry et al., 2001). Accordingly, vascular ultrasound of the carotid artery was completed on the initial screening day of this study and the distance from the angle of the mandible to each carotid bifurcation was recorded. Individuals enrolled in the study also completed several rounds of neck pressure application on the initial screening day. Individuals were enrolled in the study if these distances were within the accessible range of inflatable portion of the neck collar. Additionally, individuals only continued to the experimental day if an adequate seal could be attained with the neck collar during several practice rounds on the initial screening day.

Other Methods

The Valsalva maneuver is another non-invasive method of assessing baroreflex function. In the Valsalva maneuver, an individual forcefully exhales against a closed glottis for 15-20 sec. This straining serves to increase thoracic and abdominal pressure and elicit characteristic blood pressure and heart rate responses which can be divided into four phases and used to study baroreflex function (HAMILTON, 1936). In phase one, Valsalva straining begins and increases in intrathoracic pressure promote a temporary increase in venous return, cardiac output, and blood pressure. This transient increase in blood pressure elicits a reflexive bradycardia. In phase two, continued increases in intrathoracic pressure restrict venous return to the heart and elicit a fall in cardiac output and blood pressure. This reduction in blood pressure is accompanied by a reflexive increase in heart rate. In phase three, the participant releases the Valsalva hold and begins to breathe normally. This release serves to decrease intrathoracic pressure, temporarily reduce aortic transmural pressure, and is accompanied by a reflexive increase in heart rate and vascular resistance. In phase four, venous return to the heart is restored and cardiac output is increased. This increase in cardiac output occurs against a backdrop of increased vascular resistance and causes blood pressure to increase above baseline levels. This increase in blood pressure is accompanied by a reflexive reduction in heart rate. Baroreflex function is commonly studied by analyzing the relationship between falling blood pressure and increased heart rate or sympathetic nerve activity in phase two of the Valsalva maneuver. Additionally, baroreflex function may assessed by analyzing the degree of blood pressure “overshoot” and reflexive bradycardia accompanying phase four of the Valsalva maneuver (Eckberg, 1980b; Korner et al.,

1976; La Rovere et al., 2008; Wehrwein & Joyner, 2013). The primary advantages to the Valsalva maneuver include that it can be easily employed in both research and clinical settings. The primary disadvantage to the Valsalva maneuver assessments of baroreflex function include that the maneuver may influence chemoreceptor or pulmonary afferents (Looga, 1997; Mateika et al., 2002) or promote cardiopulmonary baroreceptor activation (Smith et al., 1996), all of which may confound derived arterial baroreflex assessments.

In contrast to other methods which utilize mechanical or pharmacological blood pressure manipulation, another commonly used non-invasive approach to the assessment of baroreflex function is through the analysis of spontaneous fluctuations in blood pressure and heart rate. The most common quantification approaches used in spontaneous baroreflex assessment include the sequence method (Parati et al., 1988) and the spectral method (Robbe et al., 1987). These methods operate on the premise that sensitivity of baroreflex control of heart rate can be determined by relating spontaneously occurring rising and falling blood pressure to baroreflex mediated changes in heart rate interval (La Rovere et al., 2008; Wehrwein & Joyner, 2013). The proposed advantage of spontaneous techniques include that they do not require a perturbation to the system to investigate baroreflex function and therefore may represent a “closed loop” model of arterial baroreflex function within a given state. However, these approaches are limited in that they only characterize baroreflex responses over a small range of spontaneously occurring blood pressure fluctuations and rely on the invalid assumptions that the “closed loop” blood pressure/heart rate relationship is linear and reflects only feedback and not feedforward responses (Diaz & Taylor, 2006). As a result of these limitations, spontaneous baroreflex assessments provide limited insight into baroreflex function when compared with more direct assessments which perturb the system (Lipman et al., 2003).

The modified Oxford method, developed by Ebert, Cowley, and Rudas (Ebert & Cowley, 1992; Rudas et al., 1999), is the gold-standard method for assessing arterial baroreflex function. In this technique, the vasoactive drugs nitroprusside and phenylephrine are used to reduce and increase arterial pressure over a relatively short time course (~3 min). During these infusions, sympathetic nerve activity is directly measured via microneurography as described by Sundlof and Wallin (Sundlöf & Wallin, 1977). The average values in the period preceding the drug infusion protocol indicate the operating point of heart rate, resting arterial pressure and sympathetic nerve activity. The relationship (weighted linear regression) between muscle

sympathetic nerve activity and diastolic blood pressure provides an index of the sensitivity of arterial baroreflex control of sympathetic nerve activity. Similarly, the relationship (weighted linear regression) between heart rate and systolic blood pressure serves as an index of the sensitivity of arterial baroreflex control of heart rate (Rudas et al., 1999; Sundlöf & Wallin, 1977). If used in combination with measures of muscle sympathetic nerve activity, this approach provides the most direct assessment of sympathetic regulation of blood pressure. Another advantage of this technique is that the vasoactive drugs serve to systemically alter blood pressure across all both carotid and aortic baroreceptor locations making the derived responses highly integrative. Disadvantages of this technique include the possibility that the vasoactive drugs directly influence baroreceptor populations or end organ responses. A challenge of this approach is that adequate muscle sympathetic nerve recordings must be obtained to gain insight into sympathetic vascular regulation. Unlike the non-invasive approaches detailed above, blood pressure is artificially impacted by drug infusion and therefore cannot be used to gauge baroreflex function. Furthermore, this technique is more invasive than other baroreflex assessment approaches in its requirement of microneurography and intravenous drug administration. Collectively, these challenges typically restrict the use of this technique to studies conducted in resting individuals and protocols which prioritize muscle sympathetic nerve recordings (La Rovere et al., 2008; Wehrwein & Joyner, 2013).

In this study, we utilized the brachial vascular conductance responses to sympathoexcitatory neck pressure stimulus as an index of the responsiveness of the peripheral vascular arm of the baroreflex. Studies conducted in our laboratory have similarly used this model to characterize changes in baroreflex control of the peripheral vasculature following pharmacological beta-blockade (Pellinger & Halliwill, 2007) and small muscle mass exercise (Buck et al., 2015). However, it is important to note that sympathetic vascular control can be more directly assessed by relating measured changes in sympathetic nerve activity to changes in a vascular outcome variable (blood flow, vascular resistance/conductance) in response to a sympathetic stressor (Tymko et al., 2021; Young et al., 2021). This measurement is commonly referred to as neurovascular transduction or sympathetic vascular transduction and describes the translation of postganglionic sympathetic nerve traffic into blood vessel tone. Neurovascular transduction may be impacted by alterations in neurotransmitter or co-transmitter release or reuptake from sympathetic nerve terminals, altered vascular smooth muscle receptor density or

reactivity, or the release of vasodilator or vasoconstrictor substances which act directly on vascular smooth muscle (Halliwill, 2001). For example, Halliwill and colleagues assessed sympathetic vascular transduction following exercise or sham treatment by having participants hold a submaximal isometric forearm contraction to fatigue while simultaneously measuring muscle sympathetic nerve activity at the peroneal nerve and calf blood flow. Sympathetic vascular transduction was derived from the slope of the relationship between values of calf vascular resistance and nerve activity (Halliwill, Taylor, & Eckberg, 1996). The cold pressor test (Usselman et al., 2015) and progressive lower body negative pressure (Ray & Monahan, 2002) are also commonly used to assess sympathetic vascular transduction. Another approach in assessing neurovascular transduction is by relating muscle sympathetic nerve activity on a beat-by-beat basis to a vascular outcome variable during rest (blood flow, vascular resistance/conductance). This approach was originally proposed by Wallin and Nerhed in the 1980's (Gunnar Wallin & Nerhed, 1982), and several recent studies utilizing vascular ultrasound have continued to modify the analysis approach (Briant et al., 2016; Fairfax et al., 2013; Steinback et al., 2019; Vianna et al., 2012). While these indices provide the most direct assessment of the translation of postganglionic sympathetic outflow into vascular resistance, they are more invasive in their reliance on muscle sympathetic nerve activity recordings.

Data and Statistical Analysis

Rectal temperature, heart rate, calf blood flow, and skin blood flow data were recorded at 250 Hz (Windaq, Dataq Instruments, Akron, OH) and skin temperature was recorded at 1 Hz (eTemperature, OnSolution Pty Ltd, NSW, AU). Average values for these variables were determined across two 5 min bins at baseline and across a single 2 min bin at the indicated time point during whole-body, passive heating or normothermic recovery. Statistical analyses were conducted using GraphPad Prism 10.1.0. Participant demographic data and experimental condition data are presented as means and standard deviations. All other data is presented as means and 95% confidence intervals. Baseline values for each variable and the change in each variable with heat stress (calculated from baseline to the final measure during passive heating) were compared between age groups using unpaired, two-tailed *t* tests. A two-way (age X time) mixed model analysis of variance was used to examine the effects of passive heating and post-heating recovery on systemic cardiovascular and carotid baroreflex function in young and older adults. A priori contrasts of age-time combinations were examined within this relation and

accordingly, we did not use a multiple comparisons adjustment when significant main or interaction effects of age and/or time into heating were detected. Statistical significance was accepted with $\alpha = 0.05$.

CHAPTER IV

SYSTEMIC CARDIOVASCULAR AND CAROTID BAROREFLEX SUPPORT OF BLOOD PRESSURE DURING RECOVERY FROM PASSIVE HEAT STRESS IN YOUNG AND OLDER ADULTS

INTRODUCTION

Cardiovascular disease is the leading cause of death in the developed world and high blood pressure (hypertension) is the leading modifiable risk factor in the development of cardiovascular disease (American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, 2018). As our worldwide population is aging and blood pressure increases with advancing age such that approximately 90% of adults with normal blood pressure at age 55 or 65 will develop hypertension in their lifetime (Vasan et al., 2002), interventions aimed at blood pressure management, particularly among older individuals, are critically needed. Heat therapy, such as regular hot bath or sauna, has increasingly gained attention as an alternative, non-pharmacological means of reducing blood pressure and improving cardiovascular health. Large prospective studies suggest that regular sauna baths are associated with a reduced risk of hypertension, sudden cardiac death, coronary heart disease, cardiovascular disease, and all-cause mortality in men (Laukkanen et al., 2015; Zaccardi et al., 2017) and women (Laukkanen et al., 2018). Several intervention-based studies have likewise demonstrated that chronic heat therapy reduced blood pressure in young individuals (Brunt, Eymann, et al., 2016), women with polycystic ovarian syndrome (Ely et al., 2019), and individuals with coronary risk factors (Masuda et al., 2004), peripheral artery disease (Akerman et al., 2019), lower-limb osteoarthritis (Roxburgh et al., 2023), and heart failure (Fujita et al., 2011; Kihara et al., 2002, 2004; Kuwahata et al., 2011; Oyama et al., 2013; Tei et al., 2016).

