Pulse Wave Velocity and Electroneurophysiological Evaluation in patients of Rheumatoid Arthritis

Geetanjali Sharma* MD, Sushma Sood** MD, R. Handa† MD and H. Singh‡ MD

*Assistant Professor, **Senior Professor and Head, Department of Physiology
†Resident, ‡Senior Professor and Head, Department of Rheumatology
University of Health Sciences, Rohtak, Haryana, India

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ABSTRACT: Rheumatoid arthritis is a chronic systemic inflammatory disease of undetermined etiology involving the synovial membranes and articular structures of multiple joints and is also associated with carditis, pleuritis, hepatitis, peripheral neuropathy and vasculitis. The present study was undertaken to investigate arterial stiffness using carotid-radial and femoral-dorsalis pedis pulse wave velocity measurements and electrophysiological tests for peripheral nervous system involvement. 25 patients (aged between 20-60 years) with rheumatoid arthritis according to the criteria of the American College of Rheumatology and 25 control subjects of the same age and sex were recruited. In the motor conduction studies, out of 25 patients of Rheumatoid arthritis, 6 had clinical evidence of peripheral neuropathy. 11 patients showed pure sensory neuropathy (44%), 10 showed mixed sensory motor neuropathy (40%) while 4 showed normal motor and sensory conduction velocity. Two patients (8%) showed features of entrapment neuropathy of median nerve i.e. feature of Carpal tunnel syndrome. In the pulse wave velocity evaluation statistically significant increase in pulse wave velocity between femoral-dorsalis pedis and carotid-radial artery segments was observed in Rheumatoid arthritis patients as compared to the control group. Measurement of carotid-radial and femoral-dorsalis pedis PWV may provide a simple and non-invasive technique for identifying patients at increased risk of vascular disease in Rheumatoid arthritis.

KEY WORDS: Peripheral neuropathy; Nerve conduction; Vascular events

INTRODUCTION

Rheumatoid arthritis is a chronic systemic inflammatory disease of undetermined etiology involving synovial membranes and articular surfaces of multiple joints in a symmetrical manner. Females are affected approximately three times more than men. It begins with pain, stiffness and swelling of specific joints such as proximal interphalangeal, metacarpophalangeal and knee joints. These include rheumatoid nodules, pulmonary manifestations, pericarditis and vasculitis. Neurological manifestations in Rheumatoid arthritis include peripheral neuropathy, cervical myelopathy, entrapment neuropathy and vasculitis. Golding & Mackenzie were the first to describe a series of patients with neuropathy and rheumatoid disease. There are three causes of neuropathy in Rheumatoid arthritis; nerve entrapment- the nerve being compressed by inflamed synovium against a fixed structure, nerve ischemia and due to drugs used in Rheumatoid arthritis. Distal sensory neuropathy is frequently reported in rheumatoid arthritis where 1-10% of patients may develop vasculitic neuropathy; sensory neuropathy may occur in up to 75% patients based on clinical and electrophysiological evaluation. It is often difficult to diagnose slight or early neuropathies due to pain in the joints and limitation of movements. One of the clinical hallmarks of vasculitis i.e. systemic arteritis is the appearance of neurological findings; but by electrophysiological studies, subclinical neuropathies can be detected earlier. Nerve
conduction studies not only confirm the presence of neuropathy and also give indication of the type of neuropathy, e.g. axonal neuropathy is characterized by a reduction in amplitude of the compound muscle action potential or compound nerve action potential, demyelination neuropathy is characterized by prolonged latency and prolonged slowing of conduction and chronic compressive lesions produce localized slowing of conduction. Rheumatoid arthritis is associated with increase cardio-vascular morbidity and mortality; pulse wave velocity is an index of arterial stiffness and a marker of cardio-vascular events.

The present study is aimed to investigate the arterial stiffness using carotid-radial and femoral-dorsalis pedis pulse wave velocity measurements in patients of Rheumatoid arthritis and electrophysiological tests to find out the incidence of early peripheral nervous system involvement in patients of Rheumatoid arthritis.

**METHODOLOGY**

The present study was carried out in the Department of Physiology, Pt. B.D. Sharma University of Health Sciences, Rohtak on 50 subjects (25 patients aged between 20-60 years diagnosed as Rheumatoid arthritis clinically as per American criteria of Rheumatology and 25 control subjects matched for age and sex). The duration of disease in the patients was ranging from 10.56 ± 6.7 years (mean ± standard deviation), the DAS score was 3.1-5.1 and all patients attended the Rheumatology clinic with or without clinical evidence of neuropathy. Patients with diabetes mellitus, severe anaemia, hypothyroidism, alcoholism and other metabolic or toxic causes of neuropathy were excluded from the study.

