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EFFECT OF PASSIVE HEAT STRESS ON ARTERIAL STIFFNESS

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Abstract

Arterial compliance, the inverse of arterial stiffness, is a prognostic indicator of arterial health. Central and peripheral arterial compliance decrease with acute cold stress and may increase post exercise when exercise-induced elevations in core temperature are likely still present. Increased blood flow through the conduit arteries associated with elevated core temperature increases shear stress which in turn releases nitric oxide and other endothelial derived factors. These changes, in conjunction with supportive *in vitro* data, suggest that elevated core temperature may indirectly increase central and peripheral arterial compliance (i.e., decrease arterial stiffness). The purpose of this study was to test the hypothesis that increased core temperature decreases central and peripheral arterial stiffness, as measured with pulse wave velocity (PWV). Using Doppler ultrasound, carotid-femoral (central) and carotid-radial (peripheral) arterial PWVs were measured from eight subjects (age 37 ± 11 years; mass 68.8 ± 11.1 kg; height 171 ± 3 cm) before and during passive heat-stress induced increases in core temperature of 0.47 ± 0.05, 1.03 ± 0.12, and 1.52 ± 0.07°C (i.e., baseline, 0.5, 1.0, and 1.5°C, respectively). Changes in PWV were evaluated with a one-way repeated measures ANOVA. When analyzed as group means, neither central (677 ± 161, 617 ± 72, 659 ± 74, and 766 ± 207 cm/s; P=0.12) nor peripheral (855 ± 192, 772 ± 95, 759 ± 49, and 858 ± 247 cm/s; P=0.56) PWV changed as core temperature increased from baseline to 0.5, 1.0, and 1.5°C, respectively. However, individual changes in central (average $r = -0.89$, $P < 0.05$) and peripheral (average $r = -0.93$, $P < 0.05$) PWV with heat stress were significantly correlated with normothermic baseline PWV. In conclusion, these data suggest that the magnitude by which heat stress reduced PWV was predicated upon normothermic PWV, with the individuals having the highest normothermic PWV being most responsive to the heat stress-induced reductions in PWV.

Keywords

hyperthermia; compliance; distensibility; pulse wave velocity

INTRODUCTION

Arterial compliance, the inverse of arterial stiffness, is a prognostic indicator of arterial health (Laurent *et al.*, 2006). The acute effect of exercise on arterial compliance is dependent on exercise duration, intensity, and mode. Thirty minutes of moderate intensity (e.g., 65% VO_{2max}) aerobic exercise leads to a transient increase in central and peripheral compliance that returns to baseline after 60 min post-exercise (Kingwell *et al.*, 1997; Heffernan *et al.*, 2007). However, with short duration aerobic exercise, increases in peripheral arterial compliance are localized to the exercising limbs (Naka *et al.*, 2003;

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Sugawara *et al.*, 2003). High intensity, short-duration anaerobic exercise leads to acute decreases in central compliance, while peripheral compliance either increases or does not change (Heffernan *et al.*, 2007; Rakobowchuk *et al.*, 2009). The mechanisms responsible for these varying effects of exercise on arterial compliance are unclear.

It is well known that moderate intensity exercise can increase body temperature as much as 1.0°C in as little as 30 min (Saltin & Hermansen, 1966; Gregson *et al.*, 2002), while high intensity and short duration anaerobic exercise can increase body temperature, but not always (Deschenes *et al.*, 1998; Watson *et al.*, 2005). It is possible that the transient and inconsistent changes in arterial compliance following various types of exercise may be associated with differences in core body temperature during these exercise bouts.

Recent evidence suggest that cold stress causes acute decreases in central and peripheral compliance that may be the result (or cause) of increases in blood pressure or from sympathetic nervous system activation (Hess *et al.*, 2009). However it is unknown if the reverse occurs; that is, whether heat stress increases vascular compliance. In support of this hypothesis, direct heating of isolated iliac arteries increases vessel compliance, although these vessels were heated to a non-physiological temperature of 60°C (Mitchel *et al.*, 1994). It remains unknown whether a more physiological heating stimulus similarly increases arterial compliance.