Some of the benefits of heat therapy may be mediated during the recovery period which follows a single session of heat exposure. For example, Francisco and colleagues demonstrated the presence of sustained hypotension following whole-body heat stress in healthy, young individuals comparable to that which follows a single session of moderate intensity aerobic exercise (post-exercise hypotension), although this is not a universal finding (Amin et al., 2022; Engelland et al., 2020a, 2020b; Hemingway et al., 2023; Richey et al., 2022; Romero, Gagnon, et al., 2017). Post-heating hypotension has also been demonstrated in several (Engelland et al.,

2020b; Laukkanen et al., 2017; Neff et al., 2016; Romero, Gagnon, et al., 2017; Thomas et al., 2017), but not all (Gravel et al., 2019; Richey et al., 2022), studies among healthy older individuals and older individuals with peripheral artery disease. Like post-exercise hypotension, post-heating hypotension could contribute to cardiovascular health improvement by transiently lowering elevated blood pressure into normotensive ranges and may potentiate chronic blood pressure reductions with heat therapy (Roxburgh et al., 2023). Older individuals may stand to gain the greatest benefit of these acute and chronic blood pressure reductions as they have the highest prevalence of hypertension and are often unable or unwilling to engage in regular exercise to effectively manage their blood pressure.

Work conducted by Romero and colleagues was the first to compare the cardiovascular and neurovascular adjustments following acute heat stress between young and older individuals. They noted that blood pressure was reduced below pre-heating baseline values 30 min following 45 min of lower-limb heating in healthy older, but not young individuals (Romero, Gagnon, et al., 2017). The sustained hypotension among older individuals was due to sustained vasodilation which was not offset by post-heating elevations in cardiac output or heart rate. In contrast, both cardiac output and heart rate remained elevated above baseline values in the young individuals during post-heating recovery. A follow-up study conducted by Engelland and Romero demonstrated that this post-heating hypotension was mediated by sympathoinhibition in older, but not young individuals (Engelland et al., 2020b).

While this work provides invaluable insight into the post-heating recovery period, several gaps in knowledge remain. First, both of these previous studies utilized a mild lower-body heating modality, and thus may not reflect the post-heating recovery period which follows the whole-body heating modalities which have been used to elicit chronic cardiovascular adaptation. Additionally, the sustained hypotension and sympathoinhibition noted among older individuals following heating in this prior work could reflect attenuated baroreflex responsiveness to changes in pressure during the post-heating recovery period. To date, no study has explored baroreflex function during the post-heating recovery period.

The purpose of this study was to address these gaps in knowledge and compare the systemic cardiovascular and carotid baroreflex support of blood pressure during recovery from whole-body, passive heat stress in young and older individuals. We tested the hypothesis that the post-heating recovery period is accompanied by sustained hypotension, elevations in cardiac

output and heart rate, and vasodilation. We additionally hypothesized that the magnitude of this blood pressure reduction would be exaggerated among older individuals due to a diminished post-heating elevation of cardiac output and heart rate. Lastly, we hypothesized that the peripheral vascular response to simulated hypotension via applied neck pressure would be attenuated while cardiac and integrated carotid baroreflex responsiveness would be preserved during the post-heating recovery period.

METHODS

Ethical Approval

This study was approved by the Institutional Review Board at the University of Oregon (Protocol #08102020.012). Prior to participation, all participants provided oral and written informed consent as set forth by the Declaration of Helsinki.

Participants

Sixteen young (8 women, 8 men) and nine older (6 women, 3 men) volunteers participated in this study. All individuals were healthy with no history of cardiovascular disease and not taking prescription medications other than hormonal contraceptives. Individuals with Stage 2 hypertension (≥140 mmHg systolic blood pressure and/or ≥90 mmHg diastolic blood pressure) or a body mass index below 18.5 or above 35 $kg \cdot m^{-2}$ were excluded from the study. Individuals who were endurance training (moderate aerobic exercise > 60 min/session on ≥ 5 days per week), training for non-recreational athletic competition, or regularly engaging in a heat therapy regimen (whole-body heating ≥ 30 min/session and ≥ 3 sessions per week) were excluded from participating in the study.

Table 4.1 Participant characteristics.

	Young	Older
n	16 (8M,8F)	9 (3M,6F)
Age (yr)	22±4	65±4*
Height (cm)	169±13	171±9
Weight (kg)	69±15	72±20
Body mass index (kg/m^2)	24±4	24±5
Body fat percentage (%)	16±10	23±6
IPAQ-SF MET-min per week	2072±952	3130±2680
Systolic blood pressure (mmHg)	116±7	114±9
Diastolic blood pressure (mmHg)	71±5	68±6
Heart rate (bpm)	71±10	60±9
Left carotid bifurcation distance (cm)	31±9	35±8
Right carotid bifurcation distance (cm)	31±7	37±6*

Values are means ± standard deviation. Data were compared between groups using an unpaired *t* test; **P* < 0.05 older vs. young.

Females were studied under low hormone conditions when possible: during the early follicular phase of the menstrual cycle, placebo phase of oral contraceptive use (B. M. Lynn et al., 2007; Minson et al., 2000; Senitko et al., 2002), and/or in the absence of hormone replacement therapy (Brooks et al., 1997; Dunbar & Kenney, 2000; Tankersley et al., 1992). Before the screening and experimental study days, participants were required to abstain from over-the-counter medications for > 24 h, heavy exercise or heat stress for > 24 h, alcohol and caffeine for > 12 h, and food for 4 h (screening visit) or 2 h (study visit). Participants on a daily aspirin regimen were also asked to refrain from aspirin for one week before participating in the experimental session. Euhydration was evaluated in all participants prior to each experimental session by a first morning urine specific gravity of less than 1.024. If urine specific gravity was greater than 1.024, participants drank 3 mL water/kg of body weight before beginning the protocol. This urine sample was also used to conduct a pregnancy test on all participants of child-bearing potential before the experimental study visit.

Experimental Protocol

Participants visited the laboratory on two separate occasions. The first visit was a screening and familiarization visit and consisted of health history and physical activity (IPAQ-SF) questionnaires, height and weight measurement, and body composition estimation based on skinfold thickness measured at three standard locations. Seated resting blood pressure assessment was also performed in accordance with clinical guidelines (American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, 2018). Auscultation of the carotid arteries was performed, and if vascular sounds suggestive of reduced or turbulent carotid arterial blood flow were detected, participants were excluded from further participation in the study. Vascular ultrasound was utilized to determine the location of the carotid bifurcation, and the distance from the carotid bifurcation to the angle of the mandible was measured to ensure that the neck collar would appropriately encompass the bifurcation. Following these screening assessments, participants completed several rounds of familiarization with the neck pressure technique as described below. Participants were excluded from the study if an adequate fit and seal of the neck collar could not be obtained during this familiarization.

The second study visit was the experimental session and consisted of a normothermic baseline period, 60 min of whole-body, passive heating via water perfused suit, and 2 h of normothermic recovery. The experimental session was held in a 23.7±0.4°C laboratory environment and began between 0700 and 1000. Upon arrival to the laboratory and initial instrumentation, participants rested in the supine position and donned a two-piece water perfused suit (Med-Eng Systems, Ottowa, Canada) which covered the entire body except for the head, hands, feet, and calves (used for calf and skin blood flow measurements). A water circulating bath (HT CIRC 7L AD, Polyscience, Niles, Illinois) was used to circulate 34°C water through the suit at baseline. Following baseline measures, participants were passively heated over the course of 60 min by perfusing 50°C water through the suit. To limit heat losses during this period, participants wore a hat and were wrapped in mylar thermal and cotton blankets. If rectal temperature increased by 1°C, the temperature of the water was decreased to 45°C to prevent further increases in core temperature. In all participants, the blankets and hat were removed at the conclusion of the final measurements during passive heating and before the neck pressure measurements during the passive heating intervention. At the conclusion of the neck pressure

measurements during the passive heating intervention, 34°C was immediately recirculated through the suit for 2 h of normothermic recovery. Fluid consumption was restricted to the heating portion of the experimental visit during which time participants consumed 3 mL water/kg of body weight. Overall sweat loss was estimated by measuring fluid consumption, urine losses, and dry nude body weight at the beginning and end of the experimental session.

Measurements

Thermal

Rectal and skin temperature were determined in duplicate at baseline, every 10 min throughout passive heating, and every 30 min throughout the 2 h normothermic recovery period. Rectal temperature was measured using a rectal thermistor probe inserted ~10 cm past the anal sphincter (YSI series 400: Yellow Spring Instruments, Yellow Springs, OH). Skin temperature was measured using six thermochron temperature loggers (DS1922L, OnSolution Pty Ltd, NSW, AU) placed at standard locations on the chest, upper back, lower back, abdomen, thigh, and calf and calculated as the weighted average of these six assessment sites (chest 22%, upper back 19%, lower back 19%, abdomen 14%, thigh 14%, calf 11%) (Gagnon et al., 2015, 2016; W. F. Taylor et al., 1989). Mean body temperature was calculated as the weighted average of core temperature (90%) and mean skin temperature (10%) (Jay et al., 2007). Participants were additionally asked to rate their perceived exertion (6-20 scale) (Borg, 1982), thermal sensation (7 point scale; 1 = cold, 7 = hot) (Gagge et al., 1967, 1969), and skin wettedness (7 point scale: +3 = very wet, 0 = neutral, -3 = very dry) (Filingeri et al., 2015; Vargas et al., 2018) at baseline, every 10 min throughout passive heating, and every 30 min throughout normothermic recovery.

