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Age Related Changes in the Parasympathetic Control of the Heart

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Abstract- Age related impairment in the parasympathetic control of the heart is a causal component for increased risk of cardiovascular diseases like arrhythmia and sudden cardiac death in the elderly. Abnormal heart rate responses as a result of parasympathetic dysfunction have demonstrated altered sympatho vagal modulation of the heart in the elderly. Simple, bedside, non invasive ECG based tests designed by Ewing & Clarke assess parasympathetic function. These are heart rate responses to Deep breathing, Valsalva maneuver and to standing. Parasympathetic function was assessed by the above mentioned cardiovascular autonomic function tests in 60 elderly subjects above 60 years who were further grouped as young old (60-74 yrs) and old old (75-90 yrs). The results thus obtained were compared with young healthy subjects (18-33 yrs) who served as controls to study the effect of aging on the parasympathetic control of heart rate. There was a significant reduction in heat rate responses to Deep breathing, Valsalva maneuver and to standing indicating reduction in parasympathetic function in the elderly above 60 years. There was no significant difference in all the tests of parasympathetic function between the young old and the old old suggesting no further decline in parasympathetic function after 75 years.

Index Terms- parasympathetic, dysfunction, elderly, valsalva, aging.

I. INTRODUCTION

Majority of deaths in the older population stem from cardiovascular disorders accounting for a third of the elderly mortality. Approximately *50%* of these occur suddenly. Lethal ventricular arrhythmias are responsible for 80% of sudden cardiac deaths (1). Age related autonomic dysfunction in the cardio vascular regulatory control is a contributing factor for the increased incidence of arrhythmias in the elderly. Autonomic changes with aging include reduction in parasympathetic function and these changes are associated with high rates of cardiovascular disease and mortality (2). Aging is known to alter the neurohormonal mechanisms that control the cardiovascular system. Published reports have demonstrated a decline in sinoatrial node parasympathetic activity(3). Previous studies have demonstrated that there is parasympathetic decline in elderly leading to impaired parasympathetic control of heart rate.(4) Cardio vascular disturbances due to impaired parasympathetic control are usually subclinical and precede symptoms. So it goes unnoticed unless carefully scrutinized. Effects of aging on parasympathetic nervous system have been much studied. The impetus for continuing interest in this topic have come in part from the recognition that in a range of cardiovascular disorders including sudden cardiac death and ventricular arrhythmia, for all of which incidence rises with age, parasympathetic nervous system pathophysiology may be an important causal component. The Autonomic Nervous System mechanisms involved in the aging process are extremely complex and many questions concerning the neurologic effects of aging have yet to be answered. Some of the mechanisms associated with aging are pathologically induced but the distinction between these mechanisms and those that are part of the normal aging process remains somewhat cloudy (5). The importance to be able to differentiate between autonomic abnormalities which are associated with systemic diseases and those which are purely the consequence of the natural processes of aging is thus obvious.

Cardiac Autonomic Neuropathy is grossly under diagnosed due in part to its frequently asymptomatic presentation and in part to the non utilization of tests for its diagnosis. Ewing and Clark have designed a battery of standardized quantitative autonomic function tests to test parasympathetic function that have been widely used to assess parasympathetic control of heart (6).These tests are performed since the procedures are straight forward, reproducible, non invasive and performed bedside. This study was conducted to evaluate the association between aging and parasympathetic function by assessing the parasympathetic function in the elderly and comparing it with young healthy subjects.

II. MATERIALS AND METHODS

Subjects.

The study comprised of 90 subjects. 60 elderly subjects residing in old age homes / attending medical OPDs/ patients' attendants between the age 60-90 yrs with a normal 12 lead ECG were included in the study. Informed consent was obtained from each subject. The 60 elderly subjects above 60 yrs were further grouped as young old aged between 60 – 74 yrs(n=30) and old old aged between 75 and 90 yrs(n=30). The study was approved by the Institutional ethical Committee. The control group consisted of 30 healthy subjects who were between the age 18 – 33 yrs and with a normal 12 lead ECG. Subjects with history of hypotensive drug intake, heart or lung disease, Diabetes Mellitus, hypertension, alcohol consumption , smoking and any inter current illness like pyrexia and diarrhea were excluded from the study.

