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Assessment of Autonomic and Cardiovascular Reactivity in Response to Cold Pressor in Prehypertensive Individuals

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Modulation of the autonomic nervous system (ANS) activity allows human organism to effectively respond to challenges in the environment via changes in, for example, heart rate (HR) and blood pressure (BP). Various factors, like cold pressor test (CPT) can impact ANS activity and may be used for the assessment of ANS and cardiovascular reactivity, i.e. physiological systems response to challenges in the environment. The commonly used method to evaluate the ANS modulation is HRV (heart rate variability). The objective of the study was to compare the autonomic and cardiovascular reactivities in response to cold pressor test between prehypertensive and normotensive individuals of both genders.

Baseline HR, SBP (systolic blood pressure), DBP (diastolic blood pressure), LF (low frequency) and HF (high frequency) HRV power were recorded in 307 normotensive and prehypertensive young men and women. Immersion of the right hand into ice cold water for one minute was performed to

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compare cardiovascular reactivity to CPT between these groups. General linear model was used to test for effect of gender and prehypertension on baseline cardiovascular and HRV variables and to compare ANS and cardiovascular reactivities. Stepwise multiple linear regression analysis was used to reveal predictors of ΔSBP and ΔDBP.
Blood pressure response to CPT, negatively associated with resting blood pressure and positively associated with BMI (body mass index), was less in prehypertensive men compared with normotensive men and prehypertensive women. Gender-based differences of ΔSBP and ΔDBP may be explained by differences in blood pressure and height and by negative association between ΔSBP and resting LnLF which was less in women.
In conclusion, ANS and cardiovascular reactivities to cold press were less in prehypertensive men compared with normotensive men and prehypertensive women indicating a decrease in the ability of prehypertensive men effectively respond to challenges in the environment via changes in ANS and cardiovascular function.

Keywords: ANS and cardiovascular reactivities; cold pressor test; gender-based differences; prehypertension; heart rate variability.

1. INTRODUCTION

Until now, hypertension remains a major global health issue, it leads to severe complications and raises a risk of cardiovascular disease, brain stroke, chronic kidney disease, and premature death [1, 2]. That is why an early diagnostic and awareness of hypertension is crucial for controlling and prevention from further its development. However, there is very little literature showing specific cardiovascular and HRV characteristics of subjects only developing hypertension [3-7].

“It has been suggested that the dysfunction of autonomic nervous system is a cornerstone of hypertension pathophysiology which underlies the initiation and development of hypertension” [1,3]. The cold pressor test (CPT) is commonly used as a sympathoexcitatory maneuver and standard laboratory method to evoke stress response and to evaluate a cardiovascular reactivity to stress [8-11]. “The data regarding the differences in blood pressure (BP) response to CPT between normotensives and hypertensives are highly controversal. Such that some of previous reports have demonstrated that increase of blood pressure during CPT was significantly higher in subjects having family history of hypertension” [10], in hypertensive [8], and atherosclerotic patients [12]. “These studies provide information that cardiovascular hyperreactivity to cold stress is an important risk factor for the development of hypertension and that cold pressor test may be used as an indicator of the severity of hypertension and atherosclerosis. However, there is a series of other studies which did not find any effects of hypertension or positive family history of hypertension on BP response to CPT” [7,13,14]. Moreover, “some authors found that sympathoneural responses to the cold pressor test in individuals with essential hypertension and in those genetically predisposed to hypertension was reduced and did not support "pressor reactor" hypothesis of hypertension development [9]. Some other reports demonstrated that cold pressor test caused an increase of the blood pressure less in the hypertensive than in the normotensive subjects” [5,15,16].