Passive heat stress increases blood flow through large conduit arteries (i.e., aorta, brachial, and femoral arteries) secondary to increases in cardiac output and reductions in systemic vascular resistance, which in turn increases shear stress (Kellogg *et al.*, 2003). Increased shear stress increases nitric oxide and/or cytochrome-related hyperpolarizing factors, which are known vasodilators and modulators of vascular tone, arterial elasticity, and arterial compliance (Kinlay *et al.*, 2001; Sugawara *et al.*, 2007; Bellien *et al.*, 2010). Therefore it stands to reason that passive heat stress, through a direct affect of temperature on the vessels as shown *in vitro* (Mitchel *et al.*, 1994) and/or the release of vasodilator substances associated with increased shear stress, may increase arterial compliance and thus reduce arterial stiffness. To that end, the purpose of this study was to test the hypothesis that increases in core temperature via passive heat-stress decreases arterial stiffness.

METHODS

Subjects

Three males and five females (n = 8) participated in this study; subjects' mean ± SD age, mass and height were 37 ± 11 years, 68.8 ± 11.1 kg, and 171 ± 3 cm. Subjects were excluded if they were smokers, taking medications, hypertensive (resting systolic blood pressure >139 mmHg), obese (body mass index >30 kg/m^2), or had any self-reported cardiovascular, metabolic or neurological diseases. Although otherwise healthy, a lack of biochemistry data to confirm health status is a recognized limitation of the study. Subjects refrained from alcohol and exercise 24 h, food 4 h, and caffeine 12 h before the study. Each subject had a urine specific gravity of <1.028 prior to testing. Written informed consent was obtained from all subjects before participating in this study. Study procedures and the informed consent were approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas.

Instrumentation and measurements

Each subject was dressed in a water-perfused, tube-lined suit (Med-Eng, Ottawa, Canada) that covered the entire body, except the head, face, hands, feet, and one forearm. The water-perfused suit permitted the control of skin and core temperature by changing the temperature of the water perfusing the suit. Core temperature was measured from an ingestible pill

telemetry system (HQ, Palmetto, FL). The pill was ingested immediately on arrival at the laboratory, which was ~1 h before the onset of data collection and ~2 hours before the onset of the heat stress. Mean skin temperature was measured via the weighted average of six thermocouples attached to the skin (Taylor *et al.*, 1989). Heart rate was obtained from an electrocardiogram (HP Patient Monitor, Agilent, Santa Clara, CA) interfaced with a cardiotachometer (CWE, Ardmore, PA). Arterial blood pressure was measured by auscultation of the brachial artery via electrosphygmomanometry (SunTech, Raleigh, NC). The blood pressure cuff was placed directly on the skin, underneath the water-perfused suit. Mean arterial blood pressure (MAP) was calculated as 1/3 pulse pressure + diastolic pressure.

Arterial stiffness was measured by pulse wave velocity (PWV) using Doppler ultrasound (LOGIQ e, GE Healthcare, Milwaukee, Wisconsin) (Laurent *et al.*, 2006). PWV is the preferred method to evaluate arterial compliance (Laurent *et al.*, 2006) given that PWV is proportional to the inverse of the square root of compliance; thus, PWV decreases as arterial compliance increases (Bramwell & Hill, 1922b, a). PWV was measured with Doppler ultrasound and calculated as the distance between measurement sites divided by the time delay between the two waveforms. Central PWV was calculated from the carotid and femoral arteries, while peripheral PWV was calculated from carotid and radial arteries (Laurent *et al.*, 2006). All PWV measures were performed on the left side of the body with consistent probe location being assured by marking the skin. Because only one Doppler ultrasound probe was used, the R-wave of the ECG was used as a reference point to calculate the time delay between waveforms. Specifically, pulse transit time was calculated by subtracting the time between the peak of the R-wave and the foot of the carotid pulse from the time between the peak of the R-wave and the foot of the distal pulse (i.e., femoral for central PWV and radial for peripheral PWV) for at least ten consecutive cardiac cycles (Laurent *et al.*, 2006). A potential limitation to the design is that the foot of the pulse wave was identified visually (versus computer aided) at the point of the systolic upstroke (Heffernan *et al.*, 2007). Since measurements between sites occurred within a short time frame (~5 min), it is unlikely that there were any differences in the left ventricle isovolumic period between measurements, which would have otherwise affected measured pulse transit times (Laurent *et al.*, 2006). Carotid and femoral measurement order was randomized between subjects. Distance between arterial measurement sites was calculated by subtracting the distance from the carotid location to the sternal notch from the distance between the sternal notch and the femoral or radial site (Laurent *et al.*, 2006).

