

Medicine & Science IN Sports & Exercise

The Official Journal of the American College of Sports Medicine
www.acsm-msse.org

... Published ahead of Print

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Accepted for Publication: 10 October 2017

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The results of the present study do not constitute endorsement by the American College of Sports Medicine. The authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Grants: Bryce N. Balmain is supported by an Australian Government Research Training Program Scholarship.

Disclosures: None

Abstract

Purpose: Heart failure (HF) patients appear to exhibit altered thermoregulatory responses during exercise in the heat. However, the extent to which these responses are altered due to physiological impairments independently of biophysical factors associated with differences in metabolic heat production (H_{prod}), evaporative heat balance requirements (E_{req}) and/or body size, is presently unclear. Therefore, we examined thermoregulatory responses in 10 HF and 10 age-matched controls (CON) similar in body size during exercise at a fixed rate of H_{prod} , and therefore E_{req} in a 30°C environment. **Methods:** Rectal temperature (T_{rec}), local sweat rate (LSR), and cutaneous vascular conductance (CVC) were measured throughout 60-min of cycle ergometry. Whole-body sweat rate (WBSR) was estimated from pre-post nude body weight corrected for fluid intake. **Results:** Despite exercising at the same rate of H_{prod} (HF: 338±43; CON: 323±31W, $p=0.25$), the rise in T_{rec} was greater ($p<0.01$) in HF (0.81±0.16°C) than CON (0.49±0.27°C). In keeping with a similar E_{req} (HF: 285±40; CON: 274±28W, $p=0.35$), no differences in WBSR (HF: 0.45±0.11; CON: 0.41±0.07L/h, $p=0.38$) or LSR (HF: 0.96±0.17; CON: 0.79±0.15mg/cm²/min, $p=0.50$) were observed between groups. However, the rise in CVC was lower in HF than CON (HF: 0.83±0.42; CON: 2.10±0.79au/mmHg, $p<0.01$). Additionally, the cumulative body heat storage estimated from partitioned calorimetry was similar between groups (HF: 154±106; CON: 196±174kJ, $p=0.44$). **Conclusions:** Collectively, these findings demonstrate that HF patients exhibit a blunted skin blood flow response, but no differences in sweating. Given that HF had similar body heat storage to controls at the same H_{prod} , their greater rise in core temperature can be attributed to a less uniform internal distribution of heat between the body core and periphery. **Key words:** Cardiac failure; heat balance; temperature regulation; exercise

Introduction

While healthy individuals have a large capacity to tolerate environmental heat stress (1), patients with heart failure (HF) appear particularly susceptible to heat-related illness during heat exposure. This is evidenced by a marked increase in morbidity and mortality for these patients during bouts of hot weather and in the summer months (2-5). Upon exposure to the heat, the human thermoregulatory system engages a number of physiological mechanisms to maintain core body temperature within safe limits — appropriate effector organs initiate increases in sweating and skin blood flow to facilitate the required rate of heat dissipation from the skin surface to the surrounding environment to balance the rate of heat that is internally generated (6, 7). These heat dissipating responses are mediated by autonomic and cardiovascular adjustments; if these adjustments are attenuated, thermoregulatory control can be compromised and may increase the risk of heat-related illness. In HF, the well-documented alteration in autonomic and cardiovascular function (8), therefore, has the potential to alter thermoregulatory responses.

To date, there have been only a limited number of studies examining thermoregulation in the context of HF. Current evidence suggests that sweating responses are not impaired; but, increases in skin blood flow are attenuated in HF compared to healthy controls during passive whole-body heating (9-15). It is worth noting, however, that these studies examined HF patients in encapsulated environments (i.e., water-perfused suits and heating techniques at supra-physiological temperatures), and it is unclear whether any thermoregulatory decrements with HF are sufficient to meaningfully alter the prevailing heat strain during exercise in an open-air (non-encapsulated) environment.

Recently, we reported that skin blood flow responses were lower in HF patients compared to healthy controls during exercise in a warm environment (9). Notably, these findings were limited by the use of a fixed relative exercise intensity (% peak oxygen uptake) (16), which resulted in a much lower rate of metabolic heat production in HF (3.9 ± 0.9 W/kg) than controls (6.4 ± 1.5 W/kg); however, similar core temperature responses were observed between the two groups (9). Indeed, this may indicate that HF patients' exhibit attenuated heat loss responses. Furthermore, Benda et al (17) demonstrated that core temperature responses were similar in HF patients and controls, even when exercising at the same absolute intensity and thus, potentially the same absolute metabolic heat production. However, this study failed to take into account differences in biophysical properties associated with body size, and the management of heat content and the importance of evaporation relative to dry heat loss (convection and radiation) (18), was not considered. Additionally, sweating and skin blood flow responses were not measured. As such, the subsequent conclusions that can be drawn from the reported data in this study (17) regarding thermoregulatory control during exercise in HF patients are limited. Therefore, in order to conclusively demonstrate the extent to which HF independently alters changes in thermoregulatory responses with exercise in the heat, a HF group of similar body mass/surface area as a control group must be compared at an exercise intensity that elicits the same metabolic heat production for both groups (16, 19).

Therefore, the purpose of this study was to examine thermoregulatory responses in HF patients compared to age-matched healthy control (CON) participants of similar body size during exercise at a fixed rate of metabolic heat production in a non-encapsulated warm environment. It was hypothesised that HF patients would demonstrate a greater rise in core temperature than CON despite exercising at the same rate of metabolic heat production, secondary to an impaired cutaneous vasodilatory response (an index of skin blood flow) but without any alterations in sweating (reflecting evaporative heat loss potential).

Methods

Participants: A power calculation (G*Power version 3.1.9.2, Heinrich Heine University Düsseldorf, Düsseldorf, Germany) was performed to determine the required sample size for the study. Based on conventional α (0.05) and β (0.80) values, and an effect size of 1.51 as in a previous study (16) using a similar design (i.e., independent groups) and primary outcome variables (i.e., core temperature), a minimum of 16 participants (8 per group) was required.

