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Cardiovascular responses to heat stress in chronic heart failure

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Abstract

Clinical reports have suggested that patients with heart diseases may be particularly vulnerable to heat injury. This review examines the effects of heat stress on cardiovascular and autonomic functions in patients with chronic heart failure (CHF). Laboratory investigations have shown that cutaneous vasodilator responses to heating are impaired in patients, whereas activation of skin sympathetic nerve activation is not attenuated in CHF as compared to controls. Attenuated cutaneous vasodilation may increase the risk of a heat related illness when CHF subjects are exposed to hyperthermic conditions.

Keywords

Heart failure; autonomic control; thermoregulation; skin blood flow; skin sympathetic nerve activity; cutaneous vasodilation; heat stress

Introduction

Healthy individuals have a great capacity to withstand exposure to a hot environment and are able to survive increases in internal temperature of up to ~3 °C. However, many clinical reports demonstrate that thermal tolerance to heat stress is impaired in patients with cardiovascular diseases. In particular, cardiovascular conditions associated with ventricular dysfunction and chronic heart failure (CHF) are predisposed to heat intolerance. Elevations in skin blood flow (SkBF) and sweating are the primary heat exchange mechanisms in humans that protect against heat-related injury. These heatdissipating responses are accompanied by critical cardiovascular adjustments, which are under autonomic control. If these adjustments are ineffectual, then thermal regulation can be compromised during exercise and/or exposure to elevated environmental temperatures. Thus, the severely impaired cardiovascular and autonomic function in CHF could contribute to heat intolerance. On the other hand, heat exposure, as a stimulus to the cardiovascular system,

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Conflict of Interest

Jian Cui and Lawrence I. Sinoway declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

has been suggested as a therapeutic intervention in patients with cardiovascular diseases including CHF. The objective of this article is to present findings pertaining to cardiovascular and autonomic responses associated with passive heat stress in CHF.

Patients with cardiovascular diseases in heat waves or summer

Heat waves defined as a period of abnormally and uncomfortably hot and (usually) humid weather are associated with death and injury especially in those with prior medical conditions such as heart failure or hypertension [1, 2]. A classic example of the increased risk of heat stress was the 1995 Chicago heat wave in which 700 “excess” deaths were reported. Of the deaths investigated, 39 % had a prior “heart condition” [1]. The 2003 heat wave in Europe caused many thousands of “excess” deaths [3-5]. The 2006 heat wave in California also caused a large number of deaths and heat injuries [6]. Of note, the excess mortality associated with a heat wave increases with age [4].

In contrast to the effects of an acute period of extreme heat, the epidemiological evidence regarding seasonal effects of temperature is controversial. Some reports show that the adverse cardiac events occur at a higher frequency during summer months than spring and autumn [7-9]. In contrast, other reports suggest a lower hospitalization rate and a lower prevalence of mortality for CHF patients in summer than in winter [10, 11]. In general, blood pressure tends to be lower in the summer than in the winter and/or the spring, and this effect is most prominent in the elderly [12, 13]. We speculate these seemingly contradictory observations are due to a variety of different factors (e.g., the level and length of the heat exposure), which must be viewed with each other. Therefore, well-controlled and monitored laboratory investigations into passive heat stress have greatly added to our understanding of heat-induced illness and deaths in patient populations.

Typically, laboratory investigators have utilized a variety of methods to evoke passive heat stress. Specific approaches may employ climatic chambers; total body or limb water immersion; or using water-perfused suits, in which hot water is perfused through a tubelined suit worn by human volunteers. In all cases, an elevation in skin temperature is the primary stimulus by which internal temperature is raised.

Cardiovascular and autonomic responses to passive heating in healthy individuals

When individuals are exposed to a hot environment, core temperature rises and heat must be transferred to the environment. This necessitates a marked increase in SkBF. Specifically SkBF is estimated to increase from 300 mL/min in thermo-neutral conditions to upwards of 7500 mL/min [14, 15] or from 5-10 % to 50-70 % of total cardiac output [16]. In order to maintain arterial blood pressure in the presence of such an impressive cutaneous vasodilation, cardiac output must increase (e.g., up to 13 L/min in healthy individuals [14, 15]) and flow to noncutaneous beds must decrease. The increase in cardiac output is due mainly to an increase in heart rate as stroke volume remains constant or rises by roughly 10 % or less in young healthy heat-stressed subjects [17-19]. The redistribution of blood flow to the skin is accomplished in part by reduction in splanchnic and renal blood flow [15, 20, 21].

