Research Letter

Modulation of cardiovascular autonomic function in a healthy male during cold pressor test resulted in neurocardiogenic syncope

Sir,

The cold pressor test (CPT) is one of the recognized physiological evaluation techniques to assess cardiac autonomic functions.[1] In this test, the subject immerses one of his hands up to wrist into ice cold water (4–6°C) for 1–6 min. Blood pressure (BP) and heart rate (HR) response to CPT is monitored continuously. In normal subjects, a vascular sympathetic response is increased during CPT resulting in increased peripheral resistance.[2] The present case study reported loss of consciousness of a healthy Indian adult male while undergoing CPT.

A 29-year-old healthy, nonsmoker male having body weight, height and body surface area (BSA) of 75.9 kg, 176 cm and 1.96 m^2 respectively, participated as a volunteer for the assessment of cardiac autonomic functions by cold pressor test. The temperature of the laboratory was maintained at about 25°C which was well within the comfort zone of human beings. The electrocardiography (ECG) of the subject was measured during rest in sitting posture for 5 min and during CPT for 3 min. The participant in sitting posture dipped his left hand up to the wrist into ice cold water at 4°C. The temperature of the water was maintained at 4–5°C throughout the CPT, by monitoring with a thermometer. A plastic tray of 6 cm height was used for cold water immersion, where ice cubes were mixed with normal tap water.

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Ethical Committee of the Institute approved the test protocol. The work described was carried out in accordance with The Code of Ethics of the World Medical Association. Voluntary written informed consent was obtained from the participant before undertaking any trial on him.

The single lead ECG was recorded by Procomp Infiniti 5.0 Physiological data recorder (Thought Technology, Montreal, Canada) and various heart rate variability (HRV) indices were computed. Various time domain and frequency domain indices of the HRV were then computed from ECG waveform using Kubios HRV analysis software, version 2.1, Finland as shown in Tables 1 and 2.

The participant complained of giddiness and darkening in front of the eyes nearing the completion of CPT. The subject lost his consciousness and became unresponsive to verbal command. He was immediately shifted to a bed with a stretcher. His head was lowered slightly from the horizontal position, and both legs were raised in order to augment blood supply to the brain. The individual regained his consciousness spontaneously.

Table 1 depicts various time domain indices of HRV at rest in sitting posture, during CPT and 1 min post-CPT. The result showed that mean HR increased until 2 min of the test and then decreased drastically to 51 bpm at 3rd min of CPT. Root mean square of successive differences (RMSSDs) between R-R intervals, was found to be higher during 3rd min of CPT as compared to the resting value. NN50, the number of neighboring R-R interval that differ by > 50 ms, was found to be gradually reduced on commencement of CPT. pNN50, the proportion of beats differing by 50 ms (NN50/total number of IBIs) was highest during 2–3 min of CPT than the resting value.

Table 2 depicts various frequency domain parameters of HRV like very low frequency, low frequency (LF) and high frequency (HF) spectral power. LF and HF (in the normalized unit [nu]) were found to be increased and decreased respectively at 3rd min of CPT from baseline. Total power of HRV reduced gradually from resting condition until 2 min of the test and at 3rd min and post CPT the total power was increased by manifold. LF/HF ratio increased during CPT from the resting value, and highest value was recorded at last min of CPT.

Table 3 depicts BP responses of the individual at rest, for every 30s during CPT and at the time of syncope. Nonlinear analysis of HRV has been analyzed using

Table 1: Time domain parameters of HRV at rest during CPT and 1st min post-CPT

	Mean RR (ms)	Mean HR (bpm)	RMSSD (ms)	NN50 (numbers)	pNN50 (in %)
Resting sitting	741.4	84.5	78.6	195	32.4
CPT: 0-1 min	760.3	79.6	52.6	22	27.8
CPT: 1-2 min	687.5	88.4	30.8	8	9.1
CPT: 2-3 min	1594.0	51.5	86.0	22	68.8
Post-CPT/syncope	1215.4	53.2	72.9	22	42.3

HRV: Heart rate variability, CPT: Cold pressor test, RMSSD: Root mean square of successive differences of RR intervals, NN50: Number of pairs of adjacent RR intervals differing by more than 50 ms, pNN50: Percentage of NN50 count of RR intervals, i.e. (NN50 count/Total count of RR intervals)x100, HR: Heart rate

Table 2: Frequency domain parameters of HRV at rest during CPT and 1-min post-CPT

