CARDIAC AUTONOMIC DYSFUNCTION AMONG RHEUMATOID ARTHRITIS: A MATCHED CASE CONTROL STUDY

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ABSTRACT:
Rheumatoid Arthritis (RA) was noted to be a chronic multisystem disease of unknown aetiology. It has a progressive course with exacerbation and remissions being part of its natural history. Overall, there is a 3:1 female preponderance, but this excess is greater in young people and the age-related incidence is approximately equal in elderly people. The prevalence of rheumatoid arthritis in India is about 0.75. Multiple studies report that in the past half century, mortality among people with diagnosed RA has increased compared with the general population. The present case control study was conducted to assess the abnormalities in cardiac autonomic dysfunction among the rheumatoid arthritis patents in comparison with the age and sex matched controls. Non-invasive tests such as Sustained Hand Grip test, Cold Pressor Test and Orthostatic Hypotension were used to assess the cardiac autonomic functions. The data was entered in spreadsheet and analyzed using appropriate test of significance in EPITOOLS software. Autonomic sympathetic dysfunction was noticed among the RA patients. The cascade of inflammation and immune mediated reactions has been suggested to play a role in severe autonomic dysfunction. Early diagnosis and interventions were suggested to halt the progression of Autonomic dysfunction among RA patients helping in improving their quality of life.

Key words: Rheumatoid arthritis, autonomous dysfunction, Cold Pressor Test, Hand Grip Dynamometer test.

INTRODUCTION

Rheumatoid Arthritis is a chronic multisystem disease of unknown aetiology. It has a progressive course with exacerbation and remissions being part of its natural history. Its onset could be at any age, although it usually starts in the fourth decade of life. Overall, there is a 3:1 female preponderance, but this excess is greater in young people and the age-related incidence is approximately equal in elderly people. The prevalence of rheumatoid arthritis in India is about 0.75% with an estimation of about seven million patients in India. [1]. Rheumatoid arthritis (RA) causes premature death, disability, and lowers the quality of life. Adults suffer from arthritis equal to approximately 23% of the population. Multiple studies report that in the past half century, mortality among people with diagnosed RA has increased compared with the general population [2,3]. Several studies have shown an increased incidence of cardiovascular events in patients with RA [4,5,6] Autonomic function tests are most widely used as they are non-invasive, results are easy to reproduce, and they reflect the state of Autonomic Nervous System (ANS) throughout the body.

Although the relationship between autoimmune diseases and ANS dysfunction has been the subject of many studies, there are still controversies concerning the role of ANS dysfunction in autoimmune diseases. Studies about ANS involvement in RA are limited, with conflicting result [7].

The objective of the study was to assess and compare the cardiac autonomic dysfunction among the rheumatoid arthritis and healthy controls.

MATERIALAND METHODS

STUDY DESIGN:

The current study was a hospital based matched case control study among the patients of rheumatoid arthritis and healthy controls.

STUDY DURATION:

The study was conducted for the period of two years, including the protocol designing, data collection, analysis and report writing.

SETTINGS:

The study was performed in the Department of Physiology, Tertiary care hospital of western India.

ETHICAL CONCERNS:

The study was approved by the institutional ethics committee of a tertiary teaching hospital in Western Maharashtra India. The informed consent was obtained from each of the study participant before their enrolment into the study.

SAMPLE SIZE CALCULATIONS AND ASSUMPTIONS:

Milovanovic B et. al. in 2010 performed case control study to determine the cardiac autonomic dysfunction among the patients of rheumatoid arthritis along with other autoimmune diseases and compared with the healthy controls. Accordingly various parameters measuring cardiac autonomic dysfunctions were measured. For practical purposes we considered the average expected proportion among controls was considered as 0.05 and Odds Ratio of 4.7 among the patients of rheumatoid arthritis. Using EPITOOLS online, with 95% confidence level and 80% power the sample size was estimated to be 74. Therefore, a sample of 75 was considered optimal in each of the group (cases and controls).

SELECTION OF CASES:

The individuals visiting to Outpatient Departments of Medicine & Orthopaedics in a tertiary care institution were subjected to a thorough clinical examination and the laboratory investigations as per the clinical protocol. The potential participants aged between 30-70 years of both sexes having diagnosed rheumatoid arthritis since at least five preceding years, were selected. The cases were selected according to the criteria published by American College of Rheumatology/European League Against Rheumatism in 2010 .[8]

Pregnant females and Patients with history of Diabetes mellitus, Renal and liver diseases, Parkinson's disease, Cardiovascular diseases, Neurological diseases, were excluded from the study.