Experimental Protocol

After instrumentation, subjects were supine for approximately 30 min prior to normothermic measures so that body fluid shifts had stabilized (Pivarnik *et al.*, 1986). Water at 34°C was perfused through the suit during this period. After this resting period, central and peripheral PWV were obtained. Subjects were then exposed to a passive heat stress by perfusing 49°C water through the suit. Measures of PWV began just prior to reaching a 0.5, 1.0, and 1.5°C elevation in core temperature from pre heat-stress baseline; this corresponded to 36 ± 5, 60 ± 11, and 77 ± 15 min of heat stress, respectively. Femoral measures occurred while briefly exposing the measurement site to room temperature (~26°C); while the carotid and radial measurement sites were exposed to room temperature throughout testing. Blood pressure was measured following the last PWV at each time point.

Statistical Analysis

Heart rate and skin and core temperature were sampled at 50 Hz via a data-acquisition (Biopac System, Santa Barbara, CA). These data were averaged at each time point over the period in which PWV measures occurred. Data were analyzed using SigmaStat 3.11

(Chicago, IL). A one-way repeated measures analysis of variance (ANOVA) was used to examine cardiovascular and thermoregulatory differences across core body temperatures. Post-hoc Bonferroni follow-up t-tests were conducted if a significant main effect was identified. A Pearson Product Moment Correlation was calculated for the change in heart rate with heat stress versus change in central and peripheral PWV. A Pearson Product Moment Correlation also was calculated for the change in central and peripheral PWV versus the respective normothermic baseline PWV. All data are reported as mean ± SD. Significance was set at $P < 0.05$.

The within-subject coefficients of variation for the time between the peak of the R-wave and the foot of the carotid, femoral, and radial artery pulse wave over ten cardiac cycles were 3.3, 2.1, and 1.4%, respectively. When subjects' baseline PWV were examined on two different occasions on the same day, the coefficient of variation was 5.7%, and the correlation coefficient between measures was 0.86, a value similar to others (Heffernan *et al.*, 2007). With an alpha set 0.05, a power of 0.8, and standard deviation of 44 cm/s, eight subjects were sufficient to detect a 55 cm/s difference in PWV, a similar acute change observed by others (Kingwell *et al.*, 1997).

RESULTS

Core temperature increased 0.47 ± 0.05, 1.03 ± 0.12, and 1.52 ± 0.07°C from baseline to each measurement period ($P < 0.05$). Likewise skin temperature and heart rate increased over time ($P < 0.05$; Table 1). The only change in mean arterial pressure occurred from baseline to +0.5°C ($P < 0.05$). Diastolic blood pressure decreased over the same temperature change ($P< 0.05$; Table 1).

Averaged central PWV did not change from baseline to 0.5, 1.0, nor 1.5°C increases in core temperature ($P = 0.12$, Figure 1A). Similarly, averaged peripheral PWV did not change between these core body temperatures ($P = 0.56$; Figure 1B). When analyzed as percent change from baseline, the results were consistent with absolute values (data not shown). Correlation analysis confirmed that changes in central ($r = 0.04$, $P = 0.84$) and peripheral ($r = 0.20$, $P = 0.28$) PWV were independent of core temperature. Increased variability in PWV between subjects was due to one subject whose responses were greater than 2SD from the mean. When those observations were removed and the data re-analyzed, the findings were consistent with that reported with the entire group and thus this individual's data were included throughout.