Methods:

Autonomic function tests that evaluate the parasympathetic function were conducted on all the subjects. These are ECG based heart rate response tests to deep breathing, Valsalva maneuver and to change in posture. All of the tests were conducted between 11.30 and 13.30 hours. The temperature of the examination room was typically between 22 - 24°C. The subjects were also instructed not to have coffee, tea, cola 12 hours before the tests and were asked to have light breakfast two hours before the tests. The subject was asked to relax in supine position for 30 minutes in the laboratory prior to conducting the tests. The resting heart rate was recorded on a standard ECG from lead II, at a paper speed of 25mm/sec. The cardiovascular tests that test parasympathetic function were performed after demonstrating these tests to the subjects.

1. Deep breathing test:

The subject was trained to breathe deeply at a rate of 6 breaths/minute while sitting. The subject was asked to breathe deeply, steadily and slowly for I mm at the rate of 6 breaths/mm (5 sec inspiration and 5 sec expiration) while ECG was being continuously recorded. The heart rate change with deep breathing (deep breathing difference) was then expressed as the mean of the differences between the maximal and minimal heart rate in 6 respiratory cycles.

Deep Breathing Difference (DBD) = mean of heart rate differences in 6 breath cycles.

2. Heart rate response to Valsalva maneuver:

The subject was trained to maintain an expiratory pressure of 40 mm Hg for 10 sec. Valsalva maneuver was performed by asking the subject to blow through a mouthpiece attached to a mercury manometer and maintain a pressure of 40 mm Hg up to 15 sec (straining period not less than 7sec). A nose clip was applied and small air leakage (through a needle) incorporated in the mouthpiece to ensure that the expiratory pressure comes from the chest and that the subject does not blow with his cheeks. Throughout the Maneuver, ECG was recorded continuously and for 30 sec after release of pressure. The heart rate changes induced by the Valsalva maneuver were expressed as the ratio of the maximal tachycardia during the maneuver to the maximal bradycardia after the maneuver. This ratio was defined as the Valsalva ratio and was calculated as the ratio of maximum R-R interval after the maneuver to minimum R-R interval during the maneuver.

3. Heart rate response to standing (Postural tachycardia index, PTI):

The subject was asked to rest in a supine position for at least two minutes and to stand unaided and remain standing for about a minute. While ECG was being recorded continuously. The heart rate response to standing (postural tachycardia index) is defined as the ratio between the heart rate at beat 15 after rising to the vertical position and the heart rate at beat 30.

PTI = RR interval at 30^{th} beat / RR interval at 15^{th} beat.

Autonomic Score:

Each individual test was given a score of 0, 1, or 2 depending on whether they were normal, borderline or abnormal respectively(Table 1). The scores of individual tests are added and an overall autonomic score of 0-6 can then be obtained. This scoring by Bellavere et al provides a simple and efficient "staging" of autonomic involvement in subjects with autonomic neuropathy(7). Autonomic score of 4 – 6 is suggestive of definite cardiac autonomic neuropathy with involvement parasympathetic pathways (8).

Table 1: Scoring of Cardiovascular autonomic function tests.

Cardiovascular Indices Heart rate response tests	Normal (score **0)**	Borderline (score **1)**	Abnormal **(score 2)**
Heart rate response to Valsalva Maneuver(VR)	≥1.21	1.11 -1.20	≤1.10
Heart rate response during deep breathing. (Deep Breathing Difference or DBD in bpm)	≥15	11-14 beats/min	≤10
Heart rate response to standing(PTI)	≥1.04	1.01-1.03	≤1.00

III. RESULTS AND ANALYSIS

Statistical Treatment of the data:

Chi-square test was carried out to evaluate the significance of sex distribution between the 3 study groups. One way ANOVA was done to compare the cardiovascular indices and autonomic score between the 3 study groups. When difference was found Bonferroni test was used. The mean difference was defined as significant at $p<0.05$ level.

Table 2: Gender distribution of subjects in the 3 study groups

	control	young old	old old	
	Nos.(%)	Nos. (%)	Nos. (%)	total
Male	12 (40)	16 (53)	10 (33.3)	38
Female	18 (60)	14 (47)	20 (66.7)	52
Total	30	30	30	90

Chi square test showed no significant difference with respect to gender distribution between the study groups ($p>0.05$).

Table 3: DBD, VR, PTI and the total autonomic score in the 3 study groups with ANOVA results.

