Effects of Heat Stress on Thermoregulatory Responses in Congestive Heart Failure Patients

Jian Cui, PhD; Armin Arbab-Zadeh, MD; Anand Prasad, MD; Sylvain Durand, PhD; Benjamin D. Levine, MD; Craig G. Crandall, PhD

Background—Clinical observations suggest that tolerance to heat stress may be impaired in patients with cardiovascular diseases, particularly those associated with impaired ventricular function and congestive heart failure (CHF). However, thermoregulatory function during a controlled heat stress challenge in patients with CHF has not been studied.

Methods and Results—To test the hypothesis that thermoregulatory responses are attenuated in such patients, we assessed cutaneous vasodilation and sweat rate in patients with stable class II–III CHF and in matched healthy subjects during passive whole-body heating. Whole-body heating induced a similar increase in internal temperature (≈0.85°C) in both groups. The sweating responses in patients with CHF were not significantly different from that in control subjects. In contrast, the elevation in forearm cutaneous vascular conductance in patients with CHF was reduced by nearly 50% relative to the control subjects (3.8±0.8 versus 6.9±1.0 mL/100 mL tissue per minute per 100 mm Hg, P=0.04). Moreover, maximal cutaneous vasodilator capacity to direct local heating in patients with CHF was also significantly lower than in control subjects, suggesting that vascular remodeling may be limiting cutaneous vasodilation during hyperthermia.

Conclusions—These observations suggest that patients with CHF exhibit attenuated cutaneous vasodilator responses to both whole-body and local heating, whereas sweating responses are preserved. Attenuated cutaneous vasodilation may be a potential mechanism for heat intolerance in patients with CHF. (Circulation. 2005;112:2286-2292.)

Key Words: blood flow ■ heart failure ■ hemodynamics ■ cardiovascular diseases ■ nervous system, autonomic...
TABLE 1. Clinical Findings and Medications for Each of the Patients With Congestive Heart Failure

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LVEF indicates ejection fraction; medications, class of medication each subject was taking; and ACE inhibitor/ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

the aforementioned physiological adaptations to CHF, we hypothesized that cutaneous vasodilation and sweating responses during heat stress would be attenuated in patients with CHF.

Methods

Subjects

A total of 14 patients with CHF (10 male, 4 female; age, 51 ± 4 years; height, 177 ± 2 cm; weight, 85 ± 5 kg) and 14 healthy control subjects (10 male, 4 female; age, 51 ± 4 years; height, 176 ± 3 cm; weight, 82 ± 4 kg) matched for age, gender, body mass index, and race participated in this study (Table 1). Thirteen patients with CHF (subjects 1 to 13 in Table 1) and 13 matched control subjects participated in protocol 1. Six patients with CHF (subjects 9 to 14 in Table 1) and 6 control subjects participated in protocol 2. Patients with CHF were eligible on the basis of the following inclusion criteria: (1) New York Heart Association class II–III after stabilization; (2) ejection fraction <0.40 determined by echocardiography, (3) systolic blood pressure ≤140 mm Hg, and (4) no underlying aortic outflow obstruction as assessed by echocardiography. Patients were recruited from the heart failure clinics at Parkland Memorial Hospital and St Paul University Hospital, both teaching hospitals of the University of Texas Southwestern Medical Center at Dallas, as well as from the private practices of 2 major cardiology groups specializing in heart failure care at Presbyterian Hospital of Dallas. Patients with ischemic and nonischemic pathology were considered eligible for this study. Patients with CHF were excluded from the study if they were diagnosed with diseases known to impair thermoregulatory responses, such as diabetes mellitus.14 Table 1 lists the patients’ physical characteristics, ejection fraction, and the medication class each patient was taking. The mean ejection fraction of the healthy control subjects was 64 ± 1%. Most of the patients (12 of 14) reported that they participated in some form of aerobic exercise (eg, walking, biking, and so forth); however, none participated in a structured exercise training program. All subjects refrained from caffeine, nicotine, alcohol, and exercise 24 hours before the study. This study was approved by the institutional review boards of the University of Texas Southwestern Medical Center and the Presbyterian Hospital of Dallas. Written informed consent from each subject was obtained before participation in this study.

