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A STUDY TO EVALUATE RESPONSE OF COLD PRESSOR TEST IN PATIENTS OF MAJOR DEPRESSIVE DISORDER

Physiology

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ABSTRACT

Background: Major depressive disorder (MDD), simply depression, is a mental disorder characterized by at least two weeks of low mood that is present across most situations. MDD is associated with the development of adverse cardiovascular (CV) outcomes, including hypertension, increased left ventricular mass, coronary artery disease, arrhythmias, stroke, and myocardial infarction. CV reactivity, defined as exaggerated blood pressure and heart rate response to laboratory stressors like mental stress and cold pressor test (CPT), can predict the development of hypertension and coronary artery disease. Depressive symptoms have been shown to be associated with cardiac hyperactivity.

Aims and Objective: The aim of our study was 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 was conducted on 30 new untreated, clinically diagnosed patients of Major depressive disorder (MDD) having no other disease and control group consisting of 30 persons having no psychiatric illness.

Results: BP responses to CPT, in patients of MDD and control was compared. The mean rise in systolic (135±12.31) and diastolic BP (97±15.23) after CPT in patients of MDD was found to be statistically significant compared to mean rise in systolic (130±5.33) and diastolic BP (92±7.62) after CPT in controls.

Conclusion: From our study we conclude that depressive symptoms may be associated with cardiac hyperactivity during sympathetic nervous system (SNS) stimulation, contributing to increased Systolic and diastolic BP. These findings may have implications for the evaluation of depressive symptoms in clinical setting.

KEYWORDS

Sympathetic Nervous System; Major depressive disorder; Cold pressor test; Cardiac hyperactivity.

INTRODUCTION:

Major depressive disorder (MDD), also known simply as depression, is a mental disorder characterized by at least two weeks of low mood that is present across most situations. It is often accompanied by low self-esteem, loss of interest in normally enjoyable activities, low energy, and pain without a clear cause.[1] MDD is associated with the development of adverse cardiovascular (CV) outcomes, including hypertension, increased left ventricular mass, coronary artery disease, arrhythmias, stroke, and myocardial infarction.[2-5] It has long been accepted that there are numerous behavioural and lifestyle factors at play that confers increased cardiovascular disease (CVD) risk in those suffering from depression. Psychological stress experienced by people suffering from MDD can also cause deregulation in the sympathetic nervous system and hypothalamic–pituitary–adrenal (HPA).[6,7] This in turn has a number of deleterious downstream effects, including the development of hypertension, left ventricular hypertrophy[8], coronary vasoconstriction, endothelial dysfunction[9-11], platelet activation, and the production of pro inflammatory cytokines.[12,13] The potential consequence of this is an elevated risk in ventricular arrhythmias and MI.[14,15]

It is well established that there are number of behavioural and lifestyle factors, which are present in MDD patients that can increase the chance of developing CVD.[16] These include increased rates of smoking, alcohol intake, physical inactivity, and obesity.[17]

It has long been known that "stress" and heart disease are linked.[18,19] Stressful events like natural disasters[20] and even high stakes knockout matches, have been positively associated with an increase in acute cardiovascular events.[21] Mental stress is one of the many cognitive symptoms that people with major depression suffer from. Laboratory mental stress tests have been shown to activate sympathetic nervous outflow in the non-cardiac patient setting.[22] The cardiac sympathetic nerves are preferentially activated by such mental stress.[23] In animal models and the clinical setting[14,24], the significance of the activation of cardiac sympathetic cardiac fibres has demonstrated disturbances in heart rhythm, leading to increased risk of ventricular arrhythmias, decreased blood flow[25], left ventricular hypertrophy[8], and MI and sudden death.[11] It has been shown that in depressed CVD patients, there is an elevated resting heart rate, and this also may be due to sympathetic hyperactivity in this group of patients.[26]

CV reactivity, defined as exaggerated blood pressure and heart rate response to laboratory stressors (e.g., mental stress and cold pressor test (CPT]), can predict the development of hypertension and coronary artery disease.[27-29]

Depressive symptoms have been shown to be associated with cardiac hyperactivity. Various 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.[30-32] This is clinically important because subclinical depression, defined as some depressive symptoms without meeting the criteria for MDD[33], may have a deleterious effect on CV autonomic modulation and hemodynamic even in the absence of hypertension.

The cold pressor test (CPT) was developed by Hines and Brown[34] as a means of inducing and measuring cardiovascular reactivity.[35-46] The cold pressor test is regarded as a passive coping stressor that elicits a typical alpha-adrenergic vascular response, namely increased vascular resistance and diastolic pressure.[47-50]

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 somaesthetic 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.[51]

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 response[29], 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[52] and as an experimental pain stimulus[53] as an index for screening subjects for hypertension.[34,54]

The acute hypertensive effects of the CPT are linked to increases in SNS activity, which, in turn, increases vascular tone and, ultimately, afterload.[30,31,55,56] There are inconsistent findings regarding the relationship between CV reactions to active coping tasks such as CPT and symptoms of depression.[57-64] Thus, the present study was undertaken to examine the associations of depression with cardiac autonomic functions to active coping tasks.

