

RESEARCH ARTICLE

Depressive symptoms contribute to increased response during cold pressor test in young adult persons

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ABSTRACT

Background: The relationship between depression and disturbance of autonomic regulation has been recognized for a long time. Major depressive disorder (MDD) is associated with increased cardiovascular (CV) risk. Temperature and other environmental stressors are known to affect blood pressure and heart rate. The cold pressor test (CPT) is used clinically to evaluate the dysregulation of CV autonomic functions. **Aims and Objective:** The aim of our study is to examine the autonomic function in patients of major depression by comparing their autonomic function with those of healthy subjects. **Materials and Methods:** The study conducted on 36 fresh untreated, clinically diagnosed for MDD having no other disease and control group consisting of 36 persons having no psychiatric illness. **Results:** BP responses to CPT, in depressed and control were compared. The mean rise in diastolic BP after CPT in depressed (98 ± 16.135) was found to be statistically significant compared to controls (90 ± 8.2). **Conclusion:** Our results indicate that depressive symptoms in individuals without MDD may be associated with cardiac hyperactivity during SNS stimulation, contributing to increased diastolic BP. These findings may have clinical implications for the evaluation of depressive symptoms in healthy, young adult men.


KEY WORDS: Depression; Sympathetic Nervous System; Parasympathetic Nervous System; Cold pressor test

INTRODUCTION

Major depressive disorder (MDD), a major cause of disability worldwide, is associated with the development of adverse cardiovascular (CV) outcomes, including hypertension, increased left ventricular mass, coronary artery disease, arrhythmias, stroke, and myocardial infarction.^[1-4] Converging evidence demonstrated that patients with MDD are at increased CV risk.^[1,2]

Depression and anxiety have been related to CV disease (CVD). Further, the association between depression, anxiety,

and CVD is complex, and the mechanisms linking them have not been fully elucidated. One pathway linking psychological factors (specifically, depression and anxiety) to CVD and CV mortality that has received attention is that of CV reactivity.^[5,6] However, the relationship between anxiety and depression and CV reactivity has been inconsistent. Early studies supported the hypothesis that exaggerated responses to stress were associated with depression, and might, therefore, account for the raised risk of CVD in people with depression.^[7] In particular, a meta-analysis of 11 studies conducted from 1887 to 2001 suggested that there was a small to moderate positive correlation between CV reactivity and depressive symptoms; however, these effect sizes did not reach conventional criteria for statistical significance.^[8] Other, more recent studies have provided limited support for this hypothesis. For example, Pointer *et al.* reported that state anxiety was positively associated with blood pressure (BP) responses to cold pressor and anger recall in 50 healthy adults.^[9] In another study of 60 healthy young women who completed a speech task,

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depressive symptoms were positively associated with BP, heart rate (HR), and cardiac output (CO) responses.^[7] Thus, these studies suggested that there may be a weak, positive relationship between depressive/anxiety symptoms and CV reactivity.

Other studies have reported no differences in sympathetic activity between depressed and non-depressed participants.^[10,11] For example, Taylor *et al.* examined CV reactions to the trier social stress test. 59 older depressed patients and 20 non-depressed patients matched for age and CV risk were tested. The study revealed no significant differences in BP reactivity between depressed and non-depressed individuals.^[11] One possible explanation for the lack of association is the small sample size and consequent lack of power to detect possible effects, although studies of similar size reported significant positive correlations.^[7,9]

