

A Study of Cardiovascular and Pulmonary Responses During Cold Pressor Test (CPT) In Healthy Volunteers

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Abstract

Acute pain was induced in 35 healthy volunteer males by cold pressor test (CPT) and pulmonary parameters - respiratory rate (RR), tidal volume (TV), inspiratory and expiratory reserve volume (IRV, ERV), inspiratory capacity (IC), vital capacity (VC), forced vital capacity (FVC), FEV1, peak expiratory flow rate and forced expiratory flow rate at 75, 50 and 25% of expired FVC (FEFR 75, 50 and 25%) were measured. Acute pain parameters like pain threshold, tolerance and sensitivity were also recorded. Besides these, the cardiovascular parameters - pulse rate, systolic and diastolic blood pressure, were also measured. Comparisons were made between values recorded before, during and after cold induced pain. There was a significant increase in cardiovascular and pulmonary parameters (RR, TV, IC, IRV, ERV, VC, FVC and FVC1) during the acute pain induced by CPT, reflecting an acute state of responses secondary to sympathetic challenge. The study indicates that alterations in pulmonary and cardiovascular profile form an integral part of multidimensional responses observed during cold induced acute pain.

Key Words

Cold Pressor Test, Pulmonary Response, Acute Pain

Introduction

The cold pressor test (CPT) has been a time honoured method of testing autonomic functions in man (1, 2). The cold pressor test (immersion of the limb, usually hand or forearm, into ice-cold water), provides a sympathetic challenge without requiring patient cooperation (3). For 50 years, cold pressor test (CPT) has been extensively applied in the studies of stress, familial hypertension, coronary artery disease, drug action and human pain (4, 5,6,7). CPT produces an increase in heart rate, total vascular resistance, arterial blood pressure and cardiac output attributable to increased sympathetic vasomotor neuronal activity (3, 8, 9,10,11). Respiratory stimulation is another important event associated with acute pain (12). Increased respiratory rate along with bronchodilation could be due to sympathoadrenal discharge leading to increased circulating catecholamines levels. Another possibility could be that during cold induced pain, increased sympathetic discharge to aortic and carotid chemoreceptors may enhance their sensitivity and augment their response resulting in increased rate and depth of respiration (13). Others are of the opinion that that pain causes a chemo-reflex-independent tonic ventilatory drive (14). In literature, very few studies have been conducted to assess the changes in pulmonary functions during acute pain induced autonomic responses.

Also it is not known as to which components of pulmonary response show specific changes secondary or concomitant to the autonomic alterations induced by acute cold induced pain (13). Hence, the present study was undertaken.

Methods

Thirty-five healthy volunteer were subjects for the study. Their weight and height was recorded. A prior informed written consent was obtained from the students participating in the study.

Exclusion Criteria Included :-History of smoking, respiratory tract allergic disorders, cardiovascular disorder, fainting or seizures, frost bite, open cut or sore on hand to be immersed, fracture of limb to be immersed & Reynaud's phenomenon. Acute pain was induced in these 35 healthy volunteers by the standard cold pressor test and proceeded as follows

Procedure

Cold Pressor Test (CPT) : After the baseline record, the subjects were made to undergo cold pressor test i.e. each subject immersed his non-dominant hand in ice-cold water at $4\pm 1^{\circ}\text{C}$, contained in a large beaker, surrounded by crushed ice to maintain temperature of water at 4°C kept in a thermocol case. The subjects were instructed to inform as soon as they started feeling the pain and to take out their hand when the pain became intolerable.

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Accordingly, as they dipped their hands, two stop-watches were simultaneously started. First stop-watch was stopped when the subjects started feeling the pain and immediately the respiratory rate was recorded along with the pulse rate and blood pressure. The subjects were made to perform the vital capacity maneuver i.e. taking a deep breath and exhaling it forcefully with maximum effort.