There were no significant correlations between the change in heart rate and change in central ($r = 0.10$, $P = 0.640$) or peripheral ($r = 0.02$, $P = 0.94$) PWV. However, the change in central PWV when core temperature was increased 0.5°C ($r = -0.93$, $P < 0.001$), 1.0°C ($r = -0.94$, $P < 0.001$), and 1.5°C ($r = -0.80$, $P = 0.03$) was significantly correlated with normothermic central PWV (Figure 2). Likewise the change in peripheral PWV when core temperature was increased 0.5°C ($r = -0.88$, $P = 0.004$), 1.0°C ($r = -0.97$, $P < 0.001$), and 1.5°C ($r = -0.93$, $P = 0.002$) was significantly correlated with normothermic peripheral PWV (Figure 3).

DISCUSSION

In vitro evidence suggests that direct heating of isolated arteries increases arterial compliance (Mitchel *et al.*, 1994). Given these findings, coupled with the observation that increases in shear stress are capable of modulating arterial elasticity (Kinlay *et al.*, 2001), we tested the hypothesis that elevations in core temperature decrease central and peripheral arterial stiffness. Averaged central and peripheral arterial stiffness were unaffected by

increases in core temperature up to 1.5°C. However, individual changes in central and peripheral arterial stiffness were negatively correlated with baseline normothermic arterial stiffness; that is, the largest decreases in arterial stiffness with heating occurred in the individuals with the highest baseline stiffness.

Arterial elasticity, and thus stiffness, has passive and active elements. The structural composition of the artery wall provides the passive component, and it is unlikely that moderate heat stress (or other acute perturbations) affects this component. The active component is related to arterial tone that can be changed by acute perturbations (Kinlay *et al.*, 2001). The present data show that changes in central and peripheral arterial stiffness during passive heating are predicated on baseline stiffness. Individuals with increased normothermic arterial stiffness had a greater decrease in stiffness when hyperthermic versus those with lower baseline arterial stiffness (Figures 2 and 3). It is unknown why hyperthermia affects vessels differently depending on baseline tone. It may be that the reserve to further increase vascular compliance in an already compliant bed is diminished, resulting in the greatest increases in vascular compliance to heat stress in the more stiff vessels. It also is possible that shear stress related factors leading to increased compliance are countered by artery stiffening due to increases in sympathetic activity known to occur with heat stress (Niimi *et al.*, 1997; Cui *et al.*, 2002; Cui *et al.*, 2004). This hypothesis is supported by findings that increases in sympathetic activity are associated with decreases in arterial compliance (Swierblewska *et al.*, 2010). However, given the present findings, if this hypothesis is correct then modulation of arterial stiffness by sympathetic activity would be different between individuals having higher and lower normothermic PWV. Although not measured in the present study, it may also be that the magnitude of the elevation in sympathetic activity to heat stress was greater in the individuals with the highest normothermic arterial compliance.

Hyperthermia increases blood flow through the skin and associated conduit arteries, which would increase shear stress and promote the release of nitric oxide and/or cytochrome-related hyperpolarizing factors (Kinlay *et al.*, 2001; Bellien *et al.*, 2010); both proposed to decrease arterial stiffness (Kellogg *et al.*, 1998; Kinlay *et al.*, 2001; Kellogg, 2006; Kooijman *et al.*, 2008). Although unlikely, we cannot exclude the possibility that in the less stiff more compliant vessels while normothermic, the magnitude of the release of nitric oxide and/or cytochrome-related hyperpolarizing factors was not adequate, or the arteries were not sufficiently sensitive to these substances to cause changes in arterial tone to heat stress.