Finally, other studies have found that anxiety and depressive symptoms are associated with blunted physiological reactivity. In the largest study to date, Carroll *et al.*^[12] assessed depressive symptoms in 1608 adults. Depression scores were negatively, but modestly, associated with systolic BP (SBP) and HR reactions to the paced auditory serial arithmetic test (PASAT).^[12] In a second, large recent study, de Rooij *et al.* reported that 725 healthy Dutch participants with high depressive or anxiety scores on the hospital anxiety and depression scale exhibited more marked SBP and HR reactions to psychological stressors (i.e. Stroop, mirror-tracing, and speech tasks) than those with low depression and anxiety scores.^[13] Young *et al.* assessed trait anxiety in 832 healthy participants and found that those with higher levels of trait anxiety had lower CV reactivity than participants with low levels of anxiety.^[14] Thus, a number of studies do not support a hyper-reactivity hypothesis; rather, they suggest that blunted physiological reactivity is related to anxiety and depression. Indeed, a meta-analysis by Chida and Hamer of studies from 1950 to 2008 found that anxiety and depressive mood were associated with decreased CV reactivity.^[15] In short, larger recent studies have reported negative relationships of symptoms of anxiety and depression with CV reactivity.

However, to date, few published studies have examined hemodynamic responses (including CO and total peripheral resistance) to mental stress tests in relation to anxiety and depressive symptoms in healthy volunteers, and the pattern of such findings has not been consistent. For example, Matthews' findings suggest a vascular mechanism underpinning relationships between depression and BP reactivity,^[16] whereas Light's findings suggest a myocardial mechanism.^[7] In addition, these studies used a variety of different measures of depression (including clinical diagnosis and questionnaires) and had a limited range of active coping tasks.

Recently, it has been suggested that CV reactivity may be related to negative health outcomes and behaviors.^[12,17] One

proposed mechanism is a motivation; blunted CV reactivity may be a physiological marker of motivational dysregulation shared by people with depression and anxiety.^[18] Carroll *et al.* found lower CV reactivity to be related to PASAT performance scores and increased symptoms of anxiety and depression.^[12] Similarly, Salomon *et al.* found that participants with major depression rated speech and mirror-tracing tasks as more demanding, threatening, and stressful than participants without major depression.^[19] However, subjective ratings did not mediate the relationship between depression and blunted reactivity.

Previous researches have shown that increased CV reactivity, defined as exaggerated BP and (HR) response to laboratory stressors (e.g., mental stress and cold pressor test [CPT]), can predict the development of hypertension and coronary artery disease.^[20-22]

Depressive symptoms have been shown to be associated with cardiac hyperactivity.^[7,23,24] These studies seem to suggest that cardiac hyperactivity may well be an early manifestation of impaired autonomic modulation and increased hemodynamics, which may ultimately lead to CVD. This is clinically important because subclinical depression, defined as some depressive symptoms without meeting the criteria for MDD,^[25] may have a deleterious effect on CV autonomic modulation and hemodynamics even in the absence of hypertension.

The preceding studies indicate that the initial CP response is cutaneous vasoconstriction, increased HR, and increased arterial pressure. These responses are primarily neurogenic reflexes depending on intact peripheral innervation. It would appear that the cold stimulation excites pain and temperature fibers which enter the spinal cord in the dorsal roots and run rostral through the lateral spinothalamic, anterior spinothalamic, and spinotectal tracts. The first two tracts proceed to the thalamus and thence to the somesthetic cortex. In the medulla, they send collaterals to the reticular formation which are in intimate association with CV regulating areas in the medulla. Their excitation causes increased CO and vasoconstriction in the skin and hence increased BP. Fibers from the spinotectal tract enter the tectum which is, in part, responsible for the elaboration of reflex mechanisms. Thus, CP stimulation affects cortical, subcortical, and probably limbic structures through the reticular formation and tectum.

Temperature and other environmental stressors are known to affect HR and BP. For example, sudden and increasingly painful cold stress causes massive discharge of the sympathetic nervous system (SNS) and release of norepinephrine (NE). This sympathetic discharge triggers responses in the CV system that include arteriolar constriction increased HR, and increased cardiac contractility. These responses combine to increase BP. This is known as the pressure response²², and testing a subject with cold stress in this fashion is known as the CPT. The CPT has been used clinically to evaluate cardiac

autonomic function^[26] and as an experimental pain stimulus^[27] as an index for screening subjects for hypertension.^[28,29]

