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Original Research

The Impact of the Cold Pressor Test on Inter-arm Differences in Blood Pressure

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ABSTRACT

International Journal of Exercise Science 16(2): 875-884, 2023. A large inter-arm difference (IAD+; ≥10mmHg between arms at rest) in blood pressure (BP) at rest is linked to cardiovascular risk, and exercise can change this difference. As mechanisms for IAD are elusive, unique physiological stimuli may provide insight towards a better understanding of this phenomenon. The cold pressor test (CPT) has a potent effect on BP and acts primarily through sympathetic nervous system (SNS) stimulation, though the effects of SNS stimulation on IAD are unknown. Therefore, the purpose of the present study was to examine the effects of the CPT on IAD. BP was monitored simultaneously using two automated, auscultatory monitors (SunTech Tango) and a non-invasive hemodynamic device (Physioflow). Participants completed a CPT test, including a 15-minute rest, three pre-test BP measurements (averaged), and a three-minute water immersion (3°C; measurements at 30-sec and 2-min). Descriptive statistics were calculated, and a repeated measures ANOVA test used to compare both the absolute and relative IAD responses. The CPT induced an average absolute increase in IAD of 4.0 mmHg at 30-sec and 6.7mmHg at 2-min across all participants ($P<0.05$). Differences in both the absolute and relative IAD responses to the CPT were noted between IAD- and IAD+ individuals ($P<0.05$). Despite a consistent HR response to the CPT between groups, stroke volume was lower in IAD+ participants at 30-sec and 2-min. Sympathetic stimulation via the CPT induced changes in both the inter-arm difference in blood pressure and hemodynamics in young, apparently-healthy individuals.

KEY WORDS: Adrenergic sensitivity, sympathoexcitation, real-time hemodynamic monitoring

INTRODUCTION

Bilateral brachial blood pressure (BP) measurements often reveal an inter-arm difference (IAD) within individuals. This phenomenon has been reported in the scientific literature since the early 1900s (5). It has been recommended that health care professionals obtain bilateral resting BP measurements during initial patient screenings to improve the detection of hypertension (i.e., by not unintentionally measuring in the 'lower' arm) and to make mindful clinical decisions (i.e., by measuring the potentially 'higher' arm for decisions regarding medication or lifestyle

alteration) moving forward (8). Increasing evidence linking the potential for serious health issues in individuals with an IAD in systolic BP, only detected through bilateral BP measurement, have been uncovered over the past three decades.

A growing body of evidence has quantified and examined the associations of having a large resting IAD (IAD+; ≥10mmHg between arms). Conservative estimates place 10% of individuals (~33 million US residents, ~770 million individuals worldwide) as IAD+ at rest (23). Resting IAD+ may also be associated with structural anomalies (e.g., aortic coarctation, subclavian stenosis, aortic aneurysm, etc.) in the vascular system (6), atherosclerosis (7), peripheral vascular disease (16), and/or increased arterial stiffness (2). Moreover, a series of prospective cohort studies and meta-analyses have related being IAD+ at rest to an increased likelihood of cardiovascular mortality and all-cause mortality (4, 23, 20, 26). As such, the relatively simple measure of bilateral BP may reveal important information related to cardiovascular risk.

Likewise, the cold pressor test (CPT) is a non-invasive test that can reveal cardiovascular risk. The CPT is typically implemented by immersing a single hand or foot in ice-cold water for several minutes, thus exciting the sympathetic nervous system (SNS) and raising BP (10, 11). An appropriate physiological response to the CPT, which stimulates the SNS via nociceptor (i.e., pain receptor) activation, results in blood pressure increases ranging from 5-15mmHg in healthy individuals (15, 24, 21). It has long been proposed that hyper-reactors to the CPT (defined as ≥15mmHg increase to stimulation) may be predisposed to the development of essential hypertension in the future (9, 1, 14, 25). Further, the BP response to the CPT has also been used to diagnose autonomic dysfunction when the change in SBP is less than 10mmHg (15). Interestingly, a potential difference in the bilateral BP response to the CPT has never been examined, to our knowledge.

