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Abstract: Pulmonary events in rheumatoid arthritis (RA) reflects the involvement of pleurae, lung interstitium, and airways. Overall, pulmonary manifestations are estimated to cause 10-20% of mortalities in RA. Respiratory system involvement as extra-articular presentations of RA is common among some Saudi patients. This study aims to evaluate specific airway conductance (sGaw), airway resistance (Raw), and specific airway resistance (sRaw), using plethysmography. Comparison for deployed methods is made by forced spirometer as an indicator for obstruction among patients with RA. The study sought to use the methods to enhance lung testing among RA patients. An analytical, hospital-based study was carried out at pulmonary function test laboratory, department of respiratory care King Saud Medical City (KSMC). RA patients were selected, with an age group of 18-75years. The tests for Forced spirometer and plethysmography were carried out to assess and analyze how the respiratory mechanism was impacted by the disease. Data collected was analyzed using Statistical Package for Social Sciences (SPSS), version 21. The obstructive and mixed ventilation patterns constituted 15%; the mean values of Raw and sRaw were significantly higher compared to mean values predicted for participants selected during the study, while sGaw was significantly lower compared to mean values predicted for participants selected. Monitoring of airway resistance parameters using plethysmography can be used as indicators of lung function testing among RA patients.

Keywords: Airway resistance; plethysmography; Rheumatid Arthritis; specific airway conductance; specific airway resistance,
1. INTRODUCTION

Rheumatoid arthritis (RA) is a progressive inflammatory disorder with symptoms of pains in the joints and extra-articular manifestations (EAM). Pulmonary system involvement for EAM accounts for about 30–40% of RA patients. Pulmonary events in RA significantly affect the pleurae, airways, and interstitium. A vast range of pulmonary manifestations is associated with RA, including interstitial lung disease, airway disease, and pleural disease as effusions and thickening. Rheumatoid pulmonary nodules that are usually associated with extrapulmonary nodules are also noted. The drug that induced respiratory malfunction was also reported, particularly methotrexate, gold, sulfasalazine, and penicillamine. Anatomically, both lower and upper airways can be established in RA patients. Pulmonary complications had been documented as a significant cause of death among patients with RA compared to cardiovascular attacks. This disorder affects the body system by causing joint deformity and bone erosion—the severity of the disease projects adverse outcomes on people's immune systems. In most instances, RA can result in painful inflammations in the affected body parts. An early study was conducted in Saudi Arabia and published in the Qassim region, which used a small sample size and a simple methodology. It concluded that the prevalence of RA was 0.22%. A 2015 study of RA in Taif City had been conducted, and the results were similar to the estimated prevalence on a global scale. Notably, respiratory system involvement is one of the common EAMs in Saudi Arabia that makes early recognition significant to decrease the mortality rate. However, it can be challenging to diagnose RA because it resembles other conditions. The ability of clinicians to physically examine the signs of inflammation is helpful to determine the functional limitations. As part of the multi-disciplinary approach, monitoring lung functions among patients with RA is vital to assess lung performance. Pulmonary function testing (PFT) has multiple categories, which can be assessed and interpreted individually or together to assess the different physiological aspects regarding the respiratory system. These categories include airway functions, diffusion tests, lung volumes and ventilation, blood gases and gas exchange tests, metabolic measurements, and cardiopulmonary exercise tests. The test results may indicate both respiratory and non-respiratory disorders, like cardiac or neuromuscular diseases. Airway resistance is one of the tests used to assess airway functions as a category of PFT. Airway resistance can be measured using forced oscillation, the interrupter technique, and whole-body plethysmography. Airway resistance (Raw) is defined as the pressure difference per unit flow as gas flows into or out of the lungs. It is related to the difference between mouth pressure and alveolar pressure, divided by flow at the mouth. Such pressure difference is created mainly by the friction of gas molecules in contact with the airways. Raw is estimated in centimetres of water per litre per second (cm H\textsubscript{2}O/L/sec). On the other hand, specific airway conductance (sGaw) is calculated as airway conductance divided by the lung volume (in litres) and reported in litres per second per centimetre of water per litre of lung volume (L/sec/cm H\textsubscript{2}O/L). The lung volume at which Raw is measured is expressed as the volume of thoracic cage (VTG) that is assessed using closed shutter manoeuvre. As in figure (1), specific airway resistance (sRaw) can be calculated as equal to Raw × VTG. Because sRaw includes lung volume, and Raw, and lung volume varies inversely, sRaw is relatively stable concerning lung volume changes, so that as lung volume decreases, Raw increases, so the generation of sRaw still the same, and vice versa. sRaw is similar to sGaw because it evaluates lung volume. sGaw determines Raw only, sRaw reflects both Raw and lung volume. These forces represent maximal airflow as the elastic recoil pressure of the lung and airway resistance upstream from the equal pressure point.
Fig (1) Representation of plethysmographic measurements of lung volumes and air way resistance.  

