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Vascular stiffness in cold pressor test hyper-reactors

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Abstract

Background: The cold pressor test (CPT) is a sympathoexcitatory manoeuvre to measure cardiovascular hyperactivity which may be a sign of future hypertension development.

Aims and Objectives: To evaluate the vascular stiffness background among healthy CPT hyper-reactor (H-R) males and age and gender-matched normo-reactors (N-R).

Methods: The study was carried out in 34 healthy young males aged 19 years old. Five minutes of recordings of left middle fingertip digital pulse wave (DPW) signals (through a piezoelectric finger pulse transducer) were registered. This was followed by the application of a cold pressor. Blood pressure (BP) and heart rate (HR) during CPT were recorded, and the individuals were divided into N-Rs and H-Rs. Vascular stiffness indices like pulse wave velocity (PWV), B/A wave ratio, pulse rising time (PRT, or crest), large artery stiffness index (SI), and pulse width (PW) were compared between H-Rs and N-Rs.

Results: No significant differences were observed between the two groups across all studied parameters.

Conclusion: The results suggest there was no difference in the vascular stiffness background between CPT H-R and N-R individuals.

Keywords: cold pressor test; hyper-reactors; vascular stiffness; digital pulse wave.

Introduction

Young, healthy people who are at risk of developing hypertension in the future can be identified using a cold stressor. BP hyper-reactors have greater incidence rates of hypertension than typical reactors and respond to the CPT with an exaggerated increase in their systolic and/or diastolic BP (SBP and DBP).[1,2] It has been hypothesized that the cardiovascular response to the CPT can predict whether neurogenic hypertension will develop later on.[1] Black participants, who are more likely to develop early hypertension, exhibit higher vascular reactivity to the CPT than white participants.[3] It has been demonstrated that the CPT causes the coronary arteries of healthy participants to dilate, while for the hypertensive subjects, they constrict.[4] One study[5] accurately predicted future unfavourable cardiovascular events (such as stroke or heart attack) in asymptomatic type 2 diabetic patients, using CPT-induced coronary vasoconstriction. Therefore, the CPT has been used to pinpoint H-Rs who may develop hypertension by measuring the BP response to the external cold stimulus. As a result, it aids in the early detection of hypertension so that preventive action can be put in place to lower morbidity and mortality brought on by hypertension and its side effects. Arterial stiffness is one of the earliest indicators of increased cardiovascular disease risk and can be considered a good predictor of the development of subclinical cardiovascular dysfunction. Moreover, arterial stiffness is often increased in overweight/obese subjects before the development of hypertension.[6,7] Very limited publications have given attention to the vascular stiffness background of CPT-H-Rs. One study showed that the increase in aortic PWV, an index of vascular stiffness, during cold-water immersion was greater in H-Rs than in N-Rs.[8] The result of the latter indicated that the change in PWV was due to CPT, and there was no difference in PWV between H-Rs and N-Rs before the stressful stimulus. The increase in PWV during CPT was attributed partly to the associated increase in BP and HR and partly to vascular stiffness.[9] Another study was able to show that PWV of central arteries and the augmentation index normalized to a heart rate of 75 bpm (AIx@75) (indices of arterial stiffness) and were similar in both H-Rs and N-Rs before the CPT.[10]

Various DPW indices can be used to assess vascular stiffness. PW, specifically pulse width corresponding to 50% of the DPW's systolic peak amplitude (PW50%), correlates with systemic vascular resistance.[11] Another vascular stiffness index is PWV. PWV is the speed at which the pulse wave moves

Authors' contribution: A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article.

through the circulatory system.[12] PWV reflects arteriosclerosis and, as a result, it can be considered a cardiovascular risk marker.[13] A B/A Ratio[14] extracted from the second derivative of DPW (SDDPW) was shown to increase with age-associated increase in vascular stiffness[15] and in atherosclerosis[16]. SI reflects the stiffness of central arteries, and it increases with age[17]. The difference in the time (ΔT) required for the pressure wave to travel from the heart to the periphery (systolic peak) and back is used to calculate SI (diastolic peak). As a result of increased large artery stiffness and higher PWV in the aorta and large arteries, the interval between the systolic and diastolic peaks shortens, and consequently, the SI increases. PRT (crest) is the time from the foot of the DPW waveform to its peak[14]. PRT was found to be increased with the rise in vascular stiffness that is associated with aging[18].

