Carotid baroreflex control of heart rate is enhanced, while control of mean arterial pressure is preserved during whole-body heat stress in young healthy men

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ABSTRACT

Whole-body heat stress (WBH) results in numerous cardiovascular alterations that ultimately reduce orthostatic tolerance. While impaired carotid baroreflex (CBR) function during WBH has been reported as a potential reason for this decrement, study design considerations may limit interpretation of previous findings. We sought to test the hypothesis that CBR function is unaltered during WBH. CBR function was assessed in ten healthy male subjects (age, 26 ± 3; height, 185 ± 7 cm; weight, 82 ± 10 kg; BMI, 24 ± 3 kg/m²; mean ± sd) using 5 s trials of neck pressure (+45, +30 and +15 Torr) and neck suction (-20, -40, -60 and -80 Torr) during normothermia (NT) and passive WBH (Δ core temp ~1 °C). Analyses of stimulus response curves (four parameter logistic model) for CBR control of heart rate (CBR-HR) and mean arterial pressure (CBR-MAP), as well as separate 2-way ANOVA of the hypo- and hypertensive stimuli (factor 1: thermal condition, factor 2: chamber pressure) were performed. For CBR-HR, maximal gain was increased during WBH (-0.73±0.11) compared to NT (-0.39±0.04, mean±SE, p=0.03). In addition, the CBR-HR responding range was increased during WBH (33±5) compared to NT (19±2 bpm, p=0.03). Separate analysis of hypertensive stimulation revealed enhanced HR responses during WBH at -40, -60 and -80 Torr (condition*chamber pressure interaction, p=0.049) compared to NT. For CBR-MAP, both logistic analysis and separate 2-way ANOVA revealed no differences during WBH. Therefore, in response to passive WBH, CBR control of heart rate (enhanced) and arterial pressure (no change) is well-preserved.
INTRODUCTION

Under hyperthermic conditions, the human cardiovascular system must compete between adequate maintenance of arterial blood pressure and providing the thermoregulatory system with sufficient blood flow to participate in heat exchange from the body to the environment. Among the numerous neural and cardiovascular alterations to heat stress are: increased cardiac output (38), marked redistribution of cardiac output to the cutaneous vasculature (13, 17, 21, 23, 33), increased muscle (25) and skin sympathetic nervous activity (21) and splanchnic vasoconstriction (23, 33). Despite the accompanying reductions in total peripheral resistance, largely the result of the well-documented cutaneous vasodilation, arterial blood pressure is well-maintained in otherwise ‘unchallenged’ conditions (e.g., supine rest) during heat stress (13, 40).

As a result of this cardiovascular and thermoregulatory ‘competition’, many groups have demonstrated a compromised ability to withstand orthostatic challenges (i.e., orthostatic intolerance) during heat stress (1, 8, 17, 20, 38, 39). Consequently, numerous studies have investigated the potential mechanisms for the attenuated orthostatic tolerance during a whole-body heat stress (WBH) in humans, with some evidence suggesting the arterial baroreflex could be likely source of system failure (5, 41).

In 2000, Crandall reported that WBH reduced carotid baroreflex (CBR) control of blood pressure (i.e., carotid-vasomotor baroreflex function), while CBR control of heart rate (i.e., carotid-cardiac baroreflex) was maintained relative to normothermic conditions (5). The author speculated that the reduced responsiveness of carotid-vasomotor baroreflex might contribute to WBH-induced reductions in orthostatic tolerance. However, methodological constraints may warrant further consideration of those findings, specifically with respect to the WBH-induced reduction in the carotid-vasomotor baroreflex responses.
The use of the neck chamber technique has been well-documented in humans (10, 12, 29, 34). The technique utilizes non-invasive perturbation of the carotid baroreceptors to elicit reflex responses to hypo- and hypertensive stimuli. Multiple investigations have demonstrated that CBR responses can be dependent on the duration of the baroreceptor stimuli (9, 26, 27, 32), of which both MSNA and heart rate consistently reach their peak responses within 5 seconds of the onset of the stimulus, while stroke volume remains unchanged. In the aforementioned study by Crandall (5), a ‘stair-step’ application of neck pressure (NP: hypotensive stimuli) and neck suction (NS: hypertensive stimuli) was utilized in which the stimulus, starting at +40 mmHg, was applied for four successive cardiac cycles before being sequentially stepped to -65 mmHg at each subsequent R wave associated with the respective cardiac cycle. While meaningful baroreflex function curves can be derived from this methodology, using this technique during heat stress is problematic. As heat stress considerably increases heart rate (~40% increase from normothermia in the aforementioned study), the stimulus time of the respective neck pressures/suctions will be substantially reduced in response to WBH. Therefore, a “stair-step” method for comparison of CBR function between thermal conditions may have been inappropriate due to inherent differences of stimulus duration between normothermia (NT) and WBH, creating a scenario in which comparisons were made using data from two disparate stimuli.