“The heart rate variability (HRV) is a potentially useful noninvasive tool for the evaluation of autonomic nervous system activity and its effect on the cardiac function” [17]. “The high frequency HRV power (HF) is widely used as an index of cardiovagal activity, however interpretation of the low frequency HRV power (LF) is more controversial. It was presumed that LF power, especially, expressed in normalized units, is a marker of sympathetic modulation” [18] or reflects both sympathetic and vagal activity [19], that LF oscillations of HRV are determined mainly by the parasympathetic nervous system, and although the final pathway is predominantly vagal, LF power provides information about the modulation of vasomotor tone [20]. “The other reports suggested that LF power is not an index of sympathetic tone but rather of the baroreflex modulation of cardiac autonomic outflows” [21,22]. “On the base of previous reports and our own investigations [6], the interpretation of LF HRV power extended observations in that LF power is an index of the baroreflex modulation of cardiac autonomic outflows” [21] and accepted that LF oscillations of HRV represent sympathoinhibitory arm of baroreflex [6].

The objectives of this study were to: 1) analyze the effect of gender and prehypertension on baseline HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), LF and HF HRV power, and cardiovascular reactivity to CPT; 2) identify cardiovascular and HRV predictors of the blood pressure response to cold pressor test.

2. MATERIALS AND METHODS

A total of 307 subjects were enrolled from V.N. Karazin Kharkiv National University student population. The participants were subdivided into four groups according to gender and blood pressure according to JNC-7 classification [23], referred thereafter to as the normotensive (NT) and prehypertensive (PHT) groups (Table 1). No one prehypertensive subject had ever been treated for hypertension. According to their medical history and examination of resting ECG, subjects with cardiac rhythm abnormalities, respiratory, or metabolic diseases were excluded from the study. None of the participants routinely took medicine. The subjects were fasted > 8 hours, and were asked to refrain from alcohol, caffeine, tobacco, abstaining from recent exercise >20 hours [24]. None of the subjects participated in sports at a competitive level. All of them gave written informed consents.

The ECG was continually recorded during 5-minutes resting and CPT stages following a stabilization period. Cold pressor test was performed by immersion of the right hand (dominant for most of participants) into ice cold water at 4^{o}C for one minute. HR was obtained by digital 2-channel ECG amplifier with a sampling frequency 1000 Hz (CardioLab 2010, XAI-Medica, Ukraine), [4]. SBP and DBP were recorded at the end of resting and CPT stages by means the automatic blood pressure digital sphygmomanometer (Nissei WS-1011, Nihon Seimitsu Sokki Co., Ltd, Japan).

"The nonparametric method of fast Fourier transformation was used to represent the signal in frequency domain during the resting stage. The low frequency and high frequency HRV power were expressed in the absolute units. For their interpretation we proceeded from the assumption that HF power received from 0.15 to 0.40 Hz oscillations is a measure of the cardiovagal outflow" [17,20,21], LF power computed from low frequency oscillations ranging from 0.04 to 0.15 Hz is the sympathoinhibitory baroreflex-mediated index of cardiac autonomic regulation [6].

Data are presented as means±SE. All tests of statistical significance were 2-tailed, $p<0.05$ was considered significant (unless otherwise specified). Two-way MANOVA was used to compare age, height, BMI, resting HR, SBP, DBP, LnLF, LnHF HRV power and also responses of HR, SBP, DBP to CPT by gender and presence of prehypertension. To meet the MANOVA assumptions the outcome variables that were not normally distributed were naturally log-transformed (LF and HF power). Three-way repeated measures MANOVA was used to test for possible effects of gender, PHT, immersion of the hand into ice cold water, and their interaction on HR, SBP, and DBP. The BMI and height were used as covariates in Two-way MANCOVA and Three-way repeated measures MANCOVA.

The stepwise multiple linear regression models were constructed to assess the relative importance of gender, BMI, height, resting BP (SBPrest and DBPrest), LnLF power (LnLFrest), LnHF power (LnHFrest), HR (HRrest), and ∆HR in SBP and DBP responses (∆SBP and ∆DBP). The two-way and three-way interactions were included in the models to improve their overall fit. To avoid multicollinearity, the explanatory variables were centered before inclusion in the stepwise regression models. Statistical analysis was performed with the SPSS statistical program, version 22.