Twenty men volunteered to participate in this study; 10 HF patients who were recruited through the local Community Heart Failure Program of Gold Coast Health Services, and 10 age-matched healthy CON participants recruited from the surrounding community. Patients with HF were aged 50-75 y; New York Heart Association (NYHA) Class I-II; no recent exacerbation of HF-related symptoms and no change in medications within the past 3 months; and free from any restriction of ambulation and mobility. CON participants matched the study population for age and sex; were apparently healthy non-smokers; free from cardiopulmonary, neurological, and/or metabolic diseases and any restriction of ambulation and mobility; and were not taking any cardiovascular medications at the time of participation in the study. Prior to all testing, the study purpose and experimental protocols were disclosed, and all participants provided written and witnessed informed consent. The experimental procedures were reviewed and approved by the Griffith University Human Research Ethics Committee, and complies with the guidelines set out in the Declaration of Helsinki.

Study design: Participants visited the laboratory on two separate occasions with each visit separated by at least 48 h. Participants were required to refrain from strenuous exercise, and consuming food and beverages containing caffeine and/or stimulants for 24 h prior to visiting the laboratory. During the first visit, participants underwent pre-participation health screening and

performed a medically supervised 2-stage sub-maximal incremental cycling test on a cycle ergometer. Following a 10-min rest period (19), participants then performed a medically-supervised maximal incremental cycling test on the same cycle ergometer. During the second visit, participants completed a prolonged (60-min) constant load sub-maximal cycling test (Experimental exercise trial) in a warm ($\sim 30^{\circ}\text{C}$, $\sim 25\%$ relative humidity) laboratory environment.

Preliminary sub-maximal incremental cycling test: Sub-maximal incremental cycling tests were performed on an electronically-braked upright cycle ergometer (Lode Corival, Lode BV, Groningen, Netherlands) to determine the relationship between external workload (W) and steady-state metabolic energy expenditure and thus, the metabolic heat production (H_{prod}) required for the experimental exercise trial for each participant (19). The test comprised two 5-min sub-maximal stages at individualised external workloads predicted to incorporate the target experimental H_{prod} for the experimental exercise trial. The required experimental H_{prod} was derived using assumed gross efficiency values (17%) (20). Pulmonary gas exchange was measured via indirect calorimetry (Ultima, Cardio2, Medical Graphics Corporation, St. Paul, MN, USA) throughout.

Maximal incremental cycling test: Maximal incremental cycling tests were performed for the determination of peak exercise values (oxygen uptake and heart rate). The tests comprised a 3-min warm-up period of unloaded cycling, before the workload was increased by 10 W (HF) or 15 W (CON) every 60 s until the participant reached volitional fatigue or symptom limitation. Cardiac rhythm and pulmonary gas exchange were measured via 12-Lead electrocardiography (ECG) (X12+, Mortara Instrument, Milwaukee, WI, USA) and indirect calorimetry, respectively. Peak heart rate and oxygen uptake ($\dot{V}\text{O}_{2\text{peak}}$) were determined as the highest 60 s bin-averaged values attained during the test.

Experimental exercise trial: The experimental exercise trial comprised of 60-min of constant-load exercise on the upright cycle ergometer at an intensity eliciting a H_{prod} of 4 W/kg (9). Prior to entering the laboratory, participants were instrumented in a thermo-neutral (22°C) environment. Following instrumentation, participants entered the laboratory and were seated on the upright cycle ergometer for 10-min of quiet rest (baseline). Once the 10-min baseline period concluded, participants commenced cycling at a preferred cadence; the pre-selected workload was then be applied and participants required to maintain the workload for 60-min or until symptom limitation. All participants completed the experimental exercise trial in a similar ($p > 0.05$) ambient air temperature (HF: 29.8 ± 0.12 ; CON $29.9 \pm 0.22^\circ\text{C}$) and relative humidity (HF: 24.2 ± 0.5 ; CON $23.8 \pm 0.1\%$), and all participants were provided with fluid (i.e., water at $\sim 37^\circ\text{C}$) ad libitum.

Heart rate and rhythm, rectal (T_{rec}) and skin (T_{sk}) temperatures, skin blood flux (an index of skin blood flow), and local sweat rate (LSR) were monitored continuously, and recorded at baseline and at 10-min intervals during the cycling test. Pulmonary gas exchange variables were measured as described above, during the final 3-min of the baseline rest period, and at 10-min intervals (3-min measurement bins). Blood pressure was also measured at these time points by manual brachial artery auscultation using a mercury sphygmomanometer (Standby Model, Baumanometer, Copiague, NY, USA).

Instrumentation: Heart rate and rhythm were monitored continuously using a 12-Lead ECG. A general-purpose paediatric thermistor (Mon-a-therm, Mallinckrodt Medical, St. Louis, MO, USA) self-inserted to a depth of ~ 12 cm beyond the anal sphincter was used to measure T_{rec} . Skin temperature was measured at five sites with thermistors (MLT422/A, ADInstruments, Bella Vista, NSW, AUS), and an area-weighted mean was subsequently calculated to derive mean skin temperature (T_{sk}) as previously described (21):

$$T_{sk} = 0.15 T_{arm} + 0.15 T_{shoulder} + 0.2 T_{thigh} + 0.2 T_{calf} + 0.30 T_{back} (^{\circ}C)$$

To account for the relative contribution of core and mean skin temperatures to the rise in skin blood flow and sweating responses, mean body temperature (T_b) was subsequently calculated as (22):

$$T_b = 0.9 T_{rec} + 0.1 T_{sk} (^{\circ}C)$$

Skin blood flux (an index of skin blood flow) was measured using laser-Doppler flowmetry. Laser-Doppler probes were placed on the forearm ~3 cm distal to the cubital fossa and on the upper back ~5 cm above the scapular spine over the trapezium. Cutaneous vascular conductance (CVC) was subsequently calculated from mean skin blood flux values divided by mean arterial pressure, and reported as a change from baseline values (11). Whole-body sweat rate (WBSR) was calculated based on pre- and post-exercise changes in nude body weight corrected for fluid consumption during exercise. LSR was measured using a ventilated sweat capsule (4.1 cm²) placed on the upper back next to the laser-Doppler probe. The flow of anhydrous air through the capsule was regulated at 0.75 L/min (SV1B-AI05, Influx Measurements, Hampshire, UK). The vapour concentration of effluent air was measured using a factory-calibrated temperature and humidity transmitter (HMT310, Vaisala, Vantaa, Finland). LSR was calculated as the product of vapour concentration and flow rate, normalised to the skin surface area covered by the capsule to yield values in mg/cm²/min.