SELECTION OF CONTROLS:

After selection of cases, the age and sex matched controls were selected among the accompanying persons. The persons having signs, symptoms and history of Musculo-skeletal

disorder or known case of joint disease in the family were excluded. Also, the pregnant women, individuals with Diabetes mellitus, known renal and liver diseases, Parkinson's disease, Cardiovascular diseases, Neurological diseases, were excluded.

All the study participants were evaluated with detailed history including age, sex, duration of Rheumatoid Arthritis, duration of morning stiffness, list of painful joints, other systemic disease, history of extra-articular manifestations and treatment.

ANTHROPOMETRIC MEASUREMENTS

Height:

Standing height of the subject was measured by simply making the subject to stand against a wall on which the measuring scale was inscribed. The subject would stand bare feet on a flat floor against the wall with the feet parallel and heels, buttocks and occiput touching the wall[9].The head was held erect and facing straight ahead positioned in Frankfort Horizontal Plane in which an imaginary line could be drawn from the bottom of the eye socket(orbital margin) to the external opening of the ear (external auditory meatus).Then with the help of plastic ruler, the top most point of the vertex compressing the hair was noted on the wall. The height was expressed in meters.

Weight:

Weight of the subject was measured using OMRAN digital weighing machine scale whose least count was 0.1kilogram (kg). To ensure that body weight is evenly distributed between both feet over the centre of the scale, the subject was asked to stand still, hold head up and face forward with arms hanging freely by the sides of the body, with palms facing the thighs. Weight was measured in light weight garments without footwear [10].

Procedure of Measurement of cardiac autonomic nervous functions:

Resting pulse rate:

The subjects were asked to lie down for 10 minutes. Thereafter the Radial pulse rate was measured among the three consecutive readings was recorded and expressed as beats/ min.

The Arterial blood pressure of each subject was recorded in the right arm in sitting position. The subject was seated quietly in a chair with back support, with both feet flat on the floor. The individuals were instructed to relax as much as possible and to not talk during the measurement procedure [11]. They were instructed to come after a night sleep of at least 8 hours. The subjects were asked to refrain from ingesting any beverages like tea or coffee and alcohol for at least 12 hours prior to the study. Details of procedures were described to each subject before starting the evaluation so that subject did not develop any anxiety at the time of the tests. No strenuous physical activity was to be performed for at least 1 hour before recording the blood pressure. Blood pressure was measured by using OMRON BP digital instrument, a mode was noted after three reading.

Orthostatic Test:

Basal blood pressure was taken with the patient lying down quietly. The individual was asked to stand up and immediately a second blood pressure reading was taken. A difference of systolic blood pressure (SBP) and diastolic blood pressure (DBP) more than 20 mm Hg between the standing and lying blood pressure was considered significant for autonomic dysfunction. The postural change in systolic and diastolic blood pressure was calculated by considering the difference in supine and standing positions.

Blood pressure response to cold pressor test

The subject was asked to sit comfortably in a chair and record the baseline blood pressure. Then subject was asked to immerse his hand in cold water maintained at4 – 6 0 C for 2 minutes. Blood pressure was recorded from the other arm at the end of 2 minutes. After 2 minutes the subject was allowed to remove the hand from cold water. Then maximum increase in systolic and diastolic blood pressure was determined. In any condition where there is deficient sympathetic outflow, the cold pressor test will be expected to show a smaller rise in blood pressure.

For blood pressure response to sustained hand grip test, the subject was asked to sit comfortably in chair. Initially he/she was asked to exert maximal hand grip strength on hand grip dynamometer (0 – 100 kg. by Anand Agencies Pune), with dominant hand. First the maximum voluntary contraction (MVC) (Maximal isometric tension i.e., T max) was 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 immediately before the release of hand grip pressure. Blood pressure response to the sustained hand grip test above 15 mmHg was considered as normal, 11 – 15 mmHg as borderline and less than 10 mmHg was considered abnormal (Ewing and Clarke grading).

The information was recorded on a predesigned and pretested semi structured proforma. Double entry of the data was made into Epi-data. Further the data was entered into spreadsheet, cross-checked, and cleaned by the independent observers.

The baseline and analytical variables were noted into the predetermined tables. The appropriate test of significance was employed wherever necessary. The interpretation and statistical significance were determined based upon p value less than 0.05 and the confidence interval. References were cited according to Vancouver style.

