

## Changes in central artery blood pressure and wave reflection during a cold pressor test in young adults

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**Abstract** The relative contribution of sympathetic nervous system (SNS)-induced increase in peripheral vascular resistance on central artery blood pressure (BP) and aortic wave reflection (augmentation index; AIx) is not completely understood. Central BP and wave reflection characteristics were measured using radial artery applanation tonometry before, during a 3-min cold pressor test (CPT), and 90 and 180-s post-CPT in 15 young, healthy adults ( $25 \pm 1$  years). The CPT resulted in a greater magnitude of change in the estimated aortic systolic (31 vs. 23%,  $P < 0.05$ ) and pulse (31 vs. 13%,  $P < 0.05$ ) BP compared with the change in brachial artery BP. Additionally, the CPT resulted in an increased mean arterial pressure (MAP) ( $P < 0.05$ ) and AIx ( $10 \pm 2$  vs.  $26 \pm 2\%$ ,  $P < 0.05$ ). The change in MAP during the CPT was correlated to the change in AIx ( $r = 0.73$ ,  $P < 0.01$ ) and inversely related to roundtrip duration of the reflected wave to the periphery and back ( $r = -0.57$ ,  $P < 0.05$ ). The present study suggests that cold pressor testing results in a significant increase in arterial wave reflection intensity, possibly due to an increased MAP. However, the greater increase in systolic and pulse BP in the central compared with the peripheral circulation suggests that increased central artery wave reflection intensity contributes to increased left ventricular myocardial oxygen demand during CPT-induced hypertension.

**Keywords** Wave reflection · Blood pressure · Sympathetic nervous system

### Introduction

Increased sympathetic nervous system (SNS) traffic to resistance arteries/arterioles in skeletal muscle contributes to the onset and sustained increase in blood pressure (BP), and is a plausible mechanism for the development of hypertension (Esler 2000). Increased peripheral vascular tone of peripheral muscular arteries/arterioles has important effects on the central circulation as this leads to increased pulse wave velocity of reflected arterial pressure waves which return early to the central circulation during systole (Nichols 2005; Nichols and Singh 2002). The early return of arterial pressure waves augments the amplitude of central systolic and pulse BPs, resulting in elevated wave reflection intensity (i.e., augmentation index, AIx) which increases left ventricular (LV) afterload and myocardial oxygen demand (Nichols 2005). Additionally, the augmented central BP causes a mismatch in vascular coupling between central and peripheral arteries and thus decreases pulse pressure (PP) amplification (PPA; i.e., the ratio of peripheral PP and central PP). These changes are of clinical importance since central BP more strongly relates to vascular disease and outcome than does brachial BP (Roman et al. 2007).

Acute SNS activation with a cold pressor test (CPT) results in a robust increase in mean arterial pressure (MAP) due to increased peripheral vascular resistance via elevated vascular tone of peripheral muscular arteries/arterioles (Victor et al. 1987). However, the relative contribution of SNS activation on central artery (i.e., aorta) BP and wave reflection characteristics in healthy adults is not completely understood. Therefore, we tested the hypothesis that acute

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SNS activation would have a greater influence on central artery BP when compared with brachial BP, due to increased arterial wave reflection intensity.

## Methods

### Subjects

Fifteen young, healthy adults ( $n = 15$ ; 9 males; age range 21–29) were recruited for participation in the study. All the subjects were either sedentary or recreationally active ( $\leq 2$  days of activity/exercise per week), and none were participating in a structured exercise program. Additionally, all subjects were normotensive ( $< 140/90$  mmHg), non-smokers, non-obese (body mass index, BMI  $< 30$  kg/m<sup>2</sup>), free from overt cardiovascular disease and were not receiving medication. All measurements were performed in the morning by the same investigator in a quiet, temperature controlled room (21–23°C) following an 8–12 h overnight fast. All measurements for female subjects were completed in the early follicular phase of their menstrual cycle and no subjects were taking birth control medications. Subjects were asked to abstain from caffeine and alcohol for at least 24 h prior to visiting the laboratory. Subjects were also asked to avoid strenuous physical activity at least 24 h prior to the study day. All subjects provided written informed consent prior to participation in the study.

