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Physiology

A Comparative Study of Cardiac Autonomic Function Indices among Young and Old Healthy Individuals of Western Rajasthan by Can*W*in

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Abstract: Ageing in humans is characterized by alterations in the integrative regulation by the cardiovascular and autonomic nervous system (ANS) systems. Proper function of the ANS is achieved through a balance of parasympathetic and sympathetic out flow from the brain and this balance is shifted with advancing age towards decreased parasympathetic function and increased sympathetic discharge to the heart, vasculature and other organs. To observe the influence of aging process on autonomic nerve functions the non- invasive autonomic function tests were carried out by CAN *W*in Analysis System in 125 healthy subjects between the age group of 20 to 70 years and divided into five groups, each comprises of 25 subjects. The Parasympathetic activity was assessed by heart rate response to deep breathing (DB),30:15 ratio and valsalva maneuver(VM) and with age results of parasympathetic tests, revealed a significant linear decline in value .Assessment of sympathetic activity by blood pressure response to standing test revealed that there is linear increase in Systolic blood pressure (SBP) and blood pressure response to sustained handgrip exercise revealed a significant decline in Diastolic Blood Pressure (DBP) with age.No gender variation in both sympathetic and parasympathetic function test was observed. From this study it may concluded that ageing process substantially impaired cardiovascular autonomic nerve functions.Autonomic status will have an important bearing on determining the therapeutic strategy and drug action in the elderly in whom there may be altered responsiveness to autonomic reflexes and receptor sensitivity.

Keywords: Autonomic nervous system (ANS), CAN *W*in analysis system (Window based), Deep breathing (DB), 30:15 ratio, Valsalva maneuver, Systolic blood pressure (SBP), Diastolic blood pressure (DBP).

INTRODUCTION

The autonomic nervous system (ANS) is one of the main divisions of the nervous system. It is responsible for the regulation of visceral functions and maintenance of homeostasis of the internal milieu [1-3]. The portion of the ANS which influences the heart (cardiac autonomic nervous system) consists of a complex network of pre-ganglionic and postganglionic sympathetic and parasympathetic fibres that synapse on extrinsic and intrinsic cardiac ganglia and ultimately directly innervate cardiac myocytes [4].

The ANS is of vital importance in daily life. Its regulatory action occurs without involvement of one’s consciousness i.e. autonomously. The decline in various functions continues slowly and eventually become considerable and functionally significant as age advances. Thus physiologically, ageing refers to an impaired ability to maintain homeostasis in the face of external and/or internal challenges or stresses. As a result an individual becomes more vulnerable to these challenges and stresses and may finally succumb to one of these [3]. Both parasympathetic and sympathetic nervous system which constitute the autonomic nervous system (ANS) are affected by ageing. The two limbs sympathetic and parasympathetic and sudomotor functions of autonomic nervous system mature with time but degree of the changes due to ageing are different because of their divergent neural pathways.In old age parasympathetic involvement appears to be more frequent than sympathetic. The examination of cardiovascular tests can provide important information about appropriate function of autonomic nervous system (ANS) as well as functional capacities of effectors (heart and vessels) and other associated structures.

There is various evidence indicating relationship between aging and autonomic functions from various parts of the world. But there are few works involving this subject with conventional methods for assessing the autonomic functions of Indian origin in this field. No such work or publication is made during recent years.

Previous studies conducted for assessment of cardiac autonomic function test indices have narrow accuracy standard. So I decided to perform my study of effect of age on human autonomic functions with the Cardiovascular Analysis System Windows based (CANWIN), which is very advance and highly specific mechanized instrument. The aim of the present study is to study sympathetic and parasympathetic function tests in a group of healthy old and young subjects, to compare the results of autonomic function tests in different age groups and to find out the relationship of autonomic function tests if any with advancing age.

MATERIALS AND METHODS

The present study was carried out in the Department of Physiology in collaboration with Department of Medicine, Dr. S.N. Medical College on 125 healthy individuals of western Rajasthan between the age group of 20-70 years. A informed consent was obtained from patients after explaining the procedure in detail. The procedure was in accordance with the ethical standards of the committee of the institute.