Table 1. Participants anthropometric and resting characteristics.

	Men		Women	
	NT	**PHT**	**NT**	**PHT**
n	79	76	95	57
Age, years	20.23±0.19	20.17±0.20	20.04±0.18	20.12±0.23
Height, m	1.77±0.01***	1.75±0.01***	1.60±0.01†	1.63±0.01
BMI, kg/m^2	22.43±0.43†	24.01±0.43	22.16±0.39	23.4±0.50

*Data are expressed as means±SE; NT, normotensive; PHT, prehypertensive; n, number of participants; ***p<0.001, vs. women of similar blood pressure; †P<0.05, vs. prehypertensives of the same gender; were found from general linear model [GLM] two-way MANOVA*

3. RESULTS

Baseline hemodynamic and HRV characteristics. There was a significant main effect of gender and PHT on the resting heart rate (Fig. 1). The testing of simple effects revealed that HRrest was significantly less in normotensive men compared with women and compared with prehypertensive men.

The resting systolic blood pressure (SBPrest) was higher in men than in women, and diastolic blood pressure (DBPrest) was higher in men as a whole (significant main effect), but these differences was not significant between normotensives (Figs. 2A and 2B).

In the current study there was a significant main effect of gender on the resting LnLF HRV power and no significant gender-based and/or PHT-based-differences in the resting LnHF HRV power between groups (Figs. 3A and 3B). The testing of simple effects revealed that LnLFrest was greater in normotensive men compared with women but gender-based differences in LnLFrest between prehypertensives did not reach significant level.

When BMI was used as a covariant all the gender-based and/or PHT-based-differences in resting indices remained at the same or increased significant level. However, when height was taken into account the gender-based differences in HRrest were no longer significant, the gender-based differences in LnLFrest still were found but at lower significant level (for main effect, p=0.001 and p=0.021, without covariates and with a height as a covariate, respectively) and the gender-based differences in blood pressure increased (not shown).

Hemodynamic response to cold pressor test. The immersion of the right hand into ice-cold water for 1 minute led to an increase of HR, SBP, and DBP (p<0.001 for all variables) in all groups (not shown).

There was a significant main effect of gender and PHT on the increment of SBP and DBP, such that both SBP and DBP increased more in women than in men and prehypertensives demonstrated the less increment of blood pressures than normotensives (Figs. 4A and 4B). The further analysis of simple effects has shown that both ΔSBP and ΔDBP was less in prehypertensive than in normotensive men. However, the differences in the increment of BPs between normotensive and prehypertensive women did not reach significant level (Figs. 4A and 4B).

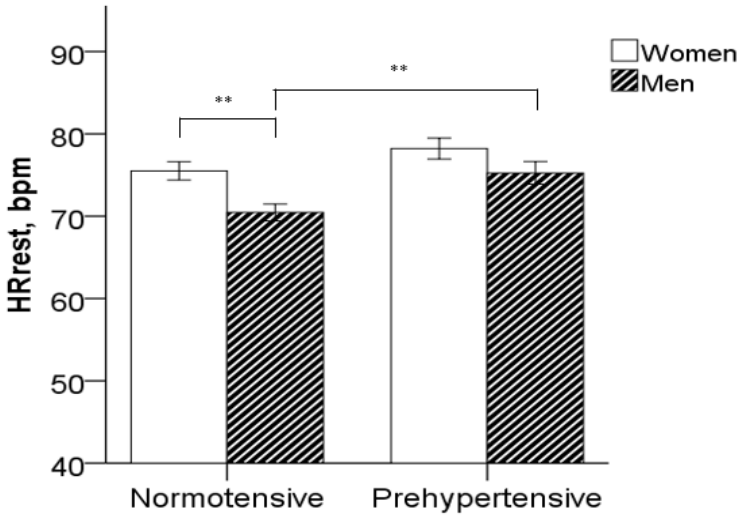

Fig. 1. Effect of gender and prehypertension on HR at rest
***p<0.01. Gender: p=0.001. Prehypertension: p=0.002. Gender* Prehypertension: P=0.393*

