

A STUDY OF CARDIOVASCULAR RESPONSES TO AUTONOMIC NERVE FUNCTIONS IN RHEUMATOID ARTHRITIS

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Background: Autonomic Neuropathy, found to be a strong predictor of sudden cardiac death, has been reported variably in patients with Rheumatoid Arthritis. **Material and method:** The study was carried out on 30 patients of rheumatoid arthritis, 20 healthy individuals as control. Patients were divided into three groups. Diagnosis of Rheumatoid Arthritis was based on the criteria developed by American Rheumatic Association. Assessment of cardiovascular autonomic nerve functions was performed using cardiovascular reflex tests. The results were complied, compared with each other and a conclusion was drawn. **Results:** Out of 30 patients in the study group, 20 patients had no autonomic neuropathy while 2 had mild autonomic neuropathy, moderate autonomic neuropathy was seen in 5 patients while 3 patients had severe autonomic neuropathy. All our patients having evidence of autonomic neuropathy had duration of rheumatoid arthritis of six or more years. Statistical analysis was performed by SPSS version 20.0. For all tests, $p < 0.05$ was considered significant. **Conclusion:** 33.33% patients had abnormal response to various cardiovascular autonomic nerve functions, 50% of which had symptoms of dysautonomia, 80% had evidence of peripheral neuropathy and all patients had duration of rheumatoid arthritis six or more years.

Key words: Rheumatoid Arthritis, dysautonomia, autonomic neuropathy.

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Introduction:

Rheumatoid arthritis is a systemic, chronic inflammatory disorder most commonly affecting the musculoskeletal system. It is characterized by symmetrical deforming polyarthritis that predominantly affects small joints such as the metacarpophalangeal, interphalangeal and metatarsophalangeal joints¹.

Apart from the joints, rheumatoid arthritis has also been implicated in involvement of skin, eye, heart, nervous and gastrointestinal systems. Being an inflammatory condition, rheumatoid arthritis affects the cardiovascular system in the form of increased intimo-medial thickness, endothelial dysfunction and in general, a higher prevalence of atherosclerosis. These extra-articular manifestations have been found to be strong predictors of decreased survival in patients of rheumatoid arthritis². Although the involvement of the central and peripheral nervous system is well known in rheumatoid arthritis, knowledge on the involvement of the autonomic nervous system is scarce³. Studies about autonomic nervous system (ANS) involvement in rheumatoid arthritis are

limited, with conflicting results. The autonomic nervous system comprises parasympathetic and sympathetic nerves⁴. Autonomic Neuropathy may present as sweating disturbances, diarrhoea or constipation, bladder dysfunction, deranged breathing control or erectile dysfunction⁵. These effects, though subtle, significantly affect the patient's quality of life. Cardiovascular Autonomic Neuropathy (CAN) which is associated with deranged heart rate control and vascular dynamics has been linked to serious complications like myocardial infarction, arrhythmias and sudden cardiac death⁶. The aim of the study was carried out to find first the incidence of various symptoms of autonomic nerve dysfunction in patients suffering from rheumatoid arthritis. Second the incidence of abnormal response to various cardiovascular autonomic nerve functions in patients of rheumatoid arthritis. Third the correlation of abnormal cardiovascular autonomic responses with symptoms of autonomic nerve dysfunction in patients suffering from rheumatoid arthritis.

Material and Methods:

This study was carried out on 30 patients of Rheumatoid arthritis admitted in medical or orthopedics ward and OPD in Mamata Medical College and 20 healthy individuals as a control group. Out of 30 patients of rheumatoid arthritis 14 were males and 16 was females. The age of the patients and control was in the range of 25 to 48 years. Patients were divided into three groups, Group I from 21 to 30 years, Group II from 31 to 40 years, Group III from 41 to 50 years. Duration of Rheumatoid arthritis in the study group varied from 1 to 15 years with a mean of 4.70 ± 3.90 years. Diagnosis of Rheumatoid Arthritis was based on the criteria developed by American Rheumatism Association⁷. A detailed clinical history and clinical examination with special reference to features of autonomic neuropathy were recorded in each case as per proforma. Patients having associated diabetes mellitus, impaired glucose tolerance, cardiorespiratory diseases, chronic renal failure, malignancy of any site, amyloid diseases, alcoholics and those on drugs like tranquilizers, antidepressants and antihypertensive were excluded from the study⁸. The various tests were performed in following order: (i) Heart rate response to Valsalva manoeuvre, (ii) Heart rate variation during deep breathing, (iii) Immediate heart rate response to standing, (iv) Blood pressure response to standing, (v) Blood pressure response to sustained hand grip. The first three tests were used to evaluate parasympathetic integrity. The other two were used for evaluating sympathetic functions⁹.