'Second stop-watch' was stopped when the subjects complained that pain was intolerable and took out their hand. The subject's hand was wrapped in a towel and when they stopped feeling the pain, they were again asked to immerse their hand in the beaker containing tap water at room temperature. All the parameters were recorded again after a gap of 5-10 minutes. The subjects were called again after a week and cold pressor test was performed on them again and in this sitting, FVC, FEV₁, FEFR75%, FEFR50%, FEFR25% (i.e. forced expiratory flow rates after 75, 50 and 25 percent of FVC had been expired) and peak expiratory flow rate (PEFR) were recorded, as soon as the subject started feeling the pain during the cold pressor test. 'Pain sensitivity' was taken as the difference between 'pain threshold' (time by 1st stop-watch i.e. when the subject started feeling pain) and 'pain tolerance' (i.e. time for which subject was able to tolerate the pain as shown by the second stop-watch). As done previously in the case of spirometry, Medspiror values were recorded again 5-10 minutes after the cold pressor test. Various 'cardiovascular' (pulse rate, systolic and diastolic blood pressure) and 'pulmonary parameters' recorded before, during and after cold induced pain were analysed.

Statistical Analysis

Mean and standard deviation were calculated for quantitative variable (respiratory rate, tidal volume, etc.) and their significance assessed by the use of appropriate statistical method. ANOVA was performed to evaluate statistically significant difference before, during and after acute pain. A 'p' value of less than .05 was considered as statistically significant.

Results

The mean age of subjects was 19.14 ± 1.28 years. The mean height and weight were 167.74 ± 5.72 cm and 63.2 ± 7.32 kg, respectively. The pain threshold in the subjects ranged from 6 to 36 sec, pain tolerance from 37 to 98 sec, and pain sensitivity from 31 to 75 sec during the cold pressor test.

A. Cardiovascular Parameters (Table 1)

The pulse rate recorded during cold induced acute pain was significantly higher ($p < 0.0001$) from both before and after cold pressor test. Systolic blood pressure showed approximately 24.5% increment during the CPT as compared to before and after the acute pain, while diastolic blood pressure showed an approximate increment of

23.6% during the CPT when compared with that before the acute pain and it was approximately 20.2% more when compared with that recorded after the CPT. The systolic and diastolic blood pressure were significantly higher during the cold pressor test as compared to before and after the cold pressor test ($p < 0.0001$) as shown in Table 1. Thus, the cardiovascular parameters (viz., pulse rate, systolic and diastolic blood pressure) showed a net increase during the cold induced acute pain as compared to those before and after the state of acute pain.

B. Respiratory Parameters (Tables 2&3)

The mean respiratory rate recorded during acute pain was significantly higher ($p < 0.0001$) than that recorded before and after the cold pressor test. Tidal volume showed a significant increase from baseline during cold induced acute pain ($p < 0.0001$). The mean tidal volume after the cold pressor test was not significantly higher than that recorded before acute pain but was significantly lower than that recorded during acute pain. Inspiratory capacity recorded during acute acute pain was significantly higher than that recorded before and after the cold induced pain. The inspiratory capacity showed an increment of approximately 9.2% during the CPT when compared to that recorded prior to the induction of acute pain. Inspiratory reserve volume recorded during acute pain was significantly higher than that recorded before and after the cold pressor test. Expiratory reserve volume recorded during the cold pressor test was significantly higher than that recorded before and after the cold induced acute pain with an average increment of 11.2% during the CPT as compared to that recorded both before and after the experimental acute pain induced by CPT. Vital capacity recorded in 35 normal healthy volunteers before, during and after experimentally induced acute pain by CPT showed a similar trend as that of respiratory rate and tidal volume i.e. it was significantly high during CPT as compared to before and after the CPT with an increment of approximately 10.1% during the CPT from the baseline i.e. prior to commencement of acute pain. The forced vital capacity recorded during the cold pressor test was significantly higher than that recorded before and after the cold induced acute pain. Forced vital capacity after one second (FVC₁) recorded during cold induced acute pain was significantly higher than that recorded before and after the cold pressor test. Peak expiratory flow rate (PEFR) recorded before, during and after the acute pain did not reveal any significant difference amongst each other. The various flow rates i.e. forced expiratory flow rate (FEFR) after 75%, 50% and 25% of FVC have been expired (FEFR75%, FEFR50% and FEFR25%) before, during and after cold pressor test showed no significant difference amongst each other. The pulse rate and the respiratory rate showed

Table 1. Cardiovascular Parameters Before, During & After Cold Pressor Test in Normal Healthy Volunteers (n = 35)