Our laboratory has previously shown that resting IAD changes acutely and consistently in response to various stimuli, including light/moderate aerobic exercise and isometric handgrip exercise (12, 22, 13). Interestingly, an absolute increase in IAD between 2-6 mmHg has been consistently noted in response to these exercise conditions. Furthermore, a distinct and divergent relative IAD response has been demonstrated between IAD+ individuals and individuals with a small IAD (IAD-; <10mmHg IAD in systolic BP) at rest (22, 13). As resting systolic BP and IAD have been shown to have a positive correlation (3), it is likely that the increase in BP and increase in IAD observed during exercise may also share some common mechanisms.

It is well known that influences on heart rate and BP during aerobic or isometric stimuli include parasympathetic withdrawal, SNS stimulation, and mechano- and metabo-receptor control, all of which may contribute to our previously observed increases in IAD with exercise. It remains equivocal, however, whether the direct stimulation of the SNS will affect IAD and related cardiovascular variables. As such, this study was the first to investigate the effect of nociceptor stimulation (i.e., SNS stimulation) on IAD. A more comprehensive understanding of the

responsiveness of IAD to various physiological mechanisms, including CPT, may provide insight into the importance of bilateral BP measurement.

Therefore, the purpose of this study was to examine the effects of the CPT on IAD and related cardiovascular variables (i.e., cardiac output, stroke volume, total peripheral resistance, and arterial compliance). The primary hypothesis was that the CPT will induce significant changes in IAD and provide insight into novel aspects of SNS control on BP regulation.

METHODS

Participants

This research was carried out fully in accordance to the ethical standards of the International Journal of Exercise Science (19). This study was approved by the Slippery Rock University Institutional Review Board. An a-priori power analysis (G*power V 3.1.9.4) with a medium effect size was used to determine a minimum adequate sample size. The following parameters revealed the need for a sample of 20 subjects to reach adequate power: F test, repeated measures ANOVA (within factors), effect size 0.4, $\alpha = 0.05$, $1-\beta = 0.8$. Young, apparently-healthy, physically-active individuals aged 18-35 years were recruited. Exclusion criteria included diagnosed cardiovascular, respiratory, and metabolic disease, signs and symptoms of chronic disease, and/or the use of prescription or over-the-counter medications that affect BP regulation or blood clotting.

Protocol

On an initial visit, participants completed an informed consent document, followed by a PAR-Q and health screening form. A standard protocol of anthropometric measurements including waist circumference (WC; cm), height, weight, and body mass index (SECA 769, Chino, CA, USA; cm, kg, and kg/m^2, respectively), and medical body composition analysis (full-body bioelectrical impedance; SECA mBCA, Chino, CA, USA; % body fat) was conducted. Researchers informed all participants of pre-test instructions before their subsequent data collection visit, which included refraining from caloric consumption for at least 4 hours, and from exercise, caffeine, and alcohol for at least 24 hours.

On a second visit, a fasting metabolic profile including total cholesterol (TC; mg/dL), low-density lipoprotein (LDL; mg/dL), high-density lipoprotein (HDL; mg/dL), HDL/LDL ratio, and blood glucose (GLU; mg/dL) was obtained via the fingerstick method and lipid/glucose analyzer (Alere Cholestech LDX® Analyzer, Freehold, New Jersey, USA). Following commonly accepted preparation steps, participants were outfitted with electrodes for 12-lead electrocardiogram (Quinton Q-Stress, Davis Medical Vista, California, USA) and non-invasive hemodynamic measurement (PhysioFlow, Nissha Medical Technologies, Buffalo, NY, USA). These measures were conducted simultaneously to bilateral BP measurements during rest, the CPT, and recovery.

Participants were seated for 15 minutes after being set up for the EKG, Physioflow, and bilateral blood pressure cuffs. After the rest period, a series of three resting BP measures were taken in a randomized hand. During the CPT, one hand (also randomly determined) was immersed in 3-5° Celsius (average) water for 3 minutes with two bilateral BP measurements taken at minutes 0:30 and 2:00. All subjects were instructed to avoid the Valsalva maneuver, holding their breath, or hyperventilating during the CPT.