### Brachial artery blood pressure and heart rate

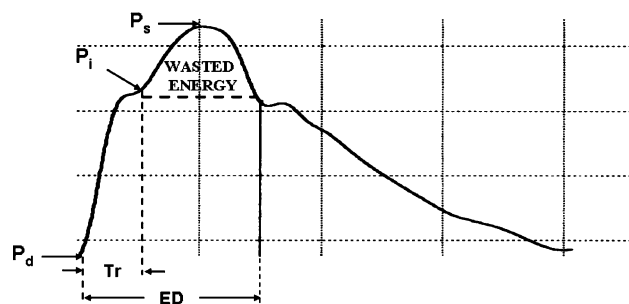
Following a 15-min rest period in a supine position, heart rate (HR) and brachial systolic and diastolic BP measurements were performed in triplicate in the right arm using an automated non-invasive BP cuff (Omron, Bannockburn, IL, USA). An average of three HR and BP measurements was used for resting values.

### Pulse wave analysis

Assessment of arterial wave reflection characteristics was performed non-invasively using the SphygmoCor system (AtCor Medical, Sydney, Australia). High-fidelity radial artery pressure waveforms were recorded by applanation tonometry of the radial pulse in the left wrist using a “pencil type” micromanometer (Millar Instruments, Houston, TX, USA). The aortic pressure waveform is derived non-invasively from the radial pulse using applanation tonometry and application of a generalized transfer function, which corrects for pressure wave amplification in the upper limb (Nichols and O’Rourke 2005). The generalized transfer function has been validated using both intra-arterially (Chen et al. 1997; Pauca et al. 2001) and non-invasively (Gallagher et al.

2004) obtained radial pressure waves. The test–retest reproducibility of this procedure was previously established by others (Wilkinson et al. 1998). In our laboratory reproducibility of AIx was evaluated by triplicate measurement on nonconsecutive days in young, healthy men with a mean coefficient of variation of 6.5% (Casey et al. 2006).

The central aortic pressure wave is composed of a forward traveling wave, generated by LV ejection and a reflected wave that is returning to the ascending aorta from the periphery (Fig. 1) (Nichols and Singh 2002). The AIx is defined as reflected wave amplitude divided by PP and is expressed as a percentage (Murgo et al. 1980). The reflected pressure wave amplitude is referred to as augmented pressure (AP) and is defined as the difference between the first (forward wave) and second systolic shoulders of the central systolic BP. The forward and reflected waves travel in opposite directions along the artery at the same velocity. The round trip travel time ( $Tr$ ) of the forward traveling wave from the ascending aorta to the major reflection site and back is measured from the foot of the forward traveling pressure wave to the foot of the reflected wave. The  $Tr$  is inversely related to arterial pulse wave velocity and arterial stiffness, and directly related to the distance to the reflecting site (Nichols and Singh 2002). AIx is an index of wave reflection intensity, which is influenced by both systemic and peripheral arterial stiffness. Wasted LV pressure energy ( $\Delta E_w$ ) is that component of extra myocardial oxygen requirement that is due to early systolic wave reflection, and can be estimated as  $2.09 \times AP(ED - Tr)$ , where 2.09 is the conversion factor for mmHg s<sup>-1</sup> to dynes s<sup>-1</sup> cm<sup>2</sup> and ED is ejection duration (Murgo et al. 1980; Nichols and Singh 2002). The aortic systolic tension time index ( $As$ ), a marker of aortic systolic stress and myocardial oxygen demand, was estimated as the integral of aortic pressure and time during ventricular systole. The aortic diastolic tension time index ( $Ad$ ), an indirect indicator of diastolic perfusion, was



**Fig. 1** Typical high-fidelity derived ascending aorta pressure waveform with pulse wave analysis components.  $P_s$  aortic systolic pressure,  $P_d$  aortic diastolic pressure,  $P_i$  inflection pressure where incident and reflected waves merge,  $Tr$  round trip travel time of reflected pressure wave to peripheral reflecting sites and back to heart,  $ED$  ejection duration. Wasted energy is the energy or force (or effort) the left ventricle must generate to overcome the late systolic augmented pressure due to wave reflection

estimated as the integral of the diastolic pressure during ventricular diastole (Nichols and O'Rourke 2005). PPA from the aorta to the periphery was estimated as the ratio of brachial PP and central aortic PP (Nichols and O'Rourke 2005). Assessment of central arterial pressure waves is described in detail by Nichols and Singh (2002).

### Cold pressor test

Following baseline peripheral and central hemodynamic measurements, a CPT was employed to evoke SNS stimulation (Koch et al. 2003). The subject's right hand was passively immersed up to the wrist in ice water (4°C) for 3 min and then withdrawn. Tonometric recordings were made during the last 15 s of the CPT (endCPT), 90- and 180-s post-CPT. Brachial BP measurements were taken prior to each tonometric recording. All the measurements were performed with the subject in the supine position.