Heart rate response to Valsalva manoeuvre: The test was performed and the results were expressed as Valsalva ratio = Longest R-R interval after manoeuvre / Shortest R-R interval during manoeuvre. The mean of three ratios was used in statistical evaluation. Valsalva ratio of 1.10 or less is defined as abnormal response, 1.21 or greater as a normal response and 1.11 to 1.20 as borderline^{10, 11}.

Heart rate variation during deep breathing: The result is then expressed as the mean of the difference between the maximum and minimum heart rate for the six measured cycles in beats a

minute. A value of ≥ 15 beats per minute is taken as normal, 11 – 14 beats per minute as borderline and ≤ 10 beats per minute as abnormal¹⁰.

Immediate heart rate response to standing: Longest R-R interval after standing / Shortest R-R interval after standing^{12, 13}.

Blood pressure response to standing: The response is taken as normal when fall in systolic blood pressure is less than 10 mmHg, borderline if it is 11 – 29 mmHg and a fall in blood pressure of 30 mmHg or more is taken as an abnormal response¹⁰.

Blood pressure response to sustained hand grip: The result was expressed as difference between the highest diastolic blood pressure recorded during hand grip and mean of the three diastolic pressure recording before the hand grip began. The rise in blood pressure is defined as abnormal if it is 10 mmHg or less, borderline if it is between 11 – 15 mmHg and normal if it is 16 mmHg or more¹⁴.

Result: A total number of 30 patients of rheumatoid arthritis and 20 controls consented to participate in the study.

Table 1: Symptoms pertaining to autonomic neuropathy and their prevalence in the study group.

	Symptoms	No. of Patients	Percentage (%)
1	Bladder dysfunction a) Retention of urine b) Incontinence	3 2	10.00 6.66
2	Impotence	1	7.14 (male)
3	Symptoms on standing a) Dizziness b) Visual impairment	2 2	6.66 6.66
4	Diarrhoea	2	6.66
5	Gustatory sweating	1	3.33

The symptoms pertaining to autonomic neuropathy were present in 5 (16.66%) patients. Impotence in one (7.14%) while 2 (6.66%) had diarrhea. One (3.33%) gave history of gustatory

sweating. Pupillary abnormalities were not observed in any patients. 8 (26.67%) patients had peripheral neuropathy. All these eight patients had sensory neuropathy in form of impairment of pain, vibration and touch sensation, motor involvement was also found in 2 (6.66%) patients who had loss of ankle jerks. None of the subjects in control group had evidence of peripheral neuropathy, based on clinical evidence only.

Table 2: Comparison of resting heart rate

	Mean Resting Heart Rate	S.D	t	p
S.G	86.49	± 9.63	2.59	< 0.02
C.G	79.91	± 6.88		

S.G: Study Group, C.G: Control Group, P <0.05 the result was significant.

All the patients had normal sinus rhythm. In study group resting heart rate varied from 71.54 to 111.11 per minute. In control group the resting heart rate varied from 69.76 to 90.90 per minute.

Table 3: Showing results of various tests in ten patients having evidence of autonomic neuropathy.

Tests of Cardiovascular responses to autonomic nerve function							
S.No	Valsalva Ratio	Heart Rate variation During deep breathing	Heart Rate Response to Standing	B.P response to Sustained hand grip	B.P response to standing	Number of Symptoms of dysautonomia	Rheumatoid factor
1	N	A	N	N	N	Nil	P
2	A	A	A	B	A	4	P
3	B	A	A	N	B	Nil	P
4	B	A	A	N	B	Nil	P
5	B	A	N	N	B	Nil	P
6	A	A	A	A	A	2	P
7	A	A	A	B	B	2	P
8	A	A	A	N	B	2	N

9	A	A	A	N	B	Nil	P
10	A	A	A	A	A	3	N

N = Normal Response, B = Borderline Response, A = Abnormal Response, P = Positive, N = Negative.

Table 4: Showing Comparison of different autonomic function tests among study group and control group.

		S.D	t	p
Valsalva Ratio				
S.G	1.40	± 0.26	4.50	<0.01
C.G	1.71	± 0.20		
Heart Rate Variation During Deep Breathing				
S.G	21.72	± 10.58	3.11	<0.01
C.G	29.53	± 3.76		
Maximum: Minimum Ratio after Standing				
S.G	1.19	± 0.14	1.69	<0.10
C.G	1.29	± 0.06		
Increase in Diastolic B.P During Hand Grip				
S.G	21.42	± 5.85	1.58	<0.10
C.G	23.83	± 4.01		
Fall in Systolic B.P on Standing				
S.G	9.27	± 9.55	1.79	<0.10
C.G	5.17	± 3.90		

S.G: Study Group,

C.G: Control Group

P <0.05 the result was significant.