Statistical Analysis

Descriptive statistics were generated for all demographic and physiological variables. Inferential statistics included the analysis of both absolute changes in IAD (mmHg) during the CPT using a one-way, repeated measures ANOVA test. Absolute and relative changes in IAD (mmHg) and hemodynamic variables were examined during the CPT and compared between IAD+ and IAD- individuals at rest using a two-way, repeated measures ANOVA test. When appropriate, multiple comparisons were performed to determine condition/time differences with a Bonferroni correction applied. An a priori α-significance level of 0.05 was used across all analyses.

RESULTS

Twenty-three individuals (IAD-, n=15; IAD+, n=8) completed all of the requirements of this study. There were no differences between anthropometric and lipid/glucose parameters in our cohort (Table 1).

Table 1. Participant Demographics.

	IAD- (n=15)	IAD+ (n=8)
Weight (kg)	76.5 ± 3.1	73.1 ± 3.8
Height (cm)	167.3 ± 3.1	169.2 ± 3.3
BMI (kg/m^2)	27.3 ± 1.6	25.5 ± 1.0
FFM (kg)	52.9 ± 3.1	55.7 ± 3.2
Body Fat Percentage (%)	29.7 ± 2.5	23.7 ± 2.7
TC (mg/dL)	188.7 ± 8.2	200.1 ± 17.0
HDL (mg/dL)	57.8 ± 3.1	49.7 ± 7.2
LDL (mg/dL)	108.6 ± 7.1	115.7 ± 13.9
non-HDL (mg/dL)	130.7 ± 7.3	140.3 ± 12.8
LDL/HDL Ratio	3.4 ± 0.2	4.2 ± 0.5
Blood Glucose (mg/dL)	90.6 ± 2.0	91.9 ± 4.2

Values are expressed as MEAN±SEM. IAD-: inter-arm difference <10mmHg; IAD+: inter-arm difference ≥10mmHg; BMI: body mass index; FFM: fat-free mass; TC: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein

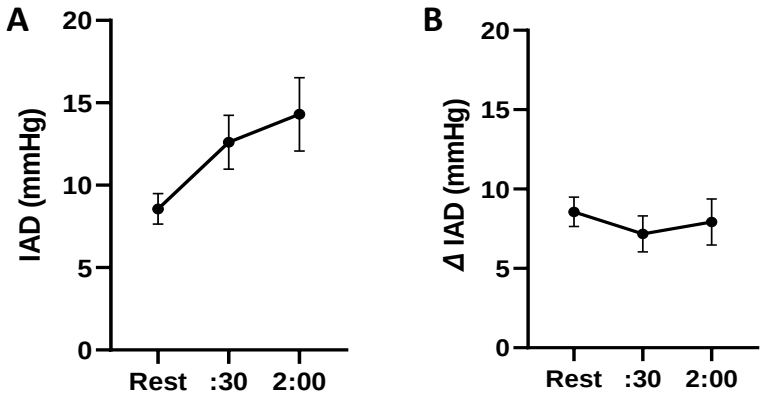

Figure 1. Effects of the Cold Pressor Test on inter-arm blood pressure difference.

Panel A – Absolute inter-arm systolic blood pressure difference (IAD). P-values: Significant difference by condition = P<0.05. Panel B – Relative inter-arm systolic blood pressure difference (ΔIAD). NSD. Time = Rest, 30 seconds, and 2 minutes.

An overall increase in the systolic IAD of 5.8±1.9 mmHg was observed during the CPT for the entire cohort. Specifically, resting systolic IAD increased from 8.5±1.6 mmHg to 12.6±1.9 mmHg and 14.3±1.9 mmHg at the 30-sec and 2-min timepoints, respectively (Figure 1A; P<0.05). There were no significant differences noted by condition in the change in systolic IAD from baseline in our cohort (Figure 1B; P>0.05).