Principally, spirometry measures changes in lung volume during forced breathing manoeuvres. The forced expiratory vital capacity (FVC) manoeuvre allows the subject to inhale maximally and then exhale as rapidly and thoroughly. The FVC test is significant and simpler. Forced expiratory volume in the first (FEV1) assesses airway responsiveness testing and exercise testing. The FEV1 and FVC (FEV1/FVC) ratios indicate airway obstruction, restriction in the lung parenchyma, or mixed picture. Forced spirometry is considered as the standard significant aspect to measure airflow hindrances. As airflow limitation develops due to increased airway resistance, measuring airway resistance may give additional information for assessing the impact of RA.

The present study investigates airway resistance among asymptomatic patients with RA. The research provides an insight into RA patients’ respiratory workup by measuring total airway resistance (Raw), specific effective airway resistance (sRaw), and Specific Airway Conductance (Gaw) using plethysmography. Also, this research explains the relationship between airway resistance and dynamic spirometer and explains how they influence lung testing among patients with RA.

2. METHODOLOGY

2.1 Study design and Setting

It was an analytical, facility-based study, conducted in the Pulmonary Function Test lab, Department of Respiratory Care, and the Outpatient Clinics of the Rheumatology Unit at the Department of Internal Medicine in King Saud Medical City (KSMC), Riyadh, KSA which is a government tertiary hospital that has been serving the people of Riyadh-KSA since 1956. The study duration was four months and was conducted from 1st of October 2019 to 1st February 2020. The study was approved by the Local Ethics Committee Board numbered (1/191)- Almaarefa University . The study obtained oral and written consent from all the participants. Also, additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

2.2 Patients and Sampling

59 Patients with RA were included. According to the American College of Rheumatology/European League against Rheumatism classification, participants were selected with age group of 18-75 years old. Patients confirmed with chronic respiratory disease symptoms prior to onset of RA, pregnant ladies, individuals who have obesity with BMI more than 35, smoking patients, Non-Arabic, and who could not speak English were excluded. Consecutive patients presenting with RA were included. All procedures performed in studies involving human participants were following the Institutional Review -Research Center-KSMC ethical standards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (ethical approval number HIRE-18-Jul19-01).

2.3.0 Pulmonary Function Tests Methods

Airway resistance and forced spirometry tests were conducted using a spirometer, body plethysmography, and
master screen PFT (CareFusion, Hochberg, Germany manufacture). The machine was calibrated on a daily basis. We used the MicroGard ® mouthpieces containing a filter to prevent infections.

### 2.3.1 Forced Spirometry

Before taking the measurement, the patient’s nose was closed with the nose clip. Also, a mouthpiece was placed between the patient’s teeth and kept the lips tightly around the mouthpiece. The participant was instructed to relax and breathe normally. Then he could breathe normally until steady tidal breathing was shown. Further, the participant was instructed to exhale as deeply as possible without any interruption, and then the patient immediately exhalas as fast and, as much (FEV1) and as long (FVC) as possible. Several normal breaths complete the manoeuvre.

### 2.3.2 Airway resistance

The body plethysmography program allows an analysis of the complete pulmonary respiratory mechanics. It includes the measurement of sRaw by registering the resistance loops and the functional residual capacity (FRCpleth) via an occlusion manoeuvre. Raw was calculated automatically. Each participant was instructed to take a seat in the closed box. The intercom system is activated automatically. Using a mouthpiece and closing the nose with the nose clip, the participant was instructed to breathe normally. Once stable tidal breathing had been obtained, the earliest after four breaths (FRCpleth) was recorded in the consistency of the end-expiratory level. The last five loops of the sRaw were recorded, and sGaw was calculated automatically. All the tests were acceptable and repeatable based on the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines.

### 2.3 Questionnaire

Detailed and well-structured questionnaire was filled for each respondent after explaining the study and its benefits. The questionnaire first was subjected to a group of ten patients, later modified, and then used for the study. The questionnaire is significant because it uses open and closed end questions to collect data. It is essential in this study because qualitative and quantitative data can be obtained.

### 2.4 Data management and Analysis

Data was entered, tested for normality, and analyzed using Statistical Package for Social Sciences (SPSS), version 21. Variables were expressed by measures of central tendency and measures of dispersion. Means comparing tests and Spearman correlation were used. All values of p<0.05 were regarded significant.

