Review Articles

Heart Failure and Thermoregulatory Control: Can Patients With Heart Failure Handle the Heat?

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ABSTRACT

Upon heat exposure, the thermoregulatory system evokes reflex increases in sweating and skin blood flow responses to facilitate heat dissipation and maintain heat balance to prevent the continuing rise in core temperature. These heat dissipating responses are mediated primarily by autonomic and cardiovascular adjustments; which, if attenuated, may compromise thermoregulatory control. In patients with heart failure (HF), the neurohumoral and cardiovascular dysfunction that underpins this condition may potentially impair thermoregulatory responses and, consequently, place these patients at a greater risk of heat-related illness. The aim of this review is to describe thermoregulatory mechanisms and the factors that may increase the risk of heat-related illness in patients with HF. An understanding of the mechanisms responsible for impaired thermoregulatory control in HF patients is of particular importance, given the current and projected increase in frequency and intensity of heat waves, as well as the promotion of regular exercise as a therapeutic modality. Furthermore, novel therapeutic strategies that may improve thermoregulatory control in HF, and the clinical relevance of this work in this population will be discussed. (*J Cardiac Fail 2017;23:621–627*)

Key Words: Cardiovascular, thermoregulation, heat.

Although healthy individuals have a high capacity to tolerate environmental heat stress,[1] individuals with heart failure (HF) appear particularly susceptible to illness during environmental heat exposure. This is seen in a marked increase in illness and death during heat waves and in the summer months for these patients.[2–5] Environmental heat exposure evokes reflex increases in sweating and skin blood flow (SkBF) to facilitate heat dissipation.[6,7] These heat-dissipating responses are mediated by autonomic and cardiovascular adjustments; if these adjustments are attenuated, thermoregulatory control can be compromised. In HF, the well-documented alteration in autonomic and cardiovascular function[8,9] has the potential to impair thermoregulatory responses. Moreover, the pharmacological management of HF patients may further compromise thermoregulatory responses. Consequently, patients with HF may be at a higher risk of heat-related illness when exposed to hot climates, particularly during exercise. The purpose of this review is to describe normal thermoregulatory mechanisms and how they may be altered in HF, and the factors that may increase the risk of heat-related illness in these patients. Additionally, therapeutic strategies that may improve thermoregulatory control in this population are discussed.

Thermoregulatory Control

The primary function of the human thermoregulatory system is to maintain core body temperature within safe limits. When humans are exposed to heat stress (ie, elevated environmental temperatures, physical activity, or a combination of both), the thermoregulatory system engages a number of physiological mechanisms to maintain heat balance. That is, the rate of

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metabolic heat production is balanced by the rate that heat is dissipated from the skin surface to the surrounding environment through a combination of dry (conduction, convection, and radiation) and evaporative heat exchange.[10,11] Heat balance can be easily disrupted, particularly during exercise and/or exposure to warm environments, because of elevations in metabolic heat production and/or a reduction (or even reversal) of dry heat transfer. The change in tissue temperature occurring because of the resultant additional heat energy stored inside the body provides thermal afferent impulses to the central nervous system.[12] Specifically, nuclei of the anterior (preoptic region) hypothalamus integrate thermal afferent information from central (core) and peripheral (skin) thermoreceptors, and subsequently send efferent signals via sympathetic pathways to appropriate effector organs to initiate (onset threshold) sustained increases in sweating and SkBF. These responses increase proportionally to the rise in core temperature, with further modification from skin temperature (thermosensitivity). Modifications of the onset threshold and thermosensitivity are indicative of central and peripheral modulations of thermoregulatory control.[13–15] In fact, the onset threshold and thermosensitivity of heat-dissipating responses represent the only way that the physiology of body temperature control can be examined.

During environmental and/or exercise heat stress, core temperature continues to rise if sweating and SkBF responses do not facilitate heat dissipation at the rate required to balance heat production.[16] Prolonged exposure to heat strain can increase the likelihood of heat-related illness.[16] Major heat-related conditions include heat stroke, which is characterized as a severe elevation in body temperature that causes body tissue and central nervous system dysfunction,[17,18] all result from insufficient heat dissipation from the body. Decreases in thermoregulatory capacity may be attributed to a combination of factors including changes in sweating, SkBF, and cardiovascular function.[19–21] Therefore, an optimally functioning sudomotor (sweating) and cutaneous vasodilatory system is necessary for humans to effectively respond to thermal challenges.