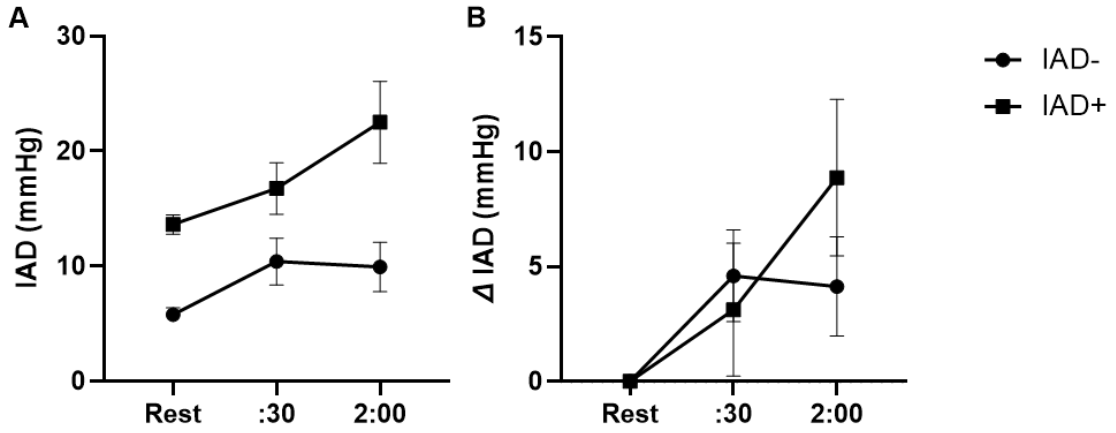

Figure 2. Effects of the Cold Pressor Test on inter-arm blood pressure differences in young, apparently-healthy individuals by group.

Panel A– Absolute inter-arm systolic blood pressure difference (IAD): P-values: group= 0.0003; time= 0.0044; GxT= 0.2256); Panel B– Relative inter-arm systolic blood pressure difference (ΔIAD: P-values: group= 0.6073; time= 0.0044; GxT= 0.2256). Groups= IAD status (IAD-= <10 mmHg and IAD+= ≥10 mmHg) ; Time= Rest, 30 seconds, and 2 minutes; GxT= group-time interaction.

Differences in the absolute systolic IAD during the CPT were noted between IAD- and IAD+ individuals (P<0.05) and time (P<0.05), though pairwise comparisons yielded no specific differences or interaction (Figure 2A). Observationally, the relative responses in the IAD- and IAD+ individuals, in which change from original baseline was examined, diverged, though no group differences existed (Figure 2B; P>0.05).