Central Hemodynamic

Blood pressure, heart rate, and cardiac output were measured in duplicate at baseline and every 30 min throughout passive heating and normothermic recovery. Blood pressure was measured using an automated auscultatory blood pressure cuff (Tango+, SunTech Medical, Raleigh, NC) and heart rate was measured using a three-lead electrocardiograph (Lead II; Cardiocap 5, Datex-Ohmeda, St. Louis, MO). Cardiac output was measured non-invasively using the open circuit acetylene washin method which has been validated in humans against the direct Fick approach (B. D. Johnson et al., 2000). Participants breathed a gas mixture containing 0.6% acetylene, 9.0% helium, 20.9% oxygen, and balanced nitrogen for 8-10 breaths via a two-way non-rebreathing valve attached to a pneumatic sliding valve. During the washin phase, breath-by-

breath acetylene and helium uptake were measured by a respiratory mass spectrometer (MGA 1100; MA Tech Services, Inc; Saint Louis, MO, USA), and total volume was measured via a pneumotach (Series 1110, Hans Rodolph, Kansas City, MO, USA) linearized and calibrated using test gases before each testing day. Stroke volume (mL) was calculated as cardiac output divided by heart rate, and systemic vascular conductance (mL/min/mmHg) was calculated as cardiac output divided by mean arterial pressure.

Calf and Skin Blood Flow

Calf blood flow was measured in duplicate at baseline and every 30 min throughout passive heating and normothermic recovery using venous occlusion plethysmography. Briefly, a venous occlusion cuff was placed around the thigh (A.T.S. Disposable Cuffs, Zimmer Biomet, Warsaw IN), an arterial occlusion cuff was placed around the ankle (A.T.S. Disposable Cuffs, Zimmer Biomet, Warsaw IN), and a mercury-in-Silastic strain gauge (Hokanson Inc., Bellevue, WA) was placed around the widest girth of the calf and connected to a plethysmograph (EC6 Plethysmograph, Hokanson Inc., Bellevue, WA). The mercury-in-Silastic strain gauge measured changes in calf volume as the venous occlusion cuff was transiently inflated to 60 mmHg for 7.5 sec out of every 15 sec. This instrumentation and protocol provided one measurement of calf blood flow every 15 sec. To ensure that measurements reflected blood flow through the calf and not the arteriovenous anastomoses of the foot, the arterial occlusion cuff around the ankle was inflated to supra-systolic pressures (250 mmHg) 1 min prior to calf blood flow measures. Calf blood flow is presented as mL/min/dL tissue. Calf vascular conductance (mL/min/dL tissue/mmHg) was calculated as calf blood flow divided by mean arterial pressure.

Skin blood flow was measured using laser Doppler flowmetry in duplicate at baseline, every 10 min throughout passive heating, and every 30 min throughout the 2 h of normothermic recovery. Two single-point (MP12; Moor Instruments, Axminster, UK) and two integrated laser Doppler probes (MP1/7-V2; Moor Instruments, Axminster, UK) were placed flush against and perpendicular to the surface of the skin of the calf. The single point probes were seated within local heating units (SH02 Skin Heater/Temperature Monitor; Moor Instruments, Axminster, UK). Cutaneous vascular conductance was calculated as skin red blood cell flux divided by mean arterial pressure. Local heating to 43.5°C at a rate of 0.1°C per second was performed on the two sites with the single-point laser Doppler probes 90 min into the 2 h normothermic recovery period to obtain maximal flux (Lorenzo & Minson, 2010; G. R. McCord et al., 2006). For these

sites, conductance values are also presented as a percentage of maximum cutaneous vascular conductance.

Carotid Baroreflex Assessments

Neck pressure was applied to assess carotid baroreflex function at baseline, at the end of the heating intervention, and every 30 minutes throughout the 2 h post-heating recovery period. Participants wore an external neck collar that enclosed the anterior two-thirds of the neck and was sealed against the mandible, collarbones, and sternum. The neck collar was connected to a bellows pressure controller (PPC-1000, Engineering Development Laboratory, Inc., Newport News, VA) and interfaced with custom software to deliver R-wave activated five-second bouts of 50 mmHg neck pressure. To minimize the influence of respiratory-induced changes in heart rate and blood pressure (Eckberg et al., 1980), each neck pressure stimulus was administered during a voluntary end expiration apnea. This apnea was maintained for 3 sec prior to neck pressure application, 5 sec during the neck pressure application, and the subsequent 7 sec after neck pressure application. This process was repeated 4-6 times to obtain high quality neck pressure applications at each time point. Each neck pressure application was preceded by 1 min of paced breathing at 0.25 Hz and consecutive neck pressure trials were separated by at least 1 min of paced breathing at 0.25 Hz (Buck et al., 2015; Pellinger & Halliwill, 2007).

During each neck pressure application, heart rate and beat-by-beat arterial blood pressure (Nexfin, BMEYE, Amsterdam, Netherlands) were continuously monitored at 250 Hz *(*Windaq*,* Dataq Instruments, Akron, OH). Brachial artery blood flow was measured via duplex ultrasonography (Phillips iE33 ultrasound with 9 MHz linear-array vascular probe, Andover, MA, USA) with an insonation angle of 60°. To ensure that brachial blood flow was reflective of arm blood flow and not flow through the arteriovenous anastomoses of the hand, a pressure cuff was placed around the wrist and inflated to 250 mmHg 1 min prior to ultrasound measurements. Measurements were made in the distal third of the upper arm, and placement locations were marked following baseline measurements to ensure that the same area was imaged for repeated measurements. A 5 sec B-mode recording was completed before each set of neck pressure trials and automated wall tracking software (Vascular Research Tools 5; Medical Imaging Applications LLC, Coralville, IA) was used to determine brachial artery diameter (cm) along the highest quality portion of this image. The retrograde and anterograde audio signal output from the Doppler ultrasound was Fourier transformed to generate a continuous analog signal of mean

blood velocity (cm/s). Brachial blood flow velocities were multiplied by artery cross-sectional area to determine brachial blood flow (mL/min). Brachial vascular conductance (mL/min/mmHg) was calculated by dividing brachial blood flow by mean arterial pressure.

Cardiac baroreflex responsiveness was evaluated as the peak heart rate response observed 1-7 sec after the onset of neck pressure, integrated carotid baroreflex responsiveness was evaluated as the peak mean arterial pressure response observed 2-9 sec after the onset of neck pressure, and peripheral vascular carotid baroreflex responsiveness was evaluated as the nadir of the brachial vascular conductance response observed 3-12 sec after the onset of neck pressure. Based on prior work conducted in both young and older individuals, these selected time windows likely encapsulated the peak responses to neck pressure application in both age groups (Fisher et al., 2009; Pellinger & Halliwill, 2007). Because changes in brachial vascular conductance with applied neck pressure were used as an index of peripheral vascular responsiveness, these values are presented as a percentage change from pre-neck pressure values. This presentation is consistent with prior work evaluating carotid baroreflex control of the vasculature (Buckwalter & Clifford, 2001; Keller et al., 2003, 2004).

Data and Statistical Analysis

Rectal temperature, heart rate, calf blood flow, and skin blood flow data was recorded at 250 Hz (Windaq, Dataq Instruments, Akron, OH) and skin temperature was recorded at 0.02 Hz (eTemperature, OnSolution Pty Ltd, NSW, AU). Average values for these variables were determined across two 5 min bins at baseline and across a single 2 min bin at the indicated time point during whole-body, passive heating or normothermic recovery. Statistical analyses were conducted using GraphPad Prism 10.1.0. Participant demographic data and experimental condition data are presented as means and standard deviations. All other data is presented as means and 95% confidence intervals. Baseline values for each variable and the absolute change in each variable with heat stress (calculated from baseline to the final measure during passive heating) were compared between age groups using unpaired, two-tailed *t* tests. Peak perceptual values during heat stress and average perceptual values across the 2 h post-heating recovery period are reported and were compared between age groups using unpaired, two-tailed *t* tests. A two-way (age X time) mixed model analysis of variance was used to examine the effects of passive heating and post-heating recovery on thermal, systemic cardiovascular, and carotid baroreflex function measures between young and older adults. *A priori* contrasts of age-time

combinations were examined within this relation and accordingly, we did not use a multiple comparisons adjustment when significant main or interaction effects of age and/or time into heating were detected. Statistical significance was accepted with $\alpha = 0.05$.

RESULTS

Participant Characteristics

Participant characteristics for the sixteen young (8 men, 8 women) and nine older individuals (3 men, 6 women) who participated in the study are presented in **Table 4.1**. Young and older individuals had similar estimated sweat losses during the experimental session [Y:0.7(0.5, 0.9) kg, O: 0.6(0.3, 0.9) kg, $P = 0.459$], which were equivalent to a sweat loss of 1.0(0.8, 1.3)% and 0.8(0.4, 1.2)% of initial body weight in young and older individuals, respectively ($P = 0.326$). Participants' perceived exertion ratings were "no exertion" at baseline [Y: 7(6, 7), O: 7(5, 9), $P = 0.425$], increased to "somewhat hard" during passive heating [peak values Y: 13(11, 15), O: 15(11, 18), $P = 0.413$], and retuned to baseline levels throughout post-heating recovery [average across 2 h recovery Y: 7(6, 7), O: 7(6, 8), $P = 0.114$]. Participants' thermal perception ratings were "neutral" at baseline [Y: 4(4, 5), O: 4(3, 4), $P = 0.194$], increased to "hot" during passive heating [Y: 7(7, 7), O: 7(7, 7), $P = 0.168$], and returned to "slightly cool" across post-heating recovery [average across 2 h recovery Y: 3(3, 4), O: 3(3, 4), $P = 0.829$] which did not differ from baseline values. Participants' ratings of skin wettedness were "neutral" at baseline [Y: 0(-1, 0), O: 0(-1, 0), $P = 0.706$], increased to "very wet" during passive heating [peak values Y: 3(2, 3), O: 3(3, 3), $P = 0.382$], and returned to baseline values across post-heating recovery [average across 2 h recovery Y: 0(0, 0), O: 0(0, 1), $P = 0.448$]. There were no differences in these perceptual responses between age groups.

Temperature

As displayed in **Figure 4.1**, there were no differences in skin temperature [Y: 34.2(34.0, 34.4)°C, O: 34.0(33.8, 34.3)°C, $P = 0.221$], core temperature [Y: 36.8(36.7, 37.0)°C, O: 36.7(36.5,37.0)°C, $P = 0.398$], or mean body temperature [Y: 36.6(36.5, 36.7)°C, O: 36.5(36.3, 36.7)°C, $P = 0.308$] between age groups at baseline. By the final measurements during passive heating (50 min), skin [Y: +3.6 (3.1, 4.1)°C, O: +4.3(3.6, 5.1)°C, $P = 0.089$), core temperature [Y: +0.8(0.7, 1.0)°C, O: +0.7(0.5, 0.9)°C, $P = 0.446$)], and mean body temperature [Y: +1.1(1.0, 1.2) °C, O: +1.1(1.0, 1.3)°C, $P = 0.834$)] were similarly elevated in young and older individuals.