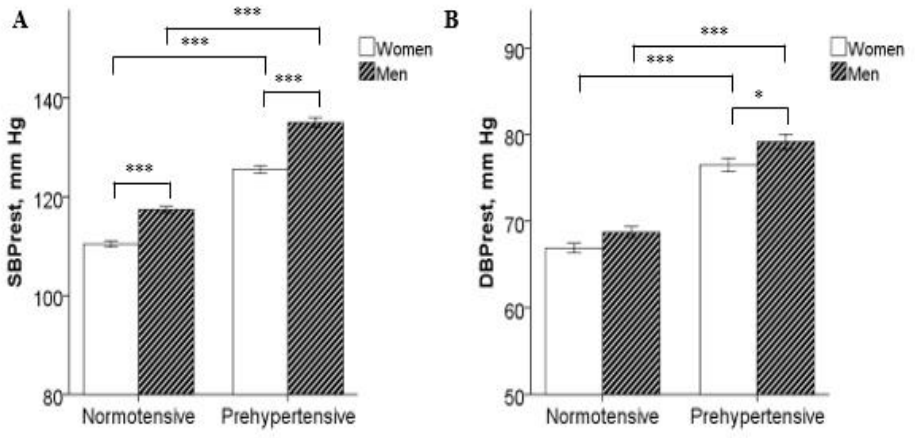

Fig. 2. Effect of gender and prehypertension on resting SBP (A) and DBP (B).
**p<0.05; ***p<0.001. For SBP, Gender: p<0.001; Prehypertension: p<0.001; Gender* Prehypertension: p=0.096. For DBP, Gender: p=0.002; Prehypertension: p<0.001; Gender* Prehypertension: p=0.557.*

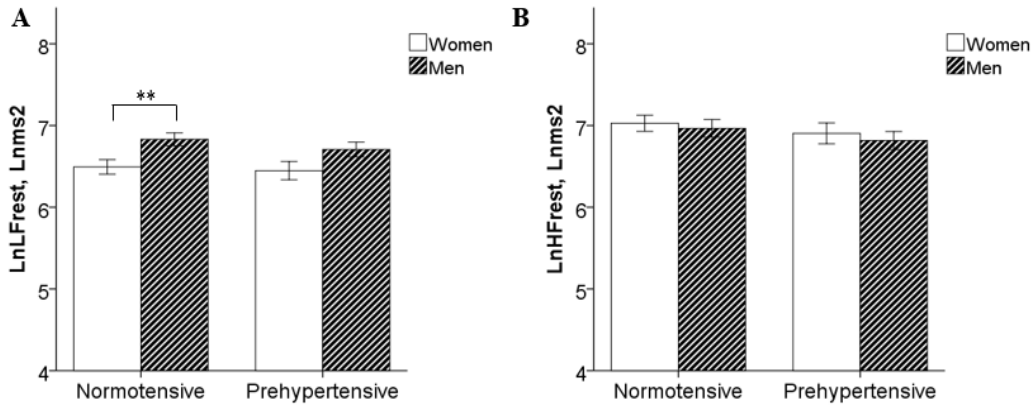

Fig. 3. Effect of gender and prehypertension on resting LnLF power (A) and LnHF power (B)
***p<0.01. For LnLFrest, Gender: p=0.001; Prehypertension: p=0.359; Gender* Prehypertension: p=0.674*