Passive whole body heating has been reported to have little effect on muscle blood flow [22-25]. This occurs in the face of significant elevations in muscle sympathetic nerve activity (MSNA) [26-30]. Thus, the individual is functioning in what has been termed a “hyperadrenergic state” [18, 31]. Considering that local (limb) heating increases muscle blood flow [22] (i.e., the direct effect of heating), and alpha-adrenergic vasoconstrictor responsiveness is preserved [32], MSNA activation evoked by whole body heating is a crucial determinant of flow distribution seen with heat stress. In young healthy individuals, the increases in SkBF, cardiac output and the reduction in splanchnic flow results in either no change, or only minimal reductions in arterial blood pressure [27, 29, 33-37].

Autonomic control of SkBF occurs via skin sympathetic nerve activity (SSNA), which includes vasoconstrictor, vasodilator and sudomotor activities. Sympathetic vasoconstrictor nerve activity leads to the release of norepinephrine and subsequent cutaneous vasoconstriction [16, 38, 39]. This vasoconstrictor component is engaged in response to cold and thermal neutral conditions [40]. The second system is a nonadrenergic sympathetically mediated vasodilator system that is engaged in warm environments [14, 16, 41, 42]. Classic studies [41, 43] demonstrate that human skin is innervated by sympathetic vasodilator nerves, since nerve blockade prevents large increases in SkBF seen with core hyperthermia in the absence of nerve blockade. However, it has never been possible to definitively confirm the specific pathways and processes involved in the skin sympathetic dilator response seen in human subjects [44]. It has been hypothesized that cholinergic sudomotor nerve activity [45] or a co-transmitter system [44, 46] are involved in the cutaneous active vasodilation, although the precise systems involved in this process remain unknown. Upon exposure to a warm/hot environment and/or exercise, the initial increase in SkBF occurs via withdrawal of the cutaneous vasoconstrictor activity [35, 47]. As internal temperature continues to increase, an active cutaneous vasodilator system is engaged [16], and accounts for 85-95 % of the rise in SkBF in hairy skin during whole-body heating [16]. Thus, a functioning cutaneous sympathetic active vasodilator system is vital for appropriate thermoregulatory responses seen during heat exposure. Moreover, a functioning sudomotor (i.e., sweating) system is absolutely necessary in order for human subjects to effectively respond to heat exposure. Under hyperthermic conditions, sudomotor/vasodilator activity is the predominant component in SSNA discharge [38, 40], and less cutaneous vasoconstrictor activity is detected in healthy individuals [38].

SkBF response to heat stress in CHF

To examine the thermoregulatory responses to whole body heat stress in patients with CHF, Cui et al. [48] assessed cutaneous vasodilation in 13 patients with stable class II–III CHF and in 13 matched healthy subjects during passive whole-body heating with a water-perfused suit. Forearm SkBF was measured from an area not covered by the tube-lined suit with laser-Doppler probes. The SkBF was also measured via venous occlusion plethysmography. Previous studies suggested that the increase in forearm blood flow during passive heat stress is predominately due to increases in SkBF [23-25]. Whole body heating induced a similar increase in skin (~4 °C) and internal temperature (~0.85 °C) in the two groups. Of note, the heat induced elevation in forearm SkBF and cutaneous vascular conductance (CVC) was much less in the CHF subjects than in the control subjects. In fact,

the increase in CVC was less than half as great in CHF as in the control subjects. Additionally, the slope of the relationship between the elevations in forearm CVC and the elevation in internal temperature was reduced in patients with CHF relative to control subjects. The maximal cutaneous vasodilator capacity to direct local heating in patients with CHF was also significantly lower than that in control subjects. However, the impaired cutaneous vasodilator response to whole body heat stress was not due to a vasodilatory ceiling effect. These results suggest that patients with CHF exhibit an attenuated cutaneous dilator response to heat stress; this is a result that is consistent with observations of Green and colleagues [49]. We posit that the attenuated cutaneous vasodilation occurs as part of an integrated response designed to prevent a reduction in blood pressure in patients with CHF who have limited cardiac output reserve. We further suggest that the tendency to protect blood pressure makes CHF patients particularly sensitive to heat injury.

SSNA response to heat stress in CHF

It is well known that autonomic control is impaired in CHF patients [50] yet resting SSNA is similar [51-53] in CHF and control subjects. To examine if the neural control of the cutaneous circulation in heat stress is altered in CHF, Cui and colleagues assessed SSNA during passive whole body heating in nine patients with stable class II-III CHF and in matched healthy subjects. Whole body heating induced similar increases in skin ($\sim 4^{\circ}\text{C}$) and internal ($\sim 0.6^{\circ}\text{C}$) temperature in the two groups. Consistent with previous observations [48, 49], the elevation in forearm CVC in patients with CHF was significantly lower than that in healthy control subjects. However, whole body heat stress evoked similar SSNA activation in CHF patients and the control subjects (Fig. 1). Thus, SSNA activation during a modest whole body heat stress is not attenuated in CHF.