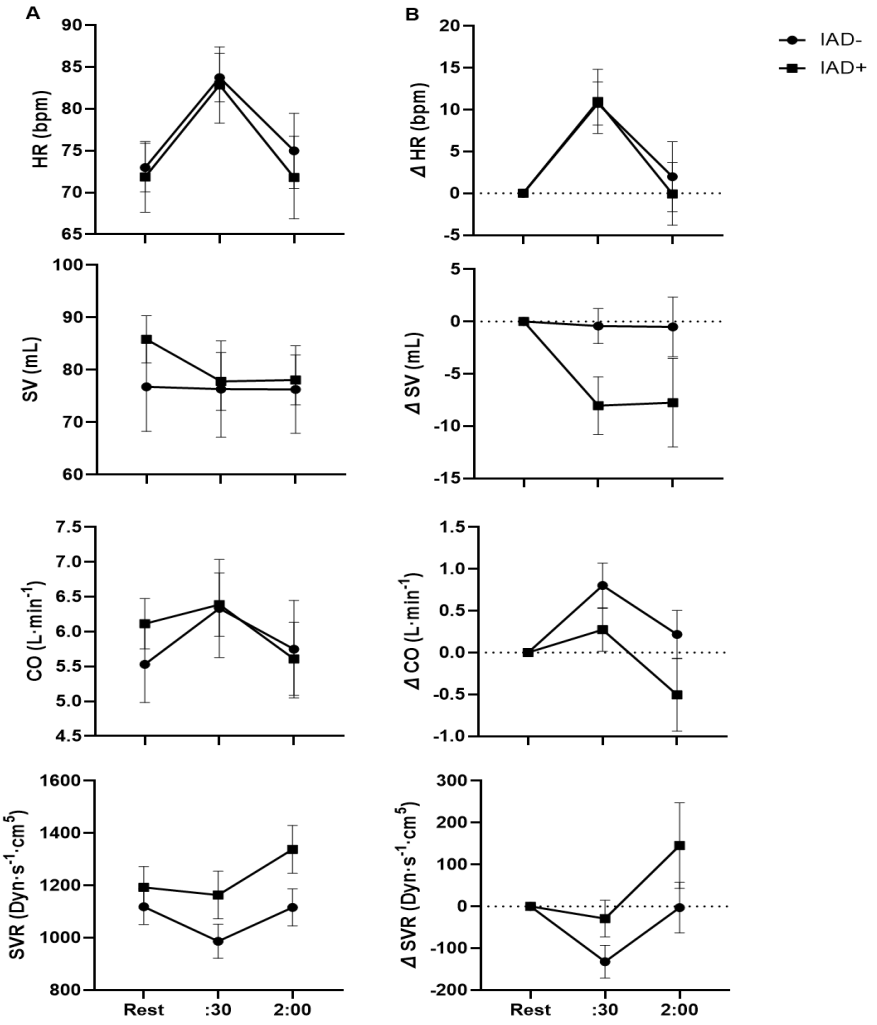

Figure 3. Effects of the Cold Pressor Test on hemodynamics in young, apparently-healthy individuals.

Panel A– Absolute hemodynamics. Heart Rate (HR): P-values: group= 0.7303; time= 0.0018; GxT= 0.9058); Stroke Volume (SV): P-values: group= 0.6614; time= 0.2230; GxT= 0.2917); Cardiac Output (CO): P-values: group= 0.8195; time= 0.0592; GxT= 0.3913); Systemic Vascular Resistance (SVR): P-values: group= 0.1147; time= 0.0621; GxT= 0.4076); Panel B– Relative hemodynamics. (HR: P-values: group= 0.8278; time= 0.0018; GxT= 0.9058); (SV: P-values: group= 0.0199; time= 0.2230; GxT= 0.2917); (CO: P-values: group= 0.0742; time= 0.0592; GxT= 0.3913); (SVR: P-values: group= 0.0921; time= 0.0621; GxT= 0.4076); Groups= IAD status (IAD-= <10 mmHg and IAD+= ≥10 mmHg); Time= Rest, 30 seconds, and 2 minutes; GxT= group-time interaction.

While no group x time interactions for absolute change in hemodynamic variables were noted, there was a significant difference in the HR response over time during the CPT (Figure 3A; $P<0.05$). Likewise, there was a trend towards significance noted in the CO and SVR values over time in the CPT (Figure 3A). When relative changes in hemodynamics were assessed during the CPT, there was a group effect for SV, wherein the IAD+ individuals had a lower SV at the 30-sec and 2-min timepoints (Figure 3B). Again, the relative HR response during the CPT changed over time, with relative CO and SVR changes also approaching significance (Figure 3B).

DISCUSSION

This study aimed to determine the effects of the CPT on systolic IAD and hemodynamics on young, apparently healthy individuals. The findings indicate that there is an effect of direct SNS stimulation on IAD. Specifically, the results demonstrated an absolute increase in IAD of ~6mmHg by 2-min across all participants, which is consistent with the range of absolute increase in IAD observed in our lab with moderate aerobic and isometric handgrip exercise stimuli (12, 22, 13). Additionally, real-time hemodynamic monitoring revealed expected cardiovascular responses to CPT.

The CPT resulted in a marked increase in IAD, however these changes were not group dependent. Further, relative changes in IAD were not different based on the resting IAD status. Previously, our lab has observed a divergent response in relative IAD change with aerobic and isometric handgrip exercise (12, 22, 13). Specifically, IAD+ individuals had little relative change in IAD during exercise, however, IAD- individuals produced large increases (22, 13). The CPT utilized in the current investigation is widely known to modulate autonomic control through sympathetic-derived pathways (15). This direct stimulus, not necessarily consistent with the two-pronged parasympathetic withdrawal and subsequent sympathetic stimulation known to alter exercising cardiovascular control, may have contributed to the response in our cohort. Additionally, the sudden onset of sympathetic stimulation in the CPT, and the robust vascular response in the CPT may have contributed to the large relative IAD. Recently, our laboratory has investigated the effect of vigorous aerobic exercise intensity and observed an increase of 16 mmHg in IAD from rest to volitional fatigue (unpublished data). This methodology permits comparison to the CPT regarding the relatively high proportions of sympathetic drive and low parasympathetic contribution at near maximal exercise.