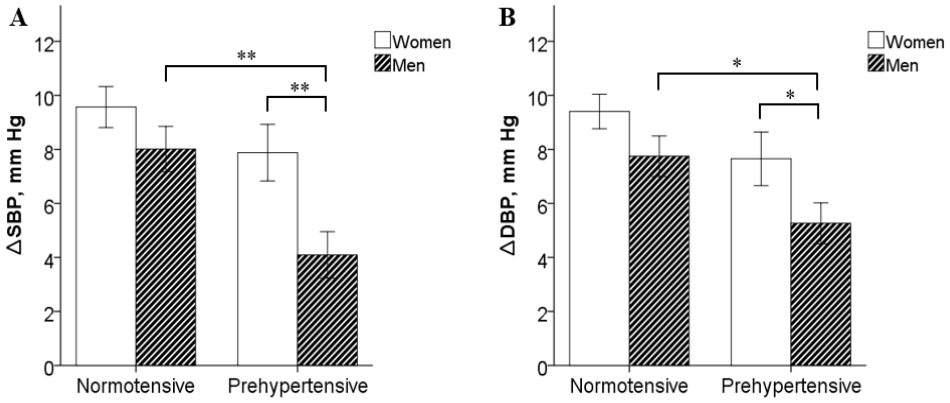

Fig. 4. Effect of gender and prehypertension on SBP (A) and DBP (B) response to cold pressor test
**p<0.05; **p<0.01. For ∆SBP, Gender: p=0.002; Prehypertension: p=0.001; Gender* Prehypertension: p=0.204. For ∆DBP, Gender: p=0.010; Prehypertension: p=0.007; Gender* Prehypertension: p=0.637.*

Table 2. Predictors of SBP and DBP responses to cold pressor tests. Final stepwise regression coefficients of the models including centered variables, two-way and three-way interactions. the reference category was normotensive men

Models	Unstandardized Coefficients		Standardized Coefficients	p
	B	Std. Error	Beta	
Model 1. Dependent variable: ∆SBP, R^2=0.235				
(Constant, mm Hg)	7.513	0.401		<0.001
∆HR, bpm	0.582	0.076	0.394	<0.001
SBPrest, mm Hg	-0.171	0.036	-0.254	<0.001
BMI, kg/m2	0.245	0.108	0.121	0.024
LnLFrest*Height, ms2*m	-14.097	4.845	-0.169	0.004
HRrest*Height, bpm*m	-0.757	0.372	-0.119	0.043
∆HR*BMI, bpm*kg/m2	0.042	0.021	0.102	0.045
Model 2. Dependent variable: ∆DBP, R^2=0.211				
(Constant, mm Hg)	7.542	0.350		<0.001
∆HR, bpm	0.339	0.100	0.262	0.001
DBPrest, mm Hg	-0.215	0.045	-0.253	<0.001
BMI, kg/m2	0.317	0.094	0.187	0.001
∆HR*Women, bpm	0.299	0.134	0.172	0.027

The increment of SBP and DBP was less in prehypertensive men compared with prehypertensive women (Figs. 4A and 4B). As a result, despite resting DBP was higher in prehypertensive men then in women (Fig. 2B), gender-based differences in DBP among prehypertensives were no longer significant during the immersion of hand into ice cold water (not shown). The analysis of simple effects revealed that gender-based differences in the increment of blood pressure between normotensive did not reach significant level (Figs. 4A and 4B).

No statistically significant gender-based and/or prehypertension-based differences were found in the increment of HR.

When BMI was taking into account by means MANCOVA, the significance level of gender- and PHT-based differences in SBP, and DBP responses was increased. However, when height was also taking into account, the gender-based differences in ∆SBP and ∆DBP were no longer significant (for main effect, p=0.002 and p=0.010 without covariates, and p=0.086 and p=0.076 with height as a covariate, for ∆SBP and ∆DBP, respectively). At this time, PHT-based differences in SBP, and DBP responses did not change (not shown).