We are surprised by these results since skin dilation is neurally mediated [16]. We suspect these results suggest that no-SSNA components of the dilatory response are abnormal. For example, whether CHF was due to a difference in sweating capacity in CHF and controls, we compared CVC at the same sweat rates in the two groups and found that, for a given sweat rate, CVC was much lower in CHF than in controls. These data support the concept that for a given level cholinergic nerve activity [45], cutaneous vasodilator responses are attenuated in CHF. Studies are necessary to further identify the determinants of the impaired dilatory response in CHF [38].

Roles of endothelial dysfunction of CHF in heat stress

Endothelium-dependent vasodilation plays a key role in vasodilatory response, while it is known that CHF induces endothelial dysfunction. The maximal peripheral vasodilator responses to forearm ischemia (the reactive hyperemia response) are known to be impaired in CHF [54, 55]. Structural changes in the cutaneous vasculature are seen in CHF [56]. CHF impairs endothelium-dependent vasodilation of the peripheral circulation [57-59] including skin [60] and nitric oxide production, and reduces the vascular responsiveness to nitric oxide [57, 61, 62]. The local heating induced cutaneous vasodilation was attenuated in patients with CHF [48], while sustained local heating causes cutaneous vasodilation via nitric oxide dependent mechanisms [63, 64]. Green and colleagues have shown a significant nitric oxide

contribution to heat-induced skin vasodilation in control subjects, but not in CHF patients [49]. Studies have shown that ~30 % of the elevation in CVC during indirect whole-body heating is mediated by nitric oxide-dependent mechanisms [65, 66]. Thus, the impaired SkBF response to whole body heating observed in CHF patients may be in part explained by impaired nitric oxide function [58, 67].

Sweating response in CHF

Whole body heating induces significant sweating responses in CHF patients [48], while the sweat rate toward the end of the moderate whole body heating in CHF patients was marginally lower (~20 %) than the control subjects [48, 68]. It should be noted that in CHF patients both SSNA and sweat rate increased during the initial period of whole body heating (e.g., internal temperature increase ~0.2-0.3 °C), while neither increased in healthy controls during this period [68]. These data support the clinical observation of excessive sweating in CHF patients when they perform simple activities of daily living. Prior clinical reports have suggested that an increased sweating rate may be an important symptom in CHF [69]. Sweat function in CHF patients is an area that should be further examined and understood.

Possible roles of pharmacologic therapy on the impaired responses to heat stress

Of note, all patients in the studies described above [48, 49, 68] were receiving a variety of vasoactive medications. Specifically, most patients were receiving beta-blockers as per clinical guidelines. Beta-blockers have been shown to attenuate the cutaneous vasodilator response seen with exercise. Thus, it is possible that the impaired cutaneous dilation seen in CHF with heat stress could have been due to beta-blockers. However, we noted impaired cutaneous dilation in CHF patients not on beta-blockers [48]. It is also possible that beta-blockers might alter the subject sweat rates [70]. However, studies performed in healthy subjects do not paint a consistent picture of the effects of blocking a sweat rate. [70-72].

Whatever the mechanism, it is important to understand that CHF patients are at a higher risk for heat stress related injury due to altered cutaneous vasodilation responses.

Cardiac function during heat stress in CHF, and possible “thermal therapy”

During heat stress, cardiac output must rise so that cutaneous beds remain perfused [15, 16]. This increase in cardiac output is associated with increased ejection fraction and tissue Doppler determinants of systolic function [73, 74], presumably these findings are due to a direct inotropic effect of heat stress [15, 16]. Heat stress also decreases ventricular filling pressures [18, 19, 75, 76] and central blood volume [73]. Of note, heat stress does not appear to alter diastolic function [74].

We pose the question of whether cutaneous vasodilation evoked by heat exposure may decrease afterload, and in turn improve vasodilatory response to stress. In CHF, reductions in cardiac output lead to an increase in vascular resistance, which over time may adversely affect the ability of the peripheral vascular to dilate in response to heat and exercise stress. We raise the possibility that warm temperatures may beneficially affect peripheral resistance

and cardiac output in CHF subjects. We further wonder whether these beneficial effects of temperate warmth are responsible for lower death rates during summer months [10, 11]. Others have previously suggested that thermal therapy (e.g., warm water baths, sauna or dry sauna, etc.) can be considered in CHF subjects [77-83]. Some have suggested that this approach increases cardiac output [81] and ejection fraction [77], improves left ventricular function [77, 83], improves endothelial function [79, 80, 84, 85], and improves the quality of life in CHF [78]. This type of beneficial modest thermal intervention has been termed “hormesis” [86, 87]. We believe controlled physiologic studies are needed to better understand heat therapy in CHF.

