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Cardiac Parasympathetic Function in Different Class Interval of Age in Type 2 Diabetes Mellitus.

Subbalakshmi N K[1]*, Prabha Adhikari[2], Shilpa N Bijoor[1], and Sathyanarayana Rao KN[3].

[1]Department of Physiology, [2] Department of Medicine, Kasturba Medical College Mangalore, Manipal University, Karnataka, India
[3]Department of Pharmacology, KS Hegde Medical Academy, Deralakatte, Mangalore, Karnataka, India.

ABSTRACT

Reduced sinus arrhythmia indicates diabetic autonomic neuropathy**.** Amplitude of respiratory sinus arrhythmia declines with aging. But no studies found on sinus arrhythmia in relation to different class interval of age in diabetes. To compare the Expiratory: Inspiratory ratio of patients with diabetes in different class interval of age with controls. In 207 patients with diabetes mellitus and 392 controls, expiratory: inspiratory ratio was obtained while breathing at 6 respiratory cycles per minute connected to limb lead II of electrocardiogram. Study and control subjects were divided into 5 subgroups with 10 years class interval (CI) as follows: CI 1: ≤ 40; CI 2: 41-50; CI 3: 51- 60; CI 4: 61-70 and CI 5: 71-80 years. In study subjects frequency of diabetes related complications in different class interval of age was noted. Statistical analysis included unpaired t, Mann-Whitney U, Chi-square, Kruskal –Wallis, and Dunn's Multiple Comparisons tests. Statistical significance was considered at $p < 0.05$. Expiratory: Inspiratory ratio was lower in study subjects in CI 2, 3, 4 and 5 compared to corresponding controls ($p < 0.001$). There was no difference in Expiratory: Inspiratory ratio between study subjects and controls in CI 1. In study group frequency of hypertension, stable angina and somatic neuropathy was higher with aging ($p < 0.0001$). Expiratory: Inspiratory ratio is lower in patients with diabetes mellitus after 40 years of age. Somatic neuropathy, hypertension and stable angina increases with aging.

Keywords: class intervals of age, Expiratory: Inspiratory ratio, diabetes complications

Corresponding author

INTRODUCTION

Heart rate fluctuates with inspiratory and an expiratory phase of respiration and is a physiological phenomenon known as respiratory sinus arrhythmia [1]. This fluctuation in heart rate is mediated through vagal nerve [2]. Therefore measure of respiratory sinus arrhythmia is widely considered as an index of parasympathetic function [3]. Heart rate response to deep breathing is a most commonly used bed side test for diagnosis of diabetic autonomic neuropathy [4], a complication of diabetes mellitus associated with sudden and unexplained death [5]. Several investigators have observed reduced cardiac parasympathetic function in diabetic patients with symptoms of autonomic neuropathy [6] and other diabetes related complications [7]. However, heart rate response to deep breathing also declines with normal aging [8, 9]. Therefore it would be appropriate to assess cardiac parasympathetic function and other diabetes related complications in different class interval of age.

Heart rate response to deep breathing could be estimated by subtracting the minimum heart rate during expiration from maximum heart rate during inspiration and expressed as beats per minute [10]. However, much simpler form of heart rate variation could be the ratio of longest R-R interval during expiration to the shortest R-R interval during inspiration [11]. Thus this study aimed to compare expiratory: inspiratory ratio between patients with type 2 diabetes mellitus and non-diabetic healthy control in different class interval of age and to find the frequency of subjects with different complications in these class interval of age.

MATERIALS AND METHODS

This was a cross sectional study done in 207 patients with type 2 diabetes mellitus and 392 non-diabetic healthy subjects. This study was done after obtaining institutional ethical committee clearance and consent from study participants.

Study group: 207 Study subjects in the study group were divided into following five subgroups based on their age**:** Group A (n = 14): aged 40 years or below; Group B (n =56) aged between 41 to 50 years; Group C (n =71) : aged between 51 to 60 years ; Group D (n = 51): aged between 61 to 70 years and Group E (n = 15): aged between 71 to 80 years. In them frequency of diabetes related clinical conditions were noted in all the different class interval of age separately.