The purpose of this study was to test the hypothesis that CBR function is preserved during WBH conditions. The neck chamber technique was used to assess CBR control of heart rate and mean arterial pressure using 5 s trials of multiple neck pressures (simulated hypotensive stimuli) and multiple neck suctions (simulated hypertensive stimuli) during NT and passive, whole-body heat stress conditions. The use of 5 s trials was chosen to standardize the carotid
baroreceptor stimulus duration between thermal conditions.

METHODS

Subjects

Ten adult male subjects voluntarily participated in this investigation (age, 26 ± 3; height, 185 ± 7 cm; weight, 82 ± 10 kg; BMI, 24 ± 3 kg/m²; mean ± sd). An all-male sample group was used in effort to eliminate the influence of sex on CBR function, as this has been previously shown both at rest, and during exercise (14, 15). All procedures conformed to the standards set by the Declaration of Helsinki. Each subject signed an informed consent that was approved by the institutional review board of the University of Texas at Arlington. Prior to participation, all subjects were familiarized with the testing protocols. Subjects were healthy, non-smokers, free of known cardiovascular and respiratory diseases, and were not using prescription or over-the-counter medications. All experiments took place in the morning or early afternoon, ~4-5 h after consuming a light meal, as instructed by investigators. Additionally, subjects were advised to not consume alcohol for 24 h before any of the scheduled experiments. Subjects were advised to not participate in exercise 24 h before any of the scheduled experiments and to refrain from the consumption of caffeinated beverages 12 h before the scheduled experiments.

Instrumentation

Subjects were dressed in a tube-lined water perfusion suit enabling the control of skin (T_{skin}) and core temperature (T_{core}) via changing the temperature of the water circulating in the suit. T_{core} was measured using a telemetric temperature pill swallowed by subjects at least 1h before any data collection (normothermic T_{core} data were identified prior to heat stress which was ~2 h post-ingestion). T_{skin} was measured from the electrical average of six thermocouples fixed to the skin (T_{sk}: 0.22 chest + 0.21 upper back + 0.19 lower back + 0.14 abdomen + 0.14 thigh + 0.11 calf) with porous adhesive tape (35). Non-invasive measures of arterial blood pressure were taken.
continuously using finger cuff photoplethysmography (Finometer Pro, Finapres Medical Systems). Arterial blood pressure was also determined by auscultation of the brachial artery (Tango+, SunTech Medical Instruments). Mean arterial blood pressures (MAP) determined by auscultation were used to calibrate MAP determined by finger cuff photoplethysmography. This was done by determining the average MAP over the 30 s period during which the auscultation-derived pressures were collected and correcting for the offset between the two measures (i.e. adjusting the finger-cuff pressure MAP to the auscultation-derived MAP)(4). This correction was performed with measures from both thermal conditions for each subject. Heart rate was collected from an electrocardiogram (ECG) signal via Cardio-Card (Nasiff Associates, Inc). Subjects were fitted with a padded, malleable lead neck chamber covering the anterior two-thirds of the neck for baroreflex testing.

Familiarization Sessions

All subjects were familiarized with the laboratory protocol, personnel, and equipment prior to completing the experimental trials. During the initial familiarization session, subjects were screened for the location of their carotid sinus bifurcation using Doppler ultrasound in efforts to ensure that the neck collar would appropriately apply the stimulus to the carotid sinus bifurcation (~2-3 cm below the mandible). Appropriate neck chamber placement was determined by fitting the collar over the anterior two-thirds of the neck and applying NP and NS to observe directionally appropriate responses. Upon proper fitting of the collar, the subjects were instructed on the end-expiratory breath hold technique and randomized NP and NS were administered similar to the experimental protocol. Typically, 1-2 of these familiarization sessions were required for ensuring the subjects were comfortable with the procedures, and consistent responses to NP and NS were observed.
Experimental protocol