Heat balance calculations: All participants were instructed to wear a light, loose fitting clothing ensemble (i.e., cotton shorts, socks and running shoes) so that dry insulation and resistance to evaporative heat loss were considered negligible. As per convention, heat balance parameters

were estimated using partitional calorimetry and calculated in W/m²; however, these values are converted in W/kg of total body mass where appropriate. Metabolic energy expenditure (*M*) was estimated as:

$$M = \dot{V}O_2 \frac{\left(\frac{RER - 0.7}{0.3} e_c\right) + \left(\frac{1 - RER}{0.3} e_f\right)}{60 \text{ BSA}} \times 1000 \text{ (W/m}^2\text{)}$$

Where: $\dot{V}O_2$ represents pulmonary oxygen uptake (in L/min), RER represents the respiratory exchange ratio (i.e., $\dot{V}CO_2 / \dot{V}O_2$) (16), e_c and e_f represent the caloric energy equivalent for the oxidation of carbohydrate (i.e., 21.13 kJ) and fat (i.e., 19.62 kJ) per litre of oxygen consumed, and BSA represents body surface area. H_{prod} was determined as the difference between *M* and the external workload (*W*) in W/m²:

$$H_{\text{prod}} = M - W \text{ (W/m}^2\text{)}$$

The rate of dry heat loss (H_{dry}) was determined as:

$$H_{\text{dry}} = R + C \text{ (W/m}^2\text{)}$$

$$R = h_r(T_{\text{sk}} - T_a) \text{ (W/m}^2\text{)}$$

$$C = h_c(T_{\text{sk}} - T_a) \text{ (W/m}^2\text{)}$$

Where: *R* and *C* represent radiant and convective heat exchange, respectively; T_{sk} and T_a represent mean skin, and ambient temperature (both in °C), respectively; and h_r and h_c are the radiant and convective heat exchange coefficients, respectively:

$$h_r = 4 \times 0.77 \varepsilon \sigma \left[\left(\frac{T_{sk} + T_r}{2} \right) + 273.15 \right]^3 \quad (\text{W} \cdot \text{m}^{-2} \cdot \text{K}^{-1})$$

$$h_c = 8.3 v^{0.6} \quad (\text{W} \cdot \text{m}^{-2} \cdot \text{K}^{-1})$$

Where: 0.77 represents the non-dimensional effective radiant surface area for a seated individual; ε represents the emissivity of the skin (0.95); σ represents the Stefan-Boltzmann constant ($5.67 \cdot 10^{-8} \text{ W} \cdot \text{m}^{-2} \cdot \text{K}^{-1}$); T_r represents the mean radiant temperature, which is assumed to equal T_a ($^{\circ}\text{C}$); and v represents air velocity (< 0.2) in m/s. Respiratory heat exchange (H_{res}) was determined as:

$$E_{res} + C_{res} = [0.0014 H_{prod}(34 - T_a) + 0.0173 H_{prod}(5.87 - P_a)] \quad (\text{W}/\text{m}^2)$$

$$P_a = \frac{\text{Relative humidity} \times P_{sa}}{100} \quad (\text{kPa})$$

$$P_{sa} = 0.1 \exp \left[18.956 - \left(\frac{4030.18}{(T_{sk} + 235)} \right) \right] \quad (\text{kPa})$$

Where: E_{res} and C_{res} represents evaporative and convective heat loss from the respiratory tract, respectively; P_a represent the evaporative and convective ambient vapour pressure; and P_{sa} represents the saturated vapour pressure. The evaporative requirement for heat balance (E_{req}) was determined as:

$$E_{req} = H_{prod} - H_{dry} - H_{res} \quad (\text{W}/\text{m}^2)$$

The calculation of E_{req} was based on mean steady-state values (i.e., average of last 10-min of exercise) from the experimental exercise trial of each heat balance parameter included in the equation. The cumulative body heat storage (S) throughout exercise was determined by:

$$S = H_{\text{prod}} - (H_{\text{dry}} + H_{\text{res}} + E_{\text{sk}}) (\text{kJ})$$

Where each heat balance parameter was converted to kJ/min and subsequently summated across the 60-min experimental trial; and the cumulative amount of evaporative heat loss from the skin (E_{sk}) was determined as (23):

$$E_{\text{sk}} = \frac{(\text{WBSR} \times 1000 \times 2426)}{1000} (\text{kJ})$$

Where: WBSR represents whole-body sweat rate (in L/h); and the number 2426 represents the latent heat of vaporisation of sweat in (J/g) (24). E_{sk} was subsequently corrected for decrements in sweating efficiency (r) (23):

$$r = 1 - \frac{w_{\text{req}}^2}{2}$$

Where w_{req} represents skin wettedness required for heat balance:

$$w_{\text{req}} = \frac{E_{\text{req}}}{E_{\text{max}}}$$

Where E_{max} represents the maximum rate of evaporation to the environment (25):

$$E_{\text{max}} = h_e (P_{\text{sa}} - P_a) (\text{W/m}^2)$$

Where: h_e is the evaporative heat transfer coefficient, calculated as the product of h_c and the Lewis number (16.5), and $P_{\text{sa}} - P_a$ represents the skin-to-air water vapour pressure gradient (in kPa).

Echocardiography: Two-dimensional (2-D) and pulsed-wave Doppler echocardiography was performed using a Vivid E9 ultrasound system (GE Healthcare, Milwaukee, WI, USA) equipped

with a 4.5 MHz sector-array probe (MS5 cardiac probe; GE Healthcare, Milwaukee, WI, USA). Parasternal and apical long-axis images were acquired at rest, 10-, 20-, 40-, and 60-min in an upright position during the sub-maximal cycling test by a single experienced sonographer. All 2-D images were acquired at frame rates of 50-80 frames/sec, and all system settings were held constant throughout the sub-maximal cycling test for each participant. All images were stored digitally and subsequently transferred to an offline workstation and analysed using Echopac software (v113; GE Healthcare, Milwaukee, WI, USA). Stroke volume was calculated as the product of left ventricular outflow tract circumference and pulsed-wave Doppler-derived blood velocity-time integral, measured immediately proximal to the aortic valve during systole. Cardiac output was quantified as the product of stroke volume and heart rate.