Parameter	Before CPT (mean ± SD)	During CPT (mean ± SD)	After CPT (mean ± SD)	p-value
Pulse rate (per minute)	82.4 ± 8.44	109.54 ± 15.73	82.20 ± 9.39	< 0.0001
Systolic BP (mmHg)	117.88 ± 10.70	146.97 ± 12.00	117.48 ± 10.53	< 0.0001
Diastolic BP (mmHg)	71.94 ± 7.50	89.14 ± 10.45	77.94 ± 8.16	< 0.0001

Table 2. Respiratory Parameter Before, During & After Cold Pressor Test (CPT) in Normal Healthy Volunteers (n = 35)

Parameter	Before CPT (mean ± SD)	During CPT (mean ± SD)	After CPT (mean ± SD)	p-value
Respiratory rate (RR) (per minute)	16.42 ± 1.83	21.68 ± 1.93	17.00 ± 1.89	< 0.0001
Tidal volume (TV) (ml)	528.57 ± 58.51	616.57 ± 77.98	548.57 ± 63.57	< 0.0001
Inspiratory capacity (IC) (ml)	2445.71 ± 509.23	2670.00 ± 514.66	2462.00 ± 502.25	< 0.0001
Inspiratory reserve volume (IRV)(ml)	1925.71 ± 465.79	2082.00 ± 480.33	1978.57 ± 476.39	< 0.0001
Expiratory reserve volume (ERV) (ml)	900.00 ± 110.48	1000.00 ± 115.68	908.57 ± 115.37	< 0.0001
Vital capacity (VC) (ml)	3371.42 ± 512.96	3710.00 ± 559.12	3440.57 ± 573.55	< 0.0001

Table 3. Respiratory Parameter Before, During and After Cold Pressor Test (CPT) in Normal Healthy Volunteers (n = 35)

Parameter	Before CPT (mean ± SD)	During CPT (mean ± SD)	After CPT (mean ± SD)	p-value
Forced vital capacity (FVC) (ml)	3762.28 ± 649.43	4220.85 ± 675.25	3911.71 ± 633.25	< 0.0001
Forced vital capacity after 1 second (FVC ₁) (ml)	3479.71 ± 676.43	3702.28 ± 716.49	3492.57 ± 708.47	< 0.001
Peak expiratory flow rate (PEFR) (l/min)	7.57 ± 1.51	7.91 ± 1.42	7.64 ± 1.61	= 0.25
Forced expiratory flow rate at 75% (FEFR 75%) (l/min)	3.33 ± 0.88	3.35 ± 0.86	3.23 ± 0.70	= 0.244
Forced expiratory flow rate at 50% (FEFR 50%) (l/min)	5.42 ± 1.17	5.45 ± 1.11	5.33 ± 0.99	= 0.699
Forced expiratory flow rate at 25% (FEFR 25%) (l/min)	6.83 ± 1.28	7.09 ± 1.26	7.01 ± 1.20	= 0.23

a positive correlation during the acute pain with coefficient of correlation ($r = 0.628$ and $p = 0.0001$) (Fig. 1). Similarly, the pain sensitivity and the tidal volume during the experimentally induced acute pain (CPT) showed a positive correlation with coefficient of correlation ($r = 0.43$; $p = 0.009$) (Fig. 2). These positive correlation show that cardiovascular and respiratory responses go hand-in-hand in response to stimulation of higher centres to prepare the individual optimally for a stressful condition like acute pain, induced in the present study by means of cold pressor test.

Discussion

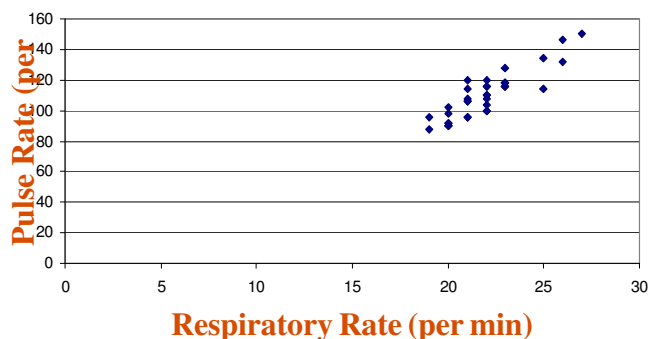
The behavioural response to a psychological stressor like cold pressor test (CPT) include somatomotor, neuroendocrine and cardiovascular components (9,

12). CPT is often used to elicit -adrenergic vasoconstriction and pressor responses (i.e. BP increase) in laboratory research on hypertension (15, 16, 17).