During normothermic testing, 33 °C water perfused the tube-lined suit for approximately 45 min before baroreceptor perturbations. Trials of neck pressure (NP, +45, +30 and +15 Torr) and neck suction (NS, -20, -40, -60 and -80 Torr) were performed in randomized order for ~28 total trials (4-5 trials per level of NP/NS) during normothermia. A minimum of 45 s was allowed to pass between each trial to enable physiological variables to return to pre-stimulus values. Following approximately 40 min of baroreflex testing during normothermia, whole-body heating was performed by perfusing water at 46 °C through the tube-lined suit. After an increase in Tcore of approximately 0.9 °C was observed, the temperature of the water was decreased (42 °C) to attenuate further increases in Tcore. After 20 min at these reduced water temperatures, baroreflex testing was repeated similar to that describe for normothermia.

Measurements and procedures

Testing was performed with subjects in the semi-recumbent (~45°) position. Cardiovascular variables were monitored and recorded on a computer equipped with a data acquisition program (Acqknowledge, Biopac). Carotid baroreflex control of heart rate (HR) and mean arterial pressure (MAP) was assessed by randomly applying single 5 s trials of NP (+45, +30, +15 Torr) and NS (-20, -40, -60, -80 Torr) as described by Potts et al. (30). Briefly, NP and NS trials were performed during an approximately 15 s breath-hold at normal end-expiration, in order to minimize the respiratory modulation of HR and MAP (11). The maximum MAP response was determined by assessing the 3 cardiac cycle interval with the largest change in MAP relative to pre-stimulus (3 cardiac cycle average) for each trial of NP and NS, typically occurring within 5-8 s following stimulus onset. This analysis has been described previously (12). For HR, the single
peak cardiac cycle response was compared to the 3 cycle average pre-stimulus heart rate for each NP/NS trial, this peak was typically observed within the first few cardiac cycles.

Carotid Baroreflex Function Curves. Carotid-cardiac and carotid-vasomotor stimulus-response curves were determined by plotting the maximal changes in HR and MAP, respectively, elicited by NP and NS against the estimated carotid sinus pressure (ECSP), which was calculated as the difference between MAP and neck collar pressure. The HR or MAP value with no manipulation of collar pressure (i.e., ECSP=MAP-0) denotes the operating point on the curve. Carotid baroreflex stimulus-response data were fit for each subject to the logistic function model described by Kent et al. (19): Dependent variable = \( A_1 \{1+\exp[A_2(\text{ECSP}-A_3)]\}^{-1} + A_4 \) where the dependent variable is HR or MAP, \( A_1 \) is the range of response of the dependent variable (maximum – minimum), \( A_2 \) is the gain coefficient, \( A_3 \) is the centering point or carotid sinus pressure required to elicit equal pressor and depressor responses, and \( A_4 \) is the minimum response. The CBR maximal gain was calculated using the equation: \( G_{\text{max}} = -A_1 A_2 /4 \). The CBR operating point gain (\( G_{\text{op}} \)) was calculated using the equation: \( G_{\text{op}} = -A_1 A_2 \exp[A_2(\text{MAP}_{\text{op}} – A_3)]/\{1+\exp[A_2(\text{MAP}_{\text{op}} – A_3)]\}^2 \). The threshold (THR) and saturation (SAT), described as the minimum and maximum ECSP, respectively, that elicit a reflex change in HR or MAP, were calculated using the following equation: \( \text{THR} = -2.944/A_2 + A_3 \) and \( \text{SAT} = 2.944/A_2 + A_3 \) (22).

Baroreceptor time-to-peak responses. Carotid-cardiac time-to-peak was determined by summing the R-R intervals from the onset of the respective stimuli to the initial R wave of the cardiac cycle associated with the peak heart rate responses. For carotid baroreflex control of MAP, the time to the peak response for each +45 and -80 Torr trial was determined during both thermal conditions. These values were calculated as the sum of the R-R intervals from the onset of the carotid stimulus to the cardiac cycle at which the largest change from pre-stimulus values
occurred. To determine if the greater time-to-peak response to NP impaired CBR control of blood pressure, the MAP at the time of the peak HR response during normothermia was compared to the MAP that occurred at the same time-point of the WBH trials (e.g., was heat impacting the carotid-cardiac baroreflex control of MAP?).

