

SYMPATHETIC FUNCTION TESTS IN BETA THALASSEMIA MAJOR PATIENTS

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ABSTRACT: Introduction and Objectives: Thalassemia is one of the most common genetic disorders that have to be treated with repeated blood transfusions which lead to many complications such as iron overload cardiomyopathy. This study was designed to evaluate early cardiovascular dysfunction in Beta thalassemia major patients by assessing sympathetic activity between study group and control group. **Material and Methods:** Present study was a cross sectional type of study and consisted of 50 normal subjects (control group) and 50 patients of beta thalassemia major (study group). Two sympathetic function tests, Cold Pressor Test (CPT) and Sustained Handgrip Test (SHG) were included in the study. After the recording of data statistical analysis of observations was done using Z test. **Results :** There was a difference in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) after cold pressor test in study group compared to control group and the difference was statistically significant. There were reduced changes in SBP in study group as compared to control group and the difference was found to be statistically significant whereas there was no statistically significant (p value >0.05) difference in changes in DBP of study group and control group.

Conclusion: Decreased cold pressor and sustained hand grip response in study group shows impaired sympathetic activity suggesting sympathetic dysfunction in the study group.

Key words: Beta thalassemia major, Cold Pressor test, Sustained Handgrip test

Abbreviations: CPT, Cold Pressor Test; DBP, Diastolic Blood Pressure; SBP, Systolic Blood Pressure; SHG, Sustained Handgrip Test

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INTRODUCTION

Beta thalassemia is the commonest single-gene disorder in the Indian population¹. Beta thalassemia major patients may need to have repeated blood transfusions throughout their life for survival, which leads to so many complications. These relate to inadequate transfusions, transfusion-related infections, sensitization, iron-overload related cardiac, endocrine and liver disturbances and toxicities of iron chelators². A few studies have documented initial cardiovascular dysfunction even in thalassemia major patients without clinical manifestation of heart failure^{3,4}.

Cardiovascular Autonomic reactivity refers to cardiovascular responses to potential stimuli, which are essentially reflexive in nature indicating cardiovascular tolerance and adaptation^{5,6}. In their study of Subclinical autonomic dysfunction in patients with beta-thalassemia, Elefterios et al⁷ evaluated the autonomic function (AF) in a consecutive series of patients with beta-thalassemia and in normal individuals. They concluded that Subclinical autonomic dysfunction

appeared to be more prevalent in beta-thalassemia patients compared to controls.

The cold pressor test (CPT) devised by Hines and Brown⁸ involves exposure of the individual to cold as a stressful stimulus. The reaction of the individual to this is measured by the change in his systolic and diastolic blood pressures after the exposure to cold stress.

The cardiovascular response to acute sympathetic stress was assessed by Sustained Hand Grip test (SHG), which evaluates the cardiovascular adrenergic function and is recommended as an investigational autonomic function test by the American Academy of Neurology⁹. The isometric hand grip exercise activates the mechanoreceptors immediately due to the increased muscle tension. The recruitment of new motor units to maintain the muscle tension, increases the excitatory state of the central nervous system and results in a possible increase in the sympathetic outflow and a decrease in parasympathetic outflow, which explain the increase in the blood pressure response¹⁰.

Present study was designed to compare the response of sympathetic nervous system to

various stressor stimuli between study group and control group.

MATERIALS AND METHODS

The present study was a cross sectional type of study conducted in the Department of Physiology and Department of Paediatric Medicine, Grant Government Medical College, Mumbai and in the Thalassemia unit of St. George Hospital, Mumbai. Before commencement of the project, approval was taken from the Institutional Ethical Committee.

The study design involved 100 individuals who were divided into two groups of 50 normal subjects (control group) and 50 patients of beta thalassemia major (study group) receiving regular blood transfusions between the age group of 8 to 20 years involving both, males and females. Patients with concomitant sickle cell anaemia or with associated congenital or acquired heart disease, diabetes mellitus, thyroid disorders or any other endocrine disorder or on long term medications for any other chronic disease were excluded from the study. Written informed consent was taken before the clinical examination of the subject.

The subjects were asked to refrain from ingesting any beverages containing caffeine and alcohol for at least 12 hours prior to the study. They were asked to report between 10a.m-12p.m. in the lab after an adequate night's sleep followed by light breakfast.