	VLF (0-0.04 Hz)			LF (0.04-015 Hz)				HF (0.15-0.4 Hz)				Total power	LF/HF
	Peak (Hz)	Power (ms^2)	Power (%)	Peak (Hz)	Power (ms^2)	Power (%)	Power (n.u)	Peak (Hz)	Power (ms^2)	Power (%)	Power (n.u)		
Resting sitting	0.031	129	4.9	0.051	1005	38.1	40.1	0.16	1497	56.8	59.7	2637	0.67
CPT: 0-1 min	0.027	245	10.4	0.089	1576	66.6	74.3	0.15	542	22.9	25.6	2364	2.908
CPT: 1-2 min	0.039	326	14.7	0.051	1197	54.1	63.5	0.18	688	31.1	36.5	2212	1.739
CPT: 2-3 min	0.019	1664	8.8	0.056	16179	85.1	93.3	0.15	1158	6.1	6.7	19001	13.98
Post-CPT/syncope	0.023	11285	72.5	0.043	3055	19.6	71.4	0.16	1224	7.9	28.6	15565	2.496

HRV: Heart rate variability, CPT: Cold pressor test, VLF: Very low frequency, LF: Low frequency, HF: High frequency

Table 3: BP responses at resting sitting, during CPT and at post-CPT

Parameters	Rest	CPT: 0-30 s	CPT: 31-60 s	CPT: 61-90 s	CPT: 91-120 s	CPT: 121-150 s	CPT: 151-180 s	Post-CPT/at the time of syncope
SBP (mmHg)	110.65±7.136	117.0±10.151	122.38±4.963	119.25±4.099	113.00±2.134	105.23±4.802	91.13±10.280	57.43±8.597
DBP (mmHg)	71.12±6.186	68.19±9.439	75.09±4.383	75.00±2.542	70.89±1.912	65.91±2.964	53.76±8.018	29.96±4.185
PP (mmHg)	39.4±5.42	48.8±4.96	47.4±3.25	44.0±1.98	42.2±2.36	39.0±4.58	38.2±1.27	27.4±2.35
MAP (mmHg)	86.12±5.801	87.22±9.106	92.81±4.774	91.55±3.170	86.73±1.73	80.00±3.413	66.47±9.078	41.61±8.949

BP: Blood pressure, CPT: Cold pressor test, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PP: Pulse pressure, MAP: Mean arterial pressure

Poincare plot (POP) and is depicted in Table 4. The result revealed that standard descriptors (SD) of POP, SD1 and SD2, decreased gradually from rest to 1st and 2nd min of CPT and increased at 3rd min of CPT, SD2 increase was more pronounced. Figure 1 depicts the POP of HRV at rest and during CPT. The HRV data for CPT has been averaged for 3 min. The present study reported cardiovascular response of a healthy adult male before and during 3 min of CPT. At 3rd min, about 5 s before completion of the test, the subject complained of giddiness and lost his consciousness.

Time domain parameters of HRV revealed that mean HR increased during first 2 min of CPT followed by a reduction in the 3rd min. It has been reported in a number of studies that CPT stimulates the sympathetic neural response.[3] RMSSD, a time domain parameter of HRV, has been reported to be associated with vagal mediated control of HR.[4] Reduction in RMSSD from commencement of the test up to 2 min has been observed in the present study. The RMSSD increased at 3rd min and post-CPT.

Frequency domain parameters like LFnu and HFnu increased and decreased respectively during first 2 min of CPT. LF spectral power mostly denotes the activity of sympathetic neural system and HF spectral power as parasympathetic neural function. At the time of syncope, the LF power reduced and HF power increased. A number of studies have confirmed that CPT causes sympathoexcitation and withdrawal of vagal activity.[1,2,5]

At last min of CPT, there is a reduction in HR and BP (HR decreased from 85 bpm at baseline to 51 bpm at last min of CPT and mean arterial pressure [MAP] fell from ± 5.80 mmHg at baseline to 66.5 ± 9.08 mmHg at last min of CPT). The bradycardia and hypotension are observed in the individuals developing neurocardiogenic syncope. This hemodynamic instability results from withdrawal of sympathetic nervous system and activation of parasympathetic discharge.

Excessive increase in LF power nu and decrease in HF power nu at last min of CPT must be a prelude to hemodynamic instability. LF power nu reduced and HF power nu increased just after CPT. Reduction in sympathetic activity post-CPT has also been observed in BP values [Table 3]. MAP was recorded to be 41.6 ± 8.95 mmHg at the time of syncope. The reduced sympathetic neural activity causes reduction in peripheral resistance

