A Case Control Study of Heart Rate Variability in Rheumatoid Arthritis female patients

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ABSTRACT

Introduction
Rheumatoid arthritis (RA) is a chronic multisystem progressive autoimmune inflammatory connective tissue disease of unknown aetiology characterized by joint swelling, joint tenderness, decreased range of motion and destruction of synovial joints, in symmetric distribution and in some cases, extra articular involvement leading to severe disability and premature mortality. Rheumatoid arthritis can begin at any age, but has its peak between 35 to 55 years of age. The prevalence of RA is around 0.5 -1% worldwide with women suffering 2-3 times more than men. Among the cases of nervous system involvement in RA, those of the peripheral nervous system are well documented; a few studies have been done to study autonomic neuropathy in rheumatoid arthritis.

Keywords: Heart Rate Variability (HRV), Rheumatoid Arthritis (RA)

Analysis of heart rate variability (HRV) nowadays has become one of the most popular non-invasive tools for the detection of early sympathetically-parasympathetically mediated changes in the autonomic nervous system dysfunction. Low variability in HR implies poor or inhibited ability to maintain internal homeostasis. Generally sympathetic influence increases HR (tachycardia response) and lowers variability of the heart rate, while parasympathetic input slows the HR (bradycardia response) and increases the variability. Low HRV is a known predictor of mortality in many clinical populations and it is associated with several cardiovascular risk factors. The present study is an attempt to an early understanding of the autonomic nervous system dysfunctions in rheumatoid arthritis patients using HRV to prevent cardiovascular morbidity and mortality in these patients.

Material and Methods
The present study was conducted in the Upgraded department of Physiology in collaboration with the Department of Medicine, S.M.S. Medical College and Hospital, Jaipur, Rajasthan from 1st June 2015 to 31st May 2016 on 45 RA female patients between the age group of 35-45 years taken from the Department of Medicine, S.M.S. Hospital, Jaipur along with 45 age and BMI matched healthy female controls taken from accompanying attendants of the patients.

All subjects gave informed written consent.

Inclusion Criteria: 35-45 yrs. aged newly diagnosed Rheumatoid Arthritis female patients, as per the 2010 ACR-EULAR CLASSIFICATION CRITERIA and Age and BMI matched healthy female controls subjects in the follicular phase of regular menstrual cycle (28 days) were included in the study.

Exclusion Criteria: Pregnancy, smoker, chronic diseases and drugs affecting autonomic functions were excluded from the study.

All subjects were tested between 11 am to 1.00 pm under similar laboratory conditions and were allowed to adapt themselves to experimental and environmental condition for 30 minutes to make them comfortable, as anxiety and stress can affect autonomic functions. The subjects were asked to avoid coffee, nicotine or alcohol 24 hours prior and food 2 hours’ prior of autonomic function test. The room ambient temperature was maintained at 24-25°C. A thorough history was taken and general physical examination was done to screen out the subjects.

The assessment of Heart Rate Variability was done by recording with Polygraph (RMS Polyrite D, version 1.0) based on the principle of EKG.

For short term analysis of HRV ECG was recorded in the supine posture for 5 minute after 15 minutes of supine rest in a quiet environment.

Conclusion– Decreased heart rate variability indicates deranged cardiovascular autonomic functions in RA patients.
Following parameters of HRV were included in the study:

Frequency Domain HRV Parameter:
- TP ('Total power') in ms
- LF (Power in low frequency range) in ms²
- HF (Power in high frequency range) in ms²
- LF n.u. (normalized unit) in %
- HF n.u. (normalized unit) in %
- LF/HF ratio

The analogue ECG signals were converted to digital signal and stored in the computer for offline Frequency Domain Analysis. In the Frequency Domain analysis, the power spectrum for HRV was calculated with the Fast Fourier Transformation (FFT) based method.

Statistical Analysis: Statistical analysis was performed using SPSS software version 20 and Z-test was used to derive the level of significance.

**OBSERVATIONS AND TABLES**

**Table 1**
Comparison of anthropometric and baseline clinical characteristics of cases and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case (n=45)</th>
<th>Control (n=45)</th>
<th>Z-value</th>
<th>p-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.)</td>
<td>39.82 ± 4.11</td>
<td>38.64 ± 3.06</td>
<td>1.573</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.14 ± 2.42</td>
<td>23.29 ± 1.83</td>
<td>1.89</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>119.53 ± 7.78</td>
<td>116.78 ± 8.16</td>
<td>1.637</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81.13 ± 7.16</td>
<td>79.22 ± 7.42</td>
<td>1.242</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>HR (Beats/min)</td>
<td>79.73 ± 10.43</td>
<td>76.38 ± 12.08</td>
<td>1.408</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>RR (per min)</td>
<td>11.62 ± 1.68</td>
<td>11.38 ± 1.39</td>
<td>0.738</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (Body mass index), SBP (Systolic blood pressure), DBP (Diastolic blood pressure), HR (Heart rate), RR (Respiratory rate)</td>
<td>NS (not significant)</td>
<td>NS (not significant)</td>
<td>NS (not significant)</td>
<td>NS (not significant)</td>
<td>NS (not significant)</td>
</tr>
</tbody>
</table>