We hypothesized that sympathoexcitation via the CPT would elicit peripheral vasoconstriction and increase IAD. The present study confirmed that CPT can induce significant increases in IAD, and that this increase continued for the duration of the CPT test in IAD+ participants. In contrast, the opposite held true for IAD- participants. Hemodynamic monitoring revealed that HR at the 30-second time point was significantly increased but not sustained in either the IAD- or IAD+ groups. Interestingly, a ~2-fold increase in IAD in IAD+ individuals was noted at the 2-min time point, and this corresponded with a ~7 mL drop in SV, 150 Dyn $\cdot s^{-1} \cdot cm^5$ increase in SVR, and 722 mL reduction in CO, compared to the responses from IAD- participants. The exact CPT-induced mechanisms underlying our observed IAD and hemodynamic discrepancies remain unclear,

however, it is plausible that differences in α- and β-adrenergic receptor sensitivity exist IAD+ and IAD- individuals. Specifically, similar β-receptor sensitivity in the heart may explain the rapid increase (30-sec) and return to baseline (2-min) in HR seen in both IAD+ and IAD- individuals during the CPT. Conversely, the immediate drop in SVR in IAD- participants (30-sec) may have been evidence of augmented adrenergic β-mediated vasodilation in the vasculature compared to IAD+ individuals. Finally, a counterbalance in α-mediated vasoconstriction in IAD+ individuals (2-min) may have been further evidence of these potential vascular differences.

The findings of our investigation provide more information on the relationship between resting IAD and its response to a direct SNS stimulus for the benefit of determining risk-factor status for future cardiovascular disease or clinical decision-making. IAD responsiveness is not limited to aerobic and isometric exercise stimuli, and may have an underlying SNS influence (18). Despite both IAD and the CPT having individual clinical relevance, whether the BP response is high or low, this study is the first to examine their interaction. IAD and the CPT may have potential as diagnostic tools towards a better understanding of cardiovascular disease, but more research is needed to understand the mechanisms of nociceptor and SNS stimulation on IAD.

The findings of this study may not be generalized to all adults as our protocol specifically observed the response of CPT on IAD in young, apparently healthy individuals. Further, confounding variables to consider include the personal-life stress of the participants and extensive set-up of EKG, bilateral BP, and Physioflow systems, both of which may have elicited acute stress that could have influenced autonomic and hemodynamic control. Finally, we did not directly control the breathing rate of the participants, though advised them to breathe normally and avoid the Valsalva maneuver.

Future studies are required to elucidate mechanisms of IAD. Looking at family history, this study could be replicated using two groups of normotensive individuals: one with a family history of hypertension and one without. Further, there may be a difference in the IAD response to the CPT based on sex, as previous work has shown a predilection for increased vasodilation in females during the CPT (17). As our study is the first to our knowledge to simultaneously examine IAD and the CPT, a future study could observe the response of each sex separately to elucidate anatomical or physiological mechanisms at play.

REFERENCES

1. Barnett PH, Hines EA, Schirger A, Gage RP. Blood pressure and vascular reactivity to the cold pressor test: Restudy of 207 subjects 27 years later. JAMA 183: 845-848, 1963.

2. Canepa M, Milaneschi Y, Ameri P, AlGhatrif M, Leoncini G, Spallarossa P, Pontremoli R, Brunelli C, Strait JB, Lakatta EG, Ferrucci L. Relationship between inter-arm difference in systolic blood pressure and arterial stiffness in community-dwelling older adults. J Clin Hypertens (Greenwich) 15(12): 880-887, 2013.

3. Clark CE, Aboyans V. Interarm blood pressure difference: More than an epiphenomenon. Nephrol Dial Transplant 30(5): 695-697, 2015.

4. Clark CE, Taylor RS, Shore AC, Campbell JL. The difference in blood pressure readings between arms and survival: primary care cohort study. BMJ 344: e1327, 2012.

5. Cyriax EF. Blood pressure in war traumatisms: A possible source of error. Br Med J 2(3006): 132, 1918.

6. Durmuş G, Belen E, Bayyigit A, Kalyoncuoğlu M, Can MM. The relationship between inter-arm blood pressure difference and coronary artery disease severity calculated by the SYNTAX score. Int J Hypertens 2018: 9370417, 2018.