Statistical analysis: Statistical analysis was performed using SPSS 22.0 (SPSS Inc, Chicago, IL, USA). Between-group (HF and CON) participant characteristics and human heat balance data were assessed using independent samples t-tests. A two-way analyses of variance (HF vs CON) with repeated measures was performed to determine whether changes in hemodynamic and thermoeffector measurements differed across time. Pair-wise comparisons using Bonferroni adjustments were applied when a significant interaction was detected. A linear regression analysis was employed to determine the contributions of T_b to LSR and the change in CVC during exercise (26). Thermosensitivity was determined as the slope of the relationship between these responses and T_b (9). The onset threshold was determined by plotting LSR and mean skin blood flux values over time and visually determining the point at which these values systematically increased over three consecutive measurement intervals (22). The corresponding ΔT_b at that specific time point was taken as the onset threshold (22). Statistical significance was accepted at $p < 0.05$. All data are presented as mean \pm standard error of the mean.

Results

Participant characteristics: Twenty men; 10 patients with ischemia-induced HF (NYHA Class I-II) and 10 CON participated in the study. Participant characteristics are displayed in Table 1. There were no differences in age, body mass, and body surface area between groups ($p > 0.05$); however, left ventricular ejection fraction was lower in HF than CON ($p < 0.01$). All participants completed the maximal incremental cycling test and as expected, HF demonstrated a lower $\dot{V}O_{2\text{peak}}$ and peak power compared to CON ($p < 0.05$). Additionally, both groups consumed a similar amount of fluid during the experimental exercise trial (HF: 0.28 ± 0.13 ; CON: 0.32 ± 0.15 L; $p = 0.63$).

Cardiorespiratory responses: For both groups there were similar and significant increases in heart rate (Figure 1, Panel A, $p < 0.01$; group*time interaction: $p = 0.98$) and mean arterial pressure (Figure 1, Panel B, $p = 0.04$; group*time interaction: $p = 0.93$) from the onset of exercise. SV did not change from rest (Figure 1, Panel C, $p = 0.17$); however, there was a significant increase in CO (Figure 1, Panel D, $p = 0.01$; group*time interaction: $p = 0.74$) from the onset of exercise in both groups. In addition, ventilation was higher in HF compared to CON during exercise (HF: 44.2 ± 9.0 ; CON: 31.6 ± 8.5 L/min; group*time interaction: $p = 0.02$).

Metabolic heat production, external workload, and evaporative heat balance requirements: Mean values for H_{prod} and evaporative heat balance requirements (E_{req}) are displayed in Table 2. By design, H_{prod} was similar between HF and CON when expressed per unit total body mass ($p = 0.44$), per unit surface area ($p = 0.23$), and as an absolute value ($p = 0.25$). The external workload to attain the fixed level of H_{prod} was the same between both groups (HF: 63 ± 16 ; CON: 65 ± 20 W; $p = 0.78$). However, the corresponding relative exercise intensity (as a

percentage of $\dot{V}O_{2peak}$) was higher in HF (56 ± 14 % vs CON: 32 ± 7 %; $p < 0.01$). Since both groups performed exercise in the same environmental condition, the use of fixed rate of H_{prod} ensured that E_{req} was the same between HF and CON ($p = 0.39$). Furthermore, E_{max} and w_{req} were not different ($p > 0.05$) between groups.

Partitional calorimetry: Heat balance parameters estimated from partitional calorimetry are displayed in Table 2. Cumulative H_{prod} , H_{res} , H_{dry} , and estimated skin surface evaporation from whole-body sweat losses – after accounting for estimated decrements in sweating efficiency– E_{sk} were similar between both groups (all $p > 0.05$). As a result, the estimated cumulative body heat storage during exercise was the same between HF and CON ($p = 0.44$).

Core and mean skin temperature: During exercise, T_{rec} increased to a greater extent in HF than CON (Figure 2, Panel A, group*time interaction: $p < 0.01$). Additionally, the end-exercise change in T_{rec} was greater in HF ($0.81 \pm 0.16^{\circ}C$, v CON: $0.49 \pm 0.27^{\circ}C$; $p < 0.01$). In contrast, T_{sk} did not differ between the two groups throughout exercise (Figure 2, Panel B, group*time interaction: $p = 0.21$).

Skin blood flux and cutaneous vascular conductance: The onset threshold of skin blood flux did not differ between groups ($p = 0.63$); however, the rise in skin blood flux was lower in HF compared to CON (HF: 216 ± 33 ; CON: 326 ± 40 au; group*time interaction: $p < 0.01$). Furthermore, the thermosensitivity of CVC was lower in HF compared to CON ($p < 0.01$; Table 3) and as a consequence, the rise in CVC was lower in HF throughout exercise (Figure 3, Panel A, group*time interaction: $p < 0.01$).

Local and whole-body sudomotor sweating: The onset threshold and thermosensitivity of LSR measured on the upper back were similar between groups (both $p > 0.05$; Table 3). As a result,

there was no difference in LSR between HF and CON groups throughout exercise (Figure 3, Panel C, group*time interaction: $p = 0.67$). Similarly, no difference was observed in WBSR between groups (HF: 0.45 ± 0.11 ; CON: 0.41 ± 0.07 L/h; $p = 0.38$).

Discussion

To the best of our knowledge, this is the first study to examine time-dependent thermoregulatory responses in patients with heart failure during exercise at a fixed rate of metabolic heat production in a warm non-encapsulated environment. Our findings show that heart failure patients have a greater rise in T_{rec} than age-matched healthy controls, even when exercising at the same H_{prod} (in W/kg). Since a similar cumulative body heat storage was evident in both groups but a blunted CVC (thermosensitivity) observed in HF, the greater rise in T_{rec} in these patients may reflect an impaired ability to redistribute internal heat content among peripheral tissues.