The increments observed in the present study i.e. an increase in pulse rate (PR), systolic and diastolic BP values during cold induced acute pain are in line with those observed by Tandon *et al.* (13), Wolf and Hardy (18), Engel (19), Cuddy *et al.* (20) and Fagius *et al.* (21). Victor *et al.* (10) also reported that the cold induced increase in HR was entirely a function of sympathetic activation, because HR changes were completely abolished by -adrenergic blockade (propranolol). The typical cardiovascular response to the CPT is significant increase in both blood pressure and heart rate (22), although increase of blood pressure associated with



Fig. 1 Correlation Between Respiratory Rate and Pulse Rate During the Cold Pain (CPT) (Coefficient of correlation $r = 0.628$, $r^2 = 0.3951$, $t = 4.64$, $p = 0.0001$)

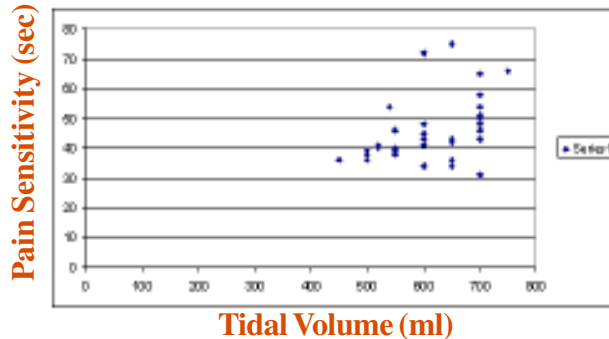


bradycardia (23, 24) or unchanged blood pressure values (10) have also been reported. It has also been reported that CPT produces significant, complementary increase in vagal tone (25). In majority of individuals, the cold pressor stimulus indicates an increase in total peripheral resistance (TPR), whereas the cardiac output may either increase or decrease. Both of these response components may be important because even substantial increases in TPR during CPT do not necessarily translate into large changes in BP (20). Also, an acute adrenergic blockage attenuates systolic BP increase to the CPT due to a reduction in cardiac output (16).

These cardiovascular responses approach a plateau for BP while heart rate starts to decrease during the 2nd minute of CPT and this normalization of heart rate may be due to decreasing pain perception at the end of stimulation (7). Skin blood flow responses to CPT are also biphasic. With prolonged CPT, cold induced vasodilatation secondary to the initial vasoconstriction is seen (3). The vasodilatation first described by Lewis as 'hunting reaction' and the normalization of heart rate both account for the relatively small BP increase during the second minute of CPT (7, 11). Summarising, CPT increases sympathetic activity through a central neural mechanism. Furthermore, it is independent of the baro reflex and can be used to test the efferent limb of the sympathetic arc.

In the present study, during the cold induced acute pain, both rate and depth of respiration increased. The increase in respiratory rate and tidal volume indicates that cold induced pain has a stimulatory effect on ventilation (13, 26). The respiratory rate and tidal volume both increase to cold pain, an effect that increases both sympathetic and para-sympathetic neural activity (3, 9). Pain alters pulmonary functions by causing a pattern of rapid, shallow breathing with a reduced number or absence of deep (sigh) breaths (12). The increase in minute ventilation during CPT is primarily due to large increase in tidal volume with only modest increase in

Fig. 2 Correlation Between Pain Sensitivity (sec) and Tidal Volume (ml) During Cold Pain (CPT) (Coefficient of correlation $r = 0.43$, $r^2 = 0.18$, $t = 2.75$, $p = 0.009$)



respiratory rate (27). In the present study, the tidal volume showed an increase during acute pain but it was not more than 50% of the vital capacity recorded during acute pain. In intact humans, breathing rate usually increases when tidal volume increases to about half the vital capacity (13). The forced vital capacity and the vital capacity showed significant increases during cold induced acute pain. This could be explained because of better muscular and voluntary effort by the subject due to general arousal response to pain during cold stress. Also the relaxation and broncho-dilatation of large airways may be contributing factor (13). FEV1, which is not effort dependent as FVC and VC and is dependent on calibre of the large airways explains the possibility of bronchodilatation in response to cold induced acute pain.