Sweating Responses in HF Patients

In a seminal study, Morgan and Nadas[22] reported that sweating was greater at rest in HF patients compared with controls. Moreover, recent studies suggest that HF patients have similar sweating responses to controls when exposed to passive whole-body heating[23,24] (Table 1). Although these findings suggest that temperature sensing, cholinergic innervation, and sudomotor function are preserved in HF, it must be acknowledged that differences in biophysical properties associated with metabolic heat production and body morphology (ie, mass and surface area) were not controlled in these studies. Given that biophysical differences are known to independently influence sweating responses,[28–32] and that the aforementioned studies did not account for these differences, it is difficult to determine whether the reported findings[22–24] are due to HF per se or are ascribed to between-group biophysical differences. Hence, we believe thermoregulatory-induced sweating in HF is an area that requires further examination.

Skin Blood Flow Responses in HF Patients

A common finding among studies examining thermoregulation in the context of HF to date is that HF patients appear to demonstrate impaired heat-induced increases in SkBF compared with controls[23–26] (Table 1). Although the mechanisms responsible for impaired SkBF in HF are not yet well understood, it may be argued that the compensatory activation of neurohumoral mechanisms that increase with severity of the condition at least partially contribute to the blunted heat-induced rise in SkBF in HF patients. Indeed, the renin-angiotensin-aldosterone system and the sympathetic nervous system are both chronically activated in HF.[8,9] Given these observations, the attenuated heat-induced cutaneous vasodilation (and accompanying changes in SkBF) in HF may be due to enhanced vasoconstrictor activity. Moreover, the attenuated SkBF response in HF may be partially explained by impaired nitric oxide (NO)-dependent vasodilation.[26] The fact that HF results in endothelial dysfunction[33,34] and reduced vascular responsiveness to NO[35,36] lend some support to this hypothesis. Although these findings suggest that HF patients demonstrate peripheral alterations in heat-induced SkBF responses, to date no study has examined the onset threshold of SkBF in response to a thermal challenge in this population. Therefore, it cannot be determined if SkBF responses in patients with HF are impaired purely from a peripheral perspective, as peripheral modulations can only be detected when changes in the thermosensitivity exist without

Table 1. A Summary of Findings From Key Studies to Date Examining Thermoregulation in the Context of HF

			Thermoregulatory Responses*	
Authors	Environment/Mode	Sample Size	Sweating	Skin Blood Flow
Morgan and Nadas[22]	Pilocarpine iontophoresis	CON = 17; HF = 14	↑	—
Zelis et al[25]	Cycling exercise in a thermo-neutral laboratory	CON = 12; HF = 9	—	↓
Cui et al[23]	Water-perfused suit (water temperature ~46°C)	CON = 14; HF = 14	↔	↓
Green et al[26]	Whole-body chamber heating at 38°C	CON = 7; HF = 7	—	↓
Cui et al[24]	Water-perfused suit (water temperature ~46°C)	CON = 9; HF = 9	↓	↓
Balmain et al[27]	Cycling exercise in a 30°C laboratory environment	CON = 8; HF = 10	↔	↓

*Arrows indicate the magnitude of response in heart failure patients (HF) compared with age- and gender-matched healthy controls (CON), where ↔ indicates that there was no significant difference in the response between HF and CON; ↑ indicates a significantly greater increase in HF compared with CON; ↓ indicates a significantly smaller increase in HF compared with CON; — indicates that the response was not assessed.

changes in the onset threshold.[37] Furthermore, although definitive studies during exercise are yet to be completed, the current evidence would imply that internal heat distribution during periods of environment heat stress might be compromised in this population.

Effect of Pharmacotherapy on Thermoregulatory Control in HF Patients

Studies examining thermoregulatory control in HF to date have included patients who continued with standard care procedures [22–27,38]; hence, it cannot be ruled out that thermoregulatory responses in HF may be influenced by concurrent use of medication. Beta-blockade is a standard, first-line therapy for HF and, although beta-blockers do not appear to influence sweating in HF, the use of this medication may possibly contribute to the lower rise in SkBF previously observed in these patients. Indeed, beta-blockers may have attenuated the heat-induced increase in cardiac output, thereby limiting the amount of blood that can be redistributed to the skin. Consistent with this suggestion is that although young healthy individuals taking beta-blockers exhibit preserved sweating responses during thermal challenges, SkBF responses are attenuated.[39,40]

In addition to beta-blockers, diuretics may also influence thermoregulation. Diuretics prevent the resorption of sodium and potassium in the distal tubules of the kidney, leading to a decrease in plasma volume.[41] In healthy individuals, a reduction in plasma volume has been shown to impair thermoregulatory increases in SkBF.[42] As such, it may be argued that taking diuretics as part of a holistic treatment strategy for HF may impair thermoregulatory control in these patients during periods of heat stress. In a classic study, Nadel et al[43] demonstrated that the core temperature onset threshold of SkBF was increased, which resulted in a lower thermoeffector output for a given core temperature when healthy individuals were dehydrated by ~3% of their individual total body mass. The fact that fluid status is an extremely fine balance in HF patients may predispose these patients to heat-related illness should they become dehydrated, particularly during an exercise challenge.