By the end of 60 min of passive heating, core temperature reached 37.8(37.6, 38.0)°C in young and 37.8(37.5, 38.1)°C in older individuals (P = 0.925). While skin temperature returned to baseline values throughout the recovery period in both age groups, core and mean body temperature remained elevated through 120 min and 90 min of post-heating recovery in young and older individuals, respectively.

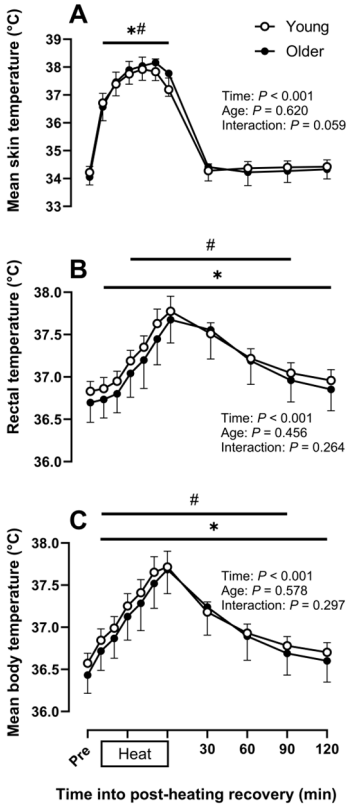

Figure 4.1 Mean skin, rectal, and body temperature at normothermic baseline (Pre), every 10 min during 60 min of passive heating, and every 30 min during 2 h of normothermic post-heating recovery in young (open circles, n = 16) and older individuals (filled circles, n = 9). Values are means ± 95% confidence intervals. Baseline values were compared between age groups using an unpaired t test. Data were analyzed using a two-way (age x time) mixed model analysis of variance; *P < 0.05 vs. baseline within young, $^{\#}P$ < 0.05 vs. baseline within older.

Central Hemodynamics

Central hemodynamic measures during whole-body, passive heating and normothermic recovery are presented in **Figure 4.2**. There were no differences in mean [Y: 85(82, 88) mmHg, O: 83(78, 88) mmHg, $P = 0.630$], systolic [Y: 115(112, 118) mmHg, O: 115(105, 125) mmHg, $P = 0.853$], or diastolic blood pressure [Y: 70(66, 74) mmHg, O: 68(63, 72) mmHg, $P = 0.425$] between age groups at baseline. Systolic blood pressure increased similarly during passive heating between age groups [Y: +7(3, 11) mmHg, O: +12(5, 20) mmHg, $P = 0.159$]. Diastolic blood pressure was reduced to a greater extent in young compared to older individuals [Y: -14(19, 10) mmHg, O: -3(6, 1) mmHg, $P = 0.001$]. As a result, mean arterial pressure was reduced with passive heating in young individuals, but maintained near baseline values in older individuals [Y: -7(11, 3) mmHg, O: +2(0, 4) mmHg, $P = 0.001$]. Mean arterial pressure remained similar to baseline through 90 min of post heating recovery in young individuals and 30 min of post-heating recovery in older individuals and was increased relative to baseline levels in both groups thereafter. This was due to increases in systolic blood pressure during post-heating recovery in young individuals at 120 min of recovery, while systolic and diastolic blood pressure were elevated above baseline values from 60 min and 90 min of recovery onward in older individuals, respectively.

Cardiac output [Y: 5.3(4.4, 6.2) L/min, O: 3.6(2.9, 4.3) L/min, $P = 0.009$] and systemic vascular conductance [Y: 63(53, 72) mL/min/mmHg, O: 44(34, 53) mL/min/mmHg, $P = 0.010$] were greater in young vs. older individuals at baseline, while heart rate [Y: 64(60, 68) bpm, O: 57(49, 65) bpm, $P = 0.071$] and stroke volume were similar between age groups [Y: 86(68, 104) mL, O: 66(48, 85) mL, $P = 0.127$]. Cardiac output [Y: +1.5(1.0, 2.0) L/min, O: +1.6(1.1, 2.2) L/min, $P = 0.738$] and systemic vascular conductance [Y: +25(19, 32) mL/min/mmHg, O: +19(11, 26) mL/min/mmHg, $P = 0.179$] increased similarly during passive heating between age groups, such that young individuals displayed a greater cardiac output and systemic vascular conductance than older individuals at all times. Cardiac output and systemic vascular conductance returned to baseline values throughout post-heating recovery in both age groups. Elevations in cardiac output with heating were supported by increases in heart rate in both young and older individuals [Y: +38(28, 49) bpm, O: +27(19, 35) bpm, $P = 0.128$]. Heart rate was elevated above baseline values 30 min into the post-heating recovery period in young individuals

but was similar to baseline values throughout recovery in older individuals. Stroke volume was reduced below baseline values in young individuals with heating [Y: -15(23, 8) mL], but was near baseline values in older individuals [O: -2(-15, +11) mL, $P = 0.052$]. Stroke volume was below baseline values 60 min into post-heating recovery in young individuals but was similar to baseline values throughout post-heating recovery in older individuals.

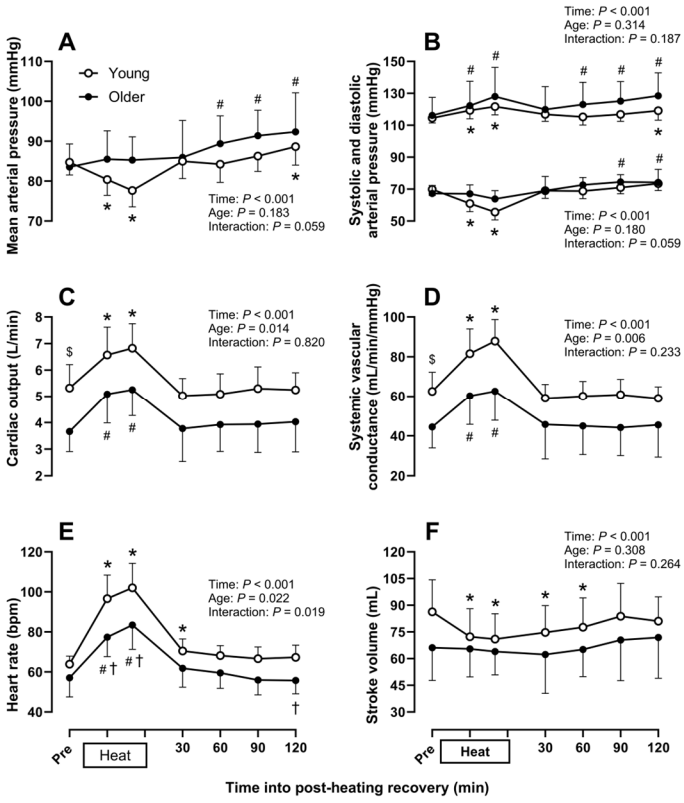

Figure 4.2 Mean (A), systolic (B), and diastolic (B) arterial pressure, cardiac output (C), systemic vascular conductance (D), heart rate (E), and stroke volume (F) at normothermic baseline (Pre) and every 30 min throughout 60 min of passive heating and 2 h of normothermic post-heating recovery in young (open circles, *n* = 16) and older individuals (filled circles, *n* = 9). Values are means ± 95% confidence intervals. Baseline values were compared between age groups using an unpaired *t* test; $^{\$}P < 0.05$ older vs. young at baseline. Data were analyzed using a two-way (age x time) mixed model analysis of variance; $^{*}P < 0.05$ vs. baseline within young, $^{\#}P < 0.05$ vs. baseline within older, $^{\dagger}P < 0.05$ older vs. young at indicated time point (interaction effect).

Calf and Skin Blood Flow

As depicted in **Figure 4.3**, calf blood flow [Y: 1.7(1.4, 2.0) mL/min/dL tissue, O: 1.1(0.6, 1.5) mL/min/dL tissue, $P = 0.010$] and vascular conductance [Y: 21(17, 24) mL/min/dL tissue/mmHg, O:13(7, 18) mL/min/dL tissue/mmHg, $P = 0.011$] were greater in young compared to older individuals at baseline. While increases in calf blood flow [Y: +3.0(2.3, 3.7) mL/min/dL tissue, O: +2.0(1.3, 2.6) mL/min/dL tissue, $P = 0.038$] and vascular conductance [Y: +41(32, 50) mL/dL tissue/mmHg, O: +23(13, 32) mL/dL tissue/mmHg, $P = 0.012$] were attenuated in older compared to young individuals during heating, these values returned to baseline values throughout post-heating recovery in both age groups. As depicted in **Figure 4.4** (Panel A)**,** cutaneous vascular conductance assessed using the integrated laser Doppler probes was similar between age groups at baseline [Y: 0.20(0.15, 0.24) a.u, O: 0.21(0.15, 0.26) a.u., $P = 0.689$], increased more with passive heating in young vs. older individuals [Y: +1.39(1.01, 1.78) a.u., O: +0.81(0.60, 1.02) a.u., $P = 0.031$], and returned to baseline values throughout post-heating recovery in both age groups. Cutaneous vascular conductance assessed using the single point laser Doppler probes (**Figure 4.4**, Panel B and C) housed within local heating units followed a similar pattern at baseline and throughout heating and post-heating recovery. When these conductance values were expressed as a percentage of maximum cutaneous vascular conductance, the increase in cutaneous vascular conductance during passive heating did not differ between age groups [Y: +33(28, 39)% CVCmax, O: +30(13, 46)% CVCmax, $P = 0.556$].