	Heart rate response to Deep breathing DBD	Heart rate response to Valsalva Maneuver VR	Heart rate response to standing PTI	Autonomic score
Controls(18-33 yrs)	15.87± 8.2	1.31± 0.20	1.05± 0.08	1.77±1.30
Young old (60-74 yrs)	7.87 ±6.25	1.08± 0.15	1.01± 0.07	4.62±1.27
Old old(75-90 yrs)	4.57± 2.76	1.04± 0.09	0.99± 0.06	5.03±1.03
ANOVA(F value)	26.661, $p=0.000^{\#}$	26.870, $p=0.000^{\#}$	6.707, $p=0.004^{\#\#}$	67.33, $p=0.000^{\#}$

$^{\#}$ significant at $p<0.0001$, $^{\#\#}$ significant at $p<0.01$

Table 4: post hoc (Bonferroni test) to compare means of DBD, VR, PTI and autonomic score between the 3 study groups

	DBD	VR	PTI	Autonomic score
Control vs young old	p=0.000*	p=0.000*	p=0.000*	p= .000*
Control vs old old	p=0.000*	p=0.000*	p=0.000*	p=0.000**
Young old vs old old	p = 0.123^{ns}	p=0.84^{ns}	p=0.46^{ns}	p=0.33^{ns}

* significant at p<0.0001, ns = not significant

IV. DISCUSSION

The mean age in years of the subjects was 24.77 ± 4.38, 67.13 ± 4.32 and 81.17 ± 4.06 in the control, young old and old old groups respectively. Cardiovascular indices (DBD, VR and PTI) obtained by performing the tests of parasympathetic function and the autonomic score are expressed as mean ± SD (Table 3) ANOVA shows significant difference between the 3 study groups. Results of post hoc test (Bonferroni test) done to compare DBD, VR, PTI and Autonomic score between the control, young old and old old is shown in table 4.There was a significant difference in the young old and old old as compared to controls in all the tests of parasympathetic function. There was no significant reduction in the heart rate response to deep breathing, Valsalva maneuver and to standing in the old old above 75 yrs as compared to young old between 60 and 75 years.

Heart rate response to Deep breathing:

There was a significant reduction in DBD in both young old and old old as compared to young subjects who served as controls .Heart rate response to breathing is a normal phenomenon and is due primarily due to fluctuations in parasympathetic output to heart. Cardiac vagal innervation decreases with age as clearly shown by a reduction in DBD that reflects respiratory sinus arrhythmia. During inspiration impulses in vagi from stretch receptors in the lungs inhibit the cardio-inhibitory area in the medulla oblangata. The tonic vagal discharge that keeps the heart rate slow decreases and heart rate rises (9). Depression of respiratory sinus arrhythmia with age also suggests a decrease in parasympathetic influence on sinus node function (10).

Healthy ageing is associated with gradual reduction of overall fluctuation in autonomic input to the heart as well as vagal index of Heart Rate Variability (11).The findings of the present study that show decline in DBD with advancing age is in conformity with the earlier studies done by Malvin et al(12) , Pandian et al (13), SJ Piha (14), Ewing et al(15), Bengt Bergstrom et al (16),Kaijser and Sachs (17), Phillip .A. Low et al(18), Braune S et al (19) and Neumann and Schmid(20).

There was no significant difference in DBD between young old and old old suggesting that there is no further decline after 75 years. This observation is similar to that of Phyllis et al who studied the association between age, aging and Heart rate Variability, an index of parasympathetic function in 585 subjects and concluded that onset of parasympathetic dysfunction is between 60 – 75 years and levels off at age >75 years(21).

Heart rate response to Valsalva Maneuver:

There was a significant reduction in VR in both young old and old old as compared to the controls.

It can thus be concluded that there is a decrease in VR in the healthy elderly above 60 years thus demonstrating involvement of parasympathetic nervous system. Heart rate response to Valsalva maneuver relies to some extent on the integrity of sympathetic as well as parasympathetic pathways. Many factors, including blood volume, antecedent period of rest, cardiac sympathetic as well as peripheral sympathetic functions and NE response affect the Valsalva maneuver. Age may affect different components of Valsalva maneuver in different directions.

This study is in conformity with the earlier studies done by Albert.B.Levin (22) & SJ. Piha (23)

The present study is not in agreement with earlier studies like Ewing et al (15), Braune S et al(19) & C Neumann and Schnmid(20). It may be due to higher upper limit of age range of

subjects (up to 90 years) in our study. The less consistent effect of age on VR likely relates to the smaller change and greater complexity of the maneuver. C Neumann (20) was of the opinion that results of the test proposed by Ewing and Clarke, however might differ between researchers because of differences in the maneuvers and equipment (they are not commercially available), and because some techniques are completely computerized whereas others are not. Previous studies have demonstrated that age related reduction in Heart Rate Variability in response to Valsalva maneuver suggested that aging is associated with impaired parasympathetic control of heart rate. There was no significant difference in VR between young old and old old suggesting that there is no further decline after 75 years. This is similar to the observation made by Phyllis et al(21) and Islam et al (24) suggesting that parasympathetic impairment seen after 60 years is not dependent on age with further advancement of age.