Vecchiet *et al.* (28) experimentally demonstrated that broncho-constriction could be brought about by means of cold stimuli applied to parietal areas metamericly connected with the bronchi (i.e. chest wall), whereas no broncho-constriction occurred in case of cold stimuli applied to the areas not connected metamericly with the bronchi. Tandon *et al.* (13) were of opinion that bronchodilation occurred during cold induced by cold pain which they attributed because of 'Herring Breuer inflation reflex', bringing about relaxation of tracheobronchial tree smooth muscle. Also the sympathoadrenal discharge during CPT leads to an increase in the circulating catecholamines (1, 20) which acts on α -adrenoceptors in the airway causing bronchodilation. Another possibility could be that during cold induced acute pain, increased sympathetic discharge to the aortic and carotid chemoreceptors may improve their sensitivity and augment their response. Increased circulating catecholamines may further increase their firing by directly acting on the chemoreceptors (13).

The various flow rates i.e. peaked expiratory flow rate (PEFR), forced expiratory flow rate, FEFR25%, 50% and 75% (i.e. 25, 50 and 75% of FVC have been expired) before, during and after cold pressor test showed no

significant difference amongst each other. Probably this finding was as a result of an increase in bronchial tone especially in upper airways and stimulation of stretch receptors by cold and reflexively induced bronchoconstriction, mediated by the vagus nerve (29). The inspiratory capacity also showed a significant increase during cold induced acute pain. Similarly, inspiratory and expiratory reserve volumes (IRV, ERV) also showed significant increments during the cold pressor test as compared to before and after the CPT. Tandon *et al.* (13) in their study, reported significant changes in expiratory and inspiratory capacities while inspiratory and expiratory reserve volume were not significantly altered. They were of opinion that the increments in these capacities may be secondary to the increase in the tidal volume. In the present study, significant increase in inspiratory capacity and reserve volumes (IRV, ERV) may be because of increase in the respiratory tone in an attempt to prepare an individual metabolically to face the acute stress (30). The pathways by which acute pain increases ventilatory drive remain speculative. According to Sarton *et al.* (14), three possible pathways are: spinal reflex pathways, activation of supra-pontine structures provoking the modulation of respiratory centres in the central nervous system and a direct effect of nociceptive afferents on the respiratory centres in the brain stem.

Conclusion

The study indicates that alterations in pulmonary and cardiovascular profile form an integral part of multidimensional responses observed during cold induced acute pain, which prepare individual to face the challenge posed by acute stressful condition.