Conclusions and Future Directions

In conclusion, cutaneous vasodilator and sweating responses to heat stress are impaired in patients with CHF. Interestingly, modest whole body heat stress does not evoke an attenuated SSNA response in CHF patients. Attenuated cutaneous vasodilation may represent an intrinsic vascular abnormality. Whatever the cause, it is clear that heat waves increase the risk of cardiac illness. Against this background, it is also important to note that modest heat exposure might be beneficial in patients with cardiac disease. Heat therapy will need to be understood and tested in subjects with CHF.

References

Papers of particular interest have been highlighted as:

* Of importance

1. Semenza JC, Rubin CH, Falter KH, Selanikio JD, Flanders WD, Howe HL, Wilhelm JL. Heat-related deaths during the July 1995 heat wave in Chicago. *N Engl J Med*. 1996; 335:84–90. [PubMed: 8649494]
2. Semenza JC, McCullough JE, Flanders WD, McGeehin MA, Lumpkin JR. Excess hospital admissions during the July 1995 heat wave in Chicago. *Am J Prev Med*. 1999; 16:269–277. [PubMed: 10493281]
3. Kovats RS, Johnson H, Griffith C. Mortality in southern England during the 2003 heat wave by place of death. *Health Stat Q*. 2006; 6–8. [PubMed: 16523675]
4. Fouillet A, Rey G, Laurent F, Pavillon G, Bellec S, Guihenneuc-Jouyaux C, Clavel J, Jouglu E, Hemon D. Excess mortality related to the August 2003 heat wave in France. *Int Arch Occup Environ Health*. 2006; 80:16–24. [PubMed: 16523319]
5. Canoui-Poittrine F, Cadot E, Spira A. Excess deaths during the August 2003 heat wave in Paris, France. *Rev Epidemiol Sante Publique*. 2006; 54:127–135. [PubMed: 16830967]
6. Knowlton K, Rotkin-Ellman M, King G, Margolis HG, Smith D, Solomon G, Trent R, English P. The 2006 California heat wave: impacts on hospitalizations and emergency department visits. *Environ Health Perspect*. 2009; 117:61–67. [PubMed: 19165388]
7. Depasquale NP, Burch GE. The seasonal incidence of myocardial infarction in New Orleans. *Am J Med Sci*. 1961; 242:468–474. [PubMed: 13885529]
8. Heyer HE, Teng HC, Barris W. The increased frequency of acute myocardial infarction during summer months in a warm climate; a study of 1,386 cases from Dallas, Texas. *Am Heart J*. 1953; 45:741–748. [PubMed: 13040270]
9. Aronow WS, Ahn C. Elderly nursing home patients with congestive heart failure after myocardial infarction living in new york city have a higher prevalence of mortality in cold weather and warm weather months. *J Gerontol A Biol Sci Med Sci*. 2004; 59:146–147. [PubMed: 14999028]