Heart response to standing (PTI):

Old group did not differ significantly from young-old with respect to heart rate response to standing.

It can be concluded that heart rate response to standing, a measure of cardiac parasympathetic function is significantly reduced in healthy elderly subjects above 60 years comprising of both the young old and old-old groups. In elderly the immediate postural reflexes are controlled neurally by sympathetic and parasympathetic nerves whereas the later neural regulation of the postural adaptation is controlled via sympathetic nerves. Since the parasympathetic nervous system is more prone to the effect of aging (9) than sympathetic function, it is likely that the transient dysregulation of postural reflexes in older subjects at the beginning of standing is due to decrease in parasympathetic activity (23). This study is in conformity with earlier studies done by G.Vita (25), J.Gert van Dijk (26), S.J.Piha (14)and C. Neumann (20). This study differs from the study of Ewing D.J et al (27) who initially promoted PTI as an age-independent test of parasympathetic function, may be due to smaller sample size of older control(10 subjects) and younger age of the older group(48-67 years).

As seen with heart rate responses to deep breathing and valsalva maneuver, heart rate response to standing (PTI) is not different between the young old and old subjects. This strengthens the possible explanation that parasympathetic dysfunction seen after 60 years does not continue to decline with further advancing age. This observation is similar to that of Phyllis et al (21) and Islam et al(24).

Autonomic score: Mean and SD of autonomic score are 1.77± 1.30, 4.62± 1.27 and 5.03±1.03 respectively. Autonomic score differed significantly between the control, young old and old old groups.

Autonomic score was significantly high in the young-old and old old ($p = 0.000$) when compared to controls suggesting the presence of severe cardiac autonomic neuropathy in the elderly. There was no difference in autonomic score between young old and old old ($p = 0.17$). Our study demonstrates reduction in parasympathetic function as suggested by significant decline in autonomic score after 60 with no further decline after 75 years. Phyllis et al(24) characterized the association between age, aging and HRV in 585 adults aged above 65 years and showed that cardiac autonomic function based on parasympathetic nervous system declines mostly at 60 – 75 years and levels off at age > 75 years.

Heart rate response to deep breathing:

Valsalva maneuver and standing that reflect integrity of parasympathetic nervous system showed a significant decline in deep breathing difference, VR and PTI in both the young-old (60 - 74 years) and old-old (75 years – 90 years) when compared to control (18 - 33) suggesting impairment of parasympathetic function in the elderly aged > 60 years. The basis for this finding is multifactorial and may be at multiple levels of neuraxis including peripheral and central mechanisms. Dysfunction in the activity of the neural portion (afferent, central or efferent) of the vagal system and the cardiac muscarinic receptor may be involved in the parasympathetic changes associated with aging (2).

The underlying mechanisms of aging are complex and uncertain. Aging is a, multifactorial process that clearly affects the Autonomic Nervous System. Its impact on the autonomic neuraxis is at multiple levels and heterogeneous. The altered autonomic function at the transition from adulthood to old age is continuation of process of modulation of autonomic function from fetal to postnatal and postnatal to adulthood. Age related changes in cardiovascular Structure and function increase the probability of disease modify the threshold at which symptoms and signs arise and affect the clinical course and prognosis.

The altered autonomic function of long term heart rate behavior with advancing age may arise from age related changes in various organs and body systems, which may interact with each other and thereby impair the function of cardiovascular autonomic regulatory systems. Altered autonomic regulation of cardiac function may contribute to the onset of cardiovascular disease and provide a substrate for malignant ventricular arrhythmia.

Additional changes in the heart with aging are structural changes in the SA node, with reduction in cell no's of such a degree (28) that the capacity for chronotropic responses might be impaired. Factors such as these could blunt cardiac responsiveness in the elderly. Cardiac electrophysiologic studies have demonstrated a progressive decline in sinoatrial conduction and sinus node recovery time with age (29).

V. CONCLUSION

According to available literature and the findings of present study, heart rate response to deep breathing, Valsalva maneuver and to standing which reflect integrity of parasympathetic function is reduced after the sixth decade even in normal healthy subjects. There was no significant difference in all the tests of parasympathetic function between the young old and old old indicating no further decline in parasympathetic function after 75 years. Physicians have to bear in mind the age related impairment of autonomic function while evaluating cardiovascular diseases in elderly.

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