Predictors of SBP and DBP responses to cold pressor test. The immersion of the hand into ice-cold water caused an increment of SBP and DBP positively associated with ∆HR and BMI and negatively associated with SBPrest and DBPrest, respectively (Table 2). The SBP response to cold stress also was reduced in subjects with high values of resting LnLF power, and this effect dependent on their height. The association between ∆DBP and ∆HR was stronger in women.

4. DISCUSSION

The main findings of our study are the following: The SBP and DBP response to CPT was less in prehypertensive men compared with normotensive men and prehypertensive women. The LnLFrest was significantly lower in normotensive women than in men. The ∆SBP was negatively associated with LnLFrest and this effect dependent on the height. In addition to negative association between ∆BP and resting blood pressure, ∆SBP and ∆DBP were positively associated with ∆HR and BMI.

"CPT as a sympathoexcitatory maneuver. The fact that the increment of blood pressure was positively associated with ∆HR supports the notion that CPT commonly is used as a sympathoexcitatory maneuver to provoke an increment in both arterial pressure and heart rate" [6-10,13-15,23].

The positive association of ∆DBP with ∆HR was even stronger in women. This fact may indicate that HR determines DBP *per se* and/or contribution of the sympathetic nervous system

into DBP response to CPT is more in women than in men.

"Baseline blood pressure as a predictor of BP response to CPT. Although the results of this study showing that the increment of SBP and DBP during cold pressor test was less in prehypertensives as a whole (significant main effect), prehypertensive men demonstrated significantly lower BP responses to cold pressor test than normotensives (significant simple effect) and prehypertensive women tended to have lower BP increments than normotensives women, are in contrast with some previous findings" [8,10,23,25], they are in agreement with other studies which did not find any effects of hypertension or positive family history of hypertension on hemodynamic functions during the cold pressor test [7,14] or also find that cold pressor test produced an increase of the arterial pressure significantly lower in the hypertensive than in the normotensive subjects [5,9,13,15,16]. The inconsistency of our data and result from some previous reports may be due to difference in ethnicity, age, stage of hypertension, and also the fact that gender, BMI, height as well as LnLFrest was not taken into account.

Gender-based differences of BP response to CPT. These results showed that the increment of SBP and DBP during CPT in women group, as a whole, was greater than in men are in congruence with some previous studies [25]. Also, as it was shown previously by Benetos and Safar, blood pressure elevation during CPT is a very common reaction in young normotensive subjects especially in those that have the lowest mean blood pressure [16]. Since in the current study women had blood pressure less than men, the increment of blood pressure was more. In addition, when height was used as a covariate, the gender-based differences in ∆SBP and DBP were no longer significant. Also, the multiple linear regression revealed that the increment of SBP was negatively associated with LnLFrest by Height interaction, such that the shorter was a participant the less LnLF power reduced increment of SBP. Also, ∆SBP was negatively associated with HRrest by Height interaction, the shorter was a participant with high HR, the more was increment of SBP. Thus, the gender-based differences of ∆SBP and ∆DBP in women may be partially explained by the lower blood pressure and short stature of women.

BMI as a predictor of BP response to CPT. As it was shown in the current study, the increment of SBP and DBP during CPT was positively associated with BMI but negatively associated with presence of prehypertension (Table 2). This finding and the fact that obesity is a major risk for essential hypertension [26] may partially explain results from some previous reports indicating higher reactivity to CPT in hypertensive subjects. However, "despite the importance of obesity in the pathogenesis and progression of hypertension due at least in part to increases in sympathetic nerve activity, increased SNS activity in various tissues appears to be differentially controlled in obesity" [26]. In addition, an obesity paradox was described, in that overweight and obese patients have a more favorable prognosis than leaner patients [27]. A promising mediator of obesity-induced SNS activation and hypertension development, is leptin [26]. However, obesity may induce selective leptin resistance, and furthermore, humans with loss-of-function mutations in leptin gene or leptin receptor have low BP despite severe obesity [28]. Thus, taking into account these findings, we cannot identify effects of prehypertension and obesity on CPT responses and it is not surprising that obesity and hypertension differently effect cardiovascular response to cold stress.

