Impaired skin blood flow response to environmental heating in chronic heart failure

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Aims We examined the thermoregulatory response to heat exposure in patients with chronic heart failure.

Methods and results Skin blood flow (SkBF) was measured in HF subjects and matched controls. Cutaneous vascular conductance (CVC) was calculated from laser-Doppler SkBF and blood pressure. To assess the nitric oxide contribution to thermoregulatory responses, subcutaneous microdialysis membranes were placed beneath the laser-Doppler probes to infuse NG-nitro-L-arginine methyl ester (L-NAME), or Ringer’s solution. Core (Tc) and skin temperatures (five sites, Ta) were continuously recorded. Subjects were studied during normothermia then at 38 °C, 50%RH within a climate chamber. Tc and Ta did not differ between HF and controls during normothermia and heating induced similar increases in both groups. During heating, CVC rose in both groups, but significantly less so in HF (HF 43.9 ± 7.8 vs. controls 58.0 ± 7.5% CVCmax, P < 0.05). L-NAME attenuated SkBF responses in the control (58.0 ± 7.5 vs. 34.6 ± 5.1% CVCmax, P < 0.001) and HF subjects (43.9 ± 7.8 vs. 27.0 ± 2.2% CVCmax, P < 0.005), with a larger effect evident in the controls (P < 0.05).

Conclusion HF patients exhibit impaired thermoregulatory responses to heat exposure. Lower SkBF in HF, which defends blood pressure during heat exposure, also predisposes these subjects to heat intolerance.

Introduction

During environmental heat exposure in humans, blood is distributed to the compliant skin vasculature to facilitate heat loss. Maximal skin blood flow (SkBF) can exceed resting cardiac output in humans1 and the potential for large decreases in peripheral vascular resistance may compromise blood pressure regulation. Competition for limited maximal cardiac output therefore exists between the skin, to subserve thermoregulatory demands, and central blood pressure regulation. Observational studies suggest that, during climatic heat waves, excess cardiovascular mortality and morbidity occur, particularly in those with a prior heart condition.2 In the 2003 heat wave in Western Europe, it was estimated that over 10 000 excess deaths occurred in France alone3 and heat stress has been linked to increased platelet count, blood viscosity, plasma cholesterol, and mortality from coronary and cerebral thrombosis.4 It has also been suggested that patients with chronic heart failure (HF) are at particular risk of complications related to heat injury5 and, anecdotally, it is clear that during summer in countries such as Australia, HF patients maintained on vasodilators and diuretics frequently have difficulty with postural dizziness, necessitating reduction in drug therapy, sometimes involving temporary cessation of prognostically important ACE-inhibitor or β-blocker therapy. Despite the clinical relevance of this problem, few studies exist in the literature investigating the mechanisms of heat intolerance in patients with compromised cardiac function.3

In a classic study, Zelis et al.6 used iontophoresis of the forearm to establish that SkBF is impaired at rest in HF patients. However, this study was not designed to compare thermoregulatory responses between HF subjects and controls and was undertaken before the era of direct Doppler SkBF measurement. In the present study, we therefore compared cardiovascular and SkBF responses of HF patients and matched controls during heat exposure in a custom-designed environmental chamber; we hypothesized that heat-induced increases in cutaneous blood flow would be impaired in subjects with HF. As there is evidence for impaired nitric oxide

KEYWORDS
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(NO)-mediated vasodilator function in conduit and resistance vessels of subjects with HF.7-9 We also hypothesized that skin microvasculature NO-mediated responses would be impaired in these subjects during whole body heating. The antagonist N(G)-nitro-L-arginine methyl ester (L-NAME) was therefore employed to determine the contribution of NO to SkBF during heat exposure in both groups.

Methods

Subjects

Seven male subjects (48.7 ± 4.6 years) were recruited from the Advanced Heart Failure service at Royal Perth Hospital (RPH) after undertaking a screening program consisting of medical history and examination, haematological, and biochemical profile. Patients were eligible if they had dilated cardiomyopathy and were in NYHA class II–III, with ejection fraction <40% by echocardiography or radionuclide ventriculography, and had been stable on their chronic therapy for at least 2 months with no clinical signs of HF. Exclusion criteria included smoking, diabetes, renal impairment, hypercholesterolaemia (total cholesterol >6.0 mmol L⁻¹), hypertension (BP >140/90 mmHg), dermatological conditions, or a history of heat intolerance. Medications, notably angiotensin-converting enzyme (ACE)-inhibitors, diuretics, digoxin, lipid lowering drugs, nitrates, and β-blockers, did not constitute exclusions. Twelve subjects were initially screened for entry to the study; four were deemed ineligible because of aspirin administration; one subject declined involvement. Aspirin constituted an exclusion because of its effects on thermogenesis.