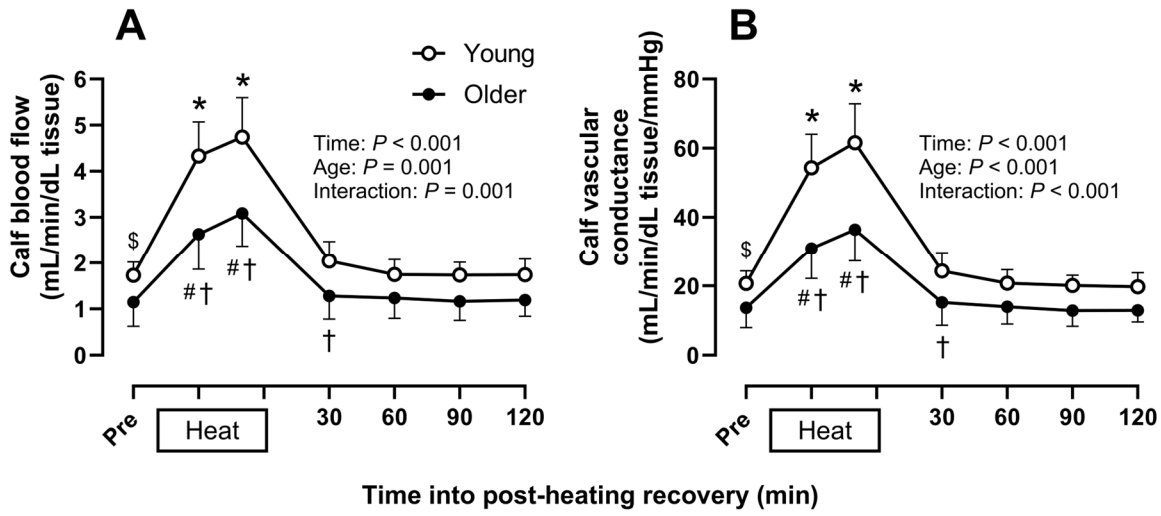

Figure 4.3 Calf blood flow (A) and vascular conductance (B) at normothermic baseline (Pre) and every 30 min throughout 60 min of passive heating and 2 h of normothermic post-heating recovery in young (open circles, *n* = 16) and older individuals (filled circles, *n* = 9). Values are means ± 95% confidence intervals. Baseline values were compared between age groups using an unpaired *t* test; $^{\$}P < 0.05$ older vs. young at baseline. Data were analyzed using a two-way (age x time) mixed model analysis of variance; $^{*}P < 0.05$ vs. baseline within young, $^{\#}P < 0.05$ vs. baseline within older, $^{\dagger}P < 0.05$ older vs. young at indicated time point (interaction effect).

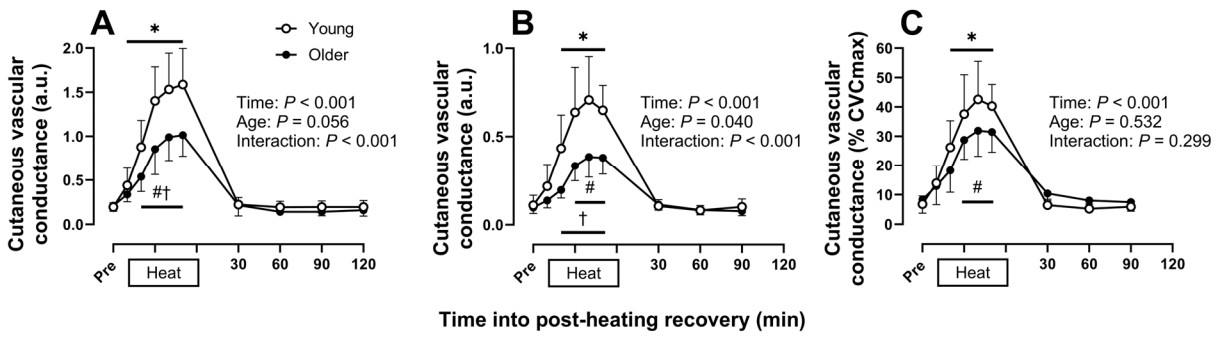

Figure 4.4 Calf cutaneous vascular conductance via integrated (A) and single point probes (B), and percent of maximal cutaneous vascular conductance via single point probes (C) at normothermic baseline (Pre), every 10 min throughout 60 min of passive heating, and every 30 min throughout normothermic post-heating recovery in young (open circles, *n* = 16) and older individuals (filled circles, *n* = 9). Values are means ± 95% confidence intervals. Due to technical challenges, maximal cutaneous vascular conductance was not obtained in one older participant (Panel C: *n* = 8 older). Baseline values were compared between age groups using an unpaired *t* test. Data were analyzed using a two-way (age x time) mixed model analysis of variance; **P* < 0.05 vs. baseline within young, #*P* < 0.05 vs. baseline within older, †*P* < 0.05 older vs. young at indicated time point (interaction effect).

Carotid Baroreflex Function

Table 4.2 displays the prevailing brachial blood flow and vascular conductance during the 3 sec end-expiratory breath hold immediately preceding neck pressure applications at each time point. **Figure 4.5** displays the heart rate, brachial vascular conductance, and blood pressure responses to simulated hypotension via applied neck pressure. Cardiac responses to neck pressure were attenuated in older compared to young individuals at baseline [Y: +7(5, 9) bpm, O: +1(0, 2) bpm, *P* < 0.001] and across all heating and post-heating recovery time points. Cardiac responses to neck pressure did not differ from baseline values at the end of passive heating [Y: +4(2, 6) bpm, O: 1(-1, 2) bpm, *P* = 0.052] or throughout post-heating recovery in young or older individuals. The brachial vascular response to neck pressure was attenuated in older compared to young individuals at baseline [Y: -28(19, 38)%, O: -14(5, 22)%, *P* = 0.035] and across all heating and post-heating recovery time points. The brachial vascular response to neck pressure was attenuated at the end of passive heating in young but not older individuals [Y: -12(8, 17)%, O: -

14(6, 21)%, $P = 0.753$] and did not differ from baseline values throughout post-heating recovery in either age group. Blood pressure responses to neck pressure were similar between age groups at baseline [Y: +5(2, 8) mmHg, O: +2(0, 5) mmHg, $P = 0.161$] and did not differ from baseline values at the end of passive heating [Y: +6(4, 8), O: 4(0, 8) mmHg, $P = 0.178$] or throughout post-heating recovery.

Table 4.2 Brachial blood flow and vascular conductance in young and older adults during passive heating and post-heating recovery.

Variable		Baseline	End of heating	Time into post-heating Recovery			
				30 min	60 min	90 min	120 min
Brachial blood flow	Young	46 (30,62)	153 (104,203)*	46 (36,57)	51 (35,66)	49 (32,66)	50 (30,70)
mL/min	Older	42 (28,55)	114 (70,159)$^{\#}$	49 (37,61)	43 (28,57)	47 (30,64)	42 (31,54)
Brachial vascular conductance	Young	0.53 (0.35,0.71)	2.25 (1.52,2.98)*	0.59 (0.44,0.73)	0.59 (0.40,0.78)	0.57 (0.37,0.76)	0.55 (0.35,0.75)
mL/min/mmHg	Older	0.48 (0.36,0.60)	1.84 (1.06,2.61)$^{\#}$	0.63 (0.44,0.81)	0.48 (0.32,0.64)	0.49 (0.32,0.65)	0.43 (0.34,0.52)

Brachial blood flow and vascular conductance at baseline, at the end of passive heating, and every 30 min throughout 2 h of normothermic recovery in young ($n = 16$) and older individuals ($n = 9$). Values are means ± 95% confidence intervals. Due to technical challenges, data was not obtained in one older participant at 60 and 90 min into post-heating recovery. Baseline values were compared between young and older adults using an unpaired *t* test. Data were analyzed using a two-way (age x time) mixed model analysis of variance, *$P < 0.05$ vs. baseline within young, $^{\#}P < 0.05$ vs. baseline within older.

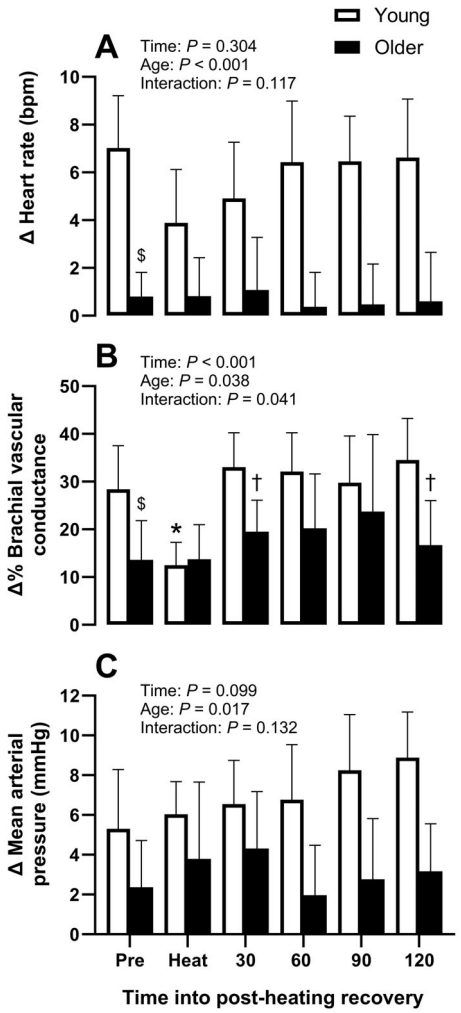

Figure 4.5 Cardiac (A), brachial vascular (B), and blood pressure (C) responses to 50 mmHg neck pressure at normothermic baseline (Pre), at the end of 60 min of passive heating, and every 30 min throughout 2 h of normothermic post-heating recovery in young (open bars, *n* = 16) and older individuals (filled bars, *n* = 9). Values are means ± 95% confidence intervals. Due to technical challenges cardiac, brachial vascular, and blood pressure responses were not obtained in one older participant at 60 and 90 min into post-heating recovery, and brachial vascular responses were not obtained in one older participant at baseline and one older participant the end of heating. Baseline values were compared between age groups using an unpaired *t* test; $^{\$}P < 0.05$ older vs. young at baseline. Data were analyzed using a two-way (age x time) mixed model analysis of variance; $^{*}P < 0.05$ vs. baseline within young, †$P < 0.05$ older vs. young (interaction effect).

DISCUSSION

Non-pharmacological lifestyle interventions such as weight loss, dietary sodium reduction, and physical exercise are a fundamental piece of the current approach to blood pressure management and recommended as a preventative measure, first-line treatment approach, and/or adjunctive treatment to individuals across all blood pressure classification criteria (American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, 2018). Within this context, heat therapy has emerged as a promising non-pharmacological therapeutic option to improve cardiovascular health and reduce blood pressure (Pizzey et al., 2021). Some of the benefits of heat therapy on blood pressure may be mediated during the recovery period which follows a single session of whole-body heat exposure. Specifically, many (Engelland et al., 2020b; Francisco et al., 2021; Laukkanen et al., 2017; Neff et al., 2016; Romero, Gagnon, et al., 2017; Thomas et al., 2017), but not all (Amin et al., 2022; Engelland et al., 2020a; Gravel et al., 2019; Hemingway et al., 2023; Richey et al., 2022), studies have demonstrated that a single session of heat stress promotes a sustained reduction in blood pressure or "post-heating hypotension." Much like post-exercise hypotension, post-heating hypotension could act to provide a meaningful "daily dose" of blood pressure reduction or mediate chronic reductions in blood pressure with regular heat therapy.