By definition, vessel compliance relates the change in volume for a given change in pressure. A more compliant vessel will have a greater increase in volume for a given increase in pressure, while the opposite will be the case for a less compliant vessel (O'Rourke *et al.*, 2002). Because of the curvilinear nature of the compliance curve, the operating point on the compliance curve influences the effect of an acute perturbation on vessel compliance. For example, cold stress acutely decreases compliance in older individuals, who have a decreased baseline arterial compliance compared to their younger counterparts (Hess *et al.*, 2009). Similarly, the effect of heat stress on arterial stiffness was dependent on normothermic values. Although we did not have adequate power to statistically compare the effects of age, it is possible the correlation between baseline stiffness and changes in PWV with heating was related to aging, given that as a group older individuals have decreased arterial compliance while normothermic (Vaitkevicius *et al.*, 1993). Nevertheless, based upon the present findings older individuals with decreased baseline compliance may have a greater capacity to increase compliance with heating.

Acute changes in arterial compliance and blood pressure are inter-related, such that blood pressure changes may lead to, or be the result of, changes in arterial compliance (Kinlay *et al.*, 2001). For example, an acute perturbation such as cold stress increases blood pressure which occurs in concert with an acute decrease in arterial compliance (Hess *et al.*, 2009). Changes in peripheral and central arterial compliance were not observed in subjects in which cold stress minimally affected blood pressure (Hess *et al.*, 2009). Although heat stress resulted in a small drop in mean arterial pressure (Table 1), it is unlikely that the magnitude of this decrease was sufficient to influence PWV (Hess *et al.*, 2009). Further, at greater increases in core temperature (i.e., +1.0 and +1.5°C), when mean arterial pressure was similar to baseline, average PWV remained unchanged, and the correlation between baseline PWV and change in PWV was independent of degree of heat stress.

The current findings have important implications for future research. First, these data support the notion that changes in arterial compliance immediately following exercise (Kingwell *et al.*, 1997) have the potential to be dependent on internal temperature. Second, technology such as beat-to-beat measures of cardiac output with Modelflow assumes arterial compliance is not changing by an acute perturbation (Wesseling *et al.*, 1993). We recently observed that on average Modelflow underestimates cardiac output during heat stress (Shibasaki *et al.*, 2011). Based on the present findings, the source of this error may be related to inter-subject variability in heat stress-induced changes in aortic compliance, with the individuals having the highest normothermic vascular stiffness perhaps being the ones with the largest changes in aortic compliance to heat stress and thus the greatest error in the Modelflow readings.

Limitations to the interpretation of the data

Whole-body heat stress causes pronounced increases in heart rate (see Table 1). Increases in heart rate via cardiac pacing independently increase PWV, indicative of decreased arterial compliance (Liang *et al.*, 1999; Lantelme *et al.*, 2002). Alternatively, decreases in arterial compliance that occur during conditions that cause tachycardia may be related to increases in sympathetic neural activity that contributed to the tachycardic response; although this effect would not explain the aforementioned effects of cardiac pacing on arterial compliance. Equally possible is that increased heart rate shortens the time available for vessel recoil and leads to vessel stiffening and thus decreased compliance (Lantelme *et al.*, 2002). Given these observations, it is possible that in the present study heat stress consistently decreased arterial stiffness in all subjects, but this response was masked and/or offset by the effect of increases in heart rate on recoil time reducing compliance; the net effect being no change in arterial stiffness. However, tachycardia-induced changes in compliance occur when heart rate is greater than 120 beats per minute (Callaghan *et al.*, 1984), which is less than the average heart rates in the current study (Table 1). These findings, coupled with an absence of a correlation between change in heart rate and changes in central and peripheral PWV, it is unlikely that heat stress induced increases in heart rate influenced PWV.