Subjects were checked for symptoms and signs of possible autonomic dysfunctions including orthostatic hypotension (light headedness, blurred vision, sensation of weakness and unsteadiness, fainting or syncope on standing), perspiration, and palpitations.

Inclusion criteria

Only healthy subjects of age group of 20 to 70 years and average body mass index of Indian origin will be included in the study.

Exclusion criteria

- Pregnant women
- Haemoglobin < 10 gm %
- Subjects having history of chronic alcohol consumption, chronic tobacco consumption in any form.
- Neurological diseases including multiple sclerosis, polyneuropathy or Guillain Barre syndrome.
- Cardiovascular diseases including hypertension, ischemic heart disease and congestive heart failure.
- Disease interfering with the autonomic functions including Diabetes mellitus, renal and liver disease.
- Subjects receiving drugs that are known to interfere with cardiac, respiratory functions such as beta blockers, sympathomimetic drugs, antihypertensive drugs, vasodilators, diuretics, adrenergic drugs, anti-arrhythmic, sedatives, hypnotics and anti-epileptic drugs.

METHOD-CAN *Win* METHOD

Following non- invasive autonomic function tests were performed by CAN *W*in Analysis System.CAN *W*in-PC is a window based Cardiac Autonomic Neuropathy (CAN) Analysis System with interpretation ,which has been unveiled by Genesis . "CAN *Win*" detects cardiac autonomic neuropathy based on Ewing battery of tests .This device can detect SNS and PNS damage and diagnose CAN. "CAN *Win*" has a complete set of accessories that required for the battery of tests. It can conduct all the maneuver and postural tests as per clinical requirements. The system uses Tacho Cardio Gram (TCG) and automatic Non Invasive Blood Pressure (NiBP) to conduct a battery of six tests. Being fully automatic, CAN *W*in eliminates the need of manual recordings , readings and calculations. Inbuilt time domain waveform analysis and BP measurements make the task of conducting all six CAN tests very easy.

AUTONOMIC FUNCTION TESTS BY CAN *Win* METHOD

Tests of predominantly parasympathetic function

Resting Heart Rate

Heart Rate variation during deep breathing (Expiration/Inspiration ratio)

While recording ECG, the subject was asked to inhale deeply for 5 seconds followed by exhalation for 5 seconds at a rate of 6 breaths per minute. The ratio between longest R-R interval during expiration and shortest R-R interval during inspiration (E/I ratio) in each respiratory cycle is calculated for evaluation. A value of 1.20 or higher was taken as normal [6].

Heart-rate response to standing (30:15 ratio)

The subject was instructed to lie down comfortably and ECG was recorded to calculate the heart rate. Then the subject was instructed to stand up within 3-4 seconds and remained motionless thereafter. The 30:15 is the ratio of the longest R-R interval at beat 30 during the inspiration/expiration cycle and the shortest R-R interval at beat 15 after standing. It examines the integrity of the efferent parasympathetic branch. The 30:15 ratio of ≥1.04 is taken as normal and value of <1.04 is considered abnormal [7].

Heart-rate response to Valsalva maneuver (VM ratio)

The subject was asked to blow out or to expire forcefully through a mouthpiece attached to the sphygmomanometer to maintain the pressure at about 40mm Hg for 15 seconds. The ECG is recorded simultaneously during this maneuver and 15 seconds afterwards to see the RR interval changes. The valsalva ratio = Longest R-R interval after maneuver (after the strain)/ Shortest R-R interval during maneuver (during the strain). The normal valsalva ratio is >1.21 and in autonomic dysfunction this ratio is <1.21[7].

Tests of predominantly sympathetic function

Blood-pressure response to standing

The BP of the subject was recorded at lying down and again when the subject stands up from supine position. In normal subjects systolic blood pressure does not fall by more than 10mm Hg and in autonomic dysfunction it falls by >20-30 mm Hg. Orthostatic hypotension was defined as a fall of ≥20 mm Hg in systolic and/or ≥10 mmHg in diastolic blood pressure from lying to standing position[8].

Blood-pressure response to Sustained handgrip (SHG)

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 press the handgrip dynamometer for at 30% of the maximal voluntary effort. The BP was recorded in contralateral arm and rise in diastolic BP was measured.