Similar to others that have examined thermoregulation in the context of HF (9, 11-15), a blunted rise in skin blood flow, as evidenced by a lower rise in CVC, was observed in HF patients compared to CON. It may be argued that the compensatory activation of neurohumoral mechanisms associated with HF contributes to the blunted cutaneous vasodilatory response (and thus, skin blood flow) in HF patients. Indeed, studies have shown that peripheral vasoconstriction is enhanced in HF patients due to an overactive sympathetic nervous system (8, 27). Thus, the reduced skin blood flow (as evidenced by a blunted CVC) in HF in the present study may be, in part, due to enhanced sympathetic activity, and/or impaired neural control of the cutaneous circulation. Aside from neural mechanisms, the attenuated skin blood flow response in HF may be explained by impaired nitric oxide (NO)-dependent cutaneous vasodilation. The fact that HF results in endothelial dysfunction (28, 29), and reduced vascular responsiveness to NO

(30), lends some support to this suggestion. Hence, impaired NO-dependent cutaneous vasodilation may have at least partially contributed to the lower rise in CVC in HF patients in the present study.

To differentiate between a central and peripheral modulation of skin blood flow responses, we examined the onset threshold and thermosensitivity of the response during exercise. In the current study, the onset threshold for skin blood flow did not differ between the two groups. However, the thermosensitivity of CVC was much lower (~5 fold) in HF than CON. Given that changes in mean arterial pressure were the same for each group, these findings suggest that skin blood flow responses in HF patients are blunted purely from a peripheral perspective, given that peripheral modulations in body temperature regulation can only be detected when changes in the thermosensitivity exist without changes in the onset threshold (22, 31). The fact that HF patients increased cardiac output during exercise to a similar extent as CON, which in theory would provide sufficient blood flow to perfuse the skin and optimize heat content management among peripheral tissues to the same degree as CON, lends some support to this suggestion.

Despite large differences in skin blood flow responses between groups, it is worth noting that the potential for net heat loss from the skin to the environment through dry (convection/radiation) and evaporative heat exchange were similar between HF and CON. Since heat storage is the cumulative difference between H_{prod} and heat dissipation, and that skin surface heat loss when exercising at the same fixed H_{prod} was similar between groups, it is not surprising that the cumulative amount of heat energy stored inside the body during exercise was also similar. Yet, T_{rec} still increased to a greater extent in HF. As such, these findings provide evidence that HF patients exhibit impairments in heat management due to a less uniform distribution of heat content between the body core and the periphery (secondary to impairments in skin blood flow

responses), and that internal heat storage is concentrated more toward the body core. Furthermore, Krack and colleagues (32) recently reported that HF leads to enhanced vasoconstriction in the gut and/or splanchnic region during exercise. As a consequence, inadequate blood flow to the gut/splanchnic region may reduce the amount of heat that is removed from this area, compounding heat accumulation and storage in the body core.

The evaporation of sweat is essential for the effective dissipation of heat from the skin surface to the surrounding environment. Previous studies have shown that in the presence of no physiological impairment to sweating, E_{req} determines WBSR under conditions permitting complete sweat evaporation (16, 18, 33). In the present study, E_{req} and WBSR (and thus, E_{sk}) were similar in HF and CON indicating no independent influence of HF on whole-body sweating. In addition to WBSR, it is well-established that irrespective of core temperature, differences in body surface area are known to influence LSR (19, 34). Because HF and CON groups in the present study were also matched for body surface area, exercise performed at a fixed H_{prod} also yielded the same H_{prod} (and thus, E_{req}) per unit body surface area. Both groups demonstrated comparable responses in LSR during exercise, secondary to a similar core temperature onset threshold and thermosensitivity of the response. Our findings suggest that thermal-afferent neural activity, sympathetic cholinergic innervation for a given thermal-afferent input, and sweat gland function may not be impaired in patients with HF. Similarly, previous studies have also shown that sweating responses, as well as skin sympathetic nerve activity are comparable between HF and control participants during passive whole-body heating (11, 12).

Although studies have previously assessed thermoregulatory responses in HF patients during exercise (9, 15, 17), it must be acknowledged that these studies utilised experimental protocols (i.e., % peak oxygen uptake) that resulted in HF patients exercising at lower levels of H_{prod}

(secondary to a lower $\dot{V}O_{2\text{peak}}$) compared to the control group. An important consideration of the current study is that we employed an experimental protocol that elicited a fixed rate of H_{prod} , combined with a fixed environmental condition, to examine thermoregulatory responses in HF patients. Indeed, this experimental approach is essential to perform an unbiased comparison of between-group thermoregulatory responses during exercise (16, 18, 19, 34). Therefore, unlike earlier studies, the differences in thermoregulatory responses reported in the present study (i.e., a greater rise in T_{rec} in HF than CON despite a similar skin surface heat loss and cumulative body heat storage content) can only be ascribed to physiological differences in body temperature regulation in HF, rather than biophysical factors.

Considerations

Despite HF exhibiting a lower skin blood flow (as evidenced by a diminished CVC) than CON during exercise, cardiac output and mean arterial pressure were similar between groups. These findings suggest that estimated peripheral vascular resistance was also the same between groups. A potential explanation for this hemodynamic discrepancy is that the greater resistance within the cutaneous vascular bed in HF was balanced out by a concomitant reduction in resistance within other vascular beds. In the present study, HF patients exhibited a greater ventilatory response during exercise than CON. We have previously shown that the work of breathing across a range of submaximal exercise intensities is higher in patients with HF compared to healthy controls (35). This higher ventilation (and thus, work of breathing) may have necessitated a greater demand for blood flow, mediated by reduced resistance, to the lungs and/or respiratory muscles, as previously suggested (36).