In order to account for the change in the systolic/diastolic period ratio as heart rate increases from NT to WBH, absolute steady-state MAP values during both thermal conditions were calculated as a function of heart rate in place of the standard MAP equation (24). First, the fraction of systole (St) of the cardiac cycle was related to HR using the following equation: \( St = 0.01 \exp(4.14-40.74/HR) \). Diastolic blood pressure (DBP) and pulse pressure (PP) were then adjusted for St in the following equation: \( MAP = DBP + St(PP) \). For completeness, MAP values from the traditional formula (i.e., \( MAP = DBP + \text{Pulse Pressure}/3 \)) are presented, as well. This correction was applied to the blood pressure measures associated with the upper-arm blood pressure cuff values.

**Statistical analysis**

The parameters for all subjects within an experimental condition were averaged to provide group mean responses. Comparisons of cardiovascular and thermal parameters between NT and WBH conditions were made using paired t-tests. Paired t-tests were used for comparison of CBR-HR and CBR-MAP response curve parameters, as well as time-to-peak indices, between thermal conditions. The statistical comparison of the separate hypotensive and hypertensive baroreceptor response variables between thermal conditions (factor 1) and the various magnitudes of NP and NS (factor 2) were made using a 2-way ANOVA. When required, multiple comparison procedures were performed using the Holm-Sidak method. Statistical significance was set at \( P < 0.05 \).
RESULTS

Thermoregulatory and cardiovascular responses to heat stress. Thermoregulatory and cardiovascular responses to passive heating are summarized in Table 1. Heat stress significantly increased core temperature (NT: 36.9 ± 0.3°C vs WBH: 37.8 ± 0.3°C, P<0.01), skin temperature (NT: 34.4 ± 0.3°C vs WBH: 38.0 ± 0.7°C, P<0.01), and heart rate (NT: 56 ± 12 bpm vs WBH: 83 ± 20 bpm, P<0.05). Systolic blood pressure significantly increased (NT: 122 ± 5 mmHg vs WBH: 129 ± 8 mmHg, P<0.05), while diastolic blood pressure (NT: 73 ± 8 mmHg vs WBH: 72 ± 11 mmHg, P=0.60) and traditionally calculated mean arterial blood pressure (NT: 89 ± 6 mmHg vs WBH: 91 ± 7 mmHg, P=0.36) remained constant. However, when adjusting for HR (i.e., the systole/diastole period ratio), there was a significant increase in MAP (NT: 87 ± 7 mmHg vs WBH: 94 ± 7 mmHg, P=0.01)

Carotid-cardiac and carotid-vasomotor stimulus-response curves. The stimulus-response relationships for the CBR control of HR and CBR control of MAP in both thermal conditions are depicted in Figures 1 and 2, respectively. For CBR control of HR, G_max (A2) was significantly higher for the heat stress group (NT: -0.39±0.04 vs WBH: -0.73±0.12, p=0.03), indicating greater carotid-cardiac baroreflex sensitivity. Further analyses revealed the G_op was also greater during WBH (-0.55±0.28) compared to NT (-0.34±0.14, p=0.04). Additionally for CBR control of HR, the responding range (A1)(p=0.03), centering point (A3)(p=0.046), and the minimum response (A4) (p=0.002) all significantly increased in response to heat stress. For CBR control of MAP during WBH, there were no differences in G_max (NT: -0.36±0.04 vs WBH: -0.43±0.03, p=0.24) or G_op (NT: -0.31±0.11 vs WBH: -0.38±0.10, p=0.20), while the minimum response (p=0.04) and threshold (p=0.02) values both significantly increased. Although not statistically significant, the centering point trended toward an increase (p=0.07) as a result of the heat stress. Taken together, the increases seen in A1, A3 and A4, combined with similar A2 values, suggest a ‘resetting’ of the baroreflex in response to hyperthermia. The aforementioned
calculated variables and the four logistic parameters associated with CBR function curves are presented in Table 2.

*Simulated Hypotension.* Figure 3 depicts group peak HR (Figure 3A) and MAP (Figure 3B) responses to simulated hypotension (i.e., NP). For response magnitude, there was not a main effect of thermal condition for HR (P = 0.63), or MAP (P = 0.16). For both HR and MAP comparisons, the main effects for chamber pressure were significant (P < 0.01).

*Simulated Hypertension.* Figure 4 depicts group peak HR (Figure 4A) and MAP (Figure 4B) responses to simulated hypertension (i.e., NS). At -40, -60 and -80 Torr, the magnitude of the HR responses was greater during WBH (thermal condition * chamber pressure interaction, p = 0.049). No significant differences were found in the magnitude of the MAP response to NS between thermal conditions (P = 0.13).