Despite the promise of post-heating recovery as a potentially valuable "window of opportunity"(Luttrell & Halliwill, 2015) in promoting blood pressure management, very little is known about the systemic cardiovascular and neurovascular mechanisms which support blood pressure regulation during recovery from passive heat stress. Furthermore, as age importantly modifies the thermoregulatory and cardiovascular responses to acute heat stress and older individuals may stand to gain the greatest benefit of post-heating reductions in blood pressure, it is scientifically and clinically important that investigations into the post-heating recovery period are conducted in both young and older individuals. Therefore, the purpose of this study was to characterize and compare the systemic cardiovascular and carotid baroreflex support of blood pressure during recovery from whole-body, passive heating in young and older individuals.

The primary finding from this study was that, contrary to our hypothesis, a single session of whole-body, passive heat stress did not promote a sustained reduction in blood pressure or "post-heating hypotension" in young or older individuals. Furthermore, the systemic cardiovascular and baroreflex responses which accompanied acute heat stress were transient and

did not persist beyond 1 h of post-heating recovery in young or older individuals despite continued elevations in core temperature.

Influence of Age on Acute Responses to Heat Stress

While this study did not aim to re-examine the age-related differences in the cardiovascular response to passive heating, a brief discussion of this topic is warranted in the capacity that these age-related differences have the potential to persist into or otherwise modify blood pressure regulation in the post-heating recovery period.

In the present study, passive heating increased skin, core, and mean body temperature similarly between age groups and the average peak change in in skin (+4.1°C), core (+1.0°C), and mean body temperature (+1.2°C) was well within the range reported by previous studies using the water perfused suit heating modality in young and older individuals over this time course (Fischer et al., 2022; Gagnon et al., 2015; Lucas et al., 2015). The heating intervention in this study promoted a large increase in calf cutaneous vascular conductance which was attenuated among older compared to young individuals. As muscle blood flow likely did not change appreciably within the uncovered calf during heating (Heinonen et al., 2011), age-related differences in cutaneous vasodilation likely mediated the attenuated increase in calf blood flow and vascular conductance observed among older individuals with heating. This is consistent with prior work which has noted attenuated increases in skin blood flow among older individuals during passive heat stress and is thought to be a consequence of age-related cutaneous microvessel remodeling, impairments in active vasodilation (Holowatz et al., 2003, 2005, 2006, 2010), attenuated efferent skin sympathetic nerve activity (Greaney et al., 2020; Stanhewicz et al., 2016), and an attenuated chronotropic and/or inotropic response of the aged heart to thermal stress (Gagnon et al., 2017; Gravel, Chaseling, et al., 2021; Greaney et al., 2015; Kenney et al., 2014; Minson et al., 1998).

Despite the attenuated cutaneous vascular responses to passive heating observed among older individuals, young and older adults displayed similar increases in systemic vascular conductance and cardiac output. In contrast, previous studies have noted that increases in cardiac output are reduced ~50% in older vs. young individuals during passive heating (Gagnon et al., 2016, 2017; Greaney et al., 2015; Minson et al., 1998). While an explanation for these differences is unclear, it is possible that the discrepancies could result from differing degrees of thermal loading or cardiovascular stress imparted by heating or differences in the physical

characteristics of the older individuals studied. Indeed, among a cohort of physically active older adults similar to that of the present study, Lucas et al. found that young and older individuals demonstrated similar increases in cardiac output (Δ cardiac output young: 1.9 L/min, older: 1.5 L/min) during whole-body, passive heating (Δ intestinal temperature ~1°C). While the similar increase in cardiac output with passive heating among young and older individuals we observed was unexpected, it afforded this investigation the unique opportunity to compare post-heating recovery responses between age groups following heat stress matched for both thermal loading and cardiovascular demand.

The increases in cardiac output with heating were mediated differently between age groups. In young individuals, increases in cardiac output were supported by increases in heart rate as stroke volume was decreased by ~15 mL with passive heating. In contrast, older individuals displayed attenuated increases in heart rate during passive heating compared to young individuals, but stroke volume was well maintained. The attenuated heart rate responses to heating among older individuals noted in the present study are consistent with most (Gagnon et al., 2016, 2017; Greaney et al., 2015; Lucas et al., 2015), but not all (Lucas et al., 2015; Minson et al., 1998), prior work. Proposed mechanisms contributing to this attenuated chronotropic response among older individuals include an age-related attenuation of parasympathetic withdrawal (J. A. Taylor et al., 1995), a lower intrinsic heart rate (Christou & Seals, 2008), or reduced adrenergic responsiveness of cardiac pacemaker cells (Ford & James, 1994); although the latter mechanism has recently been challenged (Fischer et al., 2022). In contrast with the present study, previous work has demonstrated that stroke volume is well maintained or slightly increased during passive heating in young individuals (Brothers et al., 2009; Bundgaard-Nielsen et al., 2010; Wilson et al., 2009; Wilson & Crandall, 2011). Furthermore, the ability to maintain or increase stroke volume during passive heat stress is typically either preserved (Gagnon et al., 2016, 2017; Greaney et al., 2015; Lucas et al., 2015) or reduced (Fischer et al., 2022; Minson et al., 1998) among older individuals. As cardiac inotropic function was not likely reduced among young individuals, the reduction in stroke volume observed among young individuals during heating likely reflects a reduction in central venous pressure. Exaggerated reductions in central venous pressure among young vs. older individuals during passive heating could be due to greater peripheral displacement of blood volume within the compliant cutaneous circulation or greater intravascular volume loss secondary to exaggerated sweat losses. Although we did not

assess sweat rate or changes in blood or plasma volume, young and older individuals were matched for hydration status at the beginning of the heating intervention (urine specific gravity Y: 1.016(1.011, 1.021), O: 1.017(1.011, 1.023), $P = 0.865$), were provided the same amount of water to drink during the heating (3 mL/kg body weight; Y: 208(183, 231) mL, O: 215(170, 261) mL, $P = 0.715$), and had similar estimated sweat losses over the course of the experimental visit.

These central and peripheral cardiovascular responses culminated in a ~7mmHg reduction in mean arterial pressure during heating among young individuals due to a pronounced reduction in diastolic blood pressure, while mean arterial pressure was well maintained in older individuals during heating. While prior studies have noted that mean arterial pressure is either maintained or reduced during passive heating, directionally similar pressure responses are typically seen in studies directly comparing the cardiovascular response to passive heating between age groups (Gagnon et al., 2016, 2017; Greaney et al., 2015; Lucas et al., 2015; Minson et al., 1998).

Post-Heating Recovery

The re-circulation of 34°C water allowed skin temperature to return to baseline levels during post-heating recovery, but the elevations in core temperature persisted into the post-heating recovery such that core temperature was elevated by ~0.7°C 30 min into post-heating recovery and ~0.4°C 60 min into post-heating recovery. After 90 min of post-heating recovery, core temperature was within ~0.1-0.2°C of baseline values in both young and older individuals. Similarly, previous studies conducted in both young and older individuals have noted elevations in core temperature which persist for at least 30 min and up to 80 min into the post-heating recovery period (Amin et al., 2020).

Central Hemodynamics

Contrary to our hypothesis, the current study provided no evidence of a sustained reduction in blood pressure or "post-heating hypotension" during recovery from whole-body, passive heat stress as mean arterial pressure returned to baseline within 30 min of post-heating recovery in both young and older individuals. Previous studies have produced conflicting findings with respect to the blood pressure responses following passive heating; reports of a maintenance (Amin et al., 2022; Engelland et al., 2020a; Gravel et al., 2019; Richey et al., 2022), increase (Hemingway et al., 2023), and decrease (Engelland et al., 2020b; Francisco et al., 2021; Laukkanen et al., 2017; Neff et al., 2016; Romero, Gagnon, et al., 2017; Thomas et al., 2017) in

blood pressure following passive heating have all been noted. In the same way that the profile of post-exercise hypotension is influenced by exercise, recovery, and participant characteristics (Brito et al., 2014; Halliwill, 2001; Halliwill et al., 2013; M. J. Kenney & Seals, 1993; MacDonald, 2002), it is possible that some aspect of the overall study design was not optimal in promoting the sustained post-heating hypotension which has been demonstrated previously. An interesting avenue for future research would be to investigate if there are heating modality (proportion of body surface area heated, increased hydrostatic pressure with water immersion), thermal threshold (skin, muscle, or core temperature), recovery (environmental or skin temperature, posture), or population specific (hypertensive vs. normotensive, men vs. women) attributes which are requisite in promoting a sustained reduction in blood pressure following passive heating. Interestingly, mean arterial pressure was elevated above baseline levels at 120 min of recovery in young individuals and from 60 min of recovery onward in older individuals. These elevated-post-heating blood pressure measurements may reflect the confounding influence of an increased level of participant arousal (due to the many measurements) or could reflect the circadian blood pressure rhythm as, on average, baseline blood pressures were conducted between ~1000-1100 and post heating recovery began ~1230.

Alongside the recovery of mean arterial pressure, cardiac output returned to baseline levels within 30 min of post-heating recovery in both young and older individuals and did not differ from baseline levels thereafter. While Romero et al. demonstrated sustained elevations in cardiac output 30 min into post-heating recovery in young individuals (Romero, Gagnon, et al., 2017), other studies have demonstrated a return of cardiac output to baseline values within 30 min of post-heating recovery in young and older individuals (Engelland et al., 2020b; Francisco et al., 2021; Romero, Gagnon, et al., 2017). At 30 min of post-heating recovery, cardiac output was maintained in young individuals by elevations in heart rate as stroke volume remained below baseline levels. In contrast, heart rate and stroke volume did not differ from baseline levels throughout post-heating recovery in older individuals. Previous studies have similarly demonstrated post-heating elevations in heart rate in young individuals (Francisco et al., 2021; Romero, Gagnon, et al., 2017). These elevations may stem from the direct effects of increased temperature on cardiac pacemaker cells and/or altered autonomic modulation of heart rate (Gorman & Proppe, 1984; J. M. Johnson & Proppe, 1996). The absence of post-heating elevations in heart rate among older individuals has been demonstrated by some (Gravel,

Behzadi, et al., 2021; Laukkanen et al., 2017; Richey et al., 2022; Romero, Gagnon, et al., 2017), but not all previous work (Engelland et al., 2020b; Gravel et al., 2019), and could be due to an attenuated thermal sensitivity, altered sympathovagal control of the aged heart during post-heating recovery, or as demonstrated in this study, could simply reflect a preservation of stroke volume following heating among older individuals which negates the demand for increases in heart rate to maintain cardiac output.