Control group: Control group was matched for age and gender of study subjects. 392 control subjects were further divided into five subgroups namely Group 1 (n =14): aged 40 years or below ; Group 2 (n = 143): aged between 41 to 50 years; Group 3 (n = 136) : aged between 51 to 60 years ; Group 4: (n = 92) aged between 61 to 70 years and Group 5 (n = 7): aged between 71 to 80 years.

Study protocol

Heart rate response to deep breathing was recorded in all the subjects in the morning in supine position after subjects were completely relaxed.

Procedure followed in recording heart rate response to deep breathing:

After explaining the procedure and providing sufficient trial to perform deep breathing, subjects were asked to breathe in for 5 seconds and breathe out for 5 seconds for a period of one minute while connected to limb lead II of standard electrocardiogram. All the R-R intervals were measured accurately from the ECG tracing. Heart rate response to deep breathing was expressed as ratio of longest R-R interval during expiration to shortest R-R interval during inspiration (Expiratory: Inspiratory ratio) [11].

Statistical Analysis

Unpaired 't' test was applied to unpaired data of independent observations made in two separate groups. Whenever the standard deviation between the groups was not comparable, Mann-Whitney U test was applied to unpaired data of independent observation. Chi-square test was applied when data were in frequency. Kruskal –Wallis test followed by Dunn's Multiple Comparisons Test was performed when data was of independent observations made in more than two separate groups and data was not uniformly distributed. Level of significance was tested by two tailed test. Statistical significance taken to be at $p < 0.05$.

RESULTS

Data on Expiratory: Inspiratory ratio of 207 study subjects and 392 non-diabetic healthy subjects on Expiratory: Inspiratory ratio was analysed. Findings of data analysis are presented below with suitable side headings.

Comparison of baseline characteristics of study and control groups

The mean age of study and control group did not differ significantly (55.54 ± 10.34, 54.23 ± 8.89, t = 1.61, p = 0.106). There was no significant difference in male, female distribution between study and control group (115 /92, 208 /184, Chi-square = 0.21, p = 0.639). Expiratory: Inspiratory ratio of study subjects was significantly lower compared to control group (1.27 ±0.14, 1.37 ± 0.11, Mann-Whitney U static = 21623, p < 0.0001).

Expiratory: Inspiratory ratio in different class interval of age in study and control group

Data on Expiratory: Inspiratory ratio of study and control group is presented in table 1. Expiratory: Inspiratory ratio of study and control subjects was significantly different among the different class interval of age (table 1).

Comparison of Expiratory: Inspiratory ratio between study and control group in different class interval of age

Data on comparison of Expiratory: Inspiratory ratio between study subjects and controls in different class interval of age is presented in table 2. Expiratory: Inspiratory ratio of study subjects in 41 to 50 years, 51 to 60 years, 61 to 70 years and 71-80 years had significantly lower compared to respective controls (table 2). Expiratory: Inspiratory ratio of study subjects in 40 year and below age group was not significantly different compared to control (table 2)

Clinical complications observed in study subjects

Frequency of study subjects with diabetes related complications were noted in different class interval of age separately and presented in table 3. Frequency of diabetics with hypertension, stable angina and somatic neuropathy was significantly different among the subjects in different class interval of age (table 3). Frequency of study subjects with myocardial infarction, retinopathy and micoralbuminurea did not differ significantly among the study subjects in different class interval of age (table 3).

Table 1. Comparison of Expiratory: Inspiratory ratio in different class interval of age in control and study group (Values are mean ± SD; sample size in parenthesis)

Groups	≤ 40 years	41-50 years	51-60 years	61-70 years	71-80 years	KW value	p value
Control group	1.44 ± 0.19 (n =14)	1.40 ± 0.10 (n = 143)	1.36 ± 0.11 (n = 136)	1.34 ± 0.11 (n= 92)	1.35 ± 0.12 (n = 7)	27.240	< 0.0001
Study group	1. 40 ± 0.08 (n =14)	1.33 ± 0.16 (n =56)	1.25 ± 0.11 (n =71)	1.23 ± 0.11 (n = 51)	1.18 ± 0.09 (n = 15)	32.175	< 0.0001