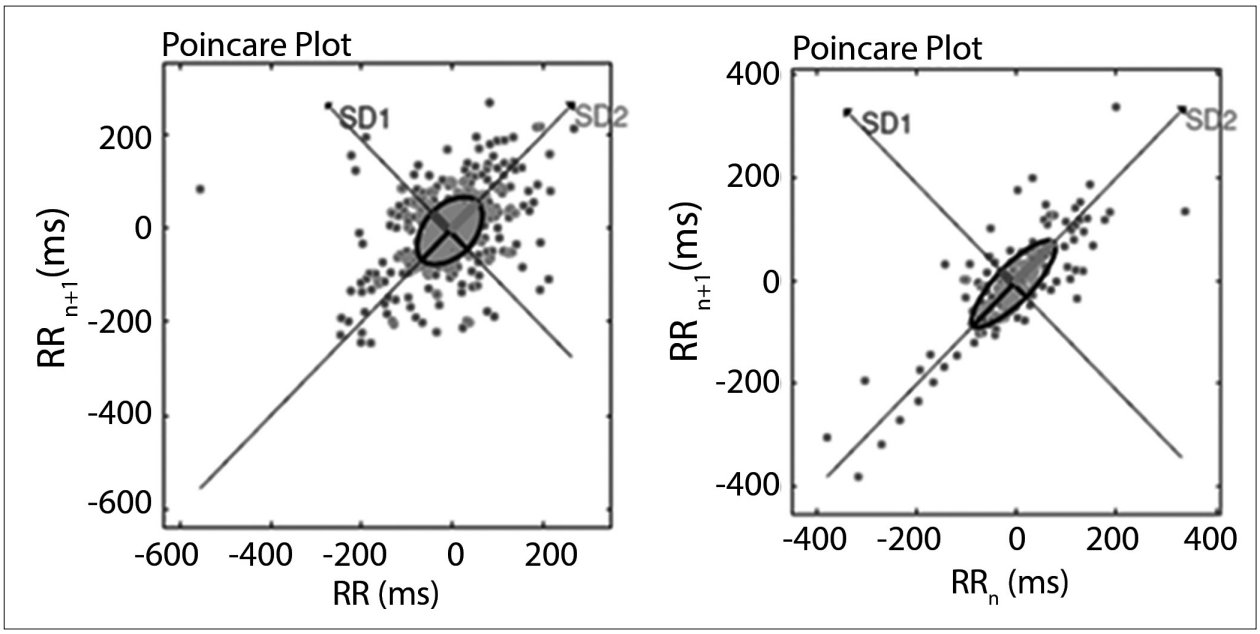

Figure 1: Poincare plot of HRV at resting sitting (Left) and during CPT (Right)

Table 4: Nonlinear analysis descriptors of HRV, SDs of Poincare plot

Variable (ms)	Rest	CPT: 1st min	CPT: 2nd min	CPT: 3rd min	Post-CPT
SD1	55.7	37.5	21.9	62.5	52.1
SD2	87.6	82.6	49.8	212.8	209.7

SD: Standard descriptor, HRV: Heart rate variability, CPT: Cold pressor test

resulting in reduced MAP. The comparatively lower value of sympathetic neural discharge as reflected in LF nu during post CPT from last min of CPT, is mainly responsible for lowest MAP in the individual at the time of syncope.

Increased sympathetic activity causing stimulation of left ventricular mechanoreceptor has been implicated in the development of syncope.[6] Activation of mechanoreceptor causes simultaneous withdrawal of sympathetic neural activity and activation of vagal input causing bradycardia and hypotension resulting in syncope. Study has also suggested that even before the activation of left ventricular mechanoreceptors, an increase in sympathetic tone can markedly reinforce vagal activity to the heart.[7]

Cold pressor test induces an immediate local and generalized vasoconstriction of the skin and skeletal muscle, which is not only due to a direct effect of cold on the skin blood vessels, but also due to stimulation of pain receptors, which activates spinal and hypothalamic reflexes.[8] Sympathoinhibition and hypotension have been reported in healthy subjects when CPT was performed after exposing them to lower body negative pressure. The similar finding has also been observed in patients undergoing hemodialysis, when CPT was performed during dialysis.[9]

The POP of HRV analysis is a nonlinear analysis of the HRV result[10] and scatter plot of the current R-R interval plotted against the preceding R-R interval. SD1, signifying short term variability, represents the dispersion of points perpendicular to the axis line of identity and is used as a marker of vagal influence. SD2, signifying long-term variability, represents the points of dispersion along the axis of the line of identity and signifies more delayed R-R interval changes correlated to sympathetic activity. When parasympathetic tone to the heart decreases, SD1 value likely decreases.[11] In the study, it was observed that SD1 value gradually decreased at 1st and 2nd min of the test, supporting the fact of HR increase during first 2 min of the test. At 3rd min of the test, SD1 increased to a maximum, even higher than the baseline value, suggestive of the higher vagal dominance over the heart and bradycardia. The SD2 value when decreases signify increased sympathetic activity.[11] During 2nd min of CPT, SD2 decreased by about 43% from baseline, suggesting sympathoexcitation. At 3rd min of CPT, SD2 increased by about 2.4 times from baseline which indicates imminent sympathetic inhibition.

The combined effect of increased vagal activity and reduced or withdrawn sympathetic drive in the individual during CPT might have led to the development of bradycardia and hypotension. This compromised blood supply to the brain could have contributed to the development of neurocardiogenic syncope.

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