Effect of Gastroesophageal Reflux Disease (GERD) on Pulmonary Function Test (PFT) and haematological parameters, RBC, MCV & RDW – Case Control Study

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ABSTRACT:

Title: Effect of Gastroesophageal Reflux Disease (GERD) on Pulmonary Function Test (PFT) and haematological parameters, RBC, MCV & RDW – Case Control Study

BACKGROUND: Gastro-oesophageal reflux disease (GERD) is defined as a condition characterized by symptoms and/or complications caused by reflux of gastric contents. The role of GERD in the causation of restrictive lung diseases has not yet been explored adequately. This study is taken up to find if there could be respiratory dysfunction much before patients become symptomatic in those suffering from GERD.

MATERIALS AND METHODS: A case-control study involving 100 adult subjects were recruited in two groups, test group of 50 patients of GERD and a control group of 50. Both the groups were further subdivided into 2 subgroups of 25 subjects each based on the presence or absence of cough. Pulmonary function tests (PFT) and Complete Blood Counts (CBC) (including all indices) were performed on all the 100 subjects. All the values were determined in test and control groups, compared and statistically analysed.

RESULTS & CONCLUSIONS: There was an overall reduction in pulmonary function in cases both with and without cough. This reduction was statistically significant for all the 4 parameters of PFT with p values being <0.002, <0.001, <0.005 and <0.05. The red cell parameters including RBC count, Hb, HCT, MCV, MCH, MCHC (all decreased) and RDW (elevated) were significantly altered in the cases relative to control subjects and statistically significant. The study showed that there was a statistically significant deterioration in PFT in GERD positive cases compared to control subjects, PFT profile favouring a restrictive pathology. The study also showed that the hematological changes related to RBC parameters were probably caused by GERD.

Keywords: GERD, PFT, RBC Indices, Case Control Study

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INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is defined as a condition characterized by worrisome symptoms and/or complications caused by reflux of gastric contents. This definition excludes occasional symptomatic reflux seen in normal individuals. In western countries, up to 20% of individuals are affected by GERD, thus making it a fairly common affliction. There are numerous risk factors for GERD including hiatus hernia, obesity, older age, alcohol abuse, tobacco use, male sex and obstructive sleep apnoea. The causal association between GERD and asthma is well discussed in the literature. However, the role of GERD in the causation of restrictive lung diseases like idiopathic pulmonary fibrosis (ITF), which has a relatively low prevalence of 16.3 – 42.7/100000, has not yet been explored adequately. Only around 10% of chronic persistent cough patients appear to display prominent GERD symptoms and GERD can be clinically ‘silent’ in up to 75% of patients with GERD-related cough. It is for this reason that an unexplained chronic cough in a non-smoker, who is not exposed to irritants or ACE inhibitors, should raise the suspicion of an underlying silent GERD. Whether there could be respiratory dysfunction much before patients become symptomatic in those suffering from GERD is not established. The present case control study has been undertaken to find out the relationship between PFT and GERD in test subjects with or without cough.

MATERIALS AND METHODS: The present case control study was conducted over a period of three months at Chettinad Hospital and research Institute. A total of hundred (100) adult subjects were recruited in two groups after obtaining informed consent: a test group of 50 patients of GERD and a control group consisting of 50 age matched subjects with no GERD. The study was initiated after getting clearance from the Institutional Ethics Committee. Both the test and the control groups were further subdivided into 2 subgroups of 25 subjects each based on the presence or absence of cough (Fig 1).

Subjects with cardiovascular disease, established respiratory diseases including COPD and asthma, chronic anaemia, liver disorders, renal diseases and malignancies were excluded from the study. PFT was performed by using Spirometer (Chestgram HI-105 Spirometer) and the following parameters were measured: Forced expiratory volume 1 s (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, and peak expiratory flow rate (PEFR). Predicted values were obtained from standard references. CBC was performed in Coulter LH780 haematology analyser. Statistical evaluation was done using IBM SPSS software (version 21) and Graphpad prism (version 7).
RESULTS: The present study was carried out on 50 control subjects and 50 cases of GERD. Average age of both the control subjects and the cases was 44 years. Duration of GERD in the cases at the time of their recruitment to the study varied from two weeks to 120 months with an average duration of 29.32 months. Duration of GERD did not show any direct correlation with degree of abnormality of PFT. The pulmonary function tests were below the lower limit of the predicted normal value of 80% in 86% and 70% of cases compared to 46% and 38% in control subjects. The odds ratios for abnormal PFT in GERD cases were 7.2 and 3.8 respectively. The findings were statistically significant at p values of 0.0001 and 0.0013 respectively. However, FEV1/FVC ratio was within normal limits in 88% of cases and the changes were not statistically significant (table 2).