Thermoregulatory Responses During Exercise in HF Patients

In addition to pharmacotherapy, exercise training is a well-recognized therapeutic modality in the management of HF[44,45] and has been shown to decrease symptoms, improve exercise capacity, and quality of life, and likely improve morbidity and mortality.[46] Accordingly, a prescribed exercise training program is now recommended standard practice for patients with HF.[44,45]

Recently, Benda et al[38] assessed core and skin temperature responses in HF patients compared with controls during prolonged exercise in a thermo-neutral environment (ie, ~22°C). Core temperature responses during exercise were similar between the 2 groups; however, an attenuated rise in skin temperature was documented in HF compared with controls. The authors concluded that the attenuated rise in skin temperature in HF may be reflective of an inability to increase SkBF, which serves to increase the convective transfer of heat from the body core to the periphery and potentially increase skin temperature. Indeed, the lower skin temperature in HF would have reduced dry heat exchange from the skin to the surrounding environment. Unfortunately, this study was not performed during exercise in the heat and, as such, it is difficult to translate these findings to a likely scenario of HF patients performing exercise outside of climate-controlled facilities—which may in fact take place outdoors in a warm environment, particularly during the summer months. Moreover, this study failed to take into account differences in biophysical properties between HF and control participants,[28–32] and sweating and SkBF responses were not measured. Therefore, the subsequent conclusions that can be drawn from the reported data regarding thermoregulatory control during exercise in HF patients are limited.[38]

More recently, we have demonstrated that thermoregulatory responses in HF patients differ from controls during exercise in a warm environment.[27] In this study, a fixed relative exercise intensity (% peak oxygen uptake) was used, resulting in a much lower rate of metabolic heat production per unit mass in HF than controls; however, core temperature responses were similar between groups. These results suggest that HF patients appear to have a disrupted ability to regulate core temperature during exercise in a warm environment. We also found that sweating responses (relative to the evaporative requirements for heat balance) were similar between the 2 groups, whereas the rise in cutaneous vascular conductance and the thermosensitivity of this response was blunted in HF compared with controls (Fig. 1). These results suggest that HF patients are potentially limited in managing a thermal load secondary to impaired SkBF responses. Given our study used a protocol based on a fixed relative intensity, we suggest future studies should look to prescribe exercise that elicits a fixed rate of metabolic heat production in watts per kilogram[28] to assess thermoregulatory control in HF patients.

Potential Strategies to Enhance Thermoregulatory Control in HR Patients

In the preceding sections, we have identified that, although HF patients appear to exhibit preserved sweating responses, heat-induced rises in SkBF are lower compared with their age-matched healthy counterparts. As such, it is within reason to suggest that HF patients are limited in their ability to manage heat content secondary to poorer circulation to the skin. Based on evidence demonstrating that endothelium-dependant vasodilation is impaired in HF,[33–36] we suspect that impaired vascular endothelial function may be a key contributor to reduced SkBF and thus, thermoregulatory control, in this population.

Although acute exercise transiently increases metabolic heat production and may increase the risk of heat-related illness