A group of seven healthy control male subjects were recruited via advertisement on the University and Hospital campuses (Table 1). Subjects were selected to match the HF group according to their age, weight, and body mass index (BMI). That is, patient to control matching was undertaken in an attempt to select a valid comparison group for the HF subjects. Aspirin constituted an exclusion owing to its effects on thermogenesis. Prior to all testing, the purpose and experimental procedures involved in the study were explained to all subjects and informed consent was obtained. The study protocol was approved by both the Royal Perth Hospital and The University of Western Australia Ethics Committee and the study procedures complied with the Declaration of Helsinki.

Experimental protocol

Subjects attended the environmental testing facility at The University of Western Australia on one occasion. They were fasted for 4 h prior to being assessed and were asked to refrain from exercise or consuming caffeine or alcohol for 24 h prior to their attendance. The study protocol (Figure 1) ran for approximately 230 min. Upon arrival, subjects were weighed on a sensitive electronic balance prior to skin cannulation. Following a 70-min stabilization period, during which they were seated under eutermic conditions (26.0 ± 3.0 °C), one of the two microdialysis sites was infused with 10 mM L-NAME (Cilinalfa, Laufelfingen, Switzerland), a inhibitor of NO synthase production, for a period of 30 min to determine the contribution of NO to SkBF under normothermic conditions. At the end of this period, baseline recordings of SkBF, BP, core temperature, and skin temperature were recorded over a period of 10 min, with BP readings taken at 3-min intervals using manual auscultation. The alternate microdialysis site was continuously perfused with Ringer’s solution, both sites perfused at a pump rate of 2 μL min⁻¹.

Following the normothermic period described earlier, subjects remained in the armchair, which was wheeled into a heated chamber set at 38 °C and 50% relative humidity for a further 90 min. All experimental measures were continuously monitored, with L-NAME administered through one site and Ringer’s solution, the control site. At the end of the 90-min protocol, 28 mM sodium nitroprusside (SNP, David Bull Laboratories, Victoria, Australia) was infused at a rate of 4 μL min⁻¹ through each microdialysis fibre for 10 min to provide a benchmark maximal vasodilation at each site.12,14

Experimental measures

The skin sites on the proximal and ventral aspect of the left forearm were shaved on the day prior to testing, to eliminate the effects of localized weal and inflammation. On the day of testing, subjects arrived wearing light, loose fitting clothing. A 12-lead ECG was used to continually monitor heart rate and rhythm.

Microdialysis fibre instrumentation and assessment of forearm SkBF

After being seated comfortably in a custom-designed armchair, the left arm was supinated and supported for insertion of microdialysis fibres and consequent measurement of laser-Doppler flux (LDF). The insertion sites were marked on the skin and cold packs were applied as temporary anaesthesia. Two microdialysis fibres (MD 2000, Bioanalytical Systems, IN, USA), containing 10 mm long 20 kDa membranes, were inserted by first placing a 25-gauge needle subdermally for threading and placement. The needles were then removed and the embedded fibres perfused with Ringer’s solution at a rate of 2 μL min⁻¹ using a microinfusion pump (Model 22, Harvard Apparatus, MA, USA). To obtain an index of SkBF, cutaneous red cell flux was measured by placing integrated laser-Doppler probes (Periflux System, Perimed AB, Sweden) above each microdialysis fibre. Each of these probes consisted of a seven ‘probe-tip’ with a transmitting fibre and a receiving fibre. The values from each ‘probe-tip’ are optically integrated into one value. This method allows measurement over a larger area in tissues with spatial variations in blood perfusion. The laser-Doppler probe signals were continuously monitored via an online software chart recorder (PowerLab, ADInstruments, NSW, Australia). At each designated study time-point, SkBF was assessed by averaging LDF, measured in perfusion units (PU), over a stable 1-min period. These data were subsequently converted to cutaneous vascular conductance (CVC), calculated as PU/MAP (mmHg); where MAP (mean arterial pressure) was calculated