The aim of the present study is to assess the vascular stiffness status of H-Rs and N-Rs during rest or inactivity using various stiffness indices extracted from DPW.

Participants and methods

Participants

In the current study, 34 healthy young male first-year medical students were included. Their age was 19 years old. All were free from any medical illness and were not taking any medication, were not smokers, and their parents did not have diabetes or hypertension. The participants were abstainers from alcohol and did not consume any vitamin supplements or antioxidative nutrients, and were on normal diets without caloric restriction. Before giving their written informed consent, each participant received a full explanation of the study. The study adhered to the standards and principles in the Declaration of Helsinki, and all procedures and protocols were approved by the department's ethical committee. Gender and other anthropometric measurements were registered.

Experimental protocol

Repeated right brachial SBP, DBP, and HR measurements were recorded in a semi-prone position after 10 minutes of complete rest using an automated sphygmomanometer (Rossmax Swiss GmbH, Tramstrasse 16, CH-9442 Berneck, Switzerland) until stable values were obtained in order to ensure the hemodynamic stability. These stable measurements (SBP, DBP, and HR) were considered baseline values or pre-CPT values. Five minutes of simultaneous recordings of left middle fingertip DPW signals (through crystal piezoelectric mechano-transducer) and lead II ECG (through three surface electrodes) were registered. The recording of DPW and ECG was achieved by LabChart Pro version 7.2 software (AD Instruments Pty Ltd, New South Wales, Australia). PowerLab Data Acquisition Unit 26T, which converts analogue signals to digital ones, was used to convert and digitally record the data on the computer for offline data analysis. Both DPW and ECG were recorded simultaneously for 60 s sampled at 1 kHz to allow for variations within the respiratory cycle. After the end of the recording time of the DPW and ECG, the volunteer was asked to immerse his left hand up to his wrist in ice-cold water for two minutes. BP and HR measurements were obtained at the end of these two minutes, and the results were considered the response of subjects to CPT. The participants who responded to CPT with ΔSBP/ΔDBP ≥ 25/20 mm Hg over the base level values were considered hyper-reactors (H-Rs).[8] Individuals whose rise in SBP and DBP was not more than 22 mm Hg and 18 mm Hg, respectively, came under the N-Rs. According to the CPT response, the participants were divided into systolic hyper-reactors (SH-R) and diastolic hyper-reactors (DH-R). For the sake of comparison of vascular stiffness indices, a number-matched control group was chosen, which included the participants with the lowest responses to CPT, who were labelled as normal reactors (N-R). This is to maximize the differences between hyper-reactors and N-R if they actually exist.

Digital pulse wave measurements

Each DPW index used in the current research was an average of about 30-40 cardiac cycles.

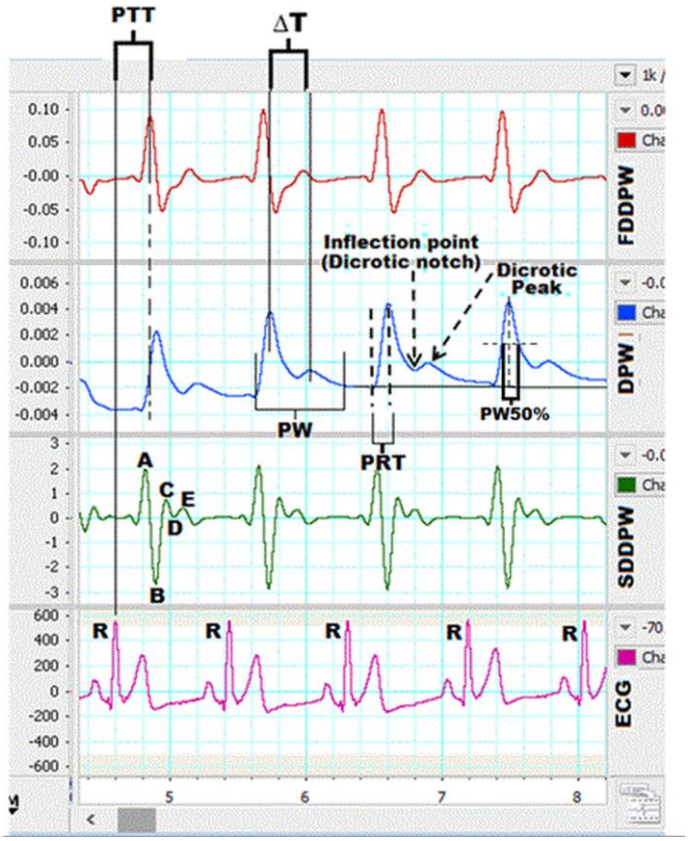

Figure 1. Typical waveform features of the digital pulse wave (DPW) and its first derivative (FDDPW) and second derivative (SDDPW). PW = Pulse wave width; PRT = Pulse Rising Time (crest); PTT = Pulse transit time; ECG = Electrocardiograph. ΔT = The time difference between DPW systolic peak and dichotic peak.