### Statistical analysis

All data are reported as mean  $\pm$  SEM. One-way ANOVA with repeated measures and pairwise comparisons with Bonferonni correction were used for the analysis of variables compared to baseline. Since Bonferonni correction was used and three pairwise comparisons (baseline vs. endCPT, baseline vs. 90-s post-CPT, and baseline vs. 180-s

post-CPT) were used, an alpha level of  $P < 0.016$  (0.05/3) was required for statistical significance for all pairwise comparisons. In addition, the difference in the magnitude of change between brachial and central pressures (from baseline to endCPT) was analyzed using independent  $t$  tests and an alpha of  $P < 0.05$  was required for statistical significance. Bivariate Pearson's correlations between change in MAP at endCPT with indices of arterial stiffness (i.e., AIx and Tr) were performed. An alpha of  $P < 0.05$  was required for significant correlations. All statistical analyses were performed using SPSS 14.0 for Windows (SPSS, Inc., Chicago, IL, USA).

### Results

All 15 subjects (mean age of  $25 \pm 1$  years; BMI =  $22.7 \pm 0.6$ ) completed the study. There was no change in HR in response to the CPT (Table 1). At endCPT, there was an increase in all components of brachial and central blood pressures ( $P < 0.05$ ). The change in systolic BP ( $31 \pm 3$  vs.  $27 \pm 3$  mmHg) and pulse BP ( $9 \pm 1$  vs.  $5 \pm 1$ ) was greater in the aorta when compared with the brachial ( $P < 0.05$ , Fig. 2). The greater change in central PP compared to brachial pulse BP resulted in a reduction in PPA ( $P < 0.05$ ). AIx increased and Tr decreased at endCPT ( $P < 0.05$ ). Changes in aortic pressure wave intensity (AIx) and Tr

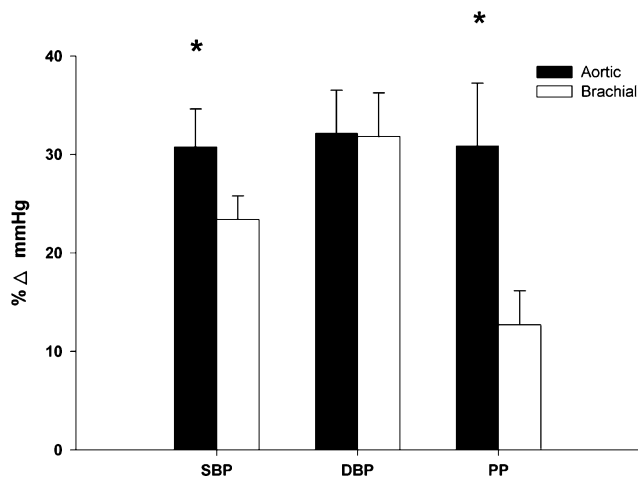
**Table 1** Hemodynamic responses to cold pressor test

Variable	Baseline	endCPT	90-s post	180-s post
Heart rate (beats/min)	58 $\pm$ 3	61 $\pm$ 3	58 $\pm$ 3	57 $\pm$ 3
Brachial SBP (mmHg)	118 $\pm$ 3	145 $\pm$ 3*	123 $\pm$ 4	120 $\pm$ 4
Brachial DBP (mmHg)	74 $\pm$ 2	97 $\pm$ 3*	78 $\pm$ 2	74 $\pm$ 2
Brachial PP (mmHg)	44 $\pm$ 4	49 $\pm$ 4*	45 $\pm$ 5	46 $\pm$ 4
Central SBP (mmHg)	103 $\pm$ 2	134 $\pm$ 3*	110 $\pm$ 3*	105 $\pm$ 3
Central DBP (mmHg)	74 $\pm$ 2	97 $\pm$ 3*	79 $\pm$ 2	75 $\pm$ 2
Central PP (mmHg)	29 $\pm$ 2	38 $\pm$ 3*	31 $\pm$ 3	31 $\pm$ 2
Mean arterial BP (mmHg)	87 $\pm$ 2	114 $\pm$ 3*	93 $\pm$ 2*	89 $\pm$ 2
AP, $P_s - P_i$ (mmHg)	3 $\pm$ 1	10 $\pm$ 1*	5 $\pm$ 1*	4 $\pm$ 1
Forward pressure, $P_i - P_d$ (mmHg)	26 $\pm$ 2	27 $\pm$ 2	26 $\pm$ 3	26.4 $\pm$ 2
PP amplification	1.55 $\pm$ 0.03	1.36 $\pm$ 0.05*	1.46 $\pm$ 0.04	1.52 $\pm$ 0.04
AIx (%)	10 $\pm$ 2	26 $\pm$ 2*	17 $\pm$ 2*	14 $\pm$ 2
Tr (ms)	163 $\pm$ 5	146 $\pm$ 4*	150 $\pm$ 4*	154 $\pm$ 5
LV ejection duration (ms)	338 $\pm$ 4	328 $\pm$ 5*	335 $\pm$ 4	335 $\pm$ 4
As (mmHg/s per minute)	1,844 $\pm$ 94	2,449 $\pm$ 142*	1,991 $\pm$ 95*	1,899 $\pm$ 102
$\Delta E_w$ (dynes s/cm <sup>2</sup> )	1,097 $\pm$ 248	3,705 $\pm$ 458*	2,110 $\pm$ 424*	1,661 $\pm$ 376