*CBR Time-to-Peak.* There was no difference in the MAP time-to-peak in response to +45 Torr (NT: 6.4±1.6 vs WBH: 7.0±1.4 s, P = 0.36) and -80 Torr (NT: 7.4±1.2 vs WBH: 6.7±2.0 s, P = 0.31) between thermal conditions. The HR time-to-peak in response to +45 Torr was significantly increased during WBH (4.1±1.3 s) compared to NT (2.8±1.7 s, P < 0.002). There was no difference in the HR time-to-peak in response to -80 Torr (NT: 1.9±1.0 vs WBH: 2.1±1.1 s, P = 0.40). Time-to-peak data for HR responses to NP are presented in Figure 5.

For each subject, the time-to-peak for HR in response to +45 Torr and -80 Torr during NT conditions was used to compare MAP at the same time-point during their respective WBH trials. It remained possible that differences in the time-course of the MAP responses during WBH could be revealed, independent of magnitude of the peak responses. Interestingly, there were no differences for the MAP at the HR time-to-peak observed during NT or WBH conditions (+45 Torr: MAP at peak HR response during NT = 5.6±4.4 vs 4.0±3.6 at same time...
point during WBH, P= 0.25, -80 Torr: MAP at peak HR response during NT = -3.4±3.8 vs -2.9±3.9 at same time point during WBH, P= 0.65).

**DISCUSSION**

The purpose of this study was to test the hypothesis that CBR function is preserved during a whole-body heat stress. The primary findings of this investigation are twofold: first, during WBH, CBR control of HR was augmented in response to NS; and second, CBR control of MAP was preserved during WBH. These findings indicate that CBR function is likely not compromised as a result of increased core temperature. Although not directly tested, it seems CBR function would be an unlikely mechanism responsible for decreased orthostatic tolerance during heat stress.

It is well-documented that passive heat stress reduces orthostatic tolerance (8, 38). As a result, multiple investigations have sought to uncover potential mechanisms responsible for this occurrence. One obvious target is the potential role of arterial baroreflex function. As heat stress results in marked cardiovascular and neural adjustments in an effort to adequately dissipate heat, possible alterations in arterial baroreflex function could, theoretically, contribute to the heat-induced orthostatic intolerance.

In the current study, as expected, CBR control of HR was reset to the prevailing HR of the WBH condition (see Table 2). Interestingly, the resetting of the CBR-HR function curve was accompanied by an increase in the $G_{\text{max}}$, $G_{\text{op}}$ and an increased responding range during WBH compared to NT (Table 2). These findings support an increased carotid-cardiac sensitivity during WBH (i.e., increased gain), and an increase in the magnitude of the end organ response (i.e., increased responding range). A further analysis of the respective hypo- and hypertensive aspects of the HR responses revealed that the increased responding range was driven exclusively
by larger responses to simulated hypertension (i.e., neck suction). Physiologically, this supports
an increased capacity of the reflex to buffer acute hypertensive challenges (at least by means of
modulating HR and, likely, cardiac output). While the HR responses to neck pressure (i.e.,
simulated hypotension) were not different between thermal conditions (Figure 1), the magnitude
of the decrease in HR in response to neck suction (i.e., simulated hypertension) was greater
during WBH (see Figure 4A). Specifically, these differences were apparent at all but the lowest
(i.e., -20 Torr) neck suction stimuli. Therefore, the increased CBR-HR responding range
observed in the complete function curves was apparently due to enhanced responsiveness to
hypertensive stimuli (and preserved response magnitude to simulated hypotension).

During heat stress, there was a delay in the time-to-peak HR response to NP (Figure 5) of
~1 s (NT: 2.8±1.7 s vs WBH: 4.1±1.3 s). While this finding suggests a potential heat-related
decrement in carotid-cardiac function during heat stress, the impact of this delay on blood
pressure regulation may be marginal. Although the modulation of HR (thus, cardiac output) can
play a role in the maintenance of arterial blood pressure, our data demonstrate the following
during WBH: 1) no reduction in the peak MAP response to NP or NS, 2) no delay in the time-to-
peak MAP response to NP or NS and 3) no difference in MAP at the time associated with the HR
time-to-peak observed during NT. Therefore, although statistically significant, the relative
impact of this HR delay does not appear to markedly impact arterial blood pressure regulation
via the CBR.