Sympathetic function test

1. Blood pressure response to cold pressor test :

The subject was asked to sit comfortably in a chair and the baseline blood pressure was recorded. Then subject was asked to immerse his hand in cold water maintained at 10⁰ C for 1 – 2 minutes; blood pressure was recorded from the other arm at the end of 2 minute. After 2 minute the subject was allowed to remove the hand from cold water. Then maximum increase in systolic and diastolic blood pressure was determined and compared with normal subjects.

2. Blood pressure response to sustained hand grip :

The subject was asked to sit comfortably in chair. Initially the subject was asked to exert maximal hand grip strength on hand grip dynamometer, with dominant hand. First the maximum voluntary contraction (MVC) (Maximal isometric tension i.e. T max) is determined and then the subject was

asked to exert 30 % of MVC for 3 minutes with dominant hand. The Blood pressure was measured in the non-exercising hand at rest and just before the release of hand grip pressure.

Statistical analysis of the observations was carried out using Z test.

RESULTS

The mean Body mass index (BMI) was 17.01±3.21 and 18.05±3.74 kg/m² in the study and control group respectively.

Table no. 1 : Comparison of SBP and DBP after CPT of subjects & Statistical analysis using 'Z' test

	Study group	Control group	P VALUE	Significance
	MEAN±S.D	MEAN±S.D		
SBP(mmHg)	105.84±7.24	110.68±8.62	0.003	Statistically significant
DBP(mmHg)	60.28±10.8	71.88±6.9	<0.0001	Statistically significant

(SBP – Systolic blood pressure, DBP – Diastolic blood pressure, CPT - Cold pressor test)

Table no. 2 : Comparison of Changes in SBP and DBP after CPT of subjects & Statistical analysis using 'Z' test

	Study group	Control group	P VALUE	Significance
	MEAN±S.D	MEAN±S.D		
ΔSBP (mmHg)	4.84±4.79	7.88±4.37	0.0013	Statistically significant
ΔDBP (mmHg)	2.56±5.81	2.24±3.71	0.7437	Not significant

There was a difference in SBP and DBP after cold pressor test in study group compared to control group and the difference was statistically significant. There were reduced changes in SBP in study group as compared to control group and the difference was found to be statistically significant whereas there was no statistically significant difference in changes in DBP of study group and control group.

Table no. 3 : Comparison of SBP and DBP after SHG of subjects

	Study group	Control group	P VALUE	Significance
	MEAN±S.D	MEAN±S.D		
SBP(mmHg)	114.84±7.98	124.04±9.45	<0.0001	Statistically significant

DBP(mmHg)	71.2±10.38	82.64±7.11	<0.0001	Statistically significant
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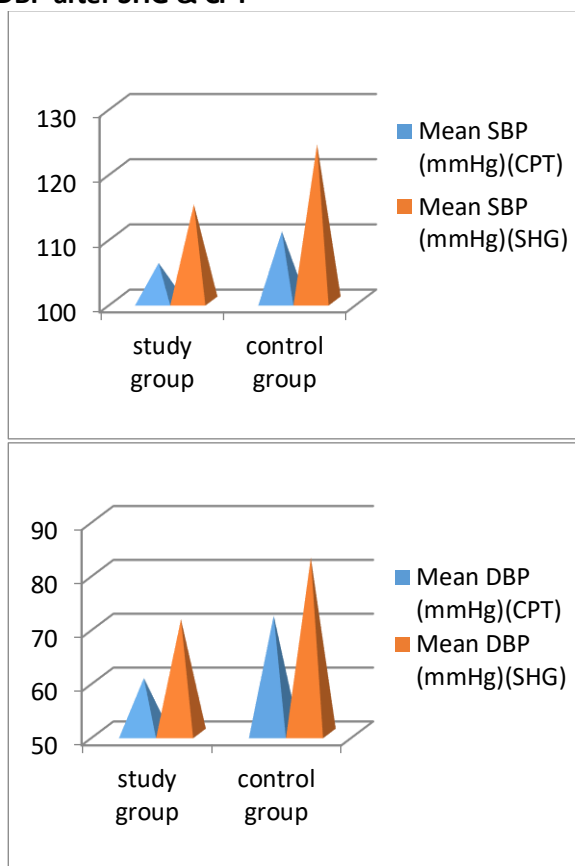
(SHG – Sustained Hand Grip)

Table no. 4 : Comparison of Changes in SBP and DBP after SHG of subjects

	Study group	Control group	P VALUE	Significance
	MEAN±S.D	MEAN±S.D		
ΔSBP(mmHg)	13.44±5.04	21.24±7	<0.0001	Statistically significant
ΔDBP(mmHg)	13.48±8.06	13±5.40	0.7276	Not significant

There was a difference in SBP and DBP after sustained hand-grip test in study group compared to control group and the difference was statistically significant. There were reduced changes in SBP in study group as compared to control group and the difference was found to be statistically significant whereas there was no statistically significant difference in changes in DBP of study group and control group.