KW value= Kruskal-Wallis Statistic

Table 2. Comparison of Expiratory: Inspiratory ratio between study and control group in different class interval of age (values are mean ± SD; sample size in parenthesis)

Class interval of age	Control group	Study group	Mann-Whitney U-statistic value	p value
≤ 40 years	1.44 ± 0.19 (n =14)	1. 40 ± 0.08 (n =14)	0.96	0.71
41-50 years	1.40 ± 0.10 (n = 143)	1.33 ± 0.16 (n =56)	2608	< 0.0001
51-60 years	1.36 ± 0.11 (n = 136)	1.25 ± 0.11 (n =71)	2404	< 0.0001
61-70 years	1.34 ± 0.11(n= 92)	1.23 ± 0.11 (n = 51)	937	< 0.0001
71-80 years	1.35 ± 0.12 (n = 7)	1.18 ± 0.09 (n = 15)	9.0	0.001

Table3. Frequency of study subjects with diabetes related complications in different class interval of age (sample size and percentage of diabetes complications are in parenthesis)

Diabetes related complications	≤ 40 years (n = 14)	41-50 years (n = 56)	51-60 years (n= 71)	61 to 70 (n = 51)	71-80 (n = 15)	Chi-square	p value
Hypertension	3 (21.42%)	21 (37.5%)	34 (47.88%)	37 (72.5%)	11 (73.33%)	21.73	0.0003
Stable angina	nil	6 (10.71%)	2 (2.81%)	13 (25.49%)	4 (26.66%)	19.4	0.0007
Myocardial infarction	nil	4 (7.14%)	13 (18.30%)	12 (23.52%)	3 (20%)	8.74	0.06
Retinopathy	1 (7.14%)	12 (21.42%)	24 (33.80%)	18 (35.29%)	3 (20%)	7.52	0.11
Microalbuminurea	1 (7.14%)	4 (7.14%)	12 (16.90%)	11 (21.56%)	2 (13.33%)	5.46	0.24
Somatic neuropathy	1 (7.14%)	16 (28.57%)	39 (54.92%)	35 (68.62%)	12 (80%)	25.67	< 0.0001
Foot ulcer	nil	5 (8.92%)	11 (15.49%)	10 (19.60%)	3 (20%)	5.38	0.25

DISCUSSION

Influence of aging on heart rate response to deep breathing is well described. Therefore we assessed the cardiac parasympathetic function of patients with diabetes mellitus compared to age and sex matched control in different class interval of age. We also investigated the frequency of other diabetes related complications with regard to different class interval of age.

All the studies investigating the effect of aging on heart rate response to deep breathing have observed decline in heart rate response to deep breathing with aging [8, 9,12]. Accordingly in the present study, both in study subjects and in control Expiratory: Inspiratory ratio was significantly different among different class interval of age (table 1). This finding suggests that detection of cardiac parasympathetic dysfunction in patients under investigation should be considered after giving allowance for natural decline in cardiac parasympathetic activity with aging.

In the present study Expiratory: Inspiratory ratio of study subjects was lower compared to control in all the class interval of age except 40 years and below age group [table2]. Study subjects in 40 years and below age group were with very low frequency of diabetes related complications. Thus we speculate that in type 2 diabetes mellitus cardiac parasympathetic function mainly coexist with other diabetes related complications.

In the present study frequency of hypertension, stable angina and somatic neuropathy was significantly higher as age advanced. Heart disease is a leading cause of morbidity and mortality [13]. Somatic neuropathy is a major cause for foot ulcer [14]. Reduced Parasympathetic activity is associated with sudden unexplained deaths [15]. Therefore it could be suggested that screening for heart disease and diabetic neuropathy should be made mandatory for all the patients with diabetes mellitus especially after 40 years of age.

CONCLUSIONS

Expiratory: Inspiratory ratio is lower in patients with diabetes mellitus after 40 years of age. Somatic neuropathy, hypertension and stable angina increases with aging.

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