10. Martinez-Selles M, Garcia Robles JA, Prieto L, Serrano JA, Munoz R, Frades E, Almendral J. Annual rates of admission and seasonal variations in hospitalizations for heart failure. *Eur J Heart Fail.* 2002; 4:779–786. [PubMed: 12453550]
- *11. Gotsman I, Zwas D, Admon D, Lotan C, Keren A. Seasonal variation in hospital admission in patients with heart failure and its effect on prognosis. *Cardiology.* 2010; 117:268–274. This epidemiological report showed that seasonal temperature had a significant effect on the rate of hospital admissions in patients with CHF. [PubMed: 21273768]
12. Halonen JI, Zanobetti A, Sparrow D, Vokonas PS, Schwartz J. Relationship between outdoor temperature and blood pressure. *Occup Environ Med.* 2011; 68:296–301. [PubMed: 20864465]
13. Alperovitch A, Lacombe JM, Hanon O, Dartigues JF, Ritchie K, Ducimetiere P, Tzourio C. Relationship between blood pressure and outdoor temperature in a large sample of elderly individuals: the Three-City study. *Arch Intern Med.* 2009; 169:75–80. [PubMed: 19139327]
14. Rowell, LB. Circulatory adjustments to dynamic exercise and heat stress: competing controls. In: Rowell, LB., editor. *Human Circulation Regulation During Physical Stress.* London: Oxford University Press; 1986. p. 363-406.
15. Rowell, LB. Thermal Stress. In: Rowell, LB., editor. *Human Circulation Regulation During Physical Stress.* London: Oxford University Press; 1986. p. 174-212.
16. Johnson, JM.; Proppe, DW. Cardiovascular adjustments to heat stress. In: Fregly, MJ.; Blatteis, CM., editors. *Handbook of Physiology - Environmental Physiology.* New York: Oxford University Press; 1996. p. 215-243.
17. Damato AN, Lau SH, Stein E, Haft JI, Kosowsky B, Cohen SI. Cardiovascular response to acute thermal stress (hot dry environment) in unacclimatized normal subjects. *Am Heart J.* 1968; 76:769–774. [PubMed: 5721834]
18. Rowell LB, Brengelmann GL, Murray JA. Cardiovascular responses to sustained high skin temperature in resting man. *J Appl Physiol.* 1969; 27:673–680. [PubMed: 5360442]
19. Minson CT, Wladkowski SL, Cardell AF, Pawelczyk JA, Kenney WL. Age alters the cardiovascular response to direct passive heating. *J Appl Physiol.* 1998; 84:1323–1332. [PubMed: 9516200]
20. Rowell LB, Brengelmann GL, Blackmon JR, Murray JA. Redistribution of blood flow during sustained high skin temperature in resting man. *J Appl Physiol.* 1970; 28:415–420. [PubMed: 5437428]
21. Rowell LB, Detry JR, Profant GR, Wyss C. Splanchnic vasoconstriction in hyperthermic man--role of falling blood pressure. *J Appl Physiol.* 1971; 31:864–869. [PubMed: 5123665]
22. Heinonen I, Brothers RM, Kemppainen J, Knuuti J, Kalliokoski KK, Crandall CG. Local heating, but not indirect whole body heating, increases human skeletal muscle blood flow. *J Appl Physiol.* 2011; 111:818–824. [PubMed: 21680875]
23. Detry JM, Brengelmann GL, Rowell LB, Wyss C. Skin and muscle components of forearm blood flow in directly heated resting man. *J Appl Physiol.* 1972; 32:506–511. [PubMed: 5026500]
24. Edholm OG, Fox RH, MacPherson RK. The effect of body heating on the circulation in skin and muscle. *J Physiol.* 1956; 134:612–619. [PubMed: 13398947]
25. 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. [PubMed: 13398924]
26. Cui J, Wilson TE, Crandall CG. Baroreflex modulation of sympathetic nerve activity to muscle in heat-stressed humans. *Am J Physiol Regul Integr Comp Physiol.* 2002; 282:R252–R258. [PubMed: 11742845]
27. Cui J, Wilson TE, Crandall CG. Phenylephrine-induced elevations in arterial blood pressure are attenuated in heat-stressed humans. *Am J Physiol Regul Integr Comp Physiol.* 2002; 283:R1221–R1226. [PubMed: 12376416]
28. Cui J, Wilson TE, Crandall CG. Muscle sympathetic nerve activity during lower body negative pressure is accentuated in heat-stressed humans. *J Appl Physiol.* 2004; 96:2103–2108. [PubMed: 14978004]