OBSERVATIONS

The study was performed with a total of seventy-five subjects among each of the case and control arms with ratio of 1:1. Observations summarized in the form of compound tables.

Table 1. Baseline characteristics of the study participants

Parameter	Male			Female		
	Cases* (n=75)	Controls* (n=75)	Significance	Cases* (n=75)	Controls* (n=75)	Significance
Age	50.69 (10.18)	48.47 (7.08)	t=1.059 p=0.2933 95%CI= -1.9625 to 6.4025	45.55 (7.08)	46.97 (5.36)	t=0.9460 p=0.3475 95%CI= -4.4752 to 1.5752
Height (cm)	161.06 (6.06)	161.12 (4.48)	t= 0.047 p=0.9626 95%CI= -2.6019 to 2.4814	152.26 (6.41)	150.73 (5.50)	t=1.0717 p=0.2877 95%CI= -1.3189 to 4.3789
Weight (kg)	66.44 (6.91)	67.24 (5.29)	t=0.5439 p=0.5883 95%CI= -3.7353	56.50 (7.77)	59.52 (11.80)	t= 1.2646 p=0.2103 95%CI= -7.7855

			to 2.1353			to 1.7455
*Heart Rate (per min)	86.00 (12.68)	81.76 (8.69)	t=1.6318 p=0.1073 95%CI=-0.9449 to 9.4249	83.03 (11.31)	79.55 (13.07)	t=1.1911 p=0.2377 95%CI= -2.3499 to 9.3099
*Systolic Blood Pressure	118.63 (7.15)	122.18 (13.31)	t=1.3900 p=0.1690 95%CI= -8.6462 to 1.5462	118.71 (8.42)	115.73 (12.02)	t= 1.2013 p=0.2338 95%CI= -1.9701 to 7.9301
*Diastolic Blood Pressure	74.75 (6.32)	72.06 (10.60)	t=1.6895 p=0.2016 95%CI= -1.4726 to 6.8526	76.35 (5.70)	75.70 (8.39)	t=0.3791 p=0.7059 95%CI= -2.7712 to 4.0712

*Measured in resting state

Table 2: Cardiac autonomic function test parameters among the cases and controls

Parameter	Cases*	Control*	Significance
Resting heart rate	85.98 (11.63)	78.6 (10.22)	t=2.03 p=0.04 95%CI = 0.1085- 11.2515
Resting Systolic Blood Pressure	123.68 (8.04)	113.42 (10.44)	t= 4.60 p=0.0001 95%CI = 5.8154 – 14.7046
Resting Diastolic Blood Pressure	76.88 (6.12)	73.15 (8.57)	t= 2.09 p=0.03 95%CI = 0.1780 – 7.2820
Fall in the Systolic blood pressure in the Cold pressor test	18.26 (6.31)	17.96 (3.42)	t= 0.70 p=0.4846 95%CI = -4.2150 – 2.0150
Fall in the Diastolic blood pressure in the Cold pressor test	12.7 (3.62)	10.64 (4.15)	t= 2.64 p= 0.009 95%CI = 0.5141 – 3.6059
Rise in the Systolic blood pressure in the Hand grip Dynamometer	6.06 (4.63)	13.32 (3.93)	t= 8.4621 p=0.0001 95%CI = -8.9632 - -5.5568
Rise in the Diastolic blood pressure in the Hand grip	14.46 (4.84)	18.8 (3.84)	t=4.97 p=0.0001 95%CI = 2.6071 – 6.0729

Dynamometer			
Orthostatic Systolic blood pressure fall	16.78 (5.91)	12.70 (3.70)	t=4.14 p=0.0001 95%CI = -6.0393 - -2.1207
Orthostatic Diastolic blood pressure fall	8.46 (4.23)	5.58 (2.25)	t=4.27 p=0.0001 95%CI = -4.2226 - -1.5374

*Mean and Standard deviation

Table 3: Comparison of cardiac autonomic dysfunction among the study participants