Table 5: Showing extent of Autonomic Nervous system damage.

	Extent of Autonomic Neuropathy	Number of Patients
1	No Autonomic Neuropathy	20 (66.67%)
2	Mild Autonomic Neuropathy	2 (6.66%)
3	Moderate	5

	Autonomic Neuropathy	(16.66%)
4	Severe Autonomic Neuropathy	3 (10.00%)

9	Moderate	Nil	8
10	Severe	3	12

Figure 1

Prevalence and Extent of Peripheral Neuropathy among patients of rheumatoid arthritis having autonomic neuropathy of varying severity.

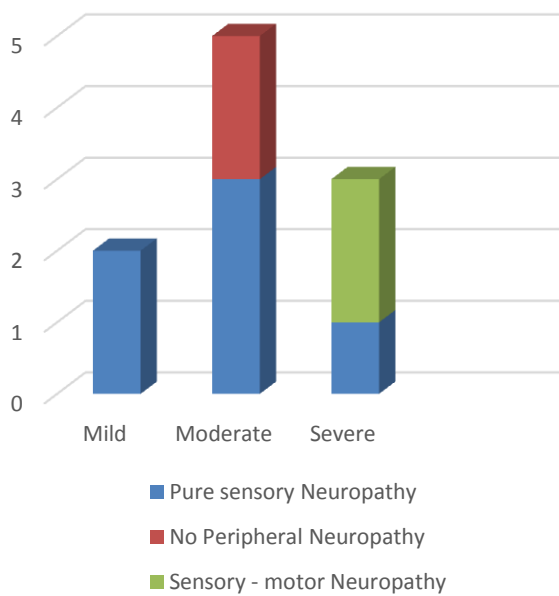


Table 6: Correlation of extent of Autonomic Neuropathy, Number of symptoms of autonomic neuropathy and Duration of Rheumatoid Arthritis.

	Extent of Autonomic Neuropathy	Number of Symptoms of Autonomic Neuropathy	Duration Of Rheumatoid Arthritis (in Years)
1	Mild	Nil	6
2	Severe	4	15
3	Moderate	Nil	11
4	Moderate	Nil	10
5	Mild	Nil	6
6	Severe	2	7
7	Moderate	2	6
8	Moderate	2	13

Discussion: In total 10 (33.33%) patients showed definite abnormal response to one or more tests of autonomic function.

Table 2, the mean resting heart rate in the study group was 86.49 ± 9.63 per minute as compared to 79.91 ± 6.88 per minute in the control group and this difference was statistically significant ($p < 0.02$)^{15,16}. None of these patients showed evidence of atrial or ventricular hypertrophy, conduction abnormalities or myocardial ischemia or infarction on ECG.

From above Table 3 in the study group 6 (20%) patients had an abnormal Valsalva ratio (< 1.10) while in 3 (10%) patients it was borderline (1.11 to 1.20). out of the 6 patients having abnormal Valsalva ratio, 5 patients had two or more symptoms of autonomic neuropathy Table 3, thus indicating that abnormal Valsalva ratio correlated well with the damage to autonomic nervous system. Also the mean value of Valsalva ratio was statistically lower in the study group than in the control group ($p < 0.01$) Table 4. These six patients with abnormal Valsalva ratio had impaired heart rate variation during deep breathing and impaired heart rate response to standing Table 3. Thus Valsalva ratio correlated well with the other tests of parasympathetic function.

Heart rate variation during deep breathing was abnormally impaired in 10 (33.33%) patients while one (3.33%) patient showed a borderline response Table 3, the mean heart rate variation during deep breathing in the study group was 21.72 ± 10.58 beats per minute as compared to 29.53 ± 3.76 beats per minute in the control group Table 4. This difference is statistically highly significant ($p < 0.01$) our result are in accordance with those of Edmonds et al^{15,16}. Out of these 10 patients with abnormal heart rate variation during deep breathing 8 had abnormal heart response to standing and 6 had abnormal Valsalva ratio Table 3. Also this test was abnormal in maximum number i.e. 10 patients of rheumatoid arthritis, so it suggests that this is the most sensitive tests of

parasympathetic function and possibly the earliest one to get impaired in the patients with autonomic neuropathy as two patients with abnormal heart rate response to deep breathing did not have any other test of autonomic function abnormal. This test correlates well with the symptoms of dysautonomia as 5 out of the 10 patients with abnormal heart rate variation during deep breathing had symptoms of dysautonomia Table 3.