The relationship of PWV to arterial compliance is described by the Bramwell-Hill equation where arterial compliance= 1/(PWV^2 * blood viscosity) (Bramwell & Hill, 1922b), and thus changes in blood viscosity have the potential to affect arterial compliance measures independent of PWV. That said, there is no known evidence to suggest that the relatively minor increase in blood temperature with passive heating (i.e. 1.5°C) is sufficient to decrease blood viscosity to the point where physiological significant increases in arterial compliance occur in the absence of changes in PWV. Secondly, the loss of hypotonic sweat throughout heating may increase blood density sufficient to increase viscosity, which would counter a direct affect of increases in blood temperature in potentially decreasing blood

viscosity (du Nouy, 1929; Merrill *et al.*, 1963). Therefore it is reasonable to assume that in this study PWV changes reflected arterial compliance.

It is recognized that passive heating is not the same as exercise-induced increases in core body temperature. However the present protocol increased core body temperature 1.5°C, an increase similarly observed after ~30 min of treadmill exercise at 70% VO_{2max} in 22°C, 37% relative humidity (Gregson *et al.*, 2002). It is possible that changes in arterial stiffness following similar exercise (Kingwell *et al.*, 1997; Heffernan *et al.*, 2007) are a due to a combination of metabolites produced during exercise, increased core body temperature, and baseline arterial stiffness.

In conclusion, using PWV as a measure of arterial stiffness, the present data show that core temperature increases up to 1.5°C above baseline with passive heating do not affect average peripheral or central arterial stiffness from a sample of individuals of varying ages. However, the subjects with the greatest normothermic arterial stiffness generally were the ones with the greatest decreases in stiffness to the heat stress. The present findings support *in vitro* observations where pronounced, and non-physiological, heating of arteries increased arterial compliance. Secondly, these observations suggest elevations in core temperature may, in part, explain previously observed post-exercise increases in arterial compliance. Lastly, prior observations of inaccuracies in Modelflow derived cardiac output may be due to the variable changes in arterial stiffness that occur during heat stress (Shibasaki *et al.*, 2011).

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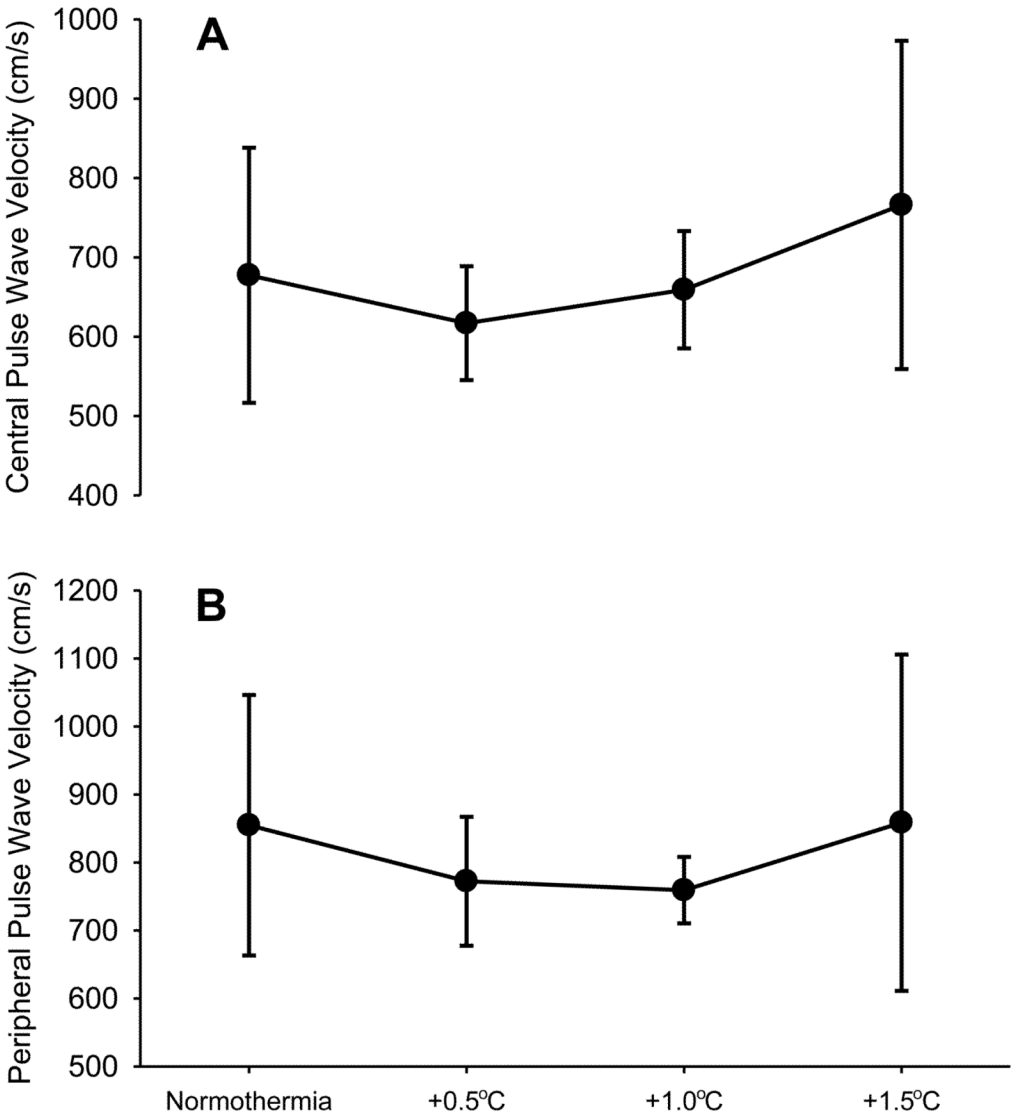