Measurements

Internal temperature (Tcore) was measured either by esophageal temperature probe (YSI) with a thermistor placed at a distance of 25% standing height or by an ingestible telemetric temperature pill (HTI Technologies). Both of these methods provide an accurate measurement of internal temperature.15,16 Mean skin temperature was obtained from the electrical average of 6 thermocouples attached to the skin.17 The subject was dressed in a tube-lined suit that permitted control of skin temperature by changing the temperature of the water perfusing the suit.18 Heart rate was obtained from the ECG signal interfaced with a cardiotachometer (CWE). Arterial blood pressure was measured from the upper arm by means of R-wave gated electrophygmonanometry (SutTech). Mean arterial pressure (MAP) was calculated as diastolic pressure plus one-third pulse pressure. Forearm skin blood flow was measured by means of 2 methods from an area not covered by the tube-lined suit. The first method uses integrating laser-Doppler probes to continuously measure skin blood flow19,20 from an area of approximately 28 mm². The second method measures forearm blood flow through venous occlusion plethysmography, with the increase in forearm blood flow during heat stress being entirely due to increases in skin blood flow.21–23 For both methods of skin blood flow assessment, vascular conductance was calculated from the ratio of blood flow to MAP. Forearm sweat rate was measured from 2.83 cm² area by means of capacitance hygrometry (Viasala), as previously described.18

Protocol 1: Thermal Response to Whole-Body Heating

In both groups, normothermic baseline data (ie, blood pressure, heart rate, forearm skin blood flow, and sweat rate) were collected, whereas 34°C water perfused the tube-lined suit worn by the subject. After ~6 minutes, whole-body heating began by elevating skin temperature to ~38°C by perfusing warm (~46°C) water through the water-perfused suit. Whole-body heating continued until Tcore increased a minimum of 0.7°C, which is sufficient to cause pronounced cutaneous vasodilation and sweating in healthy individuals.18,24,25 After this point, for patients with CHF, the heat stress continued until the patient requested the heat stress to be stopped. For the control subjects, the heating was stopped when the increase in Tcore reached the same level as the matched patient with CHF. Plethysmographic forearm blood flows and blood pressure were measured repeatedly throughout whole-body heating. After the heat...
Table 2. Hemodynamic and Thermal Responses to Whole-Body Heating in Patients With Congestive Heart Failure

<table>
<thead>
<tr>
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<th>Patients With CHF</th>
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<td>HR, bpm</td>
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MAP indicates mean blood pressure calculated from diastolic pressure plus one-third pulse pressure; HR, heart rate from ECG; Tsk, mean skin temperature; and Tcore, internal temperature.

*P<0.05 compared with normothermia; †P<0.05 compared with control subjects.

Number of subjects: 13 patients with CHF and 13 control subjects.

Results

Thermal and Hemodynamic Responses to Whole-Body Heating

Baseline Tcore was not different between groups (Table 2).
noted that in Figure 2, the subject number decreased after Tcore increased/1015°C because some subjects subjectively were unable to tolerate higher core temperatures. However, for each matched control subject, the heat stress was discontinued when Tcore increased to the same magnitude as that which occurred, heat stress was terminated for the matched subject at the same internal temperature elevation (FVC unit: mL/100 mL tissue per minute per 100 mm Hg).

Figure 2. Average increases in forearm cutaneous vascular conductance (FVC) during heat stress for both groups of subjects. FVC was calculated as forearm blood flow (measured by means of limb plethysmography) divided by mean arterial blood pressure x 100. The number of subjects in each group gradually decreased after an increase in core temperature of 0.7°C as subjects achieved their level of thermal tolerance in this experimental setting. When this occurred, heat stress was terminated for the matched subject at the same internal temperature elevation (FVC unit: mL/100 mL tissue per minute per 100 mm Hg).