**Recording of nerve conduction velocities**

The nerve conduction velocity was recorded using RMS EMG EP Mark II machine (Chandigarh). The placement of Electrodes was as per Mishra et al. The parameters recorded were:

- **Motor conduction studies**: Median, ulnar, tibial and peroneal conduction velocities (CV), distal latencies (L) and amplitudes (A).

- **Sensory conduction studies**: Sensory median and sural conduction velocity (CV), distal latencies (L) and amplitudes (A) by ring electrodes.

The cut off points for each parameter were considered as below:

- **Upper limb (motor)**: CV < 52.12, L > 3.75, and A < 10.04 are indicative of neuropathy.
- **Lower Limb (motor)**: CV < 44.2, L > 8.4 and A < 8.93 are indicative of neuropathy.
- **Upper limb (sensory)**: CV < 53.76, L > 2.72 and A < 0.088 are indicative of neuropathy.

**Lower Limb (sensory)**: CV < 41.2, L >3.63 and A < 0.22 are indicative of neuropathy.

**Recording of Pulse Wave Velocity (PWV)**

The pulse wave velocity was recorded with the help of Polywrite-4 channel machine (INCO) as from the left carotid in the neck to the left radial artery at the wrist (C-R) and from the left femoral artery just below the inguinal ligament to the left Dorsalis pedis artery in the foot (F-DP). The pulse wave at various points was recorded using pulse transducers having in built photo-detectors and light sources. Recording of arterial pulse was taken on 4 channel polygraph paper (Polywrite INCO) at a paper speed of 25 mm/sec.

**Figure 1: Polywrite for recording PWV**

For the arterial segment C-R, the pulse wave velocity was obtained by measuring the time delay between the onset of pulse waves in the carotid and radial arteries. Similarly, the time delay between the onset of pulse waves in the femoral and dorsalis pedis arteries was measured for F-DP segment. The time delay (t) of the pulse wave was measured using these points and was expressed in milliseconds. The length of the arterial segments (L) was measured on the surface of body of the patient with the help of measuring tape. The pulse wave velocity (meters/sec) was calculated by using the formula L/t. Only clearly defined tracings were analyzed (Figure 2 and 3).
Statistical analysis

The standard statistical procedure unpaired t-test (2 tailed) was used to compare values in both control and Guillain Barre Syndrome groups and ‘p’ value was derived. P<0.001 indicates statistically significant findings. The statistical analysis was done on Microsoft Office Excel 2007.

RESULTS

Out of 25 patients of Rheumatoid arthritis, 23 were females while two were males with mean age 44.4 ± 10.8 years. The mean duration of disease was 10.56 ± 6.1 years.

Conduction studies

Out of 25 patients of Rheumatoid arthritis, 6 had clinical evidence of peripheral neuropathy in the form of paraesthesia, loss of deep tendon reflexes and loss of vibration sense while remaining 19 subjects showed no clinical evidence of neuropathy. Eleven patients showed pure sensory neuropathy (44%) i.e. decrease in sensory conduction velocity, increase in latency and slight decrease in amplitude of median and sural nerve.; Ten patients showed mixed sensory motor neuropathy (40%) i.e. decrease in motor and sensory conduction velocity, slight increase in latency and markedly decrease amplitude of median ulnar, tibial and peroneal nerves. The decrease was more pronounced in lower limbs. Four subjects showed normal motor and sensory conduction velocity. Two patients (8%) showed features of entrapment neuropathy of median nerve i.e. feature of Carpal tunnel syndrome.

Table 1 shows Mean and standard deviation of motor & sensory conduction velocities.

<table>
<thead>
<tr>
<th>C V (m/s)</th>
<th>Median</th>
<th>Ulnar</th>
<th>Tibial</th>
<th>Peroneal</th>
<th>Median</th>
<th>Sural</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>RA</td>
<td>C</td>
<td>RA</td>
<td>C</td>
<td>RA</td>
</tr>
<tr>
<td></td>
<td>57.32</td>
<td>± 5.20</td>
<td>57.2</td>
<td>± 5.4</td>
<td>46.3</td>
<td>± 2.1</td>
</tr>
<tr>
<td></td>
<td>± 4.3</td>
<td>± 4.3</td>
<td>± 6.9</td>
<td>± 3.3</td>
<td>± 1.06</td>
<td>± 1.2</td>
</tr>
<tr>
<td></td>
<td>± 1.1</td>
<td>± 0.4</td>
<td>± 0.8</td>
<td>± 1.2</td>
<td>± 0.22</td>
<td>± 0.33</td>
</tr>
<tr>
<td></td>
<td>± 1.3</td>
<td>± 1.1</td>
<td>± 1.3</td>
<td>± 0.33</td>
<td>± 0.07</td>
<td>± 0.03</td>
</tr>
<tr>
<td></td>
<td>± 0.08</td>
<td>± 0.08</td>
<td>± 0.08</td>
<td>± 0.08</td>
<td>± 0.11</td>
<td>± 0.17</td>
</tr>
</tbody>
</table>