Table 2: Results of the Chi-square test; (Abn = abnormal)

<table>
<thead>
<tr>
<th>Data</th>
<th>FVC</th>
<th></th>
<th>FEV1</th>
<th></th>
<th>FEV1/FVC Ratio</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal PFT</td>
<td>Abn. PFT</td>
<td>Total</td>
<td>Normal PFT</td>
<td>Abn. PFT</td>
<td>Total</td>
</tr>
<tr>
<td>Control</td>
<td>31</td>
<td>19</td>
<td>50</td>
<td>27</td>
<td>23</td>
<td>50</td>
</tr>
<tr>
<td>Cases GERD+</td>
<td>15</td>
<td>35</td>
<td>50</td>
<td>7</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>54</td>
<td>100</td>
<td>34</td>
<td>66</td>
<td>100</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>3.807 (1.62 to 9.079)</td>
<td>7.211 (2.723 to 17.72)</td>
<td>3.273 (0.7618 to 16.44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.0013</td>
<td>&lt;0.0001</td>
<td>0.1404</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significance</td>
<td>Significant (**)</td>
<td>Significant (****)</td>
<td>Not Significant</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

When control subjects were taken as whole, the mean values with SD for FVC, FEV1, FEV1/FVC and PEF were 85.94±20.14, 81.62±19.32, 96.1±12.32 and 74.46±26.36 respectively. In comparison, the cases taken as a whole returned corresponding values of 71.4±17.96, 61.76±17.81, 86.72±12.42 and 61.56±21.74 for those parameters. There was an overall reduction in pulmonary function in cases. This reduction was statistically significant for all the 4 parameters with p values being <0.002, <0.001, <0.005 and <0.05 respectively. As is evident from the values, FEV1 was affected most and followed by FVC and PEFR (table 3). However, mean PEFR values were below normal even in control subjects.

Table 3: Comparison of all controls and all cases

<table>
<thead>
<tr>
<th></th>
<th>Controls (50)</th>
<th>Cases (50)</th>
<th>Significance</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>44.06±10.05</td>
<td>44.08±11.56</td>
<td>NS</td>
<td>0.993</td>
</tr>
<tr>
<td>FVC</td>
<td>85.94±20.14</td>
<td>70.74±17.55</td>
<td>Significant</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>FEV1</td>
<td>81.62±19.32</td>
<td>61.64±17.99</td>
<td>Significant</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>96.1±12.32</td>
<td>87.18±12.30</td>
<td>Significant</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PEFR</td>
<td>74.46±26.36</td>
<td>60.8±21.45</td>
<td>Significant</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>WBC</td>
<td>6.018±1.01</td>
<td>5.856±1.23</td>
<td>NS</td>
<td>0.723802</td>
</tr>
<tr>
<td>RBC</td>
<td>4.783±0.77</td>
<td>3.8026±0.52</td>
<td>Significant</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HGB</td>
<td>14.392±1.60</td>
<td>11.578±1.64</td>
<td>Significant</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Although there was statistically significant difference in values of FEV1/FVC ratios between cases and controls, mean values of FEV1/FVC in cases were within normal limits. In 14 of the test subjects, FEV1 was critically reduced (<40% of the predicted value; mean value 32.13%); in these, FVC and PEF were also significantly reduced with mean values of 48.14% and 29.75% respectively. However, FEV1/FVC ratio was marginally reduced (66.88%). Presence/absence of cough apparently did not influence the findings as half (4) of these subjects had cough. The mean duration of GERD was shorter in these patients (20.75 months compared to 29.32 months for the test group). When control subgroup without cough were analyzed separately, the values for FVC, FEV1, FEV1/FVC and PEF were 85.8±21.09, 86.72±20.91, 98.4±15.18 and 79.56±29.20 respectively compared to corresponding mean values of 71.4±17.96, 61.76±17.81, 86.72±12.42 and 61.56±21.74 recorded for the cough negative subgroup of cases. Of those, only the values for FEV1 and FEV1/FVC showed statistically significant differences between the two cough negative subgroups with p values of <0.001 and <0.05 (table 4).