Figure 3. Average increase in forearm sweat rate during heat stress for both groups of subjects. Whole-body heating was sufficient to induced sweating in both groups. The number of subjects in each group gradually decreased after an increase in core temperature of 0.7°C as subjects achieved their level of thermal tolerance in this experimental setting.

Maximal Cutaneous Vasodilator Capacity

Local heating of a forearm with the water spray device did not alter MAP or heart rate in either group. At the end of local heating with this device, the increase in forearm blood flow in patients with CHF (5.9 ± 1.2 mL/100 g tissue per minute) was significantly less relative to that in control subjects (10.2 ± 1.9 mL/100 g tissue per minute). This resulted in a significant attenuation in the calculated increase in forearm cutaneous vascular conductance in the patients with CHF during this mode of local heating (Figure 4). Moreover, the increase of cutaneous vasculature conductance in each CHF patient was consistently less relative to that person’s matched control subject. As outlined above, similar findings were observed with the discrete local heating protocol.

Discussion

The major novel finding of the present study is that cutaneous vasodilator responses to both whole-body and local heating are significantly reduced in patients with CHF, whereas sweating responses are not impaired in these patients. These observations suggest that impaired cutaneous vasodilation may be a key mechanism for heat intolerance in patients with CHF.

A number of studies report that adverse cardiac events occur at a higher frequency when environmental temperature is elevated,1–3 which suggests that thermal tolerance may be reduced in patients with cardiovascular disease. Patients with heart failure may be at particularly high risk because of their compromised hemodynamics and limited cardiac output reserve. However, before the present study systemic thermal regulatory responses to a heat stress challenge had not been investigated in patients with CHF. The present data clearly show that cutaneous vasodilation during whole-body heating...
is reduced in patients with CHF. On the other hand, sweat responses during the heat stress were not different between patients with CHF and control subjects (see Figure 3), suggesting intact temperature sensing, efferent sympathetic cholinergic innervation, and sweat gland function. Taken together, the present data suggest that the function of cutaneous vasodilation but not sweating is altered with CHF, and thus heat dissipation to a hyperthermic challenge will be attenuated in these patients.

The mechanism(s) for impaired vasodilator responses in patients with CHF remains speculative. At least 3 hypotheses may explain this observation: altered neural control of the cutaneous circulation, altered responsiveness to vasodilator neurotransmitters, and/or structural changes of the cutaneous vasculature. With regard to the first, control of human skin blood flow occurs through 2 distinct sympathetic pathways. The first, through sympathetic vasoconstrictor nerves, is engaged, and this sympathetic active vasodilator system is engaged, and this sympathetic active vasodilator system mediates 85% to 95% of the rise in skin blood flow in nonglabrous (ie, hairy) skin during whole-body heating. In healthy individuals, skin blood flow can increase upward to 8 L/min during pronounced whole-body heating. To maintain blood pressure in the face of a large reduction in vascular resistance that occurs with heat stress, cardiac output must increase. For example, Rowell et al have shown that during whole-body heat stress, cardiac output is capable of doubling (up to 13 L/min) in healthy individuals. Although cardiac output in patients with CHF exposed to heat stress has been shown to increase up to $\approx 3.6$ L/min per m², if this increase in cardiac output is insufficient to offset the reduction in vascular resistance, blood pressure will decrease. Such a reduction in blood pressure will evoke baroreflex mediated responses that have been shown to attenuate cutaneous vasodilation without altering sweating. Consistent with this hypothesis is the observation that blood pressure was well maintained in patients with CHF during the heat stress. Thus, attenuated cutaneous vasodilation may be necessary to prevent a reduction in blood pressure in patients with CHF with limited cardiac output reserve during heat stress, although this occurs at the expense of thermal regulatory control.

Instead of, or in combination with the aforementioned mechanism, altered nitric oxide–mediated mechanisms in patients with CHF may also impair cutaneous vasodilator responses to heating. It has been shown that production, release, and vascular responsiveness to nitric oxide is abnormal in patients with CHF, whereas studies have shown that $\approx 30\%$ of the elevation in cutaneous vascular conductance during indirect whole-body heating is mediated by nitric oxide–dependent mechanisms. Therefore, if nitric oxide production, release, and/or responsiveness are similarly attenuated in the skin of patients with CHF, this could explain a component of the observed reduction in cutaneous vasodilation during the whole-body heat stress.