29. Crandall CG, Etzel RA, Farr DB. Cardiopulmonary baroreceptor control of muscle sympathetic nerve activity in heat-stressed humans. *Am J Physiol Heart Circ Physiol*. 1999; 277:H2348–H2352.
30. Niimi Y, Matsukawa T, Sugiyama Y, Shamsuzzaman AS, Ito H, Sobue G, Mano T. Effect of heat stress on muscle sympathetic nerve activity in humans. *J Auton Nerv Syst*. 1997; 63:61–67. [PubMed: 9089540]
31. Rowell LB. Hyperthermia: a hyperadrenergic state. *Hypertension*. 1990; 15:505–507. [PubMed: 2332241]
32. Keller DM, Sander M, Stallknecht B, Crandall CG. alpha-Adrenergic vasoconstrictor responsiveness is preserved in the heated human leg. *J Physiol*. 2010; 588:3799–3808. [PubMed: 20693291]
33. Crandall CG, Zhang R, Levine BD. Effects of whole body heating on dynamic baroreflex regulation of heart rate in humans. *Am J Physiol Heart Circ Physiol*. 2000; 279:H2486–H2492. [PubMed: 11045986]
34. Cui J, Zhang R, Wilson TE, Crandall CG. Spectral analysis of muscle sympathetic nerve activity in heat-stressed humans. *Am J Physiol Heart Circ Physiol*. 2004; 286:H1101–H1106. [PubMed: 14630631]
35. Cui J, Sathishkumar M, Wilson TE, Shibasaki M, Davis SL, Crandall CG. Spectral characteristics of skin sympathetic nerve activity in heat-stressed humans. *Am J Physiol Heart Circ Physiol*. 2006; 290:H1601–H1609. [PubMed: 16306217]
36. Keller DM, Cui J, Davis SL, Low DA, Crandall CG. Heat stress enhances arterial baroreflex control of muscle sympathetic nerve activity via increased sensitivity of burst gating, not burst area, in humans. *J Physiol*. 2006; 573:445–451. [PubMed: 16581857]
37. Yamazaki F, Okuno C, Nagamatsu S, Sone R. Effects of whole-body and local thermal stress on hydrostatic volume changes in the human calf. *Eur J Appl Physiol*. 2002; 88:61–66. [PubMed: 12436271]
38. Kellogg DL Jr, Johnson JM, Kosiba WA. Selective abolition of adrenergic vasoconstrictor responses in skin by local iontophoresis of bretylium. *Am J Physiol Heart Circ Physiol*. 1989; 257:H1599–H1606.
39. Stephens DP, Aoki K, Kosiba WA, Johnson JM. Nonnoradrenergic mechanism of reflex cutaneous vasoconstriction in men. *Am J Physiol Heart Circ Physiol*. 2001; 280:H1496–H1504. [PubMed: 11247759]
40. Bini G, Hagbarth K-E, Hynninen P, Wallin BG. Thermoregulatory and rhythm-generating mechanisms governing the sudomotor and vasoconstrictor outflow in human cutaneous nerves. *J Physiol (London)*. 1980; 306:537–552. [PubMed: 7463376]
41. Roddie IC, Shepherd JT, Whelan RF. The contribution of constrictor and dilator nerves to the skin vasodilatation during body heating. *J Physiol*. 1957; 136:489–497. [PubMed: 13429515]
42. Joyner MJ, Halliwill R. Sympathetic vasodilatation in human limbs. *J Physiol*. 2000; 526:471–480. [PubMed: 10922000]
43. Edholm OG, Fox RH, Macpherson RK. Vasomotor control of the cutaneous blood vessels in the human forearm. *J Physiol*. 1957; 139:455–465. [PubMed: 13492236]
44. Kellogg DL Jr, Pergola PE, Piest KL, Kosiba WA, Crandall CG, Grossmann M, Johnson JM. Cutaneous active vasodilation in humans is mediated by cholinergic nerve cotransmission. *Circ Res*. 1995; 77:1222–1228. [PubMed: 7586235]
45. Brengelmann GL, Freund PR, Rowell LB, Olerud JE, Kraning KK. Absence of active cutaneous vasodilation associated with congenital absence of sweat glands in humans. *Am J Physiol Heart Circ Physiol*. 1981; 240:H571–H575.
46. Hokfelt T, Johansson O, Ljungdahl A, Lundberg JM, Schultzberg M. Peptidergic neurones. *Nature*. 1980; 284:515–521. [PubMed: 6154244]
47. Iwase S, Cui J, Wallin BG, Kamiya A, Mano T. Effects of increased ambient temperature on skin sympathetic nerve activity and core temperature in humans. *Neurosci Lett*. 2002; 327:37–40. [PubMed: 12098495]