Autonomous dysfunction	Individual with abnormal parameters		Significance
	Cases (%)	Controls (%)	
High resting heart rate	6 (8.00)	4 (5.33)	X^2=0.4286 p=0.51
High Resting Systolic Blood Pressure	28 (37.33)	7 (9.33)	X^2=16.43 p=0.00005
High Resting Diastolic Blood Pressure	22 (29.33)	5 (6.67)	X^2=13.05 p=0.0003
Abnormally low Systolic blood pressure in the Cold pressor test	24 (32.00)	10 (13.33)	X^2=7.45 p=0.006
Abnormally low Diastolic blood pressure in the Cold pressor test	19 (25.33)	8 (10.67)	X^2=5.47 p=0.019
Abnormally low Systolic blood pressure in the Hand grip Dynamometer	21 (28.00)	10 (13.33)	X^2=4.92 p=0.03
Abnormally low Diastolic blood pressure in the Hand grip Dynamometer	15 (20.00)	9 (12.00)	X^2=1.79 p=0.18
Significant fall in the Orthostatic Systolic blood pressure	29 (38.67)	12 (16.00)	X^2=9.70 p=0.002
Significant fall in the Orthostatic Diastolic blood pressure	24 (32.00)	10 (13.33)	X^2=7.45 p=0.006
Total	75	75	150

Cases and controls were comparable with reference to males and females as there was no significant difference observed among them. There was no significant difference in the means

of resting heart rate, resting systolic and diastolic blood pressures among the cases of rheumatoid arthritis as compared with the controls. (Table 1)

The means of resting heart rate systolic and diastolic blood pressure was significantly higher among the cases as compared with the controls. The fall in the blood pressures (both systolic and diastolic) in the cold pressor test were higher among the rheumatoid arthritis. While the rise (more than 15 mm of Hg) in the corresponding blood pressures in the hand grip dynamometer test were significantly less among the cases than controls. There also observed significantly higher fall in the orthostatic systolic and diastolic blood pressures among the cases of rheumatoid arthritis. (Table 2)

In comparison with the controls, the larger proportion of cases of rheumatoid arthritis was noticed to have higher resting heart rate as well as increased both systolic and diastolic blood pressures in the resting condition. A total of 32% and 25.33% cases had significantly higher fall in the systolic and diastolic blood pressures respectively in cold pressure test as compared with 13.33% and 10.67% among the controls. Significantly higher proportion of cases (28% & 20% respectively for systolic and diastolic blood pressure) were noticed to have abnormally less rise in the blood pressures during the hand grip test. While significantly larger proportion of individuals among the cases of rheumatoid arthritis (38.67% and 32% respectively for systolic and diastolic blood pressure) showed abnormally high fall in the orthostatic blood pressure.

DISCUSSION

Earlier some studies were conducted to note some of the cardiovascular parameters among the rheumatoid arthritis. Similar to the observations of the current study, Mittal N. et. al. (2014) also noted higher resting heart rate among the cases of rheumatoid arthritis [7]. Piha SJ et. al. (1993) studied the role of physical deconditioning in the rheumatoid arthritis, which can be a reason for higher resting heart rate among the cases as compared with the controls [10].

Abnormal blood pressure response to sustained handgrip was noted among 20% of the rheumatoid arthritis patients as compared with the controls by Bidkar MP and Ichaporia RB. They also noticed blood pressure response among 22% cases of the rheumatoid arthritis during the cold pressor test [12]. The abnormal blood pressure among the rheumatoid arthritis cases attributing the systemic inflammation was explored by Yu et al. They studied the C-Reactive Protein (CRP) among the individuals having rheumatoid arthritis. It was observed that higher levels of CRP were correlated with the systolic blood pressure among these patients [13].

The earlier authors studied the Autonomic (Sympathetic) Nervous System Involvement in Rheumatoid Arthritis Patients. A significantly higher proportion of patients of rheumatoid arthritis showed more than 30 mmHg fall in the systolic blood pressure on standing upon supine position. The current study findings were in consistency with the observed evidence [11]. Edmonds et. al. [14] also noticed characteristic tachycardia and relative bradycardia more pronounced among young controls and with the older individuals with osteoarthritis.

CONCLUSION

The present study was performed to analyse the cardiac autonomic function test among the cases of Rheumatoid Arthritis in comparison with the age and sex matched controls. The study noticed higher resting heart rate as well as resting systolic and diastolic blood pressure among the individuals having rheumatoid arthritis. Abnormally autonomic responses were noted on the cold pressor test, handgrip test and the orthostatic hypotension test among the cases as compared with the controls. Substantially higher proportion of individuals had autonomic dysfunction among the rheumatoid arthritis group than the control group. The present study observed autonomic dysfunction more pronounced among the rheumatoid arthritis patients, which can be an indicator of significant deterioration of cardiovascular health of such individuals necessitating the need of early diagnosis and treatment to halt the progression of the disease.

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