Figure 1 & 2 : Comparison of changes in SBP & DBP after SHG & CPT



DISCUSSION

CPT is a widely used experimental technique for pain or stress induction¹¹ to assess the left ventricular function¹². and to evaluate cardiac autonomic functions¹³. CPT is known to trigger a vascular sympathetic activation and an increase in blood pressure in healthy subjects.

In present study pre and post-test SBP in study group was 101.4±7.16 and 105.84±7.24 and in control group was 102.8±8.8 and 110.68±8.62 mmHg respectively. Similarly pre and post-test DBP in study group was 57.72±9.54 and 60.28±10.8 and in control group was 69.64±6.23 and 71.88±6.9 mmHg respectively. (Table no. 1 and 2) So there was increase in SBP and DBP in study group as well as in control group after CPT. But this rise in BP was relatively less in study group as compared to control group and this difference was statistically significant.(Table No. 1 & 2) Thus there was a reduced response to cold stress in study group. This may be because of sympathetic dysfunction.

It has been postulated that the pressure response to the isometric exercise is reflex in origin, which serves to increase the perfusion pressure to the active muscles, in which the blood flow is impeded by the sustained muscular contraction¹⁴. The blood pressure rise is mediated partly by a heart rate-dependent increase in cardiac output¹⁵, and partly by peripheral vasoconstriction mediated via the α -adrenergic receptors of the peripheral autonomic nervous system¹⁶. Any damage to the neurological pathways involved could lead to a diminished or absent cardiovascular response to sustained handgrip¹⁷.

In the present study pre and post-test SBP in study group was 101.4±7.16 and 114.84±7.98 and in control group was 102.8±8.8 and 124.04±9.45 mmHg respectively. Similarly pre and post-test DBP in study group was 57.72±9.54 and 71.2±10.38 and in control group was 69.64±6.23 and 82.64±7.11 mmHg respectively. (Table no. 3 & 4) Thus there was an increase in SBP and DBP in study group as well as control group but this increase was relatively less in study group as compared to control group and the difference was statistically significant.(Table No. 3 & 4) This is in accordance with study done by Nazeema Khatoun et al who has shown that in control subjects during sustained hand grip, a sharp rise in blood pressure of more than 15mmHg occurred,

however in diabetics with autonomic damage the rise in blood pressure is abnormally small¹⁸. Ziegler et al. measured plasma norepinephrine levels in response to SHG. Plasma levels of norepinephrine rose significantly in normal subjects but failed to increase in patients with central or peripheral autonomic failure¹⁹.

Thus it can be concluded that there is probably a sympathetic dysfunction in patients of thalassemia major. This could be due to chronic anaemia which may lead to a persistent sustained decrease in autonomic fluctuations as shown by Franzoni et al²⁰. This could also be because of iron overload. Iron overload causes alterations in a spectrum of cardiovascular functions, such as an endothelial impairment, alteration in oxidative stress and a proatherogenic and prothrombotic effect²¹. The alterations might also include an activation of the sympathetic cardiovascular drive, because in experimental animals iron is involved in the modulation of central nervous system receptors for dopamine that is a precursor of the adrenergic neurotransmitter norepinephrine^{22,23}.

Iron is an essential element that forms an important component of metabolic and biological processes, but when present in excess, it can produce tissue damage due to oxidative stress²⁴. Studies have shown that oxidative stress reaction can directly and functionally interact with sympathetic neurons through alterations in ion channels function and nitric oxide crowding^{25,21}. Furthermore, nitric oxide has been shown to affect central sympathetic transmission both directly and indirectly, i.e. via a vasodilatory - induced reflex activation²¹.

CONCLUSION

Decreased cold pressor and sustained hand grip response in study group shows impaired sympathetic activity in beta thalassemia major patients which may be due to chronic anemia and iron overload induced oxidative stress due to repeated blood transfusion.

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Conflict of Interest: None