CBR control of MAP was also reset during WBH (Table 2). Unlike CBR-HR function,
the resetting of the CBR-MAP function curve to an increased centering point pressure was not
associated with marked changes in curve parameters (e.g., G_{max}, responding range, G_{op}, etc.)
(Table 2). Additionally, the separate analysis of the respective hypo- (Figure 3) and hypertensive
aspects of the MAP responses supported no unique differences in CBR responsiveness between thermal conditions (unlike the CBR control of HR detailed above). However, our findings clearly support that CBR control of MAP (both CBR-MAP function curves and separate analysis of the hypo- and hypertensive aspects) is well-maintained during WBH compared to NT.

The mechanism(s) responsible for the altered CBR control of HR during WBH are not readily apparent. In response to simulated hypertension (NS), the HR response magnitude was greatly enhanced as a result of WBH (Figure 4A). In 2005, Ogoh et al. (26) reported that HR responses to 5 s trials of NP/NS were, virtually, exclusively mediated by changes in vagal activity. That is, following vagal blockade using glycopyrrolate, HR responses to 5 s trials of NP/NS were abolished. Although the aforementioned study was conducted during resting, presumably normothermic conditions, it is likely that similar mechanisms (i.e., changes in vagal responsiveness) contributed to the enhanced HR responses observed in the current study. To this end, with the expected vagal withdrawal that would accompany the WBH condition, there would be (hypothetically) a greater capacity for decreases in HR in response to neck suction, as the associated vagal activation has more ‘room’ to lower HR. However, this is not the case during dynamic exercise, a condition associated with both an increased HR and vagal withdrawal. Therefore, future studies into the mechanisms are warranted.

The findings of our study are in contrast to the work by Crandall (5). Crandall reported a decrease in both the $G_{\text{max}}$ and responding range for the CBR-MAP function curves and reported no change in basic parameters associated with the CBR-HR function curves. The author concluded that those observed changes may contribute to the well-documented reduction in orthostatic tolerance associated with heat stress in humans. The most likely reason for the clear
discrepancy between the findings of the current study and the work of Crandall is related to the nature of the application of the carotid baroreceptor stimuli used. Crandall used a ‘stair-step’ application with changes in chamber pressure occurring during successive cardiac cycles (covering a pressure range of +40 to -65 Torr). One consequence of that application is that, when used between conditions where HRs are different (e.g., NT vs WBH), the resulting duration of each pressure/suction and, ultimately, the overall baroreceptor stimulation time, are also different between conditions. As steady-state HR is increased during heat stress (~40% in Crandall’s study), the duration of the carotid baroreceptor stimuli was reduced accordingly. Considering CBR responses have been shown to be dependent on stimulus duration (9, 26, 27, 32), it is very possible that the shorter stimuli used by Crandall during WBH resulted in abbreviated HR and MAP responses compared to the findings of the current study.

The current study used 5 s trials of NP/NS during both thermal conditions to ensure consistent stimuli, regardless of the HR response to WBH. Yamazaki and Sone (41) also used the neck chamber technique to investigate the consequence of WBH on the time profile of CBR control of HR and MAP. In that study, the authors used 5-6 s trials of one hypotensive (i.e., 40 Torr) and one hypertensive (-65 Torr) stimuli and compared the timing of the peak responses between thermal conditions. The authors reported some alterations in the timing of the peak responses between thermal conditions (i.e., delayed peak MAP responses to +40 Torr and delayed peak HR responses to -65 Torr, ~1-2 s for each variable) during heat stress. In the current study, we observed no differences in the time to peak MAP responses between thermal conditions. In addition, we also examined the MAP responses during WBH at the time of the peak MAP response observed during NT. The changes in MAP during WBH trials at those times were also not different from the respective NT peak changes in MAP. Interestingly, those authors
also reported greater HR changes to the -65 Torr stimuli during WBH compared to NT. The findings of the current study support the greater HR responses to carotid-hypertensive stimulation and extend them by examining responses over a much wider range of hypertensive stimuli (both analyses of the CBR function curves and the 2-way ANOVA of the separate trials).