Resting LnLF HRV power as a predictor of BP response to CPT. Despite LF HRV power is widely used as a measure of cardiovagal activity, interpretation of LF HRV is highly controversial. It was suggested that LF HRV power provides information about the sympathetic or/and parasympathetic outflow, baroreflex modulation of cardiac autonomic outflows, vasomotor tone modulation, and mechanisms of central autonomic outflow [19-21,29]. According to our hypothesis based on ours and others previous investigations, LF power is an index of the baroreflex modulation of cardiac autonomic outflows, specifically, of the sympathetic limb of the negative feedback controlling mechanism, that is sympathoinhibitory arm of baroreflex [6]. In this study the increment of SBP was negatively associated with resting LnLF power dependently on height. This finding may indicate that in the young subjects the baseline sympathoinhibitory influences prevent from the increase of blood pressure during sympathoexcitatory maneuver - cold pressor test.

5. CONCLUSION

The SBP and DBP response to CPT, negatively associated with resting blood pressure and positively associated with BMI, was less in prehypertensive men compared with normotensive men and prehypertensive women. The gender-based differences of ΔSBP and ΔDBP may be partially explained by the lower blood pressure and short stature of women and by the fact that ΔSBP was negatively associated with resting LnLF which was less in women and that this effect dependent on the height. The ANS and cardiovascular reactivities to cold press were less in prehypertensive men compared with normotensive men and prehypertensive women indicating a decrease in the ability of prehypertensive men effectively respond to challenges in the environment via changes in ANS and cardiovascular function

6. LIMITATIONS OF THE STUDY

One of limitations of this study is that women were not controlled for menstrual cycle. Taken into account a large sample size of participants it is suggested that there would be minimal effect of gender hormones on the data.

We did not control for socioeconomic status. However, all participants were recruited from the student population of the local University; they had similar education level and lifestyle.

We did not control for a positive family history of hypertension. Although to control for a positive family history of hypertension is ideal, the level of family history hypertension awareness was very low and even participant's prehypertension awareness was inadequate and low.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

As per international standards or university standards, Participants' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

I have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

REFERENCES

1. Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G. Hypertension, blood pressure, and heart rate variability: The Atherosclerosis Risk in Communities (ARIC) study. Hypertension. 2003;42:1106-1111.
2. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. Circulation. 2016;134(6): 441–450.
3. Wu JS, Lu FH, MD, Yang YC, Lin TS, MD, Chen JJ, Wu CH, MD, Huang YH, MD, Chang CJ. Epidemiological Study on the Effect of Pre-Hypertension and Family History of Hypertension on Cardiac Autonomic Function. J Am Coll Cardiol 2008;51(19):1896-1901.
4. Shekh VE. Slow breathing has unequal effects on prehypertensives from different ethnic/racial groups. An Med Physiol. 2017;1(1):9–15.
5. VE. Shekh, EI-E Ofoegbu, EG. Adenuga, LS. Shchyrova. Different LF and HF HRV responses to cold pressor test in normotensive and prehypertensive men // BIOLOGIJA. 2018;64(4):314–320.
6. IO. Yepryntseva, L.S. Shchyrova, VE. Shekh. Effect of slow breathing on blood pressure and Valsalva ratio in prehypertensive Indian students // BIOLOGIJA. – 2019;65(2):122–131.
7. Murgan I, Beyer S, Kotliar KE, Weber L, Bechtold-Dalla Pozza S, Dalla Pozza R, Wegner A, Sitnikova D, Stock K, Heemann U, Schmaderer C, Baumann M. Arterial and retinal vascular changes in