### Table 4: Comparison of subgroups of controls and cases without cough

<table>
<thead>
<tr>
<th></th>
<th>Controls (25)</th>
<th>Cases (25)</th>
<th>significance</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>38.6±9.94</td>
<td>42.48±12.62</td>
<td>NS</td>
<td>0.549</td>
</tr>
<tr>
<td>FVC</td>
<td>85.8±21.09</td>
<td>71.4±17.96</td>
<td>NS</td>
<td>0.106</td>
</tr>
<tr>
<td>FEV1</td>
<td>86.72±20.91</td>
<td>61.76±17.81</td>
<td>Significant</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>98.4±15.18</td>
<td>86.72±12.42</td>
<td>Significant</td>
<td>&lt;0.045</td>
</tr>
<tr>
<td>PEF</td>
<td>79.56±29.20</td>
<td>61.56±21.74</td>
<td>NS</td>
<td>0.113</td>
</tr>
<tr>
<td>WBC</td>
<td>5.852±1.11</td>
<td>5.768±1.28</td>
<td>NS</td>
<td>0.962</td>
</tr>
<tr>
<td>RBC</td>
<td>5.047±0.84</td>
<td>3.663±0.48</td>
<td>Significant</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HGB</td>
<td>14.33±1.64</td>
<td>11.28±1.66</td>
<td>Significant</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCT</td>
<td>42.23±25.85</td>
<td>38.58±5.54</td>
<td>NS</td>
<td>0.134</td>
</tr>
<tr>
<td>MCV</td>
<td>83.04±4.53</td>
<td>75.44±8.53</td>
<td>Significant</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>MCH</td>
<td>27.48±3.28</td>
<td>23.71±3.34</td>
<td>Significant</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>MCHC</td>
<td>32.51±2.85</td>
<td>31.16±2.49</td>
<td>NS</td>
<td>0.106</td>
</tr>
<tr>
<td>RDW</td>
<td>14.16±1.24</td>
<td>15.97±3.43</td>
<td>NS</td>
<td>0.113</td>
</tr>
<tr>
<td>PLT</td>
<td>303.52±79.07</td>
<td>300.48±71.34</td>
<td>NS</td>
<td>0.962</td>
</tr>
</tbody>
</table>
Similarly, comparison between control and test subjects’ subgroups with cough also revealed statistically
significant differences only between the values of FEV1 and FEV1/FVC ratio (table 5). Besides; the mean
duration of GERD was shorter in cough subgroup of cases compared to the cases subgroup without cough.

**Hematological parameters:** When the controls and the cases were compared as a whole, all the red cell
parameters including RBC count, Hb, HCT, MCV, MCH, MCHC (all decreased) and RDW (elevated) were
significantly altered in the cases relative to control subjects. These changes were statistically significant.
However, in subgroup comparisons, only RBC count, Hb and MCH reductions in the cases remained as
statistically significant changes. (Table 5).

**Table 5: Comparison of subgroups of controls and cases with cough**

<table>
<thead>
<tr>
<th></th>
<th>Controls (25)</th>
<th>Cases (25)</th>
<th>significance</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>49.52±6.75</td>
<td>45.68±10.40</td>
<td>NS</td>
<td>0.496</td>
</tr>
<tr>
<td>FVC</td>
<td>86.08±19.57</td>
<td>70.08±17.48</td>
<td>Significant</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV1</td>
<td>76.52±16.45</td>
<td>61.52±18.54</td>
<td>Significant</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>93.8±8.28</td>
<td>87.64±12.42</td>
<td>NS</td>
<td>0.305</td>
</tr>
<tr>
<td>PEFR</td>
<td>69.36±22.63</td>
<td>60.04±21.56</td>
<td>NS</td>
<td>0.496</td>
</tr>
<tr>
<td>WBC</td>
<td>6.18±0.91</td>
<td>5.94±1.20</td>
<td>NS</td>
<td>0.549</td>
</tr>
<tr>
<td>RBC</td>
<td>4.518±0.61</td>
<td>3.94±0.53</td>
<td>Significant</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>HGB</td>
<td>14.44±1.58</td>
<td>11.87±1.61</td>
<td>Significant</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCT</td>
<td>42.65±4.90</td>
<td>40.39±3.92</td>
<td>NS</td>
<td>0.433</td>
</tr>
<tr>
<td>MCV</td>
<td>86.36±5.04</td>
<td>81.02±0.9</td>
<td>NS</td>
<td>0.071</td>
</tr>
<tr>
<td>MCH</td>
<td>27.56±2.94</td>
<td>24.02±3.59</td>
<td>Significant</td>
<td>&lt;0.006</td>
</tr>
<tr>
<td>MCHC</td>
<td>32.32±1.17</td>
<td>31.76±2.02</td>
<td>NS</td>
<td>0.549</td>
</tr>
<tr>
<td>RDW</td>
<td>13.98±1.12</td>
<td>15.27±2.54</td>
<td>NS</td>
<td>0.198</td>
</tr>
<tr>
<td>PLT</td>
<td>299.2±69.72</td>
<td>270.32±42.84</td>
<td>NS</td>
<td>0.433</td>
</tr>
<tr>
<td>MPV</td>
<td>8.86±0.26</td>
<td>8.62±1.10</td>
<td>NS</td>
<td>0.549</td>
</tr>
</tbody>
</table>