7. Durrand JW, Batterham AM, O'Neill BR, Danjoux GR. Prevalence and implications of a difference in systolic blood pressure between one arm and the other in vascular surgical patients. Anaesthesia 68(12): 1247-1252, 2013.

8. Frank S, Norris E, Christopherson R, Beattle C. Right- and left-arm blood pressure discrepancies in vascular surgery patients. Anaesthesia 75(3): 457-463, 1991.

9. Hines EA. The significance of vascular hyperreaction as measured by the cold-pressor test. Am Heart J 19(4): 408-416, 1940.

10. Hines EA, Brown GE. A standard stimulant for measuring vasomotor reactions: Its application in the study of hypertension. Proc Staff Meet Mayo Clin 7: 332-325, 1932.

11. Hines EA, Brown GE. The cold pressor test for measuring the reactibility of the blood pressure: Data concerning 571 normal and hypertensive subjects. Am Heart J 11(1): 1-9, 1936.

12. Holmstrup ME, Clarke MM, Conner CR, Jensen BT. An acute bout of aerobic exercise alters interarm systolic blood pressure difference. Blood Press Monit 22(2): 68-71, 2017.

13. Jensen BT, Gordon BDH, Neuscheler LS, Ace SN, Borland RK, Holmstrup ME. Characterization of resting and exercise inter-arm differences in SBP to isometric handgrip exercise in males and females. Blood Press Monit 25(5): 252-258, 2020.

14. Kasagi F, Akahoshi M, Shimaoka K. Relation between cold pressor test and development of hypertension based on 28-year follow-up. Hypertension 25(1): 71-76, 1995.

15. Lovallo W. The cold pressor test and autonomic function: A review and integration. Psychophysiology 12(3): 268-282, 1975.

16. Mehlsen J, Wiinberg N. Interarm difference in blood pressure: Reproducibility and association with peripheral vascular disease. Int J Vasc Med 2014: 841542, 2014.

17. Miller AJ, Cui J, Luck JC, Sinoway LI, Muller MD. Age and sex differences in sympathetic and hemodynamic responses to hypoxia and cold pressor test. Physiol Rep 7(2): e13988, 2019.

18. Mourot L, Bouhaddi M, Regnard J. Effects of the cold pressor test on cardiac autonomic control in normal subjects. Physiol Res 58(1): 83-91, 2009.

19. Navalta JW, Stone WJ, Lyons TS. Ethical issues relating to scientific discovery in exercise science. Int J Exerc Sci 12(1): 1-8, 2019.

20. Sharma B, Ramawat P. Prevalence of inter-arm blood pressure difference among clinical out-patients. Int J Health Sci (Qassim) 10(2): 229-237, 2016.

21. Velasco M, Gómez J, Blanco M, Rodriguez I. The cold pressor test: Pharmacological and therapeutic aspects. Am J Ther 4(1): 34-8, 1997.

22. Walsh MA, Clarke MM, Allen SA, Holmstrup ME. Lin YK, Jensen BT. Observations of the exercise-induced interarm blood pressure difference. Transl J Am Coll Sports Med 5(11): 1-6, 2020.

23. Weinberg I, Gona P, O'Donnell CJ, Jaff MR, Murabito JM. The systolic blood pressure difference between arms and cardiovascular disease in the Framingham Heart Study. Am J Med 127(3): 209-215, 2014.

24. Weise F, Laude D, Girard A, Zitoun P, Siché JP, Elghozi JL. Effects of the cold pressor test on short-term fluctuations of finger arterial blood pressure and heart rate in normal subjects. Clin Auton Res 3(5): 303-310, 1993.

25. Zhao Q, Bazzano LA, Cao J, Li J, Chen J, Huang J, Chen J, Kelly TN, Chen CS, Hu D, Ma J, Rice TK, He J, Gu D. Reproducibility of blood pressure response to the cold pressor test: The GenSalt Study. Am J Epidemiol 176(Suppl 7): S91-S98, 2012.

26. Zhou M, Gao Z, Chen F, Xu H, Dong X, Ma L. The inter-arm systolic blood pressure difference and risk of cardiovascular mortality: A meta-analysis of cohort studies. Clin Exp Hypertens 38(3): 317-324, 2016.