Values are means  $\pm$  SEM

endCPT last 15 s of cold pressor test, SBP systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure, AP augmented pressure,  $P_s$  aortic systolic pressure,  $P_i$  merging point of incident and reflected waves on aortic pressure waveform,  $P_d$  aortic diastolic pressure, AIx aortic augmentation index, Tr round trip time of reflected wave to the periphery and back to the heart, LV left ventricular, As aortic systolic tension time index,  $\Delta E_w$  wasted LV energy

\*  $P < 0.016$  versus baseline



**Fig. 2** Percentage (%) change ( $\Delta$ ) in aortic and brachial blood pressures immediately following the cold pressor test. Values are mean  $\pm$  SEM. \* $P < 0.05$  versus brachial

resulted in elevated levels of As and  $\Delta E_w$  at endCPT ( $P < 0.05$ ).

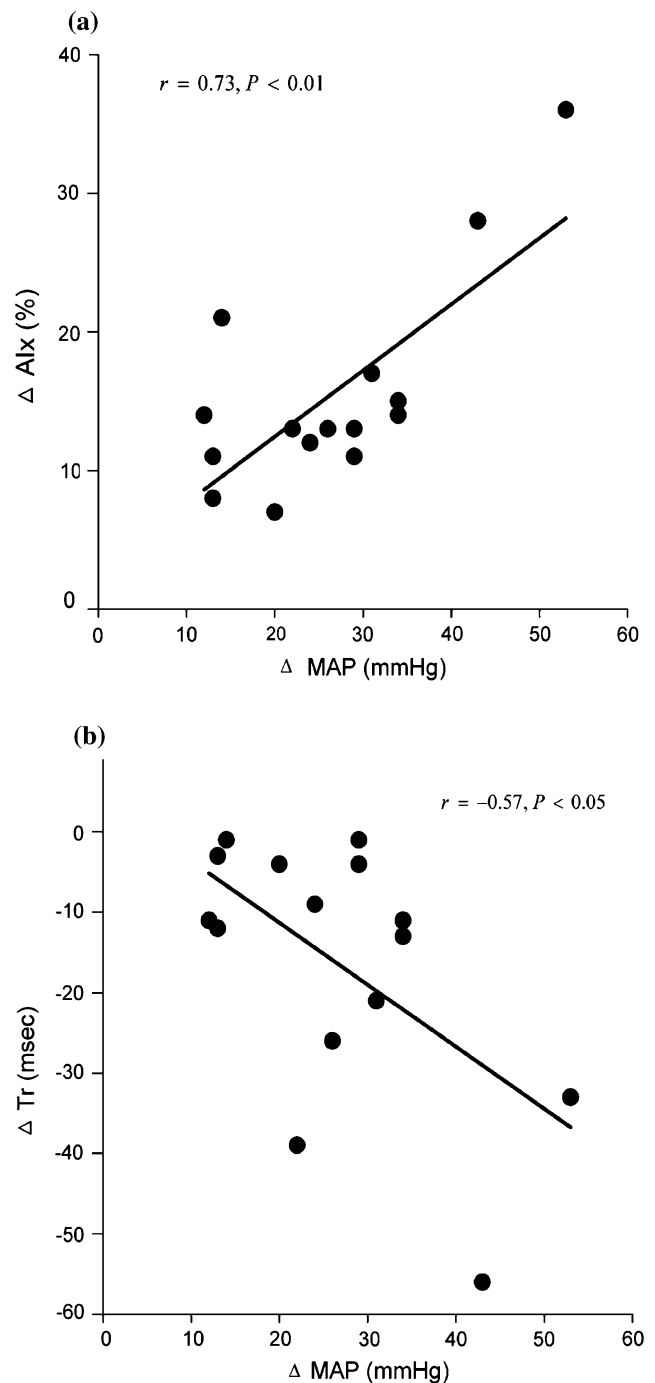
Brachial pressures did not differ from baseline values at 90-s post-CPT. Central systolic BP, AP, and MAP continued to be elevated 90-s post-CPT ( $P < 0.05$ ). This resulted in higher AIx, As, and  $\Delta E_w$  at 90 s post when compared to baseline values ( $P < 0.05$ ; Table 1). All hemodynamic variables at 180-s post-CPT were not different than baseline values.