PW was measured from the DPW foot to the point where the downstroke of the wave crosses zero baseline (**Figure 1**). The PW50% was calculated after the measurement of the wave amplitude and the width of the wave at 50% of wave amplitude (**Figure 1**). PWV is measured according to the following equation:

$$PWV = PTT/D \quad \text{Eq. 1}$$

where "D" is the artery length between the heart and the tip of the left middle finger (in meters) and is calculated as 0.5 x body height in meters[19] and pulse transit time (PTT) (in seconds) is the time difference between the R peak of the ECG and a reference point of the DPW such as the point on the upstroke of the wave that corresponds to 50% of the amplitude between apex and onset points)[20-22] (**Figure 1**). This point is marked by the maximum positive wave of the first derivative of DPW (FDDPW).

B/A Ratio was measured by dividing the amplitude of the "B" wave over the "A" wave of the SDDPW.

SI was measured according to the formula (**Figure 1**)[14]:

$$SI = h/\Delta T \quad \text{Eq. 2}$$

We can suppose that this path length is proportional to subject height (h).

From the beginning of the systolic peak (foot of the DPW) to its apex, the PRT (crest) was calculated (**Figure 1**). This time difference was normalized to the PW to lessen the impact of inter-subject variability.[23]

Statistics

All of the results were expressed using the mean and standard deviation (SD). To compare data between variables, an unpaired Student's t-test was used.

Results

The vascular indexes of SH-R and SN-R counterpart subjects are summarized in **Table 1**. The BMI ranged between 17.3-37.4 kg/m^2. The SBP ranged between 101-135 mm Hg. The DBP ranged between 60-89 mm Hg. The MBP ranged between 77-102.7 mm Hg. The HR ranged between 63-83 beat/min. The table clearly shows that there are no differences in the basic vascular stiffness indexes extracted from DPW between SH-R and SN-R volunteers. It is important to emphasize that the SN-R was chosen with the least responsive participants to CPT in terms of the change in SBP.

Table 2 provides an overview of the vascular indices of DH-R and compares them to DN-R subjects. The table unequivocally demonstrates that there are no changes between DH-R and DN-R individuals in the fundamental vascular stiffness indices retrieved from DPW. The DN-R was chosen with the least responsive participants to CPT in terms of the change in DBP.

Table 1. Blood pressure, heart rate and vascular stiffness indices extracted from digital pulse wave (DPW) in systolic hyper-reactors (SH-R) and systolic normal reactors (SN-R) volunteers.

	SH-R (N= 12)	SN-R (N = 12)	*P*
Body mass index (BMI) (kg/m^2)	23.5 ± 4.7	25.7 ± 6.1	NS
Systolic BP (mm Hg)	116.3 ± 8.5	122.2 ± 5.6	0.06
Diastolic BP (mm Hg)	74.4 ± 6.6	76.8 ± 8.4	NS
Mean BP (mm Hg)	88.4 ± 6.4	91.9 ± 6.4	NS
Heart rate (HR) (beat/min)	76.8 ± 6.9	76.2 ± 7.4	NS
PWV (m/sec)	3.5 ± 0.2	3.5 ± 0.2	NS
SI (m/sec)	6.4 ± 0.5	6.4 ± 0.5	NS
B/A ratio	-1.07 ± 0.18	-1.13 ± 0.20	NS
PRT (crest time) (msec)	105.7 ± 43.4	102.3 ± 17.1	NS
Normalized PRT to PW	23.0 ± 6.6	20.7 ± 10.1	NS
Pulse width (PW) (msec)	471.1 ± 134.2	558.5 ± 172.5	NS
Pulse width at 50% of wave amplitude (PW50%) (msec)	202.6 ± 72.4	199.6 ± 98.7	NS
Normalized PW50% to PW	0.4 ± 0.1	0.4 ± 0.1	NS

PWV = Pulse wave velocity; SI = Stiffness index; DPW = Digital pulse wave; B/A ratio = Ratio of "B" wave to "A" wave of the second derivative of DPW; PRT = Pulse rising time. PW = Pulse width.