48. Cui J, Arbab-Zadeh A, Prasad A, Durand S, Levine BD, Crandall CG. Effects of heat stress on thermoregulatory responses in congestive heart failure patients. *Circulation*. 2005; 112:2286–2292. [PubMed: 16216975]
49. Green DJ, Maiorana AJ, Siong JH, Burke V, Erickson M, Minson CT, Bilsborough W, O'Driscoll G. Impaired skin blood flow response to environmental heating in chronic heart failure. *Eur Heart J*. 2006; 27:338–343. [PubMed: 16299022]
50. Grassi G, Seravalle G, Cattaneo BM, Lanfranchi A, Vailati S, Giannattasio C, Del Bo A, Sala C, Bolla GB, Pozzi M. Sympathetic activation and loss of reflex sympathetic control in mild congestive heart failure. *Circulation*. 1995; 92:3206–3211. [PubMed: 7586305]
51. Grassi G, Colombo M, Seravalle G, Spaziani D, Mancia G. Dissociation between muscle and skin sympathetic nerve activity in essential hypertension, obesity, and congestive heart failure. *Hypertension*. 1998; 31:64–67. [PubMed: 9449392]
52. Silber DH, Sutliff G, Yang QX, Smith MB, Sinoway LI, Leuenberger UA. Altered mechanisms of sympathetic activation during rhythmic forearm exercise in heart failure. *J Appl Physiol*. 1998; 84:1551–1559. [PubMed: 9572798]
53. Middlekauff HR, Hamilton MA, Stevenson LW, Mark AL. Independent control of skin and muscle sympathetic nerve activity in patients with heart failure. *Circulation*. 1994; 90:1794–1798. [PubMed: 7923664]
54. Zelis R, Mason DT, Braunwald E. A comparison of the effects of vasodilator stimuli on peripheral resistance vessels in normal subjects and in patients with congestive heart failure. *J Clin Invest*. 1968; 47:960–970. [PubMed: 5641631]
55. Sinoway L, Minotti J, Musch T, Goldner D, Davis D, Leaman D, Zelis R. Enhanced metabolic vasodilation secondary to diuretic therapy in decompensated congestive heart failure secondary to coronary artery disease. *Am J Cardiol*. 1987; 60:107–111. [PubMed: 3300242]
56. Wroblewski H, Norgaard T, Haunso S, Kastrup J. Microvascular distensibility in two different vascular beds in idiopathic dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol*. 1995; 269:H1973–H1980.
57. Drexler H, Hayoz D, Munzel T. Endothelium function in chronic congestive heart failure. *Am J Cardiol*. 1992; 69:1596–1601. [PubMed: 1598876]
58. Kubo SH, Rector TS, Bank AJ, Williams RE, Heifetz SM. Endothelium-dependent vasodilation is attenuated in patients with heart failure. *Circulation*. 1991; 84:1589–1596. [PubMed: 1914099]
59. Andreassen AK, Gullestad L, Holm T, Simonsen S, Kvernebo K. Endothelium-dependent vasodilation of the skin microcirculation in heart transplant recipients. *Clin Transplant*. 1998; 12:324–332. [PubMed: 9686327]
60. Andersson SE, Edvinsson ML, Edvinsson L. Cutaneous vascular reactivity is reduced in aging and in heart failure: association with inflammation. *Clin Sci (Lond)*. 2003; 105:699–707. [PubMed: 12848618]
61. Ramsey MW, Goodfellow J, Jones CJ, Luddington LA, Lewis MJ, Henderson AH. Endothelial control of arterial distensibility is impaired in chronic heart failure. *Circulation*. 1995; 92:3212–3219. [PubMed: 7586306]
62. Hornig B, Maier V, Drexler H. Physical training improves endothelial function in patients with chronic heart failure. *Circulation*. 1996; 93:210–214. [PubMed: 8548890]
63. Kellogg DL Jr, Liu Y, Kosiba IF, O'Donnell D. Role of nitric oxide in the vascular effects of local warming of the skin in humans. *J Appl Physiol*. 1999; 86:1185–1190. [PubMed: 10194201]
64. Minson CT, Berry LT, Joyner MJ. Nitric oxide and neurally mediated regulation of skin blood flow during local heating. *J Appl Physiol*. 2001; 91:1619–1626. [PubMed: 11568143]
65. Kellogg DL Jr, Crandall CG, Liu Y, Charkoudian N, Johnson JM. Nitric oxide and cutaneous active vasodilation during heat stress in humans. *J Appl Physiol*. 1998; 85:824–829. [PubMed: 9729553]
66. Shastri S, Dietz NM, Halliwill JR, Reed AS, Joyner MJ. Effects of nitric oxide synthase inhibition on cutaneous vasodilation during body heating in humans. *J Appl Physiol*. 1998; 85:830–834. [PubMed: 9729554]