**DISCUSSION:** Present study was carried out on 50 cases of GERD and 50 non-GERD control subjects with
the objective of finding out if the pulmonary function is adversely affected by persistent GER and also to
ascertain if any hematological parameter shows a correlation with PFT that is significant enough to be used as
inexpensive alternative predictor of clinical outcome. Principle observations were reduction in FEV1 and FVC
values below the LLN of the predicted value in 86% and 70% of GERD positive subjects. This was statistically
significant. However, FEV1/FVC ratios were not affected. Its values, though less than what was observed in
control subjects, were close to lower limit of the normal. Although reduced FEV1 and PEF are characteristic of
airway obstruction, simultaneous reduction in FVC and nearly normal FEV1/FVC ratio favour predominant
restrictive pathology within the lung with some airway obstructive component16. Two mechanisms have been
postulated in previous studies to explain how GER causes the lung damage reflex neural mechanism occurring
at lower oesophageal sphincter during reflux and reflux of gastric content above upper oesophageal sphincter
producing upper airway injury and, if aspirated, lung disease17. It is possible that micro-aspiration of gastric acid
into the airways and lung parenchyma causes onset or exacerbation of chronic inflammation, while vagal mediated esophageal-bronchial reflex participates in the onset or worsening bronchoconstriction. It is the former mechanism that is likely to produce chronic lesion with reactive fibrosis commonly seen in restrictive diseases. As no lung biopsy was done in our cases, we cannot comment on the nature of the lesion. Our results are comparable to those of Sudarshan Murthy et al (2019), who in a study carried out on 242 subjects, found that 43.4% of their cases with erosive reflux oesophagitis had abnormal PFT with predominantly restrictive profile. In a study by Räihä et al (1992), a restrictive ventilatory defect was found to be associated with GERD in elderly patients. Raghu (2003) in his study on the role of gastroesophageal reflux in idiopathic pulmonary fibrosis, speculated that GER may be associated with the pathogenesis/progression of idiopathic pulmonary fibrosis and micro-aspiration of the gastric contents may be the initiating mechanism. We did not find any correlation between magnitude of reduction in PFT and duration of GERD. Besides, test subjects with cough had the GERD for a shorter duration of time on an average than those without cough. Along similar lines, Norderstedt et al (2006) found no correlation between the severity of reflux and severity of restrictive defect by PFT. The red cell parameters including RBC count, Hb, HCT, MCV, MCH, MCHC were decreased and RDW was elevated when GERD positive cases were compared with control subjects. This is probably related to loss of blood from erosive oesophagitis in GERD patients. The anaemia was borderline. Grant et al (2003) found an inverse correlation between an established predictor of mortality like pulmonary function tests (PFT) and RDW that was independent of confounding factors like smoking and ethnicity. However, we failed to find any correlation between PFT and RDW. That is in agreement with our earlier study on the relationship of pulmonary function tests and common haematological parameters (Vijayashree 20014).

CONCLUSION: The study showed that there was a statistically significant deterioration in PFT in GERD positive cases compared to control subjects. The parameters affected primarily were FEV1 and FVC with FEV1/FVC ratio remaining nearly normal. Such a PFT profile is in favour of a restrictive pathology underlying pulmonary changes observed in our cases. The study also showed that there was no correlation between changes in haematological parameters and PFT. The haematological changes observed were related to RBC parameters and were probably caused by GERD.

Ethical clearance- Taken from Institutional Human ethical committee, Chettinad Academy of Research and Education (CARE), Kelambakkam, Chennai.

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Conflict of Interest - Nil.

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