MATERIALS AND METHODS

The present comparative case–control study was conducted in the Department of Physiology Government Medical College, Srinagar. 30 fresh untreated patients, clinically diagnosed for MDD criteria having no other disease attending OPD of Psychiatry department of SMHS hospital, Srinagar were selected as cases. After the clinical screening of patient in the psychiatric department they were brought to the physiology department for further evaluation of autonomic function test. Control group consisting of 30 matched subjects having no psychiatric illness. The effect of CPT on BP responses was studied to evaluate cardiac autonomic functions.

Exclusion Criteria: - Patients suffering from diseases like coronary heart disease, electrolyte imbalance, diabetes mellitus, leprosy, anaemia, and pregnancy which are known to affect autonomic functions were excluded from the study.

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. A detailed history was taken and complete physical examination was carried out.

Subjects were asked to take rest in the supine position for 15 min before test. Data collection was conducted in a quiet 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.

The subjects were then asked to place one hand in 10°C water for one minute to evoke SNS stimulation and increased hemodynamics.[30,52] 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 one minute.

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.[52]

Statistical analysis was conducted using SPSS- Version 23. Numerical data are expressed as Mean ± standard deviation. Unpaired t test was used to find the level of significant in rise in Systolic and Diastolic blood pressure after CPT. "P" value < 0.05 was considered to be significant.

RESULTS

In our study we compared the systolic and diastolic BP before and after performing CPT. The mean of systolic and diastolic BP before performing CPT in patients of MDD patients was 123±9.21 mmHg and 88±12.56 mmHg respectively and was found to be statistically not significant compared to controls systolic (121±7.22) and diastolic (82±6.82). BP response in the MDD patients and control was compared for change in BP response to CPT. The mean rise in systolic BP after CPT in MDD patients (135±12.31) was found to be statistically significant compared to controls (130±5.33). Also, the mean rise in diastolic BP after CPT in MDD patients (97±15.23) was found to be statistically significant compared to controls (92±7.62) as shown in table I.

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

	Cases (Mean±SD)	Controls (Mean±SD)	P-Value (<0.05 significant)
Systolic BP before test	123±9.21	121±7.22	0.3531
Diastolic BP before test	88±12.56	82±6.82	0.9883
Systolic BP after test	135±12.31	130±5.33	0.0458
Diastolic BP after test	97±15.23	92±7.62	0.0251

DISCUSSION

This study was conducted to evaluate the acute BP responses to SNS stimulation in patients of MDD and matched healthy Adult controls. The findings of this study are that, during the CPT, subjects with depressive symptoms have higher BP than control subjects.

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 and release of norepinephrine. This sympathetic discharge triggers responses in the cardiovascular (CV) system that include arteriolar constriction, increased HR, and increased cardiac contractility. These responses combine to increase BP. This is known as the pressor response [29] and testing a subject with cold stress in this fashion is known as the cold pressor test. The cold pressor test has been used clinically as a stress test to assess left ventricular function. [65] The test is also used to evaluate cardiac autonomic function [52] and as an experimental pain stimulus. [53]

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 manoeuvre is a simple, non-invasive 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.[53] The test was once suggested as an index for screening subjects for hypertension.[34] CPT has been documented to predict the subsequent risk of hypertension in normotensive persons.[35,36,38,66]

Kessler et al and Niranjan et al in their studies have suggests that MDD is associated with increased CV adverse outcomes even in the absence of hypertension.[2,3] Nemeroff et al and Scuteri et al in their studies have also documented similar findings.[4,5] 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.[30,31,32]

Light et al have also shown an association between depressive symptoms and increased SNS activity as well as plasma catecholamine concentration during laboratory stressors.[30] Other studies have also found similar findings.[31,32] The hyperactive CV responses to the CPT in the MDD patients could be due to increased adrenergic stimulation due to altered plasma catecholamines concentration, which may ultimately increase smooth muscle vascular tone.[51] Deilliers et al and Cooper et al have found that plasma NE and 3-methoxy-4-hydroxyphenylglycol (MHPG) levels have been reported to be elevated in depressive patients.[67,68]

CONCLUSION

From our study we conclude that depressive symptoms may be associated with cardiac hyperactivity during SNS stimulation, contributing to increased Systolic and diastolic BP. These findings may have implications for the evaluation of depressive symptoms in clinical setting.

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