Peripheral Hemodynamics

The present study provided no evidence of sustained vasodilation during recovery from whole-body, passive heat stress as systemic vascular conductance, calf vascular conductance, and calf cutaneous vascular conductance returned to baseline levels within 30 min of post-heating recovery and did not differ from baseline levels thereafter in both young and older individuals. While this finding contrasts with prior work demonstrating elevations in directly heated limb blood flow and vascular conductance 30 min into post-heating recovery (Engelland et al., 2020b; Romero, Gagnon, et al., 2017; Thomas et al., 2017) and beyond (Amin et al., 2022; Gravel, Chaseling, et al., 2021), it is consistent with Francisco et al. in which brachial blood flow and vascular conductance within an indirectly heated arm remained elevated for 20 min of post-heating recovery but returned to baseline levels thereafter (Francisco et al., 2021). Our finding of a prompt recovery of skin blood flow to baseline levels contrasts with Amin et al. which noted sustained elevations in forearm skin blood flux 80 min following 30 min of chest-level hot water immersion (Amin et al., 2022). The discrepancy between these findings may relate to different degrees of thermal loading imparted during heat stress (Δ core temperature +1.0°C in the present study vs. +1.5°C in Amin et al.), the confounding influence of elevated hydrostatic pressure during passive heating (supine heating via water perfused suit in the present study vs. hot water immersion in Amin et al.), or skin blood flow assessment location (lateral calf in the present study vs. ventral forearm in Amin et al.).

It warrants mention that the recovery of skin blood flow in both age groups occurred amidst the pronounced elevations in core temperature which were evident 30 min into the post-heating recovery period. This profile is reminiscent of a post-exercise thermoregulatory profile in which heat loss responses are suppressed upon the cessation of exercise and promote sustained post-exercise elevations in core and muscle temperature (Kenny et al., 2000, 2008; Thoden et al., 1994). While no studies to our knowledge have characterized thermoeffector function which may

contribute to thermal recovery following whole-body heat stress, this remains an interesting area for future research.

Carotid Baroreflex Function

Because blood pressure is tightly regulated by the baroreflex, the sustained reductions in blood pressure during recovery from whole-body, passive heat stress noted by previous studies could result from altered baroreflex support of blood pressure during the post-heating recovery period. Along these lines, Engelland and colleagues previously noted that both blood pressure and radial sympathetic nerve activity were depressed 30 min following 45 min of leg heating among older individuals (Engelland et al., 2020b). While it has been proposed that these findings suggest a resetting of baroreflex function to reduced blood pressures and levels of sympathetic activity following heating, these adjustments could also be the result of attenuated baroreflex responsiveness to changes in pressure. Importantly, no study to date has evaluated baroreflex function in the post-heating recovery period. To fill this gap in knowledge, we evaluated the heart rate, brachial vascular, and blood pressure responses to simulated hypotension via applied neck pressure and utilized these responses as indices of carotid baroreflex control of the heart, peripheral vasculature, and integrated support of blood pressure.

While the prevailing heart rate, brachial vascular conductance, and blood pressure did not differ between age groups at baseline, older individuals displayed attenuated cardiac and vascular responses to simulated hypotension compared to young individuals at baseline and across the experimental protocol. These blunted responses culminated in a tendency for a reduced integrated carotid baroreflex support of blood pressure across the experimental protocol, although this was not statistically significant at baseline due to high level of variability in this relatively small response. Numerous studies have similarly demonstrated reductions in carotid baroreflex function with advancing age (Fisher et al., 2009, 2010; Lindblad, 1977), a phenomenon which is believed to reflect age-related impairments in the afferent, central processing, and efferent arms of the baroreflex (Monahan, 2007).

Carotid baroreflex control of heart rate was shifted upward during passive heating in young and older individuals, but remained elevated for the first 30 min of post-heating recovery in young individuals only. In both young and older individuals, the heart rate responses to neck pressure were unaltered during passive heating and throughout post-heating recovery. This finding is consistent with Krnjajic et al. which demonstrated that the peak heart rate response

across varying levels of neck pressure (+15-45 mmHg) was preserved during passive heating (Δ core temperature ~1°C) (Krnjajic et al., 2016).

Carotid baroreflex control of the vasculature was shifted upward to the prevailing increase in vascular conductance during passive heating in both young and older individuals, while the vascular responses to neck pressure were attenuated in young but not older individuals. Scremin and Kenney previously evaluated the forearm vascular conductance response to varying levels of lower body negative pressure among young and older men in different thermal conditions (normothermic, cold, and heat stress) (Scremin & Kenney, 2004). Although the study did not aim to compare vascular responses between thermal conditions, they demonstrated that lower body negative pressure (-30 mmHg) reduced forearm vascular conductance by ~47% in young and ~ 33% in older men under thermoneutral conditions and by ~42% in young and ~19% in older men during heat stress (Δ sublingual temperature 0.9°C). These general trends support our observation of attenuated brachial vascular responses to carotid baroreflex unloading in young vs. older individuals and our observation of attenuated brachial vascular responses to carotid baroreflex unloading during passive heating vs. normothermia among young individuals. However, in contrast with our findings, the heating-induced attenuation of vascular responses to baroreceptor unloading was present among both young and older men studied by Scremin and Kenney. Although an explanation for this discrepancy is unclear, it could relate to the different participant populations studied (men and women in the present study vs. men only in Scremin and Kenney) or baroreceptor populations interrogated (carotid baroreceptors in the present study vs. sinoaortic baroreceptors in Scremin et al).

The attenuated vascular responses to neck pressure during passive heating in young individuals could reflect a shift in limb blood flow distribution from the skeletal muscle circulation at normothermic baseline, which is tightly controlled by the carotid baroreflex (O'Leary et al., 1991), to the cutaneous circulation during passive heating which may (Keller, Davis, et al., 2006) or may not (Crandall et al., 1996) be responsive to carotid baroreceptor unloading. Alternatively, the vascular responses to neck pressure may have been reduced during passive heating among young individuals due to an increased competitive influence of local vasodilators within either the cutaneous or skeletal muscle circulation. Along these lines, nitric oxide, which plays a role in mediating cutaneous vasodilation during both local and whole-body heat stress (Kellogg et al., 1998, 1999; Minson et al., 2001; Shastry et al., 1998), contributes to

attenuated cutaneous adrenergic responsiveness during hyperthermia (Shibasaki et al., 2007, 2008). The absence of this heating-induced attenuation in vascular responses to neck pressure among older adults could reflect a reduced relative distribution of blood volume within the cutaneous circulation and/or a reduced competitive influence of local vasodilating factors within the skin and/or skeletal muscle circulations. This is consistent with the attenuated increases in calf and cutaneous vascular conductance observed during hyperthermia among older individuals and the well-established age-related decline in cutaneous active vasodilation (Holowatz et al., 2003, 2006a; Kenney, 1988). Despite the age-related differences during passive heating, brachial vascular responses to simulated hypotension returned to baseline levels throughout post-heating recovery in both young and older individuals. This is consistent with Engelland et al. which demonstrated that sympathetic vascular transduction, assessed as the relation between sympathetic nerve activity and leg vascular conductance during isometric handgrip, did not differ from baseline levels 30 min following of 45 min of leg heating in both young and older individuals (Engelland et al., 2020b).

Integrated carotid baroreflex support of blood pressure was shifted downward to lower prevailing blood pressures during passive heating among young individuals, while mean arterial pressure was maintained during heating in older individuals. In both young and older individuals, the blood pressure responses to neck pressure were unaltered during passive heating and throughout post-heating recovery. The preservation of blood pressure responses to neck pressure during passive heating among young individuals was somewhat surprising given the simultaneously attenuated brachial vascular responses and relatively reduced, although not significantly lower, cardiac responses and could reflect maintained or enhanced vascular responsiveness within other regional circulations (e.g., splanchnic or renal) (Minson et al., 1999). Similarly, Krnjajic et al. reported that passive, whole-body heating (Δ core temperature ~1°C) did not alter the maximum gain of carotid baroreflex control of blood pressure or the peak change in mean arterial pressure across varying levels of 5 sec applications of neck pressure (+15-45 mmHg) (Krnjajic et al., 2016).

Experimental Considerations

We evaluated carotid baroreflex function in this study using the neck pressure technique as it allowed us to conduct assessments of cardiac, peripheral vascular, and integrated baroreflex responsiveness over a short time course (each set of neck pressure trials took ~10 min) and in a

repeated fashion. These advantages permitted the characterization of the dynamic changes in baroreflex function across heating and post-heating recovery which has been largely overlooked by previous studies evaluating the post-heating recovery period at a single time point. However, despite these advantages, several methodological considerations warrant mention. First, because baroreflex mediated responses are often asymmetrical between falling and rising blood pressure stimuli (Eckberg, 1980a), our limited assessment of cardiac, vascular, and blood responses to neck pressure (simulated hypotension) may not adequately describe baroreflex responses to rising pressure stimuli (neck suction, simulated hypertension). Moreover, as we did not utilize various neck pressure/suction combinations and construct carotid baroreflex function curves, our results cannot be used to derive parameters which explain baroreflex function across its entire operating range (e.g., sensitivity, centering point, responding range, threshold). Finally, while men and women are equally represented within the younger age group studied, more women (n = 6) than men (n = 3) comprise the older age group in the current data set. We intend to minimize this limitation in the future by studying additional male participants aged 60-75. Despite this intention, it is a possibility that some of differences currently noted between age groups were unduly influenced by the underrepresentation of men among the older cohort. While sex *per se* is not thought to precipitously alter the systemic circulatory responses to passive heating (Meendering et al., 2005), it is presently unknown if the baroreflex responses to passive heat stress differ between sexes, if advancing age modifies these responses in a sex-dependent manner, and if so, how these differences impact the post-heating recovery profile.