hypertensive and prehypertensive adolescents. Am J Hypertens. 2013;26(3): 400-408.
8. Loyke HF. Cold pressor test as a predictor of the severity of hypertension. South Med J.1995;88(3):300-304.
9. Lambert EA, Schlaich MP. Reduced sympathoneural responses to the cold pressor test in individuals with essential hypertension and in those genetically predisposed to hypertension. No support for the "pressor reactor" hypothesis of hypertension development. Am J Hypertens 2004;17(10):863-868.
10. Farah K, Keshav G, Pawan S. Autonomic reactivity to cold pressor test in prehypertensive and hypertensive medical students. Indian J Physiol Pharmacol 55(3): 246-252, 2011.
11. Cheung SS. Responses of the hands and feet to cold exposure. Temperature (Austin). 2015;2(1): 105–120.
12. Voudoukis IJ. Exaggerated cold pressor response: an indicator of arteriosclerosis. Angiology 1977;28(4):248-255.
13. Czarkowski M, Chojnowski K, Osikowska-Loksztejn M, Chodakowska J. Isometric exercise and cold pressor test in young men with a family history of essential hypertension. Pol Tyg Lek. 1994;49(10-11):225-227.
14. Kasagi F. Prognostic value of the cold pressor test for hypertension based on 28-year follow-up. Hiroshima J Med Sci. 1994;43(3): 93-103.
15. Palermo A, Lattuada S, Suigo E, Libretti A. Reflex pressor response in young subjects with labile hypertension. G Ital Cardiol. 1978;8(9):996-100.
16. Benetos A, Safar ME. Response to the cold pressor test in normotensive and hypertensive patients. Am J Hypertens. 1991;4(7 Pt 1):627-629.
17. Task Force of the European Society of Cardiology, and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use Eur. Heart J. 1996;17:354-381.
18. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation. 1991;84:482–492.
19. Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: Investigation by spectral analysis. Am J Physiol Heart Circ Physiol. 1985;249:H867–H875.
20. Reyes Del Paso GA, Langewitz W, Mulder LJM, van Roon A, Duschek S. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: A review with emphasis on a reanalysis of previous studies. Psychophysiol. 2013; 50:477–487.
21. Goldstein DS, Bentho O, Park MY, Sharabi Y. LF power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. Exp Physiol. 2011;96:1255-1261.
22. Rahman F, Pechnik S, Gross D, Sewell L, Goldstein DS. LF power reflects baroreflex function, not cardiac sympathetic innervation. Clin Auton Res. 2011;21:133-141.
23. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ and the National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003;42(6):1206–1252.
24. Shekh VE. Sex and ethnic/racial differences in blood pressure and heart rate variability duriing orthostatic testing in young healthy individuals. J Phys Pharm Adv. 2016;6(3):846–59
25. Zhang M, Zhao, Q, Mills KT, Chen J, Li J, Cao J, Gu D, He J. Factors Associated With Blood Pressure Response to the Cold Pressor Test: The GenSalt Study. Am J Hypertens. 2013;26(9):1132–1139.
26. Hall JE, da Silva AA, do Carmo JM, Dubinion J, Hamza S, Munusamy S, Smith G, Stec DE. Obesity-induced hypertension: Role of sympathetic nervous system, leptin, and melanocortins. J Biol Chem. 2010;285(23):17271-17276.
27. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol. 2009;53(21):1925-1932.
28. Simonds SE, Pryor JT, Ravussin E, Greenway FL, Dileone R, Allen AM, Bassi J, Elmquist JK, Keogh JM, Henning E, Myers MG, Licinio J, Brown RD, Enriori PJ, O'Rahilly S, Sternson SM, Grove KL, Spanswick DC, Farooqi IS, Cowley MA.

Leptin mediates the increase in blood pressure associated with obesity. Cell. 2014;159(6):1404-1416.

29. Martelli D, Silvani A, McAllen RM, May CN, Ramchandra R. The low frequency power of heart rate variability is neither a measure of cardiac sympathetic tone nor of baroreflex sensitivity. Am J Physiol Heart Circ Physiol. 2014;307:H1005–H1012.

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