Immediate heart rate response to standing was impaired in 8 (26.67%) patients in the study group Table 3, our results are quite identical to the results of Edmonds et al¹⁵. On statistical analysis the difference was found to be insignificant ($p < 0.10$) Table 4, but this can be explained by the fact that 22 patients of study group had normal value thus, affecting the mean value significantly and reducing the difference between the mean value in two groups to statistically insignificant¹⁶. 5 out of these 8 patients had symptoms of dysautonomia, thereby indicating that this test correlates well with the damage to autonomic nervous system Table 3. All these 8 patients having abnormal maximum: minimum ratio had abnormal heart rate response to standing and 6 out of 8 had abnormal Valsalva ratio Table 3.

Blood pressure response to sustained handgrip was abnormal (< 10 mmHg) in 2 (6.66%) patients while another 2 (6.66%) patients showed a borderline response (11-15 mmHg) Table 3. The mean value for this test in the study group did not differ statistically from the control group ($p < 0.10$) Table 4. None of the studies are available, but it has been widely used in the diagnosis of diabetic autonomic neuropathy. All these 4 patients had symptoms of dysautonomia, thus indicating that this test correlates well with the damage to autonomic nerves Table 3. Also both the patients with abnormal results of this test also had abnormal blood pressure response to standing Table 3, thereby indicating that this test correlates well with the other tests of sympathetic function.

Blood pressure response to standing was abnormal in 3 (10%) patients while 6 (20%) patients showed a borderline response to this test Table 3. The mean value for this test in the study group did not differ statistically from the control group ($p < 0.10$)

Table 4. All the 3 patients having abnormal value for this test had symptoms of dysautonomia. Also out of these 3 patients, 2 patients had abnormal response to sustained handgrip while one patient showed borderline response to sustained handgrip Table 3. This indicates that this test correlates well with other tests of sympathetic function. This test has also not been performed on the patients of rheumatoid arthritis but widely used in diabetics to detect autonomic neuropathy.

All the 10 patients had abnormal responses to the tests of parasympathetic functions while abnormality in the tests of sympathetic functions co-existed in 3 of them and none of the patients showed evidence of sympathetic damage without co-existing evidence of parasympathetic damage. This may suggest that parasympathetic damage occurs earlier than sympathetic damage Table 3¹⁷.

When we the results of all the five tests were tabulated, we could categorized all the patients in the four groups after slightly modifying the criteria suggested by Ewing and Clarke (1982). Out of 30 patients in the study group, 20 (66.67%) patients had no autonomic neuropathy while 2 (6.66%) patients had mild autonomic neuropathy. Moderate autonomic neuropathy was seen in 5 (16.66%) patients while 3 (10%) patients had severe autonomic neuropathy Table 5^{15, 16}.

As per Figure 1 peripheral neuropathy co-existed with autonomic neuropathy in 8 patients among 10 patients giving abnormal results for the tests of autonomic neuropathy. Among the 7 patients with mild to moderate autonomic neuropathy, 5 patients had sensory neuropathy, among 3 patients with severe autonomic neuropathy one patient had pure sensory and two patients had sensorimotor neuropathy^{15, 16}. In our study in two out of 10 patients with dysautonomia, no clinical evidence of peripheral neuropathy was found. But this study was based only on clinical observation of peripheral neuropathy as we did not perform nerve conduction studies to rule out presence or absence of peripheral neuropathy in these two patients. Nerve conduction studies facility was not available at time. Also in the 20 patients with no evidence of autonomic neuropathy, we did not perform nerve conduction studies. Therefore the

observation that peripheral neuropathy did not exist in these 20 patients is also based on clinical evidence only.

As per Table 6 all our patients having evidence of autonomic neuropathy had duration of rheumatoid arthritis of six or more years, this is contrary to the results of Edmonds study¹⁵. This aspect needs further studies for definite evaluation.

Conclusion: At the end of the study, it was concluded that the incidence of various symptoms of autonomic dysfunction in patients of rheumatoid arthritis was 16.66%. Incidence of abnormal responses to various cardiovascular autonomic nerve functions in patients of rheumatoid arthritis was 33.33% and the damage to parasympathetic fibers occurred before the onset of sympathetic damage. 50% of patients having abnormal response to one or more tests of cardiovascular autonomic nerve functions had clinical evidence of peripheral neuropathy. In all the patients where duration of rheumatoid arthritis was six or more years, abnormal response to the tests of cardiovascular autonomic nerve functions was detected.

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