References

- Cummings MF, Steele PM, Meher LF, *et al.* The role of adrenal medullary catecholamine release in the response to cold pressor test. *Cardvasc Res* 1983; 17 : 189-91.
- Singh PL, Khurana L. Cardiovascular responses to cold pressor test : A test for autonomic functions. *J Ind Med Assoc* 1991; 89 (8) : 229-31.
- Lovaglio W. The cold pressor test and autonomic function : A review and integration. *Psychophysiol* 1975; 12 (3) : 268-82.
- Chang PF, Nielsen LA, Chen ACN. Dynamic changes and spatial correlation of EEG activities during cold pressor test in men. *Brain Res Bull* 2002; 57 (5) : 667-75.
- von Baeyer CL, Piira T, Chamber CT, *et al.* Guidelines for the cold pressor task as an experimental pain stimulus for use with children. *J Pain* 2005; 6 (4) : 218-27.
- Fulbright RK, Troche CJ, Studlarski P. Functional MR imaging of regional brain activation associated with the effective experience of pain. *Am J Roentgenol* 2001; 177 : 1205-10.
- Hilz MJ, Axelrod FB, Braeske K, Stemper B. Cold pressor test demonstrates residual sympathetic cardiovascular activation in familial dysautonomia. *J Neurolog Sc* 2002; 15 (196) : 81-89.
- Hines EA Jr, Brown GE. Standard stimulus for measuring vasomotor reactions: Its application in the study of hypertension. *Proc Staff Meet Mayo Clin* 1932; 7 : 332-35.
- Herd JA. Cardiovascular response to stress. *Physiol Rev* 1991; 71 (1) : 305-30.
- Victor RG, Leimbech WN, Seals DR, Wallin BG, Mark AL. Effects of the cold pressor test on muscle sympathetic nerve activity in human. *Hypertension* 1987; 9 : 429-36.
- Peckerman A, Hurwitz BE, Saab PG, *et al.* Stimulus dimension of the cold pressor test and associated pattern of cardiovascular response. *Psychophysiol* 1994; 31 : 282-90.
- Lewis KS, Whipple JK, Michael KA, Quebbeman J. Effect of analgesic treatment on the physiological consequences of acute pain. *Am J Hosp Pharm* 1994; 51 : 1539-54.
- Tandon OP, Himani A, Singh S. Pulmonary responses during cold induced acute pain. *Ind J Physio Pharmacol* 1997; 41 (1) : 16-22.
- Sarton E, Dahen A, Teppema L, *et al.* Influence of acute pain induced by activation of cutaneous nociceptors on ventilatory control. *Anesthesiol* 1997; 87 : 289-296.
- Pickering TG, Gerin W. Cardiovascular reactivity in the laboratory and the role of behavioural factors in hypertension. *Ann Behav Med* 1990; 12 : 3-16.
- Sherwood A, Allen MT, Obrist PA and Langer AW. Evaluation of beta-adrenergic influences on cardiovascular and metabolic adjustments to physical and psychological stress. *Psychophysiol* 1986; 23 : 89-104.
- Leblanc J, Dulec S, Cote J, Guard B. Autonomic nervous system and adaptation to cold in man. *J Appl Physiol* 1975; 39 : 181-86.
- Wolf S, Hardy JD. Studies on pain. Observation on pain due to local cooling and on factors involved in the 'cold pressor' effect. *J Clin Invest* 1941; 20 : 521-33.
- Engel BT. Some physiological correlates of hunger and pain. *J Exp Psycho* 1959; 57 : 389-96.
- Cuddy RP, Smulyan H, Keighley JF, *et al.* Hemodynamic and catecholamine change during a standard cold pressor test. *Am Heart J* 1966; 71 (4) : 446-54.
- Fagius J, Karhuvaara S, Sundlof G. The cold pressor test : effects on sympathetic nerve activity in human muscle and skin nerve fascicles. *Acta Physiol Scand* 1989; 137 : 325-34.
- Tassorelli C, Miceli G, Osipova V, Rossi F, Nappi G. Pupillary and cardiovascular responses to the cold pressor test. *J Auton Nerv Sys* 1995; 55 : 45-49.
- Abbound F, Eckstein J. Active reflex vasodilation in men. *Fed Proc* 1966; 25 : 1611-1617.
- Anderson NB, Lane JD, Muranaka M, *et al.* Racial differences in blood pressure and forearm vascular responses to the cold forehead stimulus. *Psychosom Med* 1988; 50 : 57-63.
- Aboussafy D, Campbell TS, Lavoie K, Aboud FE, Ditto B. Airflow and autonomic responses to stress and relaxation in asthma. *Int J Psychophysiol* 2005; 57 (3) : 195-201.
- Duranti R, Pantaleo T, Bellin F, *et al.* Respiratory responses induced by the activation of somatic nociceptive afferents in humans. *J Appl Physiol* 1991; 71 (6) : 2440-48.
- Allen MT, Sherwood A, Obrist PA. Interactions of respiratory and cardiovascular adjustments to behavioural stressors. *Psychophysiol* 1986; 23 : 532-41.
- Vecchiet L, Flacco L, Marini I, *et al.* Effects of cold stimulus of the chest wall on bronchial resistance. *Respiration* 1985; 47 : 253-89.
- Bandopadhyay P, Selvamurthy W. Respiratory changes due to extreme cold in the arctic environment. *Ind J Biometeorol* 1993; 37 : 32-35.
- Dudley DL, Holmes TH, Martin CJ, Ripley HS. Changes in respiration associated with hypnotically induced emotion, pain and exercise. *Psychoso Med* 1964; 26 : 46-57.