

## Assessment of Cardiac Sympathetic Functions in Type 2 Diabetes Mellitus Patients by Cold Pressor Test

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### Abstract

**Introduction:** Diabetes Mellitus is a well-known chronic metabolic disorder which poses as a major medical health burden in the world and in India as well. In terms of autonomic neuropathy Diabetes is associated with early vagal withdrawal, and enhanced sympathetic tone. The objective of the present study was to assess the cardiac autonomic functions using Cold Pressor test in patients with type 2 Diabetes Mellitus (DM 2) and their subsequent comparison with healthy controls subjects.

**Methods:** The Present study was performed in Department of Physiology, SMS Medical College, Jaipur recruiting 50 patients of type 2 Diabetes Mellitus (Cases) from Department of Medicine, SMS Medical College and 50 Apparently Healthy Age, Sex and BMI matched subjects (age range 35-50 years). Study conducted after obtaining approval from institutional ethics committee of SMS Medical College, Jaipur. Effects of Cold Pressor response on Systolic and Diastolic BP were used for analysis of cardiac sympathetic autonomic function.

**Results:** There was a significant decrease in cold pressor response on systolic and diastolic blood pressure in Diabetic Mellitus group as compared to the apparently healthy control subjects.

**Statistical Analysis:** For statistical analysis of data Unpaired 't' test was applied, where p-value <0.05 considered as statistically significant.

**Conclusions:** Cold pressor test can be used for diagnosing as well as determining severity of cardiac sympathetic autonomic neuropathy in patients of Diabetes Mellitus.

**Keywords:** Cold Pressor test, Systolic Blood Pressure, Diastolic Blood Pressure, Type 2 Diabetes Mellitus (DM 2).

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### Introduction

Type 2 Diabetes Mellitus is a chronic metabolic disorder impacting various complications on patient's health. One of the prominent complications is Diabetic neuropathy which can be polyneuropathy, mononeuropathy and/or autonomic neuropathy. Autonomic neuropathy can involve multiple systems including

cardiovascular, gastrointestinal, genitourinary, motor and endocrine systems [1].

Cardiac autonomic neuropathy (CAN) is common manifestation of Diabetic autonomic neuropathy. The fundamental pathology causing CAN in DM is hyperglycemia [2] and its activation of

redox and/or multiple metabolic (Polyol aldose reductase) pathways because of hyperglycemia induced oxidative stress, alteration of Na<sup>+</sup>/K<sup>+</sup>-ATPase pump function, calcium disturbance and low-grade inflammation [3,4].

This, in conjunction with reduced blood flow to nerve fibers, also contributes towards CAN [5]. Involvement of parasympathetic nervous system occurs early because of long length of vagal fibers and involvement of sympathetic system is late phenomenon [6]. This leads to early vagal withdrawal, enhanced sympathetic tone and subsequently sympathetic denervation and lastly complete autonomic denervation [7,8].

Thus, the advancement of cardiac autonomic neuropathy in Diabetes results in disruption of chief component of cardiovascular regulation, contributing to an elevated incidence of cardiovascular diseases such as heart attack, unexpected cardiac death, and silent ischemia [9-12].

Cold pressor test is a standard test to assess Sympathetic functions and has been used to identify damage to Sympathetic Nervous System in Diabetic patients. [13,14]. In present study, Cold pressor test was used to study autonomic functions in patients of Diabetes Mellitus as there is paucity of literature regarding its use in patients of Diabetes Mellitus.

### Material and Methods

The present study is a cross-sectional, comparative type of observational study. The study was conducted after obtaining approval from institutional scientific and ethics committee. The study was conducted in Department of Physiology, SMS Medical College, Jaipur, recruiting 50 patients of type 2 Diabetes Mellitus in the age range of 35-50 years with duration of disease of more than 2 years (Cases) from Department of Medicine, SMS Medical College, Jaipur and 50 apparently healthy age, sex and BMI matched subjects as controls. Individuals suffering

from any acute or chronic illness other than Diabetes Mellitus were excluded from the study. Alcoholic, Smokers and persons taking drugs affecting cardiac autonomic functions were also excluded from the study. Prior to the examination all the subjects were asked to refrain from heavy physical activity for 24 hours and from consumption of alcohol and caffeinated beverages for 12 hours. The temperature of the laboratory was kept at normal room temperature (between 25-28°C). The subjects were asked to void urine and sit comfortably to accustom the new environment. After obtaining informed consent, detailed clinical history recorded and examination was done including measurement of anthropometric parameters such as height, weight. BMI was calculated as per formulae-Weight (Kg)/Height(m<sup>2</sup>). Then the procedure of cold pressor test explained to the subjects to alleviate test anxiety. After rest for 10 minutes resting heart rate and blood pressure was recorded using automated blood pressure monitor in sitting position.

### Experimental protocol-Cold pressor test:

The baseline blood pressure was recorded. The subjects were instructed to immerse the right hand in the cold water (4 °C) for 1 minute up-to the wrist (15). The temperature of water was constantly measured throughout the process with the help of thermometer. Systolic blood pressure and diastolic blood pressure were recorded at the end of 1 min and at the end of 3 min in another arm with the help of a digital sphygmomanometer (OMRON HEM-8712, Taiwan). The rise in the systolic and diastolic pressure at the end of 1 minute and 3 minutes over baseline value was noted.

### Statistical analysis:

The testing of null hypothesis for difference of population means, at 0.05 level of significance is conducted using test statistic that follow unpaired student's 't' test. p-value <0.05 was considered as

statistically significant. Primer software version 6.0 is used for analysis of data.