### 3. RESULTS

#### 3.1 Demography of Participants

A total of 59 patients in the age group of 18-75 years participated in the study. 14.3% of the study participants were male subjects, while 85.7% were female subjects. Saudis constituted 88.6% of the participants and 12.4% were non-Saudis. The distribution of the chronicity of RA showed 60% of the participants developed RA within five years or less.

#### Table 1. Descriptive analysis of participants regarding Raw, sRaw, and sGaw (N=59).

<table>
<thead>
<tr>
<th></th>
<th>Raw cm H2O/L/sec</th>
<th>sRaw cm H2O/L/sec</th>
<th>sGaw L/sec/cm H2O/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants actual measures</strong></td>
<td>Lower Bound</td>
<td>Upper Bound</td>
<td>Lower Bound</td>
</tr>
<tr>
<td>Mean (±/ SD)</td>
<td>.54 (.27)</td>
<td>.61</td>
<td>1.23 (.47)</td>
</tr>
<tr>
<td>95% Confidence Interval for Mean</td>
<td>.47</td>
<td></td>
<td>1.11</td>
</tr>
<tr>
<td>5% Trimmed Mean</td>
<td>.52</td>
<td></td>
<td>1.2</td>
</tr>
<tr>
<td>Median</td>
<td>.5</td>
<td></td>
<td>1.13</td>
</tr>
<tr>
<td>Variance</td>
<td>.08</td>
<td></td>
<td>.228</td>
</tr>
<tr>
<td>Minimum</td>
<td>.05</td>
<td></td>
<td>.47</td>
</tr>
<tr>
<td>Maximum</td>
<td>1.88</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td>Range</td>
<td>1.83</td>
<td></td>
<td>3.01</td>
</tr>
<tr>
<td>Interquartile Range</td>
<td>.30</td>
<td></td>
<td>2.56</td>
</tr>
</tbody>
</table>

*(Table 1) demonstrates the measures of central tendency and measures of dispersion of Raw, sRaw and sGaw among the participants*
Table 2. Correlation between the mean values of the participant’s actual measures and the mean values of Predicted measures regarding Raw, sRaw, and sGaw (N=59).

<table>
<thead>
<tr>
<th>Participants actual measures</th>
<th>Predicted values</th>
<th>P- Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw (cm H₂O/L/sec)</td>
<td>.54 (.27)</td>
<td>.30</td>
</tr>
<tr>
<td>sRaw (cm H₂O/L/sec)</td>
<td>1.23(.47)</td>
<td>.98</td>
</tr>
<tr>
<td>sGaw (L/sec/cm H₂O/L)</td>
<td>.98(12 )</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Significant at P<0.05, n=59

Table (2) illustrates that the mean values of Raw and sRaw were significantly higher compared to mean values predicted for participants selected during the study. While sGaw was significantly lower compared to mean values predicted for participants selected.

Fig 2. Patterns of ventilation distribution among the participants (N=59).

Regarding figure(2), restrictive and obstructive patterns of ventilation constituted 9% and the mixed patterns entailed 10%. The standard patterns of ventilation constituted 78%, and non-specific patterns were 3%. The results noted that the majority of the participants in the study breathed normally. A minimum number of participants were subjected to the restrictive and obstructive patterns of ventilation. In the table 3, the results showed a significant negative correlation between FEV1 and Raw and significant negative correlation between FEV1 %E and sRaw. The table also revealed that there is a negative correlation between FEV1 %E and sGaw.

Table 3. Correlation between the participant’s actual measures of airway resistance parameters and forced spirometer (N=59).

<table>
<thead>
<tr>
<th></th>
<th>Raw</th>
<th>sRaw</th>
<th>sGaw</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>-.240</td>
<td>-.033</td>
<td>.009</td>
</tr>
<tr>
<td>Spearman's Correlation Coefficient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P- value</td>
<td>.070</td>
<td>.808</td>
<td>.947</td>
</tr>
<tr>
<td>FEVI</td>
<td>-.300</td>
<td>-.170</td>
<td>.165</td>
</tr>
<tr>
<td>Spearman's Correlation Coefficient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P- value</td>
<td>.022*</td>
<td>.202</td>
<td>.216</td>
</tr>
<tr>
<td>FEV1 %E</td>
<td>-.145</td>
<td>-.453</td>
<td>.507</td>
</tr>
<tr>
<td>Spearman's Correlation Coefficient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P- value</td>
<td>.279</td>
<td>.000**</td>
<td>.000**</td>
</tr>
</tbody>
</table>

** correlation is significant at the 0.01 level. *Correlation is significant at the 0.05 level.

Table 4. Correlation between the participant’s actual measures of Raw, sRaw, and sGaw with age (N=59).