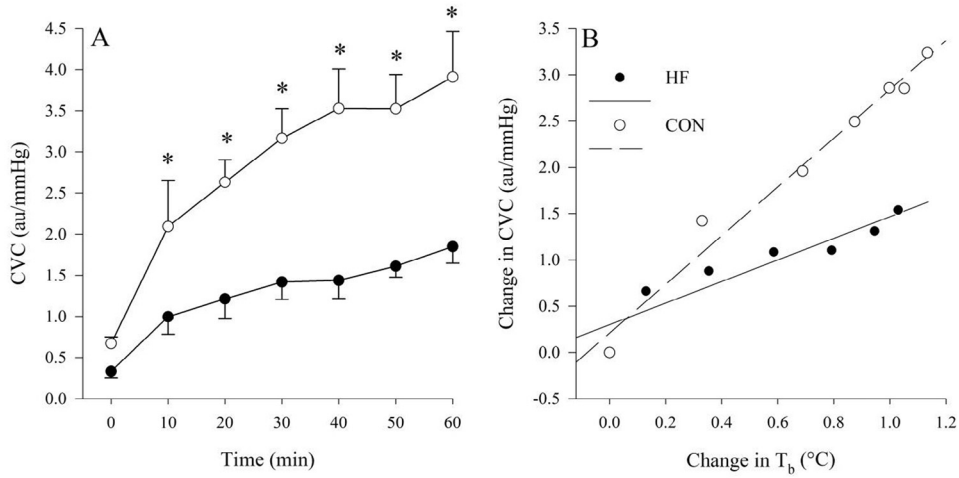

Fig. 1. CVC values recorded at 10-minute intervals during exercise (A), and changes in CVC (B) in response to increases in T_b for HF and CON participants. CON, control; CVC, forearm cutaneous vascular conductance; HF, heart failure; T_b, mean body temperature. Data are mean ± standard error of the mean. *Significantly different between groups, $P < .05$. Adapted from Balmain et al.[27]

in HF patients, regular exercise training is known to improve several physiological parameters critical to thermoregulation. Although the onset threshold of heat-dissipating responses have not been examined in response to exercise training in HF, exercise training has been shown to improve cardiac function[47–49] and improve vascular endothelial function and accompanying changes in blood flow redistribution[50–52] in this population. Additionally, exercise training has been shown to attenuate an overactive sympathetic nervous system[52–54] in these patients. As such, one may speculate that exercise training may improve thermoregulatory control by augmenting heat-induced SkBF responses and thus potential internal heat distribution in HF patients. However, this remains to be examined.

Similar to exercise training, repeated exposure to heat (ie, acclimation) reduces the absolute core temperature onset threshold of sweating and SkBF, resulting in the increase of thermo-effector output for a given core temperature.[55,56] Additionally, blood volume increases through plasma volume expansion, which allows for a larger heat-induced rise in cardiac output to facilitate a greater redistribution of blood to the skin and optimize heat content management among peripheral tissues.[57,58] Based on the evidence regarding the effects of heat acclimation in the context of HF, several studies have shown that acute and chronic exposure to heat stress via sauna therapy improves cardiac, autonomic, and circulatory function in HF patients.[59–64]

Although these studies describe the cardiovascular and autonomic benefits associated with this intervention in HF patients, it must be acknowledged that no study to date has described the impact of repeated sauna therapy on thermo-effector function in this population. It may be argued however, based on the previous findings, that repeated passive heat exposure may improve thermoregulatory control in HF patients. Indeed, sauna therapy–induced increases in cardiac output combined with improved vascular endothelial function may allow for a greater volume of blood to circulate through the cutaneous vasculature to optimize the management of changes in body heat content. Accordingly, a greater thermoregulatory-mediated rise in SkBF may serve to increase dry heat exchange, secondary to higher skin temperatures, at a given ambient temperature in HF patients following repeated sauna therapy.

Approximately 95% of the total rise in SkBF in response to heat stress is attributed to active cutaneous vasodilation, which predominately occurs via NO-dependent mechanisms.[65] Given that HF patients demonstrate impaired NO-dependent vasodilation during environmental heat exposure,[26] the NO pathway may be an important target for potential strategies aimed at improving vascular function in this population. NO formation is dependent on the presence of tetrahydrobiopterin (BH_4),[66,67] which is required to maintain the structure of NO synthase for the production of NO.[68] In conditions where BH_4 bioavailability is limited, NO synthase becomes structurally unstable and produces superoxide rather than NO.[69] Superoxide is known to oxidize BH_4, which further contributes to increased oxidative stress and vascular dysfunction.[67] Collectively, decreases in BH_4 bioavailability and subsequent increases in oxidative stress may contribute to attenuated NO-dependent vasodilation in HF patients, thereby negatively affecting peripheral, including SkBF and thus, heat content distribution and possibly even heat loss capacity.

Several studies have reported that dietary nitrate supplementation increases NO bioavailability in healthy middle-aged and older individuals and in those with hypercholesterolemia and peripheral artery disease. These studies demonstrated that nitrate supplementation serves to improve vascular endothelial function[70–74] and reduce levels of oxidative stress[75,76] via NO-dependent mechanisms. Based on these findings, it may be argued that nitrate supplementation may serve to enhance NO-dependent cutaneous vasodilation and therefore improve SkBF responses when individuals are exposed to elevated environmental temperatures. Although this is an intriguing hypothesis, nitrate supplementation in the context of thermoregulatory control has not been studied.

