NJPPP National Journal of Physiology, Pharmacy & Pharmacology

DOI: 10.5455/njppp.2015.5.160820141
http://www.njppp.com/

RESEARCH ARTICLE

CLASSICAL AUTONOMIC FUNCTION TESTS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND HEALTHY VOLUNTEERS: A COMPARATIVE STUDY

Mohan Jayabal[1], Dinesh Thangavel[1], Uma Maheswari Thiyagarajan[2], Nagashree Ramasamy[2], Venkatesan Rangan[1], Venkidusamy Subramaniyam[1]

[1] Department of Physiology, Dhanalakshmi Srinivasan Medical College & Hospital, Perambalur, Tamil Nadu, India
[2] Department of Physiology, PSG Institute of Medical Sciences & Research, Coimbatore, Tamil Nadu, India

Correspondence
Mohan Jayabal
(jmohan1@hotmail.com)

Received
01.08.2014
Accepted
16.08.2014

Key Words
Classical Autonomic Function Tests; Type 2 Diabetes Mellitus; Healthy Volunteers; Comparative Study

Background: The incidence of autonomic dysfunction has increased in the presence of type 2 diabetes mellitus and various tools have been developed for assessing it. Classical autonomic function tests are one among them.
Aims & Objectives: To compare the classical autonomic function tests in patients with type 2 diabetes mellitus and healthy volunteers.
Materials and Methods: This study was conducted at the PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India, on 30 patients with type 2 diabetes mellitus (cases) and 30 healthy volunteers (controls). Average age of the patients with diabetes mellitus was 48.53 ± 5.12 years (mean ± SD) and that of the volunteers was 47.10 ± 3.59 years (mean ± SD). After obtaining informed, written consent, cardiorespiratory parameters such as resting heart rate (HR), systolic blood pressure, and diastolic blood pressure were measured after 10 min of supine rest. Autonomic function parameters such as HR and blood pressure response to handgrip, deep breathing difference test, and Valsalva ratio were recorded in them.
Results: Statistical analysis was carried out using independent Student's *t*-test, which showed a statistically significant impairment in HR response to handgrip ($P < 0.001$), blood pressure response to handgrip ($P < 0.001$), deep breathing test ($P < 0.001$), and Valsalva ratio ($P < 0.001$).
Conclusion: Results of this study showed that significant impairment was present in patients with type 2 diabetes than in healthy volunteers, and it was more pronounced for parasympathetic system than for sympathetic system.

INTRODUCTION

Type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus or adult-onset diabetes) is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency.[1] The incidence is increasing rapidly and by 2030 it would be doubled.[2]

Autonomic nervous system (ANS) innervates almost all organ systems and is primarily involved with homeostatic regulatory mechanisms.[3] The important functions of ANS are maintenance of homeostatic conditions of the body; regulation of visceral activities; smoothening body's responses to environmental changes, stress, and exercise; and assisting endocrine system to regulate various functions.[4]

Nerve dysfunction or neuropathy associated with diabetes mellitus (DM) is called diabetic neuropathy. Autonomic neuropathy due to DM involves various systems, such as gastrointestinal, cardiovascular, sudomotor, genitourinary, and metabolic systems. Cardiac autonomic neuropathy results from injury to the autonomic nerve fibers that innervate the heart and blood vessels, which in turn results in altered heart rate (HR) control and vascular dynamics.[5]

The cardiovascular autonomic function tests (CAFTs), totally a noninvasive tool, have been scientifically well validated as evidenced by various clinical trials for assessing baroreceptor reflex. With the help of classical AFTs, subjects who are at risk of cardiac complications are found out and early intervention can be done to prevent morbidity and mortality due to DM.[6]

The noninvasive CAFTs include HR and blood pressure (BP) response to standing, deep breathing, and isometric handgrip.[7,8] In view of these facts, this study was aimed to compare the classical AFTs in patients with type 2 DM and healthy volunteers.

MATERIALS AND METHODS

This study was conducted on 30 patients with type 2 DM and 30 healthy volunteers who were motivated and recruited from the OPD of the PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India. Subjects receiving medication for any other chronic ailment, known cardiac or hypertensive patients, smokers, and alcoholics were excluded from the study. The purpose of the study, procedure, and benefits were explained in detail to the participants and informed written consent was obtained from those willing. Average age of the patients with DM was 48.53 ± 5.12 years (mean ± SD) and that of volunteers was 47.10 ± 3.59 years (mean ± SD).