While the discrepancy between the “time-to-peak” findings, particularly, the lack of an increase in the MAP time-to-peak responses to NP (+45 Torr) in the current study seem confounding, a few experimental differences are noteworthy: 1) Yamazaki and Sone tested 6 women and 3 men (we studied 10 men), 2) Yamazaki and Sone sampled their data at 100Hz (we sampled data at 200Hz) and 3) possibly most importantly was the fraction of the initial time of the MAP and HR responses that was removed during the analysis of Yamazaki and Sone. Interestingly, Yamazaki and Sone chose to subtract the “delay” (i.e., the time segment) between the onset of the carotid stimulation and the “onset” of the respective responses. Considering that it is not uncommon for some individuals’ responses to begin (and sometimes reach their peak) within the first cardiac cycle following the initiation of the stimulus, we chose not to remove this portion of the response from our analysis. While both analyses may provide insight into aspects of CBR function, we contend that removal of the initial, sometimes critical, time segment during trials may have influenced their findings in relation to those in the current study.

Perspectives & Significance:

It is well-established that heat stress reduces orthostatic tolerance. A series of studies by Wilson et al. (37) and Bungaard et al. (3) clearly showed an increase in contractility of the left ventricle during heat stress that, despite a reduced filling pressure during heat stress alone, results in maintained stroke volume. Although a positive relationship between the magnitude of the change in central venous pressure and the relative degree of orthostatic intolerance during heat
stress was not present in recent work (2), acute restoration of central venous pressure to
‘normothermic values’ (using acute volume expansion) totally alleviated the heat-induced
orthostatic intolerance (17), thus, providing evidence for reduced central venous pressure as a
likely contributor to this phenomena. Other possible factors that have been proposed as
mechanisms for the heat-induced orthostatic intolerance, such as impaired neural control of the
peripheral vasculature and redistribution of cardiac output to the skin vasculature have been
postulated (12, 16, 18). However, it appears these variables contribute minimally in comparison
to the aforementioned variables.

In conclusion, CBR control of MAP is well-maintained during passive WBH. In addition,
it appears CBR control of HR is enhanced during WBH, particularly, in response to hypertensive
stimuli (although slightly delayed during simulated hypotension). When taken together, it
appears a ‘resetting’ of the CBR occurs during hyperthermia for both HR and MAP; and while
the exact mechanisms responsible for heat-related orthostatic intolerance remain unclear, our
data indicate that CBR function is an unlikely candidate.
ACKNOWLEDGEMENT

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Table 1.

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<th>Whole-body Heating</th>
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<td>MAP adjusted, mm Hg</td>
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Values expressed as mean±SD. BMI, body mass index; BP, blood pressure; MAP, mean arterial pressure; MAP adjusted, mean arterial blood pressure as a function of heart rate; * significantly different than Normothermia (p <0.05)
### Table 2.

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<tbody>
<tr>
<td><strong>Carotid-cardiac curves</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(A_1), bpm</td>
<td>18.5 ± 2.4</td>
<td>32.5 ± 4.8*</td>
</tr>
<tr>
<td>(A_2), au</td>
<td>0.09 ± 0.01</td>
<td>0.12 ± 0.03</td>
</tr>
<tr>
<td>(A_3), mm Hg</td>
<td>90.9 ± 2.9</td>
<td>104.1 ± 5.0*</td>
</tr>
<tr>
<td>(A_4), bpm</td>
<td>46.5 ± 4.1</td>
<td>60.0 ± 6.3*</td>
</tr>
<tr>
<td>Threshold, mm Hg</td>
<td>66.1 ± 5.5</td>
<td>74.3 ± 6.9</td>
</tr>
<tr>
<td>Saturation, mm Hg</td>
<td>115.7 ± 3.0</td>
<td>133.8 ± 9.9</td>
</tr>
<tr>
<td>(G_{max}), bpm/mm Hg</td>
<td>-0.39 ± 0.04</td>
<td>-0.73 ± 0.11*</td>
</tr>
<tr>
<td><strong>Carotid-vasomotor curves</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(A_1), mm Hg</td>
<td>18.4 ± 1.8</td>
<td>21.5 ± 1.2</td>
</tr>
<tr>
<td>(A_2), au</td>
<td>0.09 ± 0.01</td>
<td>0.08 ± 0.01</td>
</tr>
<tr>
<td>(A_3), mm Hg</td>
<td>86.2 ± 3.9</td>
<td>93.3 ± 2.6*</td>
</tr>
<tr>
<td>(A_4), mm Hg</td>
<td>79.8 ± 2.7</td>
<td>84.1 ± 3.1*</td>
</tr>
<tr>
<td>Threshold, mm Hg</td>
<td>57.7 ± 5.2</td>
<td>67.8 ± 3.5*</td>
</tr>
<tr>
<td>Saturation, mm Hg</td>
<td>114.6 ± 6.0</td>
<td>118.7 ± 2.9</td>
</tr>
<tr>
<td>(G_{max}), mm Hg/mm Hg</td>
<td>-0.36 ± 0.04</td>
<td>-0.43 ± 0.03</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SE. \(A_1\), response range (maximum-minimum); \(A_2\), gain coefficient; \(A_3\), carotid sinus pressure (CSP) at midpoint (centering point); \(A_4\), minimal response; \(G_{max}\), point of greatest slope on first derivative curve of logistic function; * significantly different than Normothermia (p <0.05)
Figure Legend:

**Figure 1.** Stimulus-response relationship for carotid baroreflex (CBR) control of heart rate (HR) during normothermia (NT) and passive, whole-body heating (WBH). Each point represents mean HR responses as a function of Estimated Carotid Sinus Pressure (ECSP) defined as: ECSP = MAP-collar pressure. Lines represent mean data fitted to the logistic function model.

**Figure 2.** Stimulus-response relationship for carotid baroreflex (CBR) control of mean arterial pressure (MAP) during normothermia (NT) and passive, whole-body heating (WBH). Each point represents mean MAP responses as a function of Estimated Carotid Sinus Pressure (ECSP) defined as: ECSP = MAP-collar pressure. Lines represent mean data fitted to the logistic function model.

**Figure 3.** Baroreflex-mediated changes in heart rate (3A) and mean arterial pressure (MAP, 3B) in response to 5 s trials of simulated hypotension (i.e., Neck Pressure: +15, +30 and +45 Torr). NT, normothermia; WBH, whole-body heating. Values are mean ± SD.

**Figure 4.** Baroreflex-mediated changes in heart rate (4A) and mean arterial pressure (MAP, 4A) in response to 5 s trials of simulated hypertension (i.e., Neck Suction: -20, -40, -60 and -80 Torr). NT, normothermia; WBH, whole-body heating. Values are mean ± SD.

**Figure 5.** Baroreflex time-to-peak response time for carotid-cardiac responses to 5 s trials of simulated hypotension (i.e., Neck Pressure: +45 Torr). NT, normothermia; WBH, whole-body heating. Values are mean ± SD. * significantly different from normothermia.
Figure 1.

Estimated Carotid Sinus Pressure (mm Hg)

Heart Rate (bpm)

G_{max} = 0.73 \pm 0.11
G_{max} = 0.39 \pm 0.04
Estimated Carotid Sinus Pressure (mm Hg)

Mean Arterial Pressure (mm Hg)

\( G_{\text{max}}: -0.36\pm0.04 \)

\( G_{\text{max}}: -0.43\pm0.03 \)

NT

WBH
Figure 3.

![Graph A](image1)

![Graph B](image2)

A

- NT
- WBH

Cond = 0.625
CP = 0.002
Cond*CP = 0.064

B

- NT
- WBH

Cond = 0.162
CP = 0.001
Cond*CP = 0.949

Change in Heart Rate (bpm)

Change in MAP (mm Hg)

Chamber Pressure (Torr)
Figure 4.

**A**

Chamber Pressure (Torr)

<table>
<thead>
<tr>
<th>Chamber Pressure (Torr)</th>
<th>Change in Heart Rate (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
<td>-12</td>
</tr>
<tr>
<td>-40</td>
<td>-14</td>
</tr>
<tr>
<td>-60</td>
<td>-16</td>
</tr>
<tr>
<td>-80</td>
<td>-18</td>
</tr>
</tbody>
</table>

Legend:
- WBH
- NT

Significance:
- cond = 0.01
- CP = 0.001
- cond*CP = 0.049

**B**

Change in MAP (mm Hg)

<table>
<thead>
<tr>
<th>Change in MAP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-18</td>
</tr>
<tr>
<td>-16</td>
</tr>
<tr>
<td>-14</td>
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<tr>
<td>-12</td>
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<td>-8</td>
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<tr>
<td>-6</td>
</tr>
<tr>
<td>-4</td>
</tr>
<tr>
<td>-2</td>
</tr>
</tbody>
</table>

Legend:
- WBH
- NT

Significance:
- cond = 0.126
- CP = 0.001
- cond*CP = 0.122
Figure 5