**Table 2**
Comparison of Frequency domain HRV parameters of Case & Control group subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case (n=45)</th>
<th>Control (n=45)</th>
<th>Z-value</th>
<th>p-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total power (ms²)</td>
<td>344.649 ± 230.54</td>
<td>478.835 ± 297.16</td>
<td>2.394</td>
<td>&lt;0.05</td>
<td>Sig</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>88.043 ± 76.38</td>
<td>105.150 ± 95.62</td>
<td>0.938</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>55.359 ± 50.00</td>
<td>185.200 ± 130.52</td>
<td>6.232</td>
<td>&lt;0.001</td>
<td>HS</td>
</tr>
<tr>
<td>LF nu (%)</td>
<td>61.922 ± 10.50</td>
<td>33.198 ± 8.22</td>
<td>14.449</td>
<td>&lt;0.001</td>
<td>HS</td>
</tr>
<tr>
<td>HF nu (%)</td>
<td>38.078 ± 10.50</td>
<td>66.802 ± 8.22</td>
<td>14.456</td>
<td>&lt;0.001</td>
<td>HS</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>1.781 ± 0.61</td>
<td>0.521 ± 0.19</td>
<td>13.263</td>
<td>&lt;0.001</td>
<td>HS</td>
</tr>
</tbody>
</table>

NS (not significant), HS (Highly significant)

**RESULTS**

The mean of Total power (ms²) for the RA patients was 344.649 ± 230.54 and of the control groups was 478.835 ± 297.16. (Table 2) (p-value <0.05) (Bar diagram 1)

The mean of low frequency component LF (ms²) for RA patients was 88.043 ± 76.38 as compared to the control subjects where mean was 105.150 ± 95.62. (Table 2) (p-value <0.001) (Bar diagram 1)

The mean of high frequency component (HF ms²) for the RA patients was 55.359 ± 50.00 and of the control groups was 185.20 ± 130.52. (Table 2) (p-value <0.001) (Bar diagram 1)

**DISCUSSION**

In RA patients the morbidity and mortality is attributed more to its cardiovascular complications rather than the disease itself.

Autonomic imbalance, characterized by a hyperactive sympathetic system and a hypoactive parasympathetic system, is found in various pathological conditions including rheumatoid arthritis [9].

HRV is a non-invasive and cost effective method to assess autonomic imbalances and cardiovascular risk in RA patients [10]. There is little literature concerning HF power reflecting primarily parasympathetic influences, LF power has been shown to reflect both sympathetic and parasympathetic influences [11].

We found total power (ms²) with p value <0.05 (Table 2, Bar diagram 1), HF (ms²) and HF n.u. (%) with p value <0.001 (Table 2, Bar diagram 1 and 2) significantly lower whereas LF n.u. (%) and LF/HF ratio with p value <0.001 (Table 2, Bar diagram 2 and 3) significantly higher in RA patients as compared to healthy control group. Our study results are comparable with study conducted by Evrengul H et al (2004) [12], Janse Van Rensburg DC et al (2012) [13], Jahan K et al (2012) [14]. In this study using frequency domain HRV parameters, the RA group showed less heart rate variability compared to healthy control group.

The pathophysiological basis of the development of autonomic nerve dysfunction in RA patients is not clearly known. However contribution of a direct immunological damage to components of neural pathways can be postulated which is supported by the demonstration of circulating complement fixing auto antibodies directed against sympathetic and parasympathetic nervous structures, represented by superior cervical ganglia and vagus nerve, respectively, in patients with SLE and RA [15].
One another mechanism that is presumed for derangement of autonomic function in RA patients was an increased outflow of the sympathetic nervous system (SNS) and a decreased tone of the hypothalamic–pituitary–adrenal (HPA) axis in patients with SLE and RA. NPY is an excellent indicator of sympathetic activity. Both norepinephrine and NPY are released from sympathetic nerve terminals but there is differential release of norepinephrine and NPY, from nerve terminals. Norepinephrine is released at low stimulation frequencies, whereas norepinephrine and NPY are released together at higher stimulation frequencies.

The sympathetic nervous system plays a dual role, which presumably depends on the ligation of sympathetic neurotransmitters at either α2-adrenoceptors (proinflammatory) or β-adrenoceptors (anti-inflammatory) in the synovial tissue. The differential effects of sympathetic neurotransmitters are consistent with the concept that stimulation of β-adrenoceptors increases intracellular cAMP, which inhibits production of proinflammatory cytokines such as TNF, interferon-γ, IL-2, and IL-12 while α2-adrenergic receptor mechanisms are involved in sensitization of primary afferent sensory nerve fibers, leading to release of proinflammatory substance P into the lumen of the joint. In RA sympathetic nervous system is dominant over HPA axis so there is increased serum NPY/serum cortisol ratio which is pro-inflammatory due to uncoupling of the local inflammation from the anti-inflammatory input by the CNS. In addition, disease related factors such as depression, chronic pain, weight gain, and others may add to the uncoupling phenomenon.

Thus regular assessment of autonomic functions can be used as a biomarker for early detection and subsequent management of cardiovascular morbidity and mortality in RA patients.

CONCLUSION
It is concluded that Rheumatoid Arthritis patients have sympathetic hyperactivity and reduced parasympathetic activity, when compared with the normal subjects.

Thus, this study signifies the importance of non-invasive methods for screening of autonomic nerve functions status in RA patients. This early detection is important for timely prevention and management of severe consequences of cardiac autonomic impairment such as arrhythmias and sudden death.

STRENGTH, LIMITATIONS AND RECOMMENDATIONS
Certainly, the strength of our study is the careful selection of the subjects and an effort to rule out all possible confounding factors which can affect the results. The study was conducted in a limited time on a small sample size. Better results may be obtained with a large sample size over a longer time.

REFERENCES