Table 2. Blood pressure, heart rate and vascular stiffness indices extracted from digital pulse wave (DPW) in diastolic hyper-reactors (DH-R) and diastolic normal reactors (DN-R) volunteers.

	DH-R (N = 8)	DN-R (N = 8)	*P*
Body mass index (BMI) (kg/m^2)	25.6 ± 7.1	23.8 ± 6.0	NS
Systolic BP (mm Hg)	121.1 ± 9.8	122.8 ± 6.9	NS
Diastolic BP (mm Hg)	77.1 ± 6.2	77.6 ± 7.4	NS
Mean BP (mm Hg)	91.8 ± 5.0	92.7 ± 7.0	NS
Heart rate (HR) (beat/min)	76.1 ± 5.9	77.0 ± 5.4	NS
PWV (m/sec)	3.5 ± 0.2	3.5 ± 0.1	NS
SI (m/sec)	6.5 ± 0.7	6.5 ± 0.5	NS
B/A ratio	-1.0 ± 0.2	-1.1 ± 0.2	NS
PRT (crest time) (msec)	116.9 ± 47.9	106.1 ± 16.5	NS
Normalized PRT to PW	20.0 ± 7.4	20.7 ± 11.7	NS
Pulse width (PW) (msec)	603.2 ± 154.0	581.1 ± 155.8	NS
Pulse width at 50% of wave amplitude (PW50%) (msec)	267.8 ± 121.9	218.4 ± 84.8	NS
Normalized PW50% to PW	0.43 ± 0.1	0.39 ± 0.1	NS

PWV = Pulse wave velocity; SI = Stiffness index; DPW = Digital pulse wave; B/A ratio = Ratio of "B" wave to "A" wave of the second derivative of DPW; PRT = Pulse rising time. PW = Pulse width.

Discussion

The provocative cold pressor test (CPT), which results in widespread sympathetic activation, promotes excessive arteriolar constriction and hence raises blood pressure.[24] Because of this, CPT is used to evaluate the neural control of the cardiovascular system by submerging one hand in ice-cold water and observing the increased vascular reactivity that is brought on by the stimulation of sensory pain as well as emotional stimulation that raise blood pressure and heart rate.[25,26] In this study, we observed no differences in the vascular stiffness background between CPT H-Rs and N-Rs. to maximize the differences in the vascular stiffness between the two groups, if they existed, we chose the N-Rs with the lowest response to CPT (in terms of ΔSBP/ΔDBP). The lack of differences in the PWV and DPW indices includes both SH-R and DH-R groups. The observation extends to denote that the vascular stiffness similarity of both groups includes the central elastic arteries (indexed by SI) and peripheral muscular conduit arteries (indexed by finger-heart PWV). These results are in agreement with those reported by others[8], who measured the PWV of the central arteries in H-R and N-R. Moreover, the results of the current study also agree with those reported by others.[10] Therefore, it is possible to suggest that the exaggerated response of H-R to CPT is not due to the differences in their vascular tone background (and consequently the stiffness). Vascular tone is determined by many competing vasoconstrictor and vasodilator factors acting on the blood vessel, and the autonomic nervous system is one of the main ones that influence it.[27] This led us to the conclusion that the autonomic nervous system activity was similar in both H-R and N-R.

Limitations of the study

Two main limitations of our study should be considered. Firstly, the data of this preliminary study is small to draw a conclusion that can apply to other age groups or gender. If the difference in vascular stiffness really exists, it may be difficult to detect it with the current small sample size. Therefore, a larger scale research could be needed, with control groups pair-matched for known risk factors of hypertension. Secondly, the choice of a healthy and exclusively young male cohort allowed the assessment of normal physiological responses to CPT in this particular population group without the influence of gender, significant sex hormone variations, and diseases like atherosclerosis and arteriosclerosis; but as a result, we are unable to apply our results to those who are older or female populations.

Conclusion

Hyper-reaction to CPT in young, healthy males is not due to the differences in the vascular tone background (and consequently the vascular stiffness). The vascular stiffness of SH-R and DH-R is comparable to that of normal reactor counterparts.

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