The present study used partitioned calorimetry to estimate changes in net heat loss from the skin surface to the environment. With respect to the evaporation of sweat, this method cannot fully

determine if all sweat secreted on the skin surface evaporated to the environment. However, skin wittedness required for heat balance was the same between both groups. Thus, if there was any dripping of sweat, it is likely that both groups dripped sweat to the same extent. In addition to the evaporation of sweat, it is worth noting that skin temperature (and thus, dry heat loss) was similar between groups in the present study, despite HF exhibiting a lower skin blood flow than CON. Indeed, we measured skin temperature using the standard practice of thermistors placed on the skin surface; however, this method does not necessarily represent sub-dermal tissue temperature, but rather acts as an interface temperature between the body ‘shell’ and the surrounding environment. Consequently, the dynamics of heat exchange at the skin surface via convection/radiation and evaporation will likely dilute the effect of differences of skin blood flow on our measurement of skin temperature, particularly for the relatively modest (albeit practical) degree of heat strain induced in the present study.

While both groups in the present study were matched for age, gender, and body mass and surface area, it is worth noting that body fat percentage was not taken into consideration. It is known that the specific heat capacity of fat tissue (2.97 kJ/kg/°C) is lower than lean tissue (3.66 kJ/kg/°C) (37). Consequently, a similar cumulative body heat storage would have theoretically elevated core temperature in individuals with a greater body fat percentage. Recently, Dervis and colleagues (37) demonstrated that a 20% difference in body fat percentage between experimental groups may lead to a greater change in core temperature in the group with a higher body fat percentage. Given that BMI was similar in HF and CON in the present study, it is unlikely that a 20% difference in body fat percentage existed between groups. Therefore, it is within reason to suggest that any thermoregulatory implications due to the influence of body fat percentage in the present study were negligible.

This study examined NYHA Class I-II HF patients, which limits the generalization of our findings to those patients with mild disease. Furthermore, the present study examined stable, well-compensated HF patients who continued with standard care procedures, which included taking a variety of cardiovascular medications. For example, beta-blockers have been shown to attenuate skin blood flow responses during thermal challenges in young healthy individuals (38). Indeed, given that beta-blockade is a standard first line therapy for HF, and that all HF patients in the present study were taking beta-blockers, we cannot exclude the possibility that the thermoregulatory responses observed in HF may have been confounded by concurrent use of medication. Whilst we recognise the confounding influence of cardiovascular medications, we did not attempt to discontinue standard care procedures to allow for the extrapolation of data to the broader population of patients with compensated HF, and daily situations.

Perspectives and significance

Determining how HF influences thermoregulatory responses during exercise has important mechanistic and practical implications. There is now strong evidence that regular physical activity in HF leads to a reduction in the severity of HF-related symptoms, decreased morbidity and mortality and improved health-related quality of life (39, 40). Hence, therapeutic exercise, prescribed through rehabilitation programs, remains a key HF management strategy. Whilst many centre-based rehabilitation programs may be run in climate-controlled indoor facilities, individuals with HF are encouraged to undertake regular, home-based exercise (39, 40). For individuals with mild disease (i.e., NYHA Class I-II), this may entail exercise performed in varied environments (including outdoors and/or hot ambient conditions) and across a broad range of exercise intensities (including high-intensity exercise, implying high levels of metabolic heat production). Thus, the findings of the present study could contribute to improvements in the

management of the disease, particularly through the development of clear, clinical guidelines for the performance of physical activity outside of climate controlled facilities (e.g., outdoors) for HF patients.

Conclusion

During exercise at a fixed H_{prod} per unit mass, the findings of the present study demonstrate that rises in core temperature are greater in HF relative to CON, despite a similar potential for dry and evaporative skin surface heat loss and therefore, estimated cumulative body heat storage. While sweating appears preserved in HF, cutaneous vasodilation is greatly attenuated. As such, it appears that patients with HF are limited in their ability to regulate core temperature, secondary to poorer transport of internal heat to peripheral tissues.

Acknowledgements

The results of the present study do not constitute endorsement by the American College of Sports Medicine. The authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Grants

Bryce N. Balmain is supported by an Australian Government Research Training Program Scholarship.

Disclosures

None

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Figure legends

Figure 1. HR (Panel A), MAP (Panel B), SV (Panel C), and CO (Panel D) for HF and CON participants recorded at 10-min intervals during the sub-maximal cycling test. HR: heart rate; MAP: mean arterial pressure; SV: stroke volume; CO: cardiac output; HF: heart failure; CON: control. Data are mean \pm SEM.

Figure 2. T_{rec} (Panel A) and T_{sk} (Panel B) for HF and CON participants recorded at 10-min intervals during the sub-maximal cycling test. T_{rec} : rectal temperature; T_{sk} : skin temperature; HF: heart failure; CON: control. Data are mean \pm SEM. [†]Significant group*time interaction, $p < 0.05$.

Figure 3. CVC (Panel A) and LSR (Panel C) values recorded at 10-min intervals during the sub-maximal cycling test, and changes in CVC (Panel B) and LSR (Panel D) in response to increases in T_b for HF and CON participants. CVC: mean cutaneous vascular conductance; LSR: local sweat rate T_b : mean body temperature; HF: heart failure; CON: control. Data are mean \pm SEM. [†]Significant group*time interaction, $p < 0.05$.