A review of studies of cold stress indicates that cold immersion effects cannot be understood without considering affective states such as pain. Appenzeller (1970) points out that the response to CP is partly due to the pain induced by the ice water. Edes and Dallenbach (1936) took subjective reports by 5s which indicated that the sensation passed through several stages from a feeling of cold, increased cold, pain, to increased pain, which leveled off, decreased pain, and then cold alone. This evidence indicated that the sensations of cold and pain were mediated by separate classes of fibers since the cold sensation was present throughout while pain had a later onset and earlier disappearance. Wolf and Hardy (1941) reported a pain study which provided reports of the progression of pain states occurring with various water temperatures. It was found that BP increased, leveled off, and decreased in direct proportion of the reported pain, and so the BP response seems to be associated with the pain rather than the cold sensation *per se* (Wolf and Hardy, 1942). Importantly, the two sensations (cold and pain) can be perceived independently and the perception of pain is directly correlated with changes in peripheral response. This view is supported by Hilgard (1969).

The acute hypertensive effects of the CPT are linked to increases in SNS activity, which, in turn, increases vascular tone and, ultimately, afterload.^[7,23,30,31]

In brief, there are inconsistent findings regarding the relationship between CV reactions to active coping tasks such as CPT and symptoms of depression. Thus, the objectives of the present study were to examine the associations of depression with cardiac autonomic functions to active coping tasks and to examine whether these associations remained after statistical adjustments for performance and self-reported stress.

MATERIALS AND METHODS

The present quantitative, retrospective, and comparative case-control study was conducted in the Department of Physiology, in SIMMER Medical College, Surat. This study was approved by the Institutional Ethical Committee. After the prior permission of Dean of Institute Ethical Committee and Heads of the concerned departments and approval from university, 36 fresh untreated, clinically diagnosed for MDD criteria having no other disease attending OPD of Psychiatry Department of SMIMER hospital, Surat were selected as cases. After the clinical screening of patient in the psychiatry department they were brought to the physiology department for further evaluation of autonomic function test. Control group consisting of 36 were selected from Surat Municipal Corporation staff having no psychiatric illness.

The effect of CPT on BP responses was studied to evaluate cardiac autonomic functions. Patients suffering from other

conditions known to affect autonomic functions were excluded from the study, for example, diabetes mellitus, coronary heart disease, electrolyte imbalance, leprosy, anemia, and pregnancy.

Subjects

The nature of the CPT was explained to subjects beforehand to allay their apprehension. Laboratory thermometer was used to record the temperature of ice-cold water so as to maintain the temperature at 10°C.

Written informed consent was taken from the subjects and controls before the tests and the procedure was explained to them. A detailed history was taken and complete physical examination was carried out.

Procedure

Subject was asked to take rest in the supine position for 15 min before test. Data collection was conducted in a quiet, temperature-controlled (23±1°C) room with dimmed lighting and at the same time of the day (±2 h) to minimize potential diurnal variations in vascular reactivity. Immediately following the baseline measurements, in sitting position, subject's BP was recorded by sphygmomanometer with 12 cm cuff width first by palpatory and then by auscultatory method.

Then, the subject was asked to place one hand in freezing 10°C water for 1 min to evoke SNS stimulation and increased hemodynamics.^[7,26] During the CPT, a research assistant made sure the participant kept their hand in the water throughout the entire task. The BP was then recorded from the right arm, and maximum BP value was noted. The subject was instructed to indicate if he/she was unable to keep the hand immersed in cold water for 1 min.

At the end of it, systolic and diastolic BP was again measured from the other arm before removing the hand from cold water. Normally, there is an increase in systolic BP by 10–20 mm of Hg and diastolic BP by 0–10 mm of Hg.^[26]

Statistical analysis was conducted using SPSS – statistics – 20. Numerical data are expressed as Mean ± standard deviation. Quantitative data, i.e., the difference in diastolic BP before and after CPT between the study groups (depressed and healthy age and sex-matched controls) analyzed using unpaired t test. “*P*” < 0.05 is considered to be significant.