### Results:

The results of the study are summarized in Table 1 to Table 4. Both cases and controls were Age, Sex and BMI matched. No significant differences exist between resting cardiovascular parameters between

both the groups whereas significant differences in systolic blood pressure at 1 minute and diastolic blood pressure at 1 and 3 minutes after start of cold pressor test between cases and controls were present. The mean duration of Diabetes Mellitus in study was  $7.6 \pm 2.4$  years with majority of cases have duration of disease more than 5 years.

**Table 1: Demographic parameters of study population**

S.N.	Parameter	Diabetes Mellitus patients (cases) Mean $\pm$ SD	Healthy controls Mean $\pm$ SD
1	Age (Years)	$44.76 \pm 5.09$	$44.90 \pm 5.20$
2	Gender (M: F Ratio)	4:1	3.7:1.3
3	Height(m)	$1.63 \pm 0.08$	$1.62 \pm 0.09$
4	Weight(kg)	$72.88 \pm 12.01$	$71.64 \pm 13.08$
5	BMI (kg/m <sup>2</sup> )	$27.44 \pm 4.77$	$27.47 \pm 5.86$
6	Duration of Disease (years)	$7.6 \pm 2.4$ years	

\* Significant

**Table 2: Cardio Vascular Parameters of study population**

S.N.	Parameter	Diabetes Mellitus patients (cases) Mean $\pm$ SD	Healthy controls Mean $\pm$ SD
1	Resting Systolic blood pressure (mmHg)	$115.04 \pm 9.04$	$114.56 \pm 10.86$
2	Resting Diastolic blood pressure (mmHg)	$73.00 \pm 7.35$	$73.24 \pm 8.65$
3	Resting Heart rate (Beats per minute)	$77.52 \pm 6.39$	$80.78 \pm 9.85$

\* Significant

**Table 3: Effect of cold pressor test on systolic and diastolic blood pressure**

S. N.	Parameter	Diabetes Mellitus patients (cases) Mean $\pm$ SD	Healthy controls Mean $\pm$ SD
1	Systolic blood pressure at 1 minute (mmHg)	$120.52 \pm 8.52$	$125.64 \pm 10.72^*$
2	Diastolic blood pressure at 1 minute (mmHg)	$78.32 \pm 7.22$	$86.32 \pm 7.48^*$
3	Systolic blood pressure at 3 minutes (mmHg)	$121.84 \pm 8.66$	$125.64 \pm 10.72$
4	Diastolic blood pressure at 3 minutes (mmHg)	$79.00 \pm 7.02$	$84.08 \pm 7.24^*$

\* Significant

**Table 4: Distribution of patients as per duration of disease**

Duration of Disease (Years)	No. of patients
$\geq 2$ to $< 5$ years	07
$\geq 5$ years to $< 8$ years	20
$\geq 8$ years to $< 10$ years	13
$\geq 10$ years	10

## Discussion

The cold pressor test (CPT), which measures the response of the blood pressure after the stimulus of external cold, has long been a standard test for characterization of sympathetic function of heart [16]. The CPT is well known to cause a global activation of the sympathetic system and result in significant arteriolar vasoconstriction, with a subsequent increase in blood pressure [17].

In the present study there was no significant difference in resting systolic and diastolic blood pressure before start of cold pressor test. After providing cold stimulus with cold pressor test there was significant difference in systolic blood pressure at 1 minute and diastolic blood pressure at 1 and 3 minutes of test between cases and controls. So, it is evident that there was a significant decrease in cold pressor response on systolic and diastolic blood pressure in Diabetic group as compared to healthy controls.

The results were similar to study done by Luft.D et al.,1996 which observed a significant decrease in cold pressor response on systolic and diastolic pressure at end of 1 minute in type 1 Diabetes Mellitus patients with mean duration of disease of more than 12 years than control group [18]. Our results were also similar to study done by Krishna BH et al ., They conducted their study on 30 type 2 Diabetes Mellitus and observed a blunted blood pressor response during cold pressor test [19]. The mean duration of the Diabetes in this study was more than 7 years.

Similar results were also observed in study done by Sinha S et al., 2017 on rural population of type 2 Diabetic Mellitus patients. Significant decrease in cold pressor response on systolic and diastolic pressure was observed in their study [20]. The results of our study were contrary to findings of Bashir.M et al., (2018) They

found a significant increase in cold pressor response on systolic and diastolic pressure in young type 1 Diabetes Mellitus patients on comparison with healthy controls [15].

Attenuated cold pressor response on changes in blood pressure suggests a sympathetic dysfunction in patients whereas exaggerated cold pressor response can be due to parasympathetic dysfunction with compensatory sympathetic predominance. Impaired parasympathetic functions was observed in patients of Diabetes Mellitus with less duration of disease [15] whereas impaired sympathetic function was observed in studies done on Diabetic patients with more duration of disease (more than 5 years) [18-20].

In our study, the mean duration of Diabetes is more ( $7.6 \pm 2.4$  years) and an attenuated blood pressure response to cold stress in patients of Diabetes Mellitus indicate towards impairment of sympathetic nervous system activity on provocative cold stimuli. This can be explained as in Diabetic cardiac autonomic neuropathy there is impairment of parasympathetic function in early stages of Diabetes resulting in increased sympathetic reactivity followed by sympathetic function impairment with progression of disease [6]. Thus, the results of cold pressor test for assessment of cardiac autonomic functions in patients of Diabetes Mellitus depends on severity of autonomic neuropathy.

## Conclusion

Cold pressor test can be used for diagnosing as well as determining severity of autonomic neuropathy in patients of Diabetes Mellitus.

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