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Subject characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Controls</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.7 ± 4.6</td>
</tr>
<tr>
<td>BMI</td>
<td>25.7 ± 2.2</td>
</tr>
<tr>
<td>Plasma lipids (mmol L⁻¹)</td>
<td>4.6 ± 0.6</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>HDL-C</td>
<td>3.0 ± 0.4</td>
</tr>
<tr>
<td>Resting blood pressure (mmHg)</td>
<td>100 ± 5</td>
</tr>
<tr>
<td>Systolic</td>
<td>63 ± 4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76 ± 4</td>
</tr>
<tr>
<td>Resting mean arterial pressure (mmHg)</td>
<td>100 ± 5</td>
</tr>
<tr>
<td>Resting heart rate (b.p.m.)</td>
<td>71 ± 5</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>27 ± 2</td>
</tr>
<tr>
<td>End-diastolic diameter (cm)</td>
<td>6.8 ± 0.3</td>
</tr>
<tr>
<td>VO2 peak (mL kg⁻¹ min⁻¹)</td>
<td>18.9 ± 2.3</td>
</tr>
</tbody>
</table>

Values are means ± SE. Resting arterial pressures differed significantly between the groups. All analyses were performed using paired t-tests.
as \( (\langle SBP - DBP \rangle \times 0.33) + DBP \) from contemporaneous blood pressure measures in the contralateral arm. Values were then expressed relative to the maximal CVC achieved during infusion of 28 mM SNP, as \%CVCmax, the preferred method of data expression adopted in the literature.11,13,15–17

Assessment of core and mean skin temperature
A thermocouple consisting of a thin flexible plastic probe (RET-1, Physitemp Instruments, NJ, USA) was placed approximately 6 cm beyond the anal sphincter and connected to an isolated pre-amplifier (BAT-12, Physitemp Instruments) for the measurement of core temperature. We selected rectal temperature as an index of core temperature (Tc) because, although it has longer response time than other measures, it is an accurate method for assessment of Tc during heating.18

Whole-body mean skin temperature (Tsk) was determined from the mathematical weighted sum of measures,19 derived from separately placed skin thermistors (MLT409, ADInstruments) taped in position using Fixomull air permeable woven surgical tape. Thermistors were placed just below the sternal notch on the anterior chest wall, the midpoint of the lateral surface of the left forearm, the midpoint of the anterior surface of the left thigh, and the midpoint of the lateral surface of the lower left leg. Tsk was calculated as: 

\[
T_{sk} = 0.3(T_{sternum} + T_{forearm}) + 0.2(T_{thigh} + T_{calf})
\]

Data analysis
All data were recorded continuously at 40 Hz using a 16-channel computerised data-acquisition system (PowerLab and Chart5, AD-Instruments). Post hoc mean data were calculated, over 1-min periods, at designated study time-points. Baseline data were averaged from three 1-min measures, collected 90 min after microdialysis probe placement. Following chamber entry, 1-min averages for all variables were recorded at 10, 15, 30, 45, 60, 75, and 90 min. Changes in all variables over time were assessed using a mixed model approach (PROC MIXED, SAS, SAS Institute, NC, USA). This model was adjusted for age and BMI, used group as a fixed factor, case control pair as a random factor, time as a continuous variable, and examined the group x time interaction as the primary term of interest. Although weight was used as a matching criterion, BMI is a function of weight and therefore, only BMI was included in the model. All of these comparisons were performed on the baseline, 75, and 90 min data sets, unless otherwise indicated, with significance set at the 5% probability level. Results were recorded as mean values ± standard errors. Paired t-tests were used to compare data at baseline and also 90 min post-chamber entry.

Sample size was based on a power test performed on data investigating the effect of L-NAME infusion on \%CVCmax responses to body heating. In the study of Kellogg et al.,17 L-NAME was associated, on average, with a 15% difference in CVC (SD 8%). Assuming \( \alpha = 0.05 \), six subjects are required to demonstrate a difference with L-NAME with \( \beta \) of 80%.

Results
Subject characteristics
The aetiology of five of the HF patients (NYHA class II–III) was idiopathic dilated cardiomyopathy, the remaining subjects had ischaemic HF. Haemoglobin concentration was 139 ± 5 g L\(^{-1}\), haematocrit 41 ± 2%, and creatinine 95 ± 7 \( \mu \)L min\(^{-1}\). All patients were treated with an ACE-inhibitor and diuretics, three were on selective \( \beta \)-blockade, three received carvedilol, two were anticoagulated with warfarin, three were on digoxin, two on amiodarone, and one patient was treated with a statin. No subjects were taking nitrates. There was no significant difference in age, BMI, or plasma lipids between groups (Table 1). The HF subjects exhibited significantly lower blood pressures, possibly reflecting medication use in these subjects.