Ewing and Clarke grading [9]:

a) Normal ≥16 mmHg
b) Borderline 11-15 mmHg
c) Abnormal <10 mmHg

RESULTS

Table-1: Comparison of resting heart rate (rhr) of different groups

Age (in years)	Mean of Resting Heart rate in bpm	SD	P value
20-30	75.64	9.68	<0.05
31-40	75.52	10.97	
41-50	76.16	7.36	
51-60	78.44	9.30	
61-70	81.4	10.40	

All values expressed as mean & SD; with significant p value (<0.05).

Table-2: Comparison of e:i of different groups

Age (in years)	Mean(E:I ratio)	SD	P value
20-30	1.53	0.55	0.0002
31-40	1.39	0.29	
41-50	1.22	0.15	
51-60	1.21	0.1	
61-70	1.18	0.2	

All values expressed as mean & SD; with very significant p value (<0.01).

Table-3: Comparison of 30:15 ratios of different groups

Age (in years)	Mean of 30:15 Ratio	SD	P value
20-30	1.19	0.35	<0.089
31-40	1.15	0.29	
41-50	1.13	0.27	
51-60	1.03	0.22	
61-70	1.02	0.1	

All values expressed as mean & SD; with non significant p value(>0.05).

Table-4: Comparison of valsalva maneuver ratio of different groups

Age (in years)	Mean of val. Man.	SD	P value
20-30	2.23	1.08	<0.75
31-40	2.19	1.4	
41-50	2.16	1.66	
51-60	1.92	0.82	
61-70	1.84	1.26	

All values expressed as mean & SD; with non-significant p value(>0.05).

Table- 5: Comparison of orthostatic fall in systolic blood pressure among different groups

Age (in years)	Mean (SBP mmHg)	SD	P value
20-30	4.08	6.28	0.47
31-40	0.72	6.04	
41-50	2.76	6.92	
51-60	0.4	7.68	
61-70	3.04	13.13	

All values expressed as mean & SD; with non-significant p value(>0.05)

Table-6: Comparison of rise in dbp after sustained hand grip (shg) among different groups

Age (in years)	Mean (DBP mmHg)	SD	P value
20-30	13.72	6.84	<0.05
31-40	13.44	7.37	
41-50	12.04	9.59	
51-60	12.16	13.94	
61-70	5.28	15.5	

All values expressed as mean & SD; with significant p value(<0.05)

DISCUSSION

The present study was carried out in 125 healthy subjects in the age range of 21-70 years, to assess the influence of age on autonomic nervous function. The subjects were distributed into five age groups. Total 25 subjects (20%) were included in each group. Out of the total 125 subjects, 66(52.8%) were females and 59 (47.2%) were males. Evaluation of status of autonomic nervous system was done with the help of a non-invasive device, Cardiac Autonomic Neuropathy Analysis System, 'CAN *Win*". The measured parameters of autonomic function tests are discussed below:-

Parameters for assessment of parasympathetic activity

Resting Heart Rate Resting heart rate reflects the balance of parasympathetic and sympathetic influences at the sinoatrial node, with higher heart rate indicating a decreased parasympathetic influence or over activity of the sympathetic influence. Increased resting heart rate is a predictor of cardiovascular mortality in subjects with and without diagnosed cardiovascular disease. [66].According to Table no.1, Mean RHR of Group A, Group B, Group C ,Group D and Group E was 75.6 ±9.68, 75.52±10.97, 76.16±7.36, 78.44±9.30 and 81.4±10.40 respectively .Our study shows that resting heart rate increases with age with significant results (p-value <0.05) ,which is similar to the findings of Shaileja modithya[10].

Heart Rate variation during Deep Breathing

(Expiration/Inspiration Ratio):- In healthy young individuals breathing at A normal rate, the HR varies with the phases of respiration i.e., HR accelerates during inspiration and decelerates during expiration, this is known as sinus arrhythmia. Sinus arrhythmia is a normal phenomenon and is due to fluctuations in parasympathetic output to the heart. Baroreceptors are solely responsible for resting vagal tone in the normally breathing individuals.