Figure 1

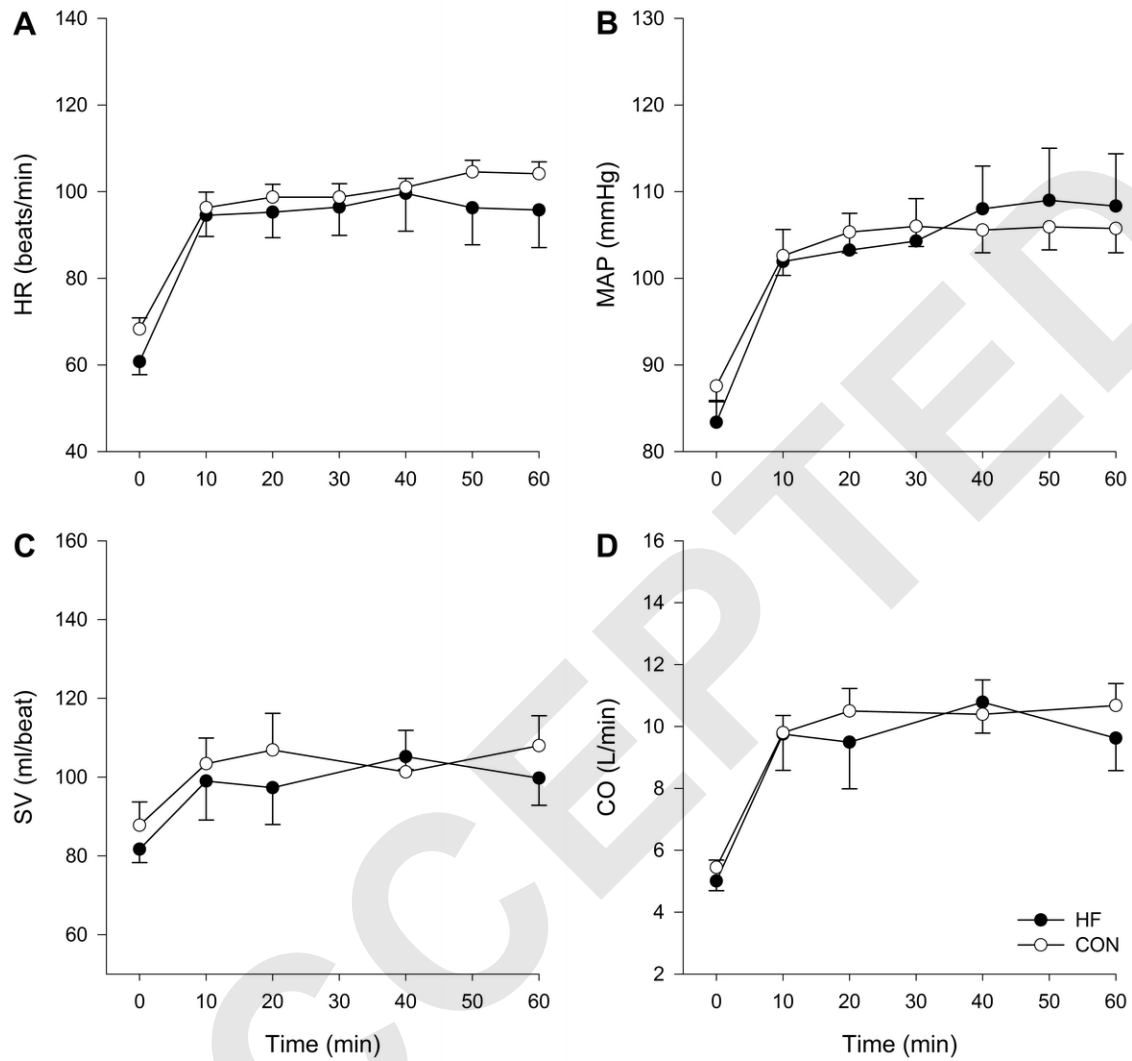


Figure 2

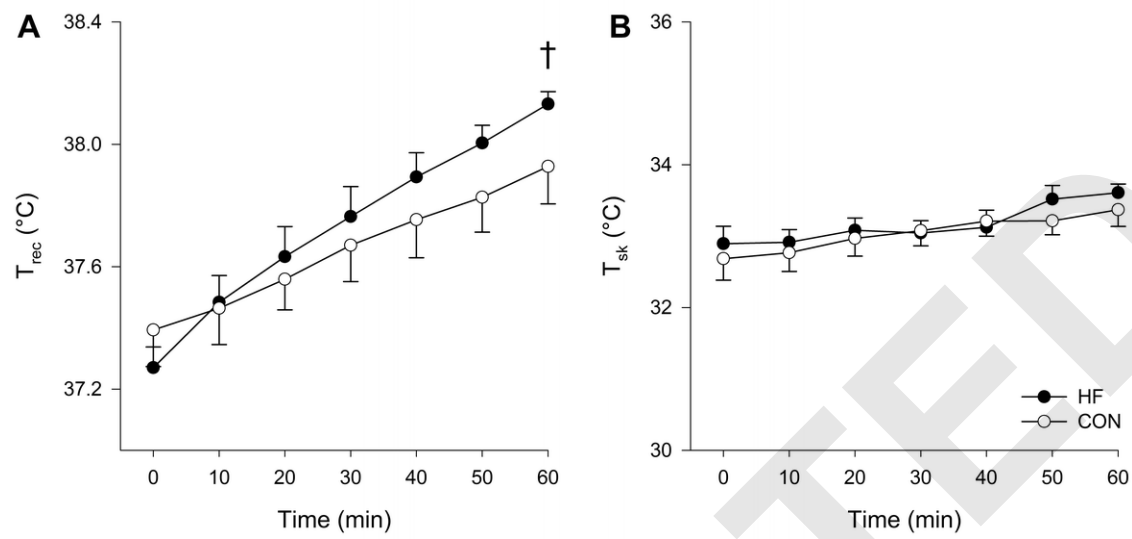


Figure 3

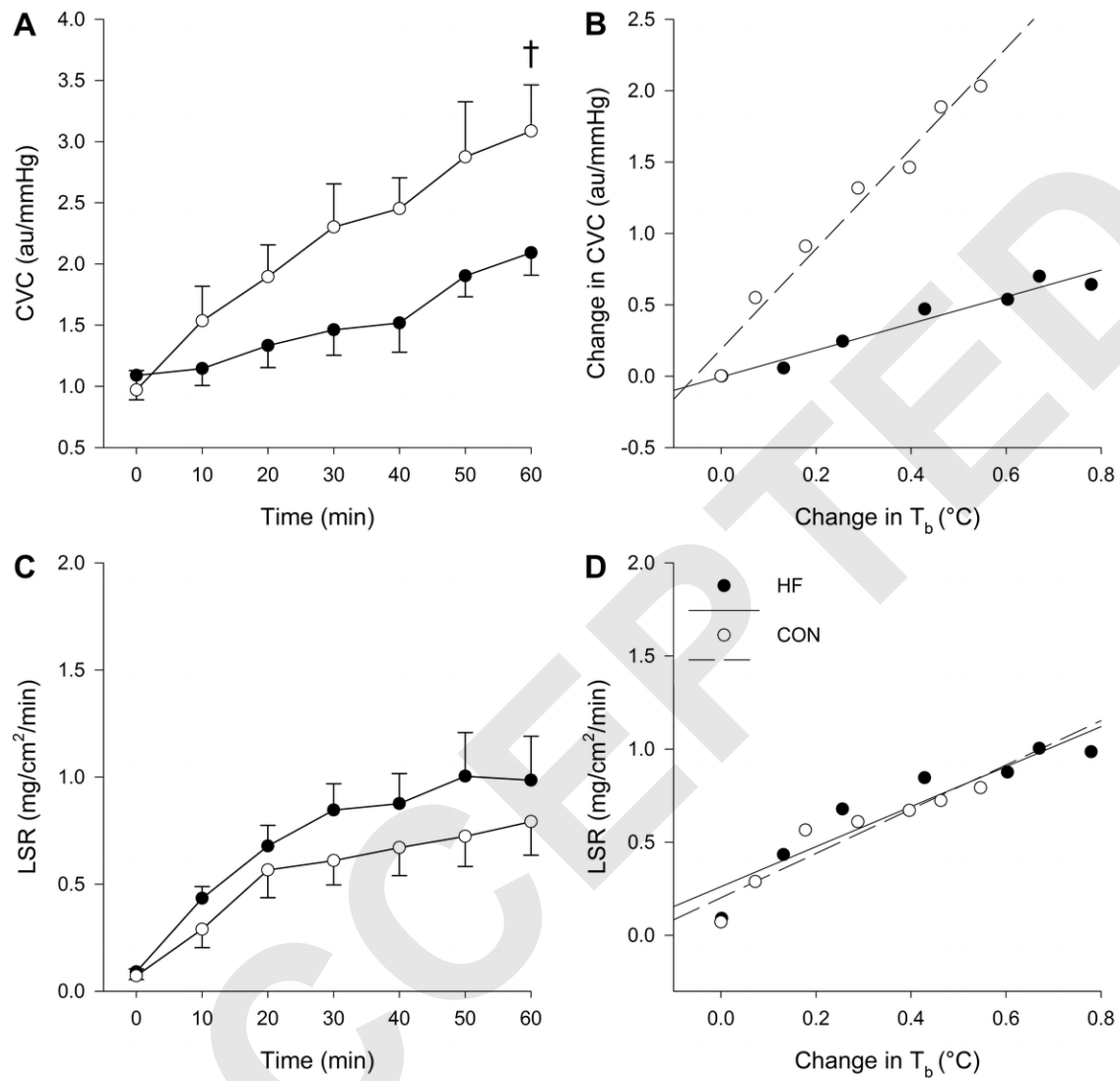


Table 1. Participant characteristics

<i>Demographic and functional measures</i>	HF	CON
Age (yr)	62 ± 7	61 ± 7
Height (m)	1.7 ± 6.0	1.8 ± 5.7
Body mass (kg)	90 ± 13	84 ± 12
Body mass index (kg/m ²)	29.3 ± 4.6	25.9 ± 3.2
Body surface area (m ²)	2.0 ± 0.2	2.0 ± 0.2
Resting mean arterial pressure (mmHg)	89 ± 4	93 ± 3
Resting heart rate (beats/min)	62 ± 12	64 ± 7
Peak heart rate (beats/min)	118 ± 15	151 ± 22
$\dot{V}O_{2\text{peak}}$ (L/min)	1.7 ± 0.4	2.9 ± 0.5*
$\dot{V}O_{2\text{peak}}$ (ml/kg/min)	19.1 ± 5.2	34.1 ± 6.6*
Peak power (W)	118 ± 24	211 ± 48*
Left ventricular ejection fraction (%)	44 ± 11	66 ± 8*
New York Heart Association Class (I:II)	3:7	
<i>Cardiovascular medications</i>		

ACE inhibitors	8 (80%)
Beta-blockers	10 (100%)
Diuretics	8 (80%)
Lipid-lowering	6 (60%)
Anti-coagulants	4 (40%)

Data are mean \pm SD. HF: heart failure participants; CON: control participants; $\dot{V}O_{2peak}$: peak oxygen uptake; ACE: angiotensin-converting-enzyme. *Significantly different between HF and CON participants, $p < 0.05$.

Table 2. Mean heat balance parameters for HF and CON groups

	HF	CON
<i>Metabolic heat production and evaporative heat balance requirements</i>		
H_{prod} (W)	338 \pm 43	323 \pm 31
H_{prod} (W/kg)	3.8 \pm 0.5	3.9 \pm 0.3