Core and skin temperature responses
At baseline, \( T_c \) averaged 35.8 ± 0.1°C in controls and 36.1 ± 0.1°C in the HF subjects (Figure 2A, \( P = 0.09 \), paired t-test). Increases in \( T_c \) from baseline was significantly related to time by the mixed model approach (\( P < 0.001 \)) and the \( T_c \) increase from baseline to 90 min of heating was significant in both controls (36.1 ± 0.1°C, \( P = 0.03 \)) and HF subjects (36.4 ± 0.3°C, \( P = 0.002 \)) when compared with paired t-test. However, the magnitude of increase in \( T_c \) did not differ between the groups (\( P = 0.72 \) for time x group interaction by mixed models approach).

At baseline, \( T_{sk} \) averaged 31.1 ± 0.9°C in controls and 30.9 ± 1.0°C in HF subjects (\( P = 0.89 \), paired t-test; Figure 2B). Chamber heating increased \( T_{sk} \) significantly in both groups (\( P = 0.0001 \), mixed models time effect) with significant differences between baseline and peak \( T_{sk} \) in both groups by paired t-test (35.2 ± 0.9°C controls \( P = 0.002, 35.5 ± 0.1°C \) HF; \( P = 0.0001 \)). However, no significant difference existed in the magnitude of change in \( T_{sk} \) with chamber heating between groups (\( P = 0.52 \) for time x group interaction by mixed models approach).
Impaired SkBF in chronic heart failure

Figure 2 (A) Core (Tc) and (B) mean skin (Tsk) temperature responses to heat exposure in the environmental chamber in control (open circle) and HF (closed square) subjects. At baseline, Tc and Tsk did not significantly differ between control and HF subjects when compared with t-tests. Chamber heating increased Tc (P < 0.001) and Tsk (P < 0.0001) significantly in both groups (mixed models time effect), but no significant difference existed in the magnitude of change in Tc or Tsk with chamber heating between groups (mixed models time x group interaction).

Haemodynamic responses

MAP differed significantly between groups at baseline and throughout the protocol (P < 0.001 for group effect by mixed models approach, Table 1, Figure 3A), although no time x group interaction was evident (P = 0.72). The change in heart rate in response to chamber heating differed significantly between the groups (P < 0.05 for time x group interaction by mixed models approach). Heart rate rose from 62.7 ± 1.8 at baseline to 76.8 ± 2.1 b.p.m. following chamber heating in controls and from 71.3 ± 5.5 to 76.4 ± 5.0 b.p.m. in HF subjects.

CVC responses

Effect of chamber heating on %CVCmax responses within and between groups

The %CVCmax responses of control and HF groups to chamber heating at the Ringer’s sites are presented in Figure 4A. At baseline, %CVCmax in the site perfused with Ringer’s solution averaged 14.8 ± 3.2% in HF subjects and 14.8 ± 2.6% in control group, data which did not differ significantly (P = 0.99, paired t-test). Following chamber entry, the interaction between group and time at the Ringer’s sites using the mixed models approach differed significantly (P = 0.0277). Figure 4B presents Ringer’s site %CVCmax data which corresponded with a given change in Tc from baseline (Figure 4B) within subjects. Based on the data provided earlier, controls exhibited consistently higher responses than the HF subjects for levels of rise in Tc.

Effect of NO inhibition with L-NAME on %CVCmax responses groups

In control subjects, mixed models analysis revealed significant time (P < 0.001) and interaction (P < 0.001) effects between the Ringer’s and L-NAME sites following chamber entry. The peak (i.e. 90 min) %CVCmax observed in response to chamber heating at the Ringer’s site (58.0 ± 7.5%) was significantly higher (P = 0.006) than that observed at the L-NAME treated site (34.6 ± 5.1%, paired t-test; Figure 5A). Differences were also evident between sites at the 60 min (P = 0.019) and 75 min (P = 0.015) time-points. Similarly, mixed models analysis revealed significant time (P < 0.001) and interaction (P < 0.005) effects between the Ringer’s and L-NAME sites following chamber entry in HF subjects. Peak %CVCmax at the Ringer’s site (43.9 ± 7.8%) was significantly higher than that at the L-NAME treated site (27.0 ± 2.2%, P = 0.027; Figure 5B), although no such differences were evident at other heating time-points in this group. When mixed models analysis was performed on the differences between Ringer’s and L-NAME sites, there was a significant difference between the groups (P < 0.05).