67. Katz SD, Biasucci L, Sabba C, Strom JA, Jondeau G, Galvao M, Solomon S, Nikolic SD, Forman R, LeJemtel TH. Impaired endothelium-mediated vasodilation in the peripheral vasculature of patients with congestive heart failure. *J Am Coll Cardiol.* 1992; 19:918–925. [PubMed: 1552112]
- *68. Cui J, Boehmer JP, Blaha C, Lucking R, Kunselman AR, Sinoway LI. Chronic heart failure does not attenuate the total activity of sympathetic outflow to skin during whole-body heating. *Circ Heart Fail.* 2013; 6:271–278. This study showed that the cutaneous vasodilation during heat stress was significantly attenuated, while the response of skin sympathetic nerve activity to heat stress was not altered in CHF patients when compared with healthy control subjects. [PubMed: 23395933]
69. Morgan CL, Nadas AS. Sweating and congestive heart failure. *N Engl J Med.* 1963; 268:580–585.
70. Mack GW, Shannon LM, Nadel ER. Influence of beta-adrenergic blockade on the control of sweating in humans. *J Appl Physiol.* 1986; 61:1701–1705. [PubMed: 3023274]
71. Freund BJ, Joyner MJ, Jilka SM, Kalis J, Nittolo JM, Taylor JA, Peters H, Feese G, Wilmore JH. Thermoregulation during prolonged exercise in heat: alterations with beta-adrenergic blockade. *J Appl Physiol.* 1987; 63:930–936. [PubMed: 2820920]
72. Pescatello LS, Mack GW, Leach CN Jr, Nadel ER. Thermoregulation in mildly hypertensive men during beta-adrenergic blockade. *Med Sci Sports Exerc.* 1990; 22:222–228. [PubMed: 2355819]
73. Crandall CG, Wilson TE, Marving J, Vogelsang TW, Kjaer A, Hesse B, Secher NH. Effects of passive heating on central blood volume and ventricular dimensions in humans. *J Physiol.* 2008; 586:293–301. [PubMed: 17962331]
74. Brothers RM, Bhella PS, Shibata S, Wingo JE, Levine BD, Crandall CG. Cardiac systolic and diastolic function during whole body heat stress. *Am J Physiol Heart Circ Physiol.* 2009; 296:H1150–H1156. [PubMed: 19218504]
75. Wilson TE, Tollund C, Yoshiga CC, Dawson EA, Nissen P, Secher NH, Crandall CG. Effects of heat and cold stress on central vascular pressure relationships during orthostasis in humans. *J Physiol.* 2007; 585:279–285. [PubMed: 17901119]
76. Wilson TE, Brothers RM, Tollund C, Dawson EA, Nissen P, Yoshiga CC, Jons C, Secher NH, Crandall CG. Effect of thermal stress on Frank-Starling relations in humans. *J Physiol.* 2009; 587:3383–3392. [PubMed: 19417092]
- *77. Oyama J, Kudo Y, Maeda T, Node K, Makino N. Hyperthermia by bathing in a hot spring improves cardiovascular functions and reduces the production of inflammatory cytokines in patients with chronic heart failure. *Heart Vessels.* 2013; 28:173–178. This recent study demonstrated that two weeks of repeated moderate heat exposure improved ventricular ejection fraction and cardiothoracic ratio in CHF patients. Moreover, the inflammatory responses decreased after the treatment. [PubMed: 22231540]
78. Michalsen A, Ludtke R, Buhning M, Spahn G, Langhorst J, Dobos GJ. Thermal hydrotherapy improves quality of life and hemodynamic function in patients with chronic heart failure. *Am Heart J.* 2003; 146:E11.
79. Imamura M, Biro S, Kihara T, Yoshifuku S, Takasaki K, Otsuji Y, Minagoe S, Toyama Y, Tei C. Repeated thermal therapy improves impaired vascular endothelial function in patients with coronary risk factors. *J Am Coll Cardiol.* 2001; 38:1083–1088. [PubMed: 11583886]
80. Kihara T, Biro S, Imamura M, Yoshifuku S, Takasaki K, Ikeda Y, Otsuji Y, Minagoe S, Toyama Y, Tei C. Repeated sauna treatment improves vascular endothelial and cardiac function in patients with chronic heart failure. *J Am Coll Cardiol.* 2002; 39:754–759. [PubMed: 11869837]
81. Tei C, Horikiri Y, Park JC, Jeong JW, Chang KS, Toyama Y, Tanaka N. Acute hemodynamic improvement by thermal vasodilation in congestive heart failure. *Circulation.* 1995; 91:2582–2590. [PubMed: 7743620]
82. Weber AA, Silver MA. Heat therapy in the management of heart failure. *Congest Heart Fail.* 2007; 13:81–33. [PubMed: 17392618]
83. Kisanuki A, Daitoku S, Kihara T, Otsuji Y, Tei C. Thermal therapy improves left ventricular diastolic function in patients with congestive heart failure: a tissue doppler echocardiographic study. *J Cardiol.* 2007; 49:187–191. [PubMed: 17460879]
84. Tei C, Shinsato T, Miyata M, Kihara T, Hamasaki S. Waon therapy improves peripheral arterial disease. *J Am Coll Cardiol.* 2007; 50:2169–2171. [PubMed: 18036456]

85. Shinsato T, Miyata M, Kubozono T, Ikeda Y, Fujita S, Kuwahata S, Akasaki Y, Hamasaki S, Fujiwara H, Tei C. Waon therapy mobilizes CD34+ cells and improves peripheral arterial disease. *J Cardiol*. 2010; 56:361–366. [PubMed: 20843662]
86. Rattan SI. Hormesis in aging. *Ageing Res Reviews*. 2008; 7:63–78.
87. Radak Z, Chung HY, Koltai E, Taylor AW, Goto S. Exercise, oxidative stress and hormesis. *Ageing Res Reviews*. 2008; 7:34–42.

Figure 1. Mean skin sympathetic nerve activity (SSNA), cutaneous vascular conductance (CVC), and sweat rate (SR) responses to whole body heating

During the initial period of heating, mean skin temperature (Tsk) increased, but the internal temperature (Tcore) did not rise. In the later period of whole-body heating, Tsk was clamped at ~38 °C, whereas the Tcore increased. Mean body temperature (Tbody) was calculated as follows: $0.9 \times T_{core} + 0.1 \times T_{sk}$. CHF indicates chronic heart failure (From Cui J, et al., “Chronic Heart Failure Does Not Attenuate the Total Activity of Sympathetic Outflow to Skin During Whole-Body Heating,” *Circ Heart Fail.*, 2013;6: 271-278, with permission from the American Heart Association).