*= p<0.05; **= p<0.01; others= p<0.001; C= control group; RA= Rheumatoid group

Pulse Wave velocity

Table 2 shows mean and standard deviation of pulse wave velocity evaluation. There was a significant increase in pulse wave velocity of both Femoral-Dorsalis pedis and Carotid-Radial artery segments in rheumatoid arthritis patients as compared to the control group. (Figure 4)

<table>
<thead>
<tr>
<th>PWV</th>
<th>C-R</th>
<th>PWV</th>
<th>F-DP</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>RA</td>
<td>C</td>
<td>RA</td>
</tr>
<tr>
<td>5.81</td>
<td>±</td>
<td>7.03</td>
<td>±</td>
</tr>
<tr>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>1.1</td>
<td>3.48</td>
<td>1.1</td>
<td>4.7</td>
</tr>
</tbody>
</table>
The present study showed that there was an increased incidence of peripheral neuropathy in Rheumatoid arthritis i.e. 21 out of 25 patients (84%). Although clinical features like paraesthesia, absent distal tendon reflexes and absent vibration sense are good indicators of peripheral neuropathy, the peripheral neuropathy in rheumatoid arthritis is mainly subclinical. Our results indicated that peripheral nervous involvement mainly manifested as mild sensory (44%) and mixed sensory motor neuropathy in median, tibial, peroneal and sural nerves (40%). Entrapment neuropathy was seen in only two patients that too in the median nerve (8%). This nerve involvement was ranging from axonal neuropathy as evident by marked decrease in amplitude as compared to motor conduction velocity to segmental demyelination in some cases. This finding is consistent with the findings of Lanzillo et al\textsuperscript{15} in which 21 out of 26 (80.7\%) of the patients exhibited sensory motor neuropathy and of Yazdchi et al\textsuperscript{16} where sensory motor neuropathy was observed in 57.1\% and pure sensory neuropathy in 35.7\% subjects. Agarwal et al\textsuperscript{17} in 2008 also found sensory motor type of neuropathy to be the most common type in patients of Rheumatoid arthritis. Similar results were also reported by Aneja et al\textsuperscript{1} where entrapment neuropathy was reported in 9% cases, pure sensory involvement in 12% subjects, 20% showed mixed sensory motor neuropathy while 12% cases showed pure motor neuropathy. Rheumatoid arthritis is associated with increased cardio-vascular mortality. Chronic inflammation may impair vascular function and lead to increased arterial stiffness which is an important determinant of cardio-vascular risk.\textsuperscript{18} Pulse wave velocity is defined as the velocity of the arterial pulse as it moves along the vessel wall. It is an indicator of arterial elasticity.\textsuperscript{19} A close association between increased PWV and atherosclerosis development has been reported.\textsuperscript{20} In the present study, PWV was evaluated in 25 patients of Rheumatoid arthritis and the results showed statistically significantly increase in PWV in F-DP and C-R artery segment. These findings are in consistent with Yildiz\textsuperscript{10}, Kaisa\textsuperscript{14} and Klocke\textsuperscript{18}. The inflammation in rheumatoid arthritis may impair endothelial function, arterial compliance and arterial elasticity and may act as a contributory factor in the initiation or progression of atherosclerosis.\textsuperscript{22,23} In the present study, 18 patients were C-reactive protein and rheumatoid antibody positive which is again predictive of atherosclerosis which is again in consistent with the statement made by Ridker\textsuperscript{24}. 

**CONCLUSION**

Thus to summarize, occlusive vascular disease in the vasa nervosum was considered to be the major cause of peripheral neuropathy and inflammation in vessels may impair vascular function and lead to increase in pulse wave velocity. The same reasoning has been theorized by Weller\textsuperscript{25} and Wong et al\textsuperscript{22}. Further, pulse wave velocity and electrodiagnostic tests are non-invasive techniques and should be recommended in patients of Rheumatoid arthritis as a routine for early detection of peripheral neuropathy and for identifying vascular involvement.

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**REFERENCES**