Discussion

The present study is the first to compare the effects of whole body heating on skin vasodilation, and the contribution of NO to this vasodilation, in healthy subjects and those with chronic HF. Using a climate chamber to induce a controlled hot ambient environment, we observed...
significant lower CVC responses to chamber heating in HF subjects, despite both groups entering the chamber with similar core and skin temperatures, and experiencing similar changes in these variables across the heating period. This result demonstrates that the physiological response to heating is abnormal in HF subjects.

During passive heating in healthy humans, demand for blood flow to the skin is increased in order to facilitate the process of thermoregulatory heat loss. The large capacitance of the skin vasculature may lead to competition for limited cardiac output between blood flow distribution to the skin and the requirement for BP regulation. This competition is particularly germane in patients with HF, in whom reduced cardiac output may predispose to a greater risk of heat intolerance in these subjects. Heat waves may be attenuated as a counter-regulatory response to heating, in HF subjects, possibly because of the effect of nitrates or b-blockers; or the well-established chronotropic incompetence characteristic of these patients.

The above findings are consistent with those of the classic physiological study of Zelis et al., which performed plethysmographic assessment of forearm blood flow in the presence and absence of skin epinephrine iontophoresis; the subtraction of iontophoretic flow from total forearm flow taken to represent forearm skin volume. They demonstrated impaired resting SkBF in HF subjects and also impaired blood flow in HF subjects during a brief period of ‘strenuous’ exercise. Our data from the Ringer’s infusion site reinforce their conclusion, that the deceased cutaneous vasodilation in HF may contribute to the heat intolerance often seen in these subjects.

Previous studies in healthy subjects indicate that the rise in SkBF because of increase in core temperature is mediated in part by NO. In the present study, we observed a significant contribution of NO to heat-induced skin vasodilation in controls, but less evidence for a contribution in HF subjects; significant L-NAME-induced constriction was evident at several of the heating time-points in controls but only at the final time-point in HF subjects. This raises the possibility...
that the impaired SkBF response to heating observed in HF subjects may be in part explained by impaired NO function, a finding consistent with the impaired NO bioactivity in both conduit and resistance vessel beds of HF patients.7–9 Nonetheless, CVC measures remained significantly elevated relative to normothermia even in the presence of L-NAME in both groups, suggesting that other dilators mediate a substantial component of the response to heating. Future studies, employing similar microdialysis techniques, should investigate the impact of combined and independent inhibition of other known dilator agents and the possibility of synergistic interaction between these agents in HF.

There are several important limitations of the present study. Based on previous studies which utilized hot water perfusion suits,11,15,16,25,26 we assumed that 38°C 50%RH would be sufficient to invoke a physiologically significant increase in $T_C$ in both the control and HF subjects. The purpose of our study was primarily to emulate a naturally occurring hot environment and, despite the magnitude being modest, the rise in $T_C$ and $T_{Sk}$ was significant in both groups. It is likely, however, that longer exposure or exposure to a higher temperature or humidity, or addition of exercise to the environmental stress, would result in different thermoregulatory responses between the groups and this will be an interesting avenue for future studies.

Another limitation is that responses of the HF patients may have been confounded by concurrent medication use, although subjects were administered selective $\beta$-blockers and a recent carefully performed study indicated that $\beta$-adrenoceptors play no role in mediating cutaneous vasodilation at rest or during whole body heating.27 In those HF patients on carvedilol, $\alpha$-blockade might be expected to produce higher blood flows, rather than the impaired responses we observed. We did not attempt to discontinue therapy, partly on ethical grounds, but also because we wished to describe the responses of ‘typical’ patients. In any event, there was no difference in CVC responses to heat exposure in the subgroup of HF subjects administered carvedilol, indicating that exaggerated $\alpha$-adrenoceptor activity is unlikely to be responsible for the impaired blood flow responses to the skin in CHF. Our data are valid in their description of the potential impact, in HF patients receiving optimal contemporary management, of living in a warm climate on the performance of tasks of daily living. Finally, thresholds for sweating and active vasodilation are influenced by cardiorespiratory fitness and it is possible that the lower SkBF responses we observed in HF subjects may, in part, relate to decreased cardiorespiratory fitness levels in these individuals. Although our control subjects were sedentary and we matched activity levels, future studies should carefully characterize and match cardiorespiratory fitness levels between groups.

In conclusion, HF patients exhibit impaired thermoregulatory responses to heat exposure. Lower SkBF in HF, which defends blood pressure during heat exposure, also predisposes these subjects to heat intolerance.

Conflict of interest: none declared.

References