Conclusions

In conclusion, this study presents novel data displaying the time course of thermal, systemic cardiovascular, and neurovascular recovery from whole-body, passive heat stress in young and older individuals. Contrary to our hypothesis, we found no evidence of a sustained reduction in blood pressure during post-heating recovery, and the systemic cardiovascular and baroreflex responses which accompanied acute heat stress were transient and did not persist beyond 1 h of post-heating recovery in young or older individuals. While these findings do not support the notion that the post-heating recovery period, like the post-exercise recovery period, promotes robust and sustained alterations in the systemic cardiovascular and baroreflex support of blood pressure, future studies are warranted to determine if heating modality, recovery, or participant characteristics influence the expression of the post-heating recovery profile.

CHAPTER V

CONCLUSIONS

Since Fitzgerald's early observation that his daily jogs improved his own labile hypertension (Fitzgerald, 1981), decades of research have established the post-exercise recovery period as a discrete physiological phenomenon distinct from both the stressed and rested state which promotes clinically relevant reductions in blood pressure, is marked by alterations in both central and peripheral cardiovascular control, and plays an important role in potentiating adaptation to exercise training. As highlighted by Luttrell and Halliwill, this collective knowledge has allowed the post-exercise recovery period to emerge as a valuable "window of opportunity" during which risk factors in many disease states can be attenuated and beneficial cardiovascular adaptation may be mediated (Luttrell & Halliwill, 2015). However, despite the integral nature of the recovery period to any given stress response and the demonstrated value of these investigations within the context of exercise stress, our understanding of the physiology of recovery remains in its relative infancy with respect to the various stresses encountered by humans.

This dissertation examines the post-stress recovery period from a new perspective: heat stress. Much like exercise, heat stress is a profound thermoregulatory, cardiovascular, and autonomic stressor which may act through shared and unique mechanisms to promote a similarly distinct and valuable post-stress recovery period. Indeed, many (Engelland et al., 2020b; Francisco et al., 2021; Laukkanen et al., 2017; Neff et al., 2016; Romero, Gagnon, et al., 2017; Thomas et al., 2017), but not all (Amin et al., 2022; Engelland et al., 2020a; Gravel et al., 2019; Hemingway et al., 2023; Richey et al., 2022), studies have demonstrated that a single session of heat stress promotes a sustained reduction in blood pressure or "post-heating hypotension." Like post-exercise hypotension, post-heating hypotension may contribute to cardiovascular health improvement by transiently lowering elevated blood pressure into normotensive ranges and may potentiate chronic blood pressure reductions with regular heat therapy (Roxburgh et al., 2023).

Despite the promise of the post-heating recovery period as a mediator of beneficial cardiovascular adaptation, very little is known about the systemic cardiovascular and neurovascular mechanisms which support blood pressure regulation in the post-heating recovery period. Furthermore, as advancing age increases the prevalence of hypertension and alters the thermoregulatory and cardiovascular responses to acute heat stress, it is clinically and

scientifically important that investigations into the post-heating recovery period are conducted in both young and older individuals. Therefore, the overarching purpose of this dissertation was to characterize and compare the systemic cardiovascular and carotid baroreflex support of blood pressure following whole-body, passive heat stress in young and older individuals.

We tested the hypothesis that the post-heating recovery period is accompanied by sustained hypotension, elevations in cardiac output and heart rate, and vasodilation; and that the magnitude of this blood pressure reduction would be exaggerated among older adults due to a diminished post-heating elevation of cardiac output and heart rate. Lastly, we hypothesized that the peripheral vascular response to simulated hypotension via applied neck pressure would be attenuated while cardiac and integrated carotid baroreflex responsiveness would be preserved during the post-heating recovery period. The primary finding from this study was that, contrary to our hypothesis, a single session of whole-body, passive heat stress did not promote a sustained reduction in blood pressure or "post-heating hypotension" in young or older individuals. Furthermore, the systemic cardiovascular and baroreflex responses which accompanied acute heat stress were transient and did not persist beyond 1 h of post-heating recovery in young or older individuals despite continued elevations in core temperature. While these findings do not support the notion that the post-heating recovery period, like the post-exercise recovery period, promotes robust and sustained alterations in the systemic cardiovascular and baroreflex support of blood pressure, our novel characterization of the time course of thermal, systemic cardiovascular, and neurovascular recovery from whole-body, passive heat stress in young and older individuals fills gaps in knowledge as we begin to understand the post-heating recovery profile and highlights important considerations and key avenues for future research.

IMPLICATIONS AND FUTURE DIRECTIONS

The notable absence of post-heating hypotension in the present study combined with the largely conflicting findings surrounding the presence and absence of the post-heating hypotension reported in the literature suggests that post-heating hypotension is not a robust and highly reproducible phenomenon across heating modalities, recovery characteristics, and participant populations. While we feel it is premature to conclude that post-heating hypotension does not occur given the dearth of studies evaluating blood pressure regulation in the post-heating recovery period, the highly variable methods employed, and the conflicting findings

yielded, our negative results highlight the need for additional research to determine if there are heating modality (proportion of body surface area heated, changes in hydrostatic pressure with water immersion), thermal threshold (skin, muscle, or core temperature), recovery (environmental or skin temperature, posture), or population specific (hypertensive vs. normotensive, men vs. women) attributes which are requisite in promoting a sustained reduction in blood pressure following passive heating. This research would parallel the considerable body of work devoted to exploring the effect of exercise modality, intensity, and duration on the magnitude and duration of post-exercise hypotension (Pescatello, 2005). Moreover, in the same way that we have defined the FITT (Frequency, Intensity, Time, Type) principles with respect maximizing the beneficial adaptations which accompany exercise training (Pescatello, Franklin, et al., 2004), a key unanswered question within the growing body of research on heat therapy, is whether an optimal dose of heat exposure exists which maximizes cardiovascular benefit. We propose that that an improved understanding of the post-heating recovery period and the heating modality, thermal loading, population, and recovery characteristics which modify it are an important consideration in addressing this question. Alternatively, if it is determined that acute heat stress does not consistently yield a post-stress hypotensive response, this is a crucial piece of information which should inform the overall clinical utility of heat therapy as a cardiovascular therapeutic option.

Another challenge within this field is that previous examinations of the post-heating recovery period in young vs. older individuals have conducted assessments at a single time point: 30 min into post-heating recovery (Engelland et al., 2020b; Romero, Gagnon, et al., 2017). While these studies offered a valuable snapshot of blood pressure regulation in the post-heating recovery period, this picture was incomplete and did not describe the dynamic changes which may occur throughout the post-heating recovery period and the total duration of these responses. The integrative, repeated measures, and prolonged nature of the present study sought to address this gap in knowledge. We demonstrated that core temperature progressively declined between 30- and 60-min of recovery but was relatively stable within ~0.1-0.2°C of baseline values thereafter. Along these lines, the elevations in heart rate and reductions in stroke volume which accompanied heating in young individuals persisted 30-60 min into the post-heating recovery period and recovered thereafter. Moreover, from 60 min of recovery onward we observed paradoxical responses as blood pressure increased in young and older individuals. As a whole,

this data demonstrates that the physiology of post-heating recovery likely differs across time and/or across the recovery of core temperature. As future research seeks to classify the post-heating recovery period as a truly "distinct" phenomenon apart from both the heat stressed and rested state, we assert that post-heating assessments should be conducted not only early in the recovery period when core temperature is markedly elevated, but also in the later recovery period once core temperature has stabilized. We contend that this is a particularly important consideration with respect to studying recovery from passive heat stress because, unlike recovery from exercise stress in which there is a discrete "end" of exercise, it is difficult to objectively determine the definitive "end" of passive heating.

Another aim of this research was to determine the extent to which the marked cutaneous vasodilation which accompanies hyperthermia persists into the post-heating recovery period and contributes to sustained post-heating vasodilation and hypotension. Unfortunately, as we did not observe sustained vasodilation or post-heating hypotension, we are unable to speak to the latter half of this research question. However, our observation of a prompt recovery of skin blood flow in the post-heating recovery period amidst pronounced and sustained elevations in core temperature is reminiscent of a post-exercise thermoregulatory profile in which heat loss responses are suppressed upon the cessation of exercise and promote sustained post-exercise elevations in core and muscle temperature (Kenny et al., 2000, 2008; Thoden et al., 1994). While no studies to our knowledge have characterized thermoeffector function which may contribute to thermal recovery during recovery from whole-body heat stress, this remains an interesting area for future research.

Finally, as the baroreflex tightly regulates blood pressure in the short term, the sustained nature of the blood pressure reductions following acute heat stress documented by previous studies suggested that baroreflex support of blood pressure may be altered in the post-heating recovery period. This study was the first to our knowledge to characterize baroreflex function in the post-heating recovery period as we evaluated the heart rate, brachial vascular, and blood pressure responses to simulated hypotension via applied neck pressure and utilized these responses as indices of carotid baroreflex control of the heart, peripheral vasculature, and integrated support of blood pressure. Unfortunately, as post-heating hypotension was not observed in this study our results do not speak to the baroreflex adjustments which may underlie post-heating hypotension should it occur. Notwithstanding this limitation, several interesting

observations warrant consideration. First, we demonstrated that while brachial vascular responses to neck pressure were attenuated during passive heating in young individuals, they did not differ from baseline values throughout the post-heating recovery period in young and older individuals suggesting that baroreflex control of the peripheral vasculature is quickly restored following acute heat stress. Furthermore, we demonstrated that carotid baroreflex control of heart rate and blood pressure was not attenuated during or following whole-body, passive heat stress in young individuals. Interestingly, older individuals did not display changes in any indices of carotid baroreflex responsiveness during heating or post-heating recovery. These cumulative findings demonstrate that cardiac, peripheral vascular, and integrated carotid baroreflex responsiveness is not altered during the post-heating recovery period.

Collectively, this dissertation examines if passive heat stress may be an alternate way to open the "window of opportunity" posed by post-stress recovery. Our examination of the systemic cardiovascular and carotid baroreflex support of blood pressure during recovery from passive, whole-body heating among young and older individuals represents the most comprehensive characterization of the post-heating recovery profile conducted to date, and in doing so, fills several gaps in knowledge and highlights important considerations and avenues for future research. We hope that this research not only contributes to the growing body of work exploring the clinical utility of heat therapy as a blood pressure management strategy, but also acts more broadly to expand our view of the physiology of recovery to consider not only recovery from exercise stress, but also the various environmental stressors encountered by humans, and most importantly, those environmental stressors which may be leveraged to promote chronic beneficial adaptation.

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