Figure 1.
Mean ± SD central (A) and peripheral (B) pulse wave velocity at baseline normothermia and after core temperature increases of 0.5, 1.0, and 1.5°C. There were no significant differences across temperatures.

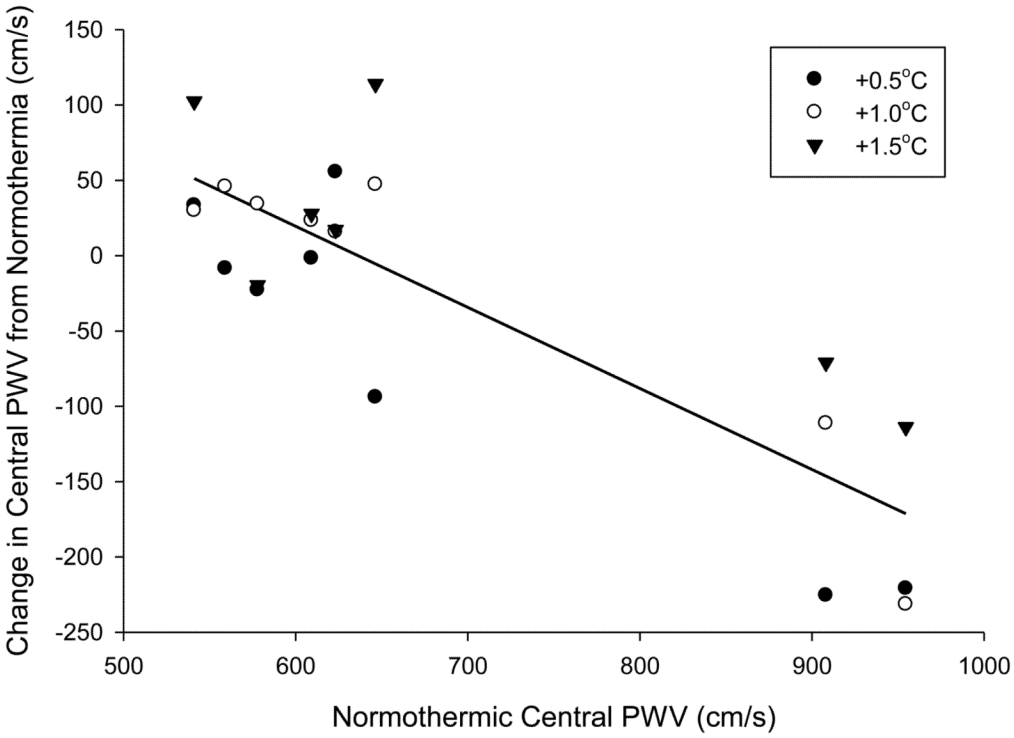

Figure 2.