Parameters: Basal physiological parameters such as HR, systolic blood pressure, and diastolic blood pressure (DBP) were recorded after 10 min of supine rest using digital BP monitor (CH 432B; Citizen, Japan). Classical AFT parameters such as HR and BP response to isometric handgrip and deep breathing, and Valsalva ratio were recorded by explaining the procedure.

Handgrip dynamometer: HR and BP responses to isometric handgrip were recorded using handgrip dynamometer. After 5 min of rest, the subjects were asked to grip the handgrip dynamometer as maximally as possible with the dominant hand, and the reading was noted. The subjects were instructed to grasp a dynamometer and sustain a fixed, isometric contraction for 3 min at 30% of maximum effort. The BP was recorded just before releasing the grip.

Deep breathing test: HR was calculated from ECG recording. Lead II ECG recording was done in supine resting position for 5 min. Respiration probe was tied at the level of fourth intercostals space, and the subject was instructed to breathe slowly and deeply. The subjects were asked to inspire deeply for 5 s and expire maximally for 5 s for 6 cycles. The ratio of shortest respiratory rate (RR) interval (fastest HR) in inspiration to longest RR interval (slowest HR) in expiration was calculated for each subject, which is called as expiration/inspiration ratio (E/I ratio).

Valsalva ratio: The subjects were asked to forcefully exhale against a closed glottis into a tube connected to the sphygmomanometer and sustain the pressure at 40 mmHg for 15 s and Lead II ECG was recorded. Valsalva ratio, which is the ratio of the longest RR interval in phase 4 to the shortest interval in phase 2, was calculated.

Ethics: The study was conducted after obtaining clearance from the Institute Ethics Committee for human studies and caries less than minimal risks.

Statistical analysis: Data for all parameters were collected per the study protocol and were entered in Microsoft Office Excel database. Data were analyzed using Student's *t*-test and Mann–Whitney *U*-test according to the normality of the distribution of data for cross-sectional comparison of two groups. Statistical analyses were done at 5% level of significance and $P < 0.05$ was considered as statistically significant.

RESULTS

Average age of the patients with DM was 48.53 ± 5.12 years (mean ± SD) and that of volunteers was 47.10 ± 3.59 years (mean ± SD).

Diastolic blood pressure rise after handgrip between cases and controls: The mean rise in DBP after handgrip in cases was 3.20 ± 1.54 mmHg and that for controls was 10.13 ± 1.89 mmHg. There was a significant rise in DBP after handgrip in controls when compared to that of cases, and the *P*-value was <0.001, which is statistically significant.

Heart rate rise after handgrip between cases and controls: The mean rise in HR after handgrip in cases was 6.47 ± 2.27 beats/min and that for controls was 11.00 ± 2.45 beats/min. There was a significant rise in HR after handgrip in controls than in cases as the *P*-value was <0.001.

Deep breathing difference in cases and controls: The mean deep breathing difference in cases was 1.099 ± 0.05 and that for controls was 1.255 ± 0.11. There was a significant difference in E/I ratio between cases and controls as the *P*-value was <0.001.

Valsalva ratio between cases and controls: The mean Valsalva ratio in cases was 1.20 ± 0.12 and for controls was 1.40 ± 0.05. There was a significant difference in Valsalva ratio between cases and controls as the *P*-value was <0.001.

Table 1: Comparison of basal physiological parameters between the cases and controls

Parameters	Cases (*n* = 30)	Controls (*n* = 30)
HR (beats/min)	77.16 ± 10.9	75.56 ± 8.79
SBP (mmHg)	114.53 ± 10.31	112.23 ± 10.64
DBP (mmHg)	72.78 ± 7.13	73.77 ± 9.34
RR (beats/min)	17.42 ± 1.12	18.13 ± 1.61

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory rate. Values are expressed as mean ± SD. Analysis done by Student's unpaired t-test.