<table>
<thead>
<tr>
<th></th>
<th>Raw</th>
<th>sRaw</th>
<th>sGaw</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spearman's Correlation Coefficient</td>
<td>.241</td>
<td>.293</td>
<td>-.298</td>
</tr>
<tr>
<td>P- value</td>
<td>.069</td>
<td>.026*</td>
<td>.23*</td>
</tr>
</tbody>
</table>

** correlation is significant at the 0.01 level. *Correlation is significant at the 0.05 level.
Fig 4. Distributions of Raw means of participants and predicted values according to the age groups.

Fig 5. Distributions of $s_{\text{Raw}}$ means of participants and predicted values according to the age groups.

Fig 6. Distributions of $s_{\text{Gaw}}$ means of participants and predicted values according to the age groups.
4. **DISCUSSION**

Nowadays, whole-body plethysmography is considered an essential aspect of pulmonary function testing, particularly in necessary diagnostic procedures to assess lung volumes and airway resistance. It applies Boyle-Mariotte's gas law to assess the pressure difference of the closed box and flows measured at the subject's mouth by breathing out of the box. Our results demonstrated that obstructive and mixed patterns of ventilation constitute around 15% based on the spirometer. The results revealed that the mean values of Raw and sGaw were significantly higher than the mean of predicted values regarding airway parameters. The mean values of sGaw are significantly lower compared with the mean of predicted values. Topalovic and his colleagues in 2015 published an article about airways resistance and specific conductance to diagnose obstructive airways diseases. They concluded that Raw and sGaw are significant factors contributing to the differentiation and diagnosis of obstructive airways diseases. Our results revealed a significant negative correlation between FEV1 and Raw, a significant correlation between FEV1 %E and sRaw. The American Thoracic Society (ATS)/ERS Task Force reported that airflow resistance is rarely used to identify airflow obstruction in clinical practice. The results noted that extrathoracic or large central intrathoracic airways resistance can be determined comparable to peripheral intrathoracic airways. The results reported the airway resistance measurement using whole-body plethysmography, which is a unique study in RA patients. Still, there is nothing unique about the importance of resistive parameters to respiratory diagnoses. sGaw is sensitive to upper airway involvement in vocal cord dysfunction and vocal cord paralysis. Smith and colleagues concluded that spirometry failed to assess bronchodilator reversibility in 15% of patients. There was a possibility of clinical responses and obstruction of reversible airways to bronchodilator. Still, those patients could be identified by changes in sGaw or TGV. Further, our results demonstrated a significant positive correlation between age and sRaw, while a negative correlation between age and sGaw was reported. Such significant results need further investigations to detect either age as a physiological variation or their outcomes of RA as the cause. Aging changes in resistive properties were investigated earlier as soon as the body plethysmograph technique was developed to measure airway resistance by Briscoe and Dubois. They established that measuring specific airway resistance at low flow close to FRC was, on average, similar in childhood and old age. To our knowledge, there are meagre information regarding the respiratory assessment of airway resistance using plethysmography in RA patients. The previous studies mainly measured such values using forced oscillation technique FOT. Sokai, et al. 2020 assessed respiratory impedance, respiratory resistance (Rrs) and reactance (Xrs), at different oscillatory frequencies during tidal breathing. They interpreted the findings of PFTs included FOT with chest CT images, and concluded that the impedance results reflect abnormalities in pulmonary functions and structures in patients with RA. Yoshitaka et al. 2019 examined long-term changes in pulmonary function and respiratory impedance (Zrs) as assessed by FOT of 42 patients with RA. They found Zrs combined with spirometry may be beneficial to evaluate alterations in respiratory functions of RA.

5. **CONCLUSION**

Measurement of airway resistance parameters using plethysmography showed significant correlations with force spirometry. In Patient with RA, the obstructive and mixed patterns of ventilation had been shown in 15% of the participants. Those patients may have higher airway resistance and lower conductance compared with predicted. Functional monitoring of airway resistance using plethysmography among patients with RA for lung involvement can be used as a tool for lung function testing. It provides more information regarding the airway flow and ventilation patterns among patients with RA.

6. **ACKNOWLEDGMENTS**

The authors of this research would like to acknowledge Almaarefa University and Research Centre - King Saud Medical City for providing facilities for conducting this study.
We also appreciate the patients who took part in the exercise and provided samples for the study. Thanks to the deanship of postgraduate studies and research at the International University of Africa, Sudan.

7. **AUTHOR CONTRIBUTION STATEMENT**

Prof Ahmed, Dr. Tarig and Dr. Abdulrhman conceptualized and gathered the data with regard to this work. Prof Asma, Dr. Wael and Dr. Saitah analyzed these data and necessary inputs were given towards the designing of the manuscript. All authors discussed the methodology and results and contributed to the final manuscript.

8. **CONFLICT OF INTEREST**

Conflict of interest declared none.

9. **REFERENCES**