RESULTS

The mean of diastolic BP before CPT in depressed (84 ± 9.27) was found to be statistically not significant compared to controls (82 ± 9.27). BP response in the depressed and control was compared for change in BP response to CPT. The mean rise in diastolic BP after CPT in depressed (98 ± 16.135) was found

to be statistically significant compared to controls (90 ± 8.2) as shown in Table 1.

DISCUSSION

We sought to evaluate the acute BP responses to SNS stimulation in healthy, young adult control, and depressed case. Accordingly, the novel findings of this study are that, during the CPT, individuals with depressive symptoms have higher BP than control subjects.

CPT is a valuable tool to investigate the sympathetic and parasympathetic function of the autonomic nervous system. The CPT which is considered to be a sympathoexcitatory maneuver is a simple, noninvasive and validated test of sympathetic activation. The HR and BP responses to CPT could be used as indicators of global sympathetic activation, and thus, of cardiac status.^[31] The test was once suggested as an index for screening subjects for hypertension.^[28] Several studies have indicated that the CV response to the CPT can predict the future development of hypertension. Recent epidemiological evidence suggests that MDD is associated with increased CV adverse outcomes even in the absence of hypertension.^[1-4] However, the association between adverse CV functioning and depressiveness remains poorly understood. It has been proposed that altered autonomic modulation and increased hemodynamics may be early indicators of SNS hyperactivity in those individuals with high depression symptoms.^[7,23,24] For instance, Light *et al.*^[7] reported that healthy women with depressive symptomatology showed higher cardiac hyperactivity, increased brachial BP, and increased plasma NE to laboratory stressors compared with those with low depression symptomatology. Similarly, we observed higher BP response during SNS stimulation in depressed as compared to healthy adults. Previous studies have shown an association between depressive symptoms and increased SNS activity as well as plasma catecholamine concentration during laboratory stressors.^[7,23,24] The hyperactive CV responses to the CPT in the depressed group could be driven by increased adrenergic stimulation due to altered plasma catecholamines concentration, which may ultimately increase smooth muscle vascular tone. Hines and Brown's (1932) study revealed that subjects could be distinguished into three categories (normals, hyperreactors, and hypertensives) on the basis of baseline and CP responses

in BP. Normals showed the lowest basal and response BP levels, hypertensives the highest, with hyperreactors in between. These results were confirmed by additional studies (Hines and Brown, 1933, 1936, 1939; and Hines, 1940). A number of other investigations (Briggs and Oerting, 1933; Pickering and Kissen, 1936; Ayman and Goldshine, 1938; Yates and Wood, 1936; Shapiro, 1961) confirmed or found results very similar to those obtained by Hines and Brown. There is also reported evidence showing abnormal autonomic nervous system function in depression, specifically regarding increased sympathetic activity and poor vagal control. Several studies have examined cerebrospinal fluid, plasma or urinary levels of NE and its major central nervous system metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG). Devilliers and Cooper found that plasma NE and/or MHPG levels have been reported to be elevated in depressive patients.^[32,33] Our findings correlate with the study of Adamis and Ball, Nakagawara *et al.*, Shinagawa and Hughes, who showed that depressed patients have higher BP levels and it may be due to increased sympathetic activity and poor vagal control.

A potential limitation of our study is that we did not measure HR during the CPT, which has shown good reproducibility in short-term test studies.

CONCLUSION

Our results indicate that depressive symptoms may be associated with cardiac hyperactivity during SNS stimulation, contributing to increased diastolic BP. These findings may have clinical implications for the evaluation of depressive symptoms in healthy, young adult men.

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Table 1: Comparison of the rise of diastolic BP (mm of Hg) before and after cold pressor test between depressed and control groups

Variables	Diastolic BP before test	Diastolic BP after test
	Mean±SD	Mean±SD
Control	82±10.26	90±8.2
Case	84±9.27	98±16.135
P value	0.3	0.009

BP: Blood pressure

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