Table 2: Comparison of autonomic function parameters among the study participants

Parameter	Group	Mean ± SD	p-Value
DBP rise after handgrip	Cases	3.20 ± 1.54	< 0.001*
	Controls	10.13 ± 1.89	
Heart rate rise after handgrip	Cases	6.47 ± 2.27	< 0.001*
	Controls	11.00 ± 2.45	
E/I ratio	Cases	1.099 ± 0.05	< 0.001*
	Controls	1.255 ± 0.11	
Valsalva ratio	Cases	1.20 ± 0.12	< 0.001*
	Controls	1.40 ± 0.05	

*DBP, diastolic blood pressure; E/I, expiration/inspiration ratio. Values are expressed as mean ± SD. Analysis done by Student's unpaired t-test. * Statistically significant.*

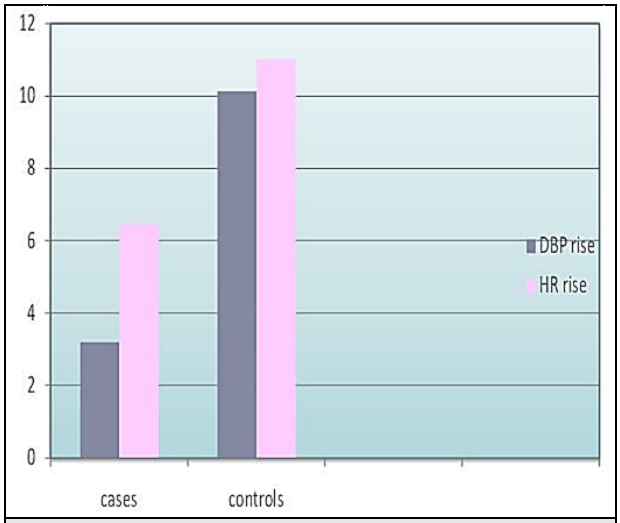

Figure 1: DBP, HR rise after hand grip between cases and control

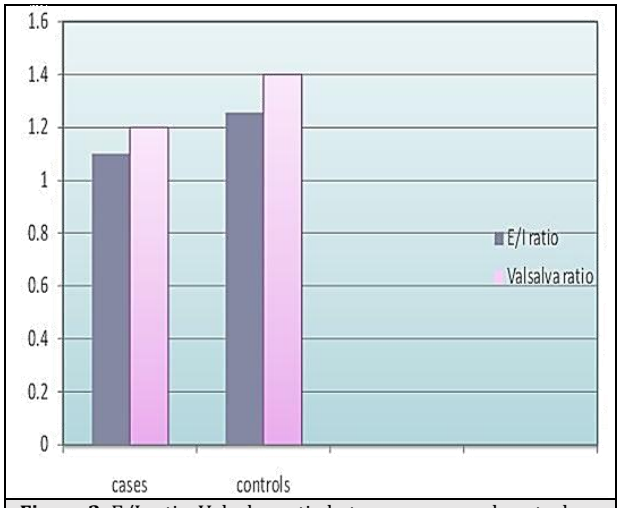

Figure 2: E/I ratio, Valsalva ratio between cases and control

DISCUSSION

Type 2 DM is typically a metabolic disorder associated with a 10-year-shorter life expectancy.[9] Pathogenic pathways responsible for autonomic neuropathy in DM are production of advanced glycation end products, increased oxidative stress with increased free radical production, activation of the polyol and protein kinase C pathways, activation of poly-ADP-ribosylation, and activation of genes involved in neuronal damage. Imbalance in the free radical mechanism also contributes to the pathogenesis of autonomic dysfunction in DM.[10,11]

Vagus nerve controls most part of parasympathetic activity. Nerve impairment is first seen in long fibers. Hence, parasympathetic nerve impairment is the first and foremost manifestations of autonomic neuropathy in DM. Sympathetic nerve impairment follow later, which starts at the apex of the ventricles and proceeds toward the base.[12]

In our study, patients with DM were found to have both sympathetic and parasympathetic dysfunctions. DBP rise after handgrip dynamometer test in cases showed minimal rise in BP (3.20 ± 1.54 mmHg) compared to controls (10.13 ± 1.89 mmHg) who showed a defect in the efferent sympathetic vasomotor tone. This is similar to a study done by consensus committee of the American Autonomic Society.[13]