In addition to altered responsiveness to vasoactive agents, structural changes in the cutaneous vasculature of patients with CHF may result in attenuated vasodilator responses to a heat stress. Sustained local heating causes cutaneous vasodilation through nitric oxide–dependent mechanisms. The present and previous findings show that local heating-induced cutaneous vasodilation is attenuated in patients with CHF. These observations are consistent with those of others showing that patients with CHF exhibit attenuated endothelium-dependent vasodilation of the peripheral circulation, including skin. However, it is recognized that the present results do not permit the discrimination between altered responsiveness to vasodilator agents, such as nitric oxide, from possible structural changes in the cutaneous vasculature with CHF, previously shown in these patients. With regard to the latter, in patients with CHF, structural alterations of cutaneous terminal arterioles have been reported, and these alterations may decrease distensibility and

Patients with CHF are characterized by an increase in sympathetic activity and increased plasma norepinephrine. Given these observations, attenuated cutaneous vasodilator responses during heat stress in patients with CHF could be due to enhanced cutaneous vasoconstrictor neural activity and/or reduced cutaneous active vasodilator activity, perhaps through a baroreflex mediated response.
increase stiffness of the cutaneous microvascular bed. Taken together, these findings suggest that attenuated vascular responsiveness to vasodilator agents and/or structural changes in the cutaneous vasculature may at least partially explain the observed attenuated vasodilator responses to whole-body heating.

Study Limitations
Like all treated patients with CHF, patients in the present study were taking a variety of cardiovascular medications. Patients in the present protocol did not take diuretics from when they woke up in the morning through the end of the study, but no other medications were withheld. This approach was selected because of concerns of the risk of exposing a patient with CHF to a severe heat stress in the absence of appropriate medical therapy. Thus, we cannot exclude the possibility that a drug or a combination of drugs may attenuate cutaneous vasodilation during exercise in healthy subjects taking β-blockers. However, in the present study, the magnitude of cutaneous vasodilation in the patients taking β-blocking agents was not different from the subjects not taking a β-blocker. Nevertheless, it is difficult to identify whether altered cutaneous vasodilatory responses in patients with CHF was attributed to CHF, medications used to treat this illness, or a combination of both. Importantly, regardless of the mechanism leading to the observed responses, patients with CHF who are treated for this disease will be at a higher risk for a heat-related injury because of altered cutaneous vasodilation during heat stress. Finally, studying patients receiving modern therapy, including ACE inhibitors/angiotensin receptor antagonists and β-blockers, allows the extrapolation of the results of this study to the broader population of patients with compensated CHF exposed to environmental heat stress.

The severity of the symptoms associated with CHF probably will change along the course of the illness. In the present study, the duration from the onset of the illness to the thermal assessment was not controlled (average, 45±10 months; range, 4 to 108 months). It is possible that variations in cutaneous vasodilator responses between patients with CHF could be explained on the basis of duration from the onset of the illness. To investigate this question, we assessed the magnitude of the elevation in forearm cutaneous vascular conductance relative to the duration from the onset of the illness and found that the correlation coefficient was very low (R=0.03) This finding strongly suggests that the magnitude of cutaneous vasodilatory impairment was unrelated to the duration of the illness. Exercise training improves thermoregulatory responses, enhances endothelial function in healthy individuals, and even can reverse systemic endothelial dysfunction in patients with heart failure. Thus, the exercise habits of the subjects might affect cutaneous vasodilator response to whole-body and local heat stresses. Twelve of the 14 subjects with CHF self-reported participat-


23. Roddie IC, Shepherd JT, Whelan RF. Evidence from venous oxygen saturation measurements that the increase in forearm blood flow during body heating is confined to the skin. J Physiol. 1956;134:444–450.


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