During inspiration, neuronal activity of inspiratory neurons in the medulla besides initiating inspiration also discharge to Nucleus of tractus solitarius (NTS), Nucleus ambiguous (NA), and inhibit both the relay centers of the baroreceptors, NTS-NA pathway. This leads to inhibition of cardiac vagal motor discharge which in turn leads to an increase in HR during inspiration and decrease in HR during expiration [1].

Table 2 shows comparison of E:I ratio among different groups. Mean E:I ratio of Group A, Group B, Group C, Group D and Group E was 1.53±0.55, 1.39±0.29, 1.22±0.15, 1.21±0.10 and 1.18±0.2 respectively. There was a significant linear decline in E/I ratio with advancing age (p value 0.002).

Our results are supporting the earlier studies done by, Iain A D O'Brien, Paul O' Hare *et al.* [11], Vita G *et al*. [12], Sampo J Piha *et al*. [13],Ewing *et al*. [7,9].Vita G *et al.* [12] attributed this decline to reduction in number of fibers in the vagus nerve, increase in empty Schwann cell bands and accumulation of pigments in neurons as the age advances.

Heart –rate response to standing (30:15 ratios)

When subject assumes an erect posture, from supine posture, gravity causes pooling of blood in the lower limbs. As a result venous return, cardiac output and arterial BP decreases. This leads to decreased stretch of baroreceptors, activation of vasomotor center, which leads to increased sympathetic discharge, decreased vagal tone instantaneous increase in HR. On standing the heart rate increases until it reaches maximum at about the 15th beat, after which it slows down to a stable state at about 30th beat. The ratio of R-R intervals corresponding to the 30th and 15th heart beat is called the 30:15 ratios [14].

Table no. 3 shows comparison of heart rate response to standing among different age groups. Mean 30:15 ratio of Group A, Group B, Group C, Group D And Group E was 1.19±0.35, 1.15±0.29, 1.13±0.27, 1.03±0.22 and 1.02±0.1 respectively with a p value of <0.08,which is found to be non significant. Thus heart rate response to orthostatic test was found to reduce linearly with advancing age in our study.

Our findings are in conformity with earlier studies done by Weiling W *et al*. [15], Lain A D O'Brien *et al*. [11], Bengt Bergstrom *et al*. [16], Vita *et al*. [12], Chu T S *et al*. [17], J Gert Van Dijk *et al.* [18], Piha S J [13].

Heart- rate response to Valsalva maneuver (VM ratio): Is characterized by a decrease in the pulse pressure and tachycardia during the strain and blood pressure overshoot and bradycardia following the strain. The Valsalva manoeuvre tests the integrity of both sympathetic & parasympathetic divisions of the autonomic nervous system.

The hemodynamic changes during the manoeuvre are mediated via baroreceptors. With parasympathetic affection, the baroreceptor mediated reflex bradycardia response to elevated blood pressure will be reduced. Heart rate response to Valsalva manoeuvre was evaluated in all the subjects.

Table 4 shows comparison of Valsalva Maneuver ratio (VM ratio) among different age groups.Mean VM ratio of Group A, Group B ,Group C ,Group D And Group E was 2.23±1.08,2.19±1.4,2.16±1.66,1.92±0.82 and 1.84±1.26 respectively with a p-value <0.75 ,which is non-significant..

This correlates with the study conducted by Jain A D O'Brien *et al.* [11], Chu T S *et al*. [17], Philip A low *et al*. [19], S J Piha [13], Zeigler D *et al*. [20], Gautschy *et al*. [21], RomeroVecchione *et al*.[61]. Our results were not in agreement with Kaijser & Sachs [22], Neumann & Schmid [23].

Parameters for assessment of sympathetic activity

Blood-pressure response to standing : With change of posture from supine to standing the autonomic nervous system acts to produce a rise in heart rate and vasoconstriction in order to maintain blood pressure. Vasoconstriction is mediated through sympathetic innervations to blood vessels during standing. Blood pressure response to standing was evaluated in all the subjects. The values in various age groups for fall in systolic blood pressure on orthostatic test are shown in Table No 5. Mean orthostatic Fall in systolic BP of Group A,Group B ,Group C, Group D And Group E was 4.08±6.28, 0.72±6.04, 2.76±6.92, 0.4±7.68 and 3.04±13.13 respectively with a p- value <0.47,which is found to be non significant.