Deep breathing test that is specific for parasympathetic activity found out that E/I ratio is less in cases than that in controls. Hence, in patients with DM the parasympathetic impairment is significant. This finding is similar to a study done by Sundkvist et al.[14]

Valsalva ratio was less in cases than in controls. It is more sensitive test for both sympathetic and parasympathetic activities. Our study showed impairment of autonomic system in which parasympathetic impairment was more than sympathetic impairment. Our finding correlated with other studies.[15,16]

Our study gives a solid evidence of impairment of cardiac autonomic activity with dysfunction of both sympathetic and parasympathetic systems with slightly more impairment of parasympathetic system.

CONCLUSION

We conclude that the results of this study confirm the presence of autonomic dysfunction in patients with type 2 DM and classical AFTs can be used as a

validated tool for assessing it. A more detailed study involving more number of patients with DM is warranted to come to a definite conclusion.

ACKNOWLEDGMENT

We thank the management of the PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, and Dhanalakshmi Srinivasan Medical College and Hospital, Perambalur, Tamil Nadu, and colleagues who helped us to carry out this project.

REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047–53.
2. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J (Eds.). Diabetes mellitus. In: Harrison's Principles of Internal Medicine, 18th edn. New York: McGraw-Hill Professional. 2012. pp. 2968–3002.
3. Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. Williams Textbook of Endocrinology, 12th edn. Philadelphia, PA: Elsevier/Saunders. pp. 1371–1435.
4. Pal GK, Pravati Pal, Nanda N. Autonomic nervous system: Functional organization. In: Textbook of Medical Physiology, 2nd edn. New Delhi: Ahuja Publishing House, 2011. pp. 201–208.
5. Pop-Busui R, Kirkwood I, Schmid H, Marinescu V, Schroeder J, Larkin D, et al. Sympathetic dysfunction in type 1 diabetes: Association with impaired myocardial blood flow reserve and diastolic dysfunction. J Am Coll Cardiol. 2004;44:2368–74.
6. Ewing DJ, Martin CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care. 1985;8:491–2.
7. Malliani A, Montano N. Autonomic balance. In: Dynamic Electrocardiography, 1st edn. New York: Futura-Blackwell, 2004. p. 48. http://dx.doi.org/10.1002/9780470987483.ch6.
8. Mathias CJ, Bradley WG, Daroff RB, Fenichel GM, Janokovic J (Eds.). Disorders of the autonomic nervous system: Autonomic dysfunction in paediatric practice. In: Neurology in Clinical Practice, 4th edn. Philadelphia, PA: Butterworth-Heinemann, 2004. p. 2406.
9. Ganong WF. Cardiovascular regulatory mechanisms. In: Review of Medical Physiology, 22nd edn. San Francisco, CA: McGraw-Hill, 2005. pp. 597–602.
10. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetic Care. 2003;26:1553–79.
11. Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. Q J Med. 1980;49:95–108.
12. Steven M, Raffel D, Allman KC, Dayanikli F, Ficaro E, Standford T, et al. Cardiac sympathetic dysinnervation in diabetes implications for enhanced cardiovascular risk. Circulation. 1998;98:961–8.
13. Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. Neurology. 1996;46:1470.
14. Sundkvist G, Lilja B, Almer LO. Deep breathing, Valsalva, and tilt table tests in diabetics with and without symptoms of autonomic neuropathy. Acta Med Scand. 1982:211(5):369–73.
15. Smith SA. Diagnostic value of the Valsalva ratio reduction in diabetic autonomic neuropathy: Use of an age-related normal range. Diabet Med. 1984;1;295–7.
16. Pfeifer MA, Cook D, Brodsky J, Tice D, Reenan A, Tice D, et al. Quantitative evaluation of cardiac parasympathetic activity in normal and diabetic man. Diabetes. 1982;31:339–45.

Cite this article as: Jayabal M, Thangavel D, Thiyagarajan UM, Ramasamy N, Rangan V, Subramaniyam V. Classical autonomic function tests in patients with type 2 diabetes mellitus and healthy volunteers: A comparative study. Natl J Physiol Pharm Pharmacol 2015;5:68-71.
Source of Support: Nil
Conflict of interest: None declared