H_{prod} (W/m ²)	166 \pm 16	160 \pm 7
E_{req} (W/m ²)	140 \pm 15	136 \pm 7
E_{max} (W/m ²)	201 \pm 5	199 \pm 11
w_{req}	0.70 \pm 0.08	0.69 \pm 0.06
<i>Cumulative heat balance parameters estimated using partitional calorimetry</i>		
H_{prod} (kJ)	1111 \pm 201	1121 \pm 121
H_{dry} (kJ)	66 \pm 19	67 \pm 22
H_{res} (kJ)	83 \pm 22	92 \pm 18
E_{sk} (kJ)	808 \pm 159	772 \pm 154
S (kJ)	154 \pm 106	189 \pm 177

Data are mean \pm SD. HF: heart failure participants; CON: control participants; H_{prod} : metabolic heat production; E_{req} : evaporative requirements for heat balance; E_{max} : maximum

rate of evaporation possible in the ambient environment; w_{req} : skin wettedness required for heat balance.

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Table 3. Onset threshold and thermosensitivity of thermoeffector responses

	HF	CON
<i>Onset threshold of thermoeffector responses ($\Delta^{\circ}\text{C}$)</i>		
Skin blood flux	0.08 \pm 0.05	0.06 \pm 0.06
Local sweat rate	0.08 \pm 0.06	0.03 \pm 0.04
<i>Thermosensitivity of thermoeffector responses</i>		
Cutaneous vascular conductance (au/mmHg/ $^{\circ}\text{C}$)	0.89 \pm 0.64	4.02 \pm 2.06*
Local sweat rate (mg/min/cm ² / $^{\circ}\text{C}$)	1.32 \pm 0.48	1.22 \pm 0.75

Data are mean \pm SD. HF: heart failure participants; CON: control participants. * Significantly different between HF and CON participants, $p < 0.05$.