Bivariate Pearson's correlation analysis demonstrated a relation between the change in MAP and the change in AIx ( $r = 0.73$ ,  $P < 0.01$ ; Fig. 3a). There was also a relation between the change in MAP and the change in Tr ( $r = -0.57$ ,  $P < 0.05$ ; Fig. 3b).

## Discussion

The primary finding of the present study was that the magnitude of change in central systolic and pulse BP is greater than the magnitude of change in brachial artery BP following an acute elevation in SNS activity via CPT. Additionally, we found that the change in MAP during the CPT was related to the changes in wave reflection characteristics (AIx and Tr). Together, these findings suggest that an increased amplitude and/or early return of the arterial reflected pressure wave from the periphery during acute SNS elevation contributes to the increased AIx in young healthy adults.

Mean arterial pressure is a key determinant of arterial stiffness and wave reflection intensity (Laurent et al. 1993). Accordingly, the change in MAP during CPT showed a strong correlation with the change in AIx ( $r = 0.73$ ) and was inversely related with the change in Tr ( $r = -0.57$ ). The increase in MAP observed in the present study is likely



**Fig. 3** Relation between change ( $\Delta$ ) in mean arterial pressure (MAP) and **a** aortic augmentation index (AIx) and **b** round trip travel time of the peripheral reflecting sites and back to the heart (Tr)

due to increased total peripheral vascular resistance due to  $\alpha$ -adrenergic vasoconstriction of muscular arteries and arterioles elicited by the acute cold and/or pain stress (Dinenno et al. 2001). Vasoconstriction of peripheral muscular arteries and arterioles also leads to an increase in pulse wave velocity (PWV) (Geleris et al. 2004) and possibly a decrease in the distance of peripheral reflecting sites (i.e.,

more proximal reflecting sites). Although PWV was not directly assessed in the present study, Tr was decreased. A decrease in Tr indicates that the reflected wave returns early to the ascending aorta and merges with the incident wave during systole and augments the aortic pressure. The early return of the reflected wave leads to greater LV myocardial oxygen demand (systolic tension time index, As) and thus requires a greater LV energy (i.e., wasted energy,  $\Delta E_w$ ) to overcome this added augmentation of pressure (Nichols 2005). The results indicate that the augmentation of the central pressure wave during the CPT resulted in a 33% increase in As and a threefold increase in LV  $\Delta E_w$ .

The results are in agreement with two previous studies that demonstrated CPT causes an increase in AIx. Geleris et al. (2004) demonstrated that the magnitude of change in AIx during CPT is comparable to the AIx changes observed during isometric handgrip exercise, another test of sympathetic activation. Edwards et al. (2006) showed that acute whole body exposure to cold (via an environmental chamber) for 30 min resulted in increases in AIx and central pressures. However, the results differ from these studies in several ways. First, Geleris et al. (2004) reported only brachial artery BP before and after CPT, whereas we derived at both central and peripheral BP and demonstrated that central BP increases more than peripheral BP upon acute SNS activation. Second, the CPT in this study was used experimentally to increase MAP via SNS activation, not to examine the effects of whole body cooling. This allowed us to manipulate SNS activity without the confound of a decreased core body temperature, thus isolating the acute changes in vascular resistance and MAP on central artery BP and wave reflection characteristics. Although SNS activity was not measured, the CPT evokes acute increases in SNS activity, as measured by microneurography (Dishman et al. 2003; Lambert and Schlaich 2004; Schobel et al. 1998) and plasma catecholamine levels (Pascualy et al. 1999; Schobel et al. 1998).

In conclusion, acute SNS activation via CPT results in greater increases in systolic and pulse BP in the central circulation when compared to the peripheral circulation. Additionally, CPT in young healthy adults results in an increase in AIx, possibly due to an increased MAP. Increased central artery wave reflection intensity also contributes to increased LV myocardial oxygen demand during acute SNS activation-induced hypertension.

**Conflict of interest** There are no conflicts of interest to disclose.

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