Correlation between central pulse wave velocity (PWV) at normothermia versus the change in central PWV after core temperature increases of 0.5, 1.0, and 1.5°C. The correlation was significant at +0.5°C ($r = -0.93$, $P < 0.001$), +1.0°C ($r = -0.94$, $P < 0.001$), and +1.5°C ($r = -0.80$, $P = 0.03$). Line of best fit is the average of all temperature responses. The addition of an outlier datapoint with a baseline PWV of 559 cm/s and change in PWV at +1.5°C of 652 cm/s does not change the significance of the statistical outcome.

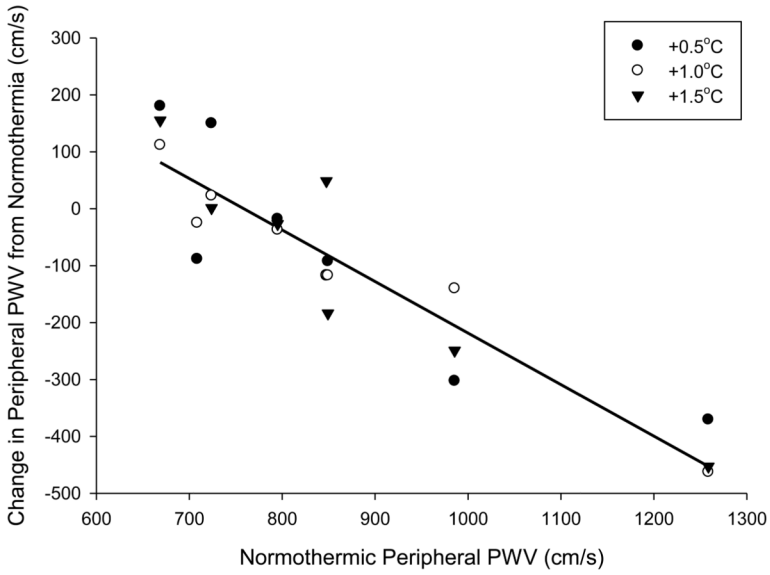

Figure 3.

Correlation between peripheral pulse wave velocity (PWV) at normothermia versus the change in peripheral PWV after core temperature increases of 0.5, 1.0, and 1.5°C. The correlation was significant at +0.5°C ($r = -0.88$, $P = 0.004$), +1.0°C ($r = -0.97$, $P < 0.001$), and +1.5°C ($r = -0.93$, $P = 0.002$). Line of best fit is the average of all temperature responses. The addition of an outlier datapoint with a baseline PWV of 709 cm/s and change in PWV at +1.5°C of 737 cm/s yields a non-significant correlation ($r = -0.53$, $P = 0.18$).

Table 1

Thermal and hemodynamic responses at normothermia and after subjects' core temperatures were increased approximately 0.5, 1.0, and 1.5°C.

	Normothermia	+0.5°C	+1.0°C	+1.5°C
Mean Skin Temperature (°C)	34.2 ± 0.6	38.0 ± 0.4*	38.6 ± 0.4*	38.9 ± 0.3
Core Temperature (°C)	37.16 ± 0.16	37.63 ± 0.15*	38.18 ± 0.20*	38.67 ± 0.18*
Mean Arterial Pressure (mmHg)	82 ± 5	77 ± 5*	81 ± 5	81 ± 6
Systolic Blood Pressure (mmHg)	111 ± 10	109 ± 9	115 ± 10	115 ± 11
Diastolic Blood Pressure (mmHg)	68 ± 4	62 ± 6*	64 ± 3	63 ± 6
Heart Rate (beats/min)	58 ± 6	84 ± 11*	99 ± 10*	108 ± 13*

*Significant difference from the prior temperature stage ($P < 0.05$).