Our findings are correlated with Kaijser & Sachs [22], Lain AD O'Brein [11], Bengt Bergstrom *et al*. [16], Chu TS *et al*. [17], J gert Van Dijk *et al*. [18], S J Piha [13] and Neumann & Schmid [23]. They did not observe any significant fall in systolic blood pressure with advancing age.

Blood pressure response to sustained handgrip exercise

In the hand grip test, there is an increase in both heart rate and blood pressure. The cardiovascular responses to isometric exercise are mediated partly by the influence of cardiovascular centers and partly by metabolic or mechanical changes, or both, in response to contraction of the muscle that activate small fibbers in the afferent limb of the reflex arc. The response is a rise in diastolic pressure, more than 15 mm of Hg and rise in the heart rate by about 30 per cent. The blood pressure rise is due to increased sympathetic activity, heart rate rise is due to decreased parasympathetic activity [11]. In our study a gradual decrease in heart rate response was observed.

Table 6 shows comparison of rise in DBP after sustained handgrip exercise among different age groups. Mean rise in DBP after sustained handgrip exercise of Group A,Group B ,Group C, Group D And Group E was 13.72 ± 6.84, 13.44±7.37, 12.04±9.59, 12.16±13.94 and 5.28±15.5 respectively with a p-value of <0.05,which is found to be significant.

Thus, sympathetic function as assessed by sustained handgrip exercise, was reduced significantly in subjects above 60 years indicating, late onset of decline in sympathetic efficiency in normal subjects, with advancing age. The results of our study are significant, (p-value<0.05).

Our findings are matching with the findings of Kaijser and Sachs [22], He observed a decreased blood pressure response to sustained handgrip test in older (above 60 yrs) subjects, due to reduced effector organ sensitivity. Our results differ with earlier studies done by Vita G *et al*. [12], J Gert Van Dijk [18], S J Piha [13], Zeigler D *et al*. [20] and Neumann & Schmid [23] in that they did not observe any significant decline in blood pressure response to sustained handgrip with advancing age.

Gender related variations in autonomic nervous functions:-In our study cardiovascular test were performed in 66 (52.8 %) females and 59(47.2%) males. No significant sex variation was observed in autonomic nervous function in our study. Our results are in accordance with Lain AD O'Brien *et al*.[11], Kaijser& Sachs *et al*.[22], Bengt Bergstrom *et al*.[16], Philip A *et al*.[19], Zeigler D *et al*.[20] & Neumann & H Schmid[23]. Our findings were not in agreement with Chu T S *et al*. [17], Age link N W *et al*.[24].

CONCLUSION

We assessed parasympathetic activity by heart rate response to deep breathing, heart rate response to valsalva manoeuvre and heart rate response to orthostatic test. The results of these tests, revealed a significant linear decline in values with advancing age. Decline in parasympathetic activity observed in our study may be attributed to reduction in number of vagal fibres and decrease in biosynthesis and hydrolysis of acetylcholine with advancing age.

Assessment of sympathetic activity by blood pressure response to orthostatic test revealed that there is linear increase in systolic blood pressure and diastolic blood pressure response to sustained handgrip exercise revealed a significant decline with age. With advancing age, changes in neurons such as pigment accumulation, Schwann cell demyelination, neuronal loss and axonal degeneration has been reported. The decline in sympathetic efficiency in subjects above 60 years of age as observed in our study may be due to progressive reduction in pre ganglionic sympathetic neurons of intermediolateral column of spinal cord beginning in the adult life as reported by Philip A Low. [19] .No significant variation in the values of males & females was found in the tests used to study sympathetic & parasympathetic activity.

Hence based on the results of above study it is concluded that increasing age has an important role in declining autonomic functions. Thus, the knowledge of autonomic status will have an important bearing on determining the therapeutic strategy and drug action in the elderly in whom there may be altered responsiveness to autonomic reflexes and receptor sensitivity.

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