A potentially more viable dietary intervention strategy aimed at improving thermoregulatory control is folic acid supplementation. Recent published work demonstrates that folic acid and its active metabolite, 5-methyltetrahydrofolate, increases vascular BH_4 production in healthy older individuals and in patients with metabolic and coronary artery disease.[77–79] Data from these studies suggest that subsequent improvements in vascular function and accompanying changes in peripheral, including SkBF, with folic acid supplementation are mediated through NO-dependent mechanisms. Given that HF patients exhibit impaired circulation to the periphery,[23–26] folic acid supplementation may serve to improve SkBF responses through NO-dependent mechanisms and, thus, thermoregulatory control in this population.

In contrast to strategies aimed at increasing SkBF in HF patients, an alternative approach to improving thermoregulatory control in this population would be to use strategies that enhance sweating responses and, thus, evaporative heat exchange. Because sweating responses appear to be preserved in HF patients, this may be an important consideration if impairments in SkBF are sufficient to alter dry heat exchange from the skin surface to the surrounding environment. It is well understood that the potential for evaporation is increased substantially with increasing air movement.[32,80,81] As such, a simple and cost-effective cooling strategy to enhance the evaporation of sweat during heat exposure is the use of an electric fan.

Until recently, most public health guidance suggested that electric fans are not effective in preventing heat-related illness at ambient temperatures greater than ~35 to 37°C.[82] This was based on the assumption that the gradient for dry heat exchange is reversed (provided that the ambient temperature was greater than skin temperature) and an increase in air velocity (with the use of a fan) across the skin surface would accelerate dry heat gain and consequently "accelerate body heating." However, evidence suggests that the use of electric fans when ambient temperature exceeds that of skin temperature may need to be reconsidered.[80] Indeed, Jay et al[80] recently demonstrated that fans protect against cardiovascular and thermal strain in young and older healthy individuals up to at least an ambient temperature of 42°C (irrespective of relative humidity), which is much higher than the limit suggested by the Centers for Disease Control and Prevention and the World Health Organization.[82] The increase in dry heat gain associated with using electric fans during heat waves increases the evaporative requirements for sweating to attain heat balance. Consequently, sweating responses increase, and the increase in air velocity (with a fan) further facilitates the evaporation of sweat. As a result, this will lead to a higher rate of net heat loss from the skin, which may serve to be protective during heat stress despite a higher rate of convective heat gain.[32] Because thermoregulatory sweating responses appear to be preserved in those individuals with HF, the use of an electric fan may be an effective cooling strategy—even when the ambient temperature exceeds that of the skin; however, further work in this area needs to be undertaken, particularly in clinical populations.

Clinical Relevance

Impaired thermoregulatory responses should be considered in patients with HF because they may contribute to heat-related illness and therefore adversely affect health outcomes during everyday activities, particularly during bouts of hot weather. Individuals should be made aware of their potential susceptibility to temperature extremes, and education should be provided to address simple strategies to avoid overheating. Relevant advice may include wearing appropriate clothing; ensuring access to electric fans where possible, particularly when performing indoor exercise activities; controlling the ambient temperature and ventilating the home environment; timing activities to avoid extremes of temperature; and undertaking activity modification for energy conservation. Monitoring of fluid status should also be reviewed regularly with the intent that requirements for fluid restrictions and use of diuretics may change from season to season as temperature and patient activity varies.

With respect to physical activity, program attendance and general participation in exercise are likely to be better if environmental issues do not pose a significant barrier. Although current guidelines provide information on recommended levels of physical activity with associated long- and short-term outcomes,[44,45] there are no recommendations regarding the levels of physical activity that can be safely performed in the heat. Exercise training should, where possible, be conducted in air-conditioned or well-ventilated facilities, and this should be a consideration when choosing venues to run such programs. Similarly, the home environment should also be considered when prescribing exercise to be undertaken outside of a health facility. Exercise prescription may also need to be modified if heat-related fatigue is problematic; as such, exercise intensity and rest periods can be adapted accordingly.

Conclusion

Recent observations clearly show that HF patients are susceptible to heat-related illness. This increased susceptibility appears to be mediated by diminished heat-induced increases in SkBF. We suspect that impaired intrinsic vasodilator pathways combined with a reduced cardiac reserve may contribute to this response in these patients. Although theoretical at this point, routine exercise, acclimation, and the use of electric fans might be beneficial in protecting against heat-related illness in patients with HF. Additional studies examining mechanisms of temperature regulation in HF, as well as potential therapeutic strategies to improve thermoregulatory control in this population, are needed to optimize treatment and management of these vulnerable patients when exposed to heat stress.

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Disclosures

None.

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