Pulmonary Diffusing Capacity in Polycytemic States Before and After Phlebotomy*

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RANKIN, McNEILL and FORSTER† have shown that the diffusing capacity of the lung for carbon monoxide (DLCO) is low in severely anemic subjects without pulmonary disease, and that increasing the hemoglobin concentration by transfusion raises the DLCO toward normal values.

Observations on the diffusing capacity in clinical states characterized by an increase in hemoglobin concentration have been conflicting. However, Burgess and Bishop, using the breath-holding method for determining the DLCO have recently shown that it is elevated in subjects with polycythemia vera and decreases when the red cell mass and hemoglobin concentration are reduced.

Figure 1: Pulmonary physiologic data in polycytemic subjects.

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In this investigation, the effect of various polycythemic disorders on alveolar capillary gas transfer as measured by the breath-holding DLCO has been studied. Particular attention has been directed to changes in the DLCO after reduction of red cell mass and hemoglobin concentration by phlebotomy.

**Subjects and Methods**

Hematologic and pulmonary function studies including DLCO were completed on nine polycythemic subjects before and after phlebotomy. Eight subjects had absolute polycythemia and one relative polycythemia. Four subjects had polycythemia vera with increased red cell mass, palpable spleen, normal ventilatory function and normal arterial oxygen saturation. In one (H.V.), myelofibrosis and extramedullary hematopoiesis was proved by bone marrow and liver biopsies. Three patients had absolute polycythemia secondary to arterial hypoxemia on the basis of pulmonary dysfunction. This group included one with al-
veolar hypoventilation of neuromuscular origin, one with pulmonary emphysema and one with a diffusion disorder of unknown etiology. One obese woman with absolute polycythemia lacked supporting criteria for polycythemia vera and maintained normal arterial oxygen saturation in spite of restrictive and obstructive ventilatory impairment and a clinical picture of chronic bronchitis. In this study she is categorized as absolute polycythemia, unclassified.

The one subject with relative polycythemia had a high normal red cell mass and a low normal plasma volume. Ventilatory studies showed a marked degree of restriction, obstruction, hyperinflation and abnormal intrapulmonary gas mixing consistent with his clinical diagnoses of chronic bronchitis and pulmonary emphysema. However, his arterial oxygen saturation was normal on three determinations more than one month apart.

The red blood cell mass was estimated with hexavalent radioactive chromium (Cr⁵¹) as described by Beierwaltes. Ferrokinetic studies were performed as described by Huff et al. The plasma volume was estimated from data derived from extrapolation of the plasma iron clearance curve to "0" time. The total blood volume was obtained from the sum of the red cell mass and plasma volume estimations determined simultaneously although independently.

Spirometric studies were performed with a 13.5 liter Collins respirometer. Results are expressed as volumes BTPS and predicted values are those of Kory and associates. Residual volume was determined by Meeneley's modification of the closed circuit helium dilution method. Intrapulmonary mixing of inspired gas was assessed by measuring the per cent increase in N₂ between 750 and 1250 ml expired air after a single breath of 100 per cent O₂. Arterial oxygen saturation was measured by the method of Van Slyke and Neil, the dual beam oximeter and the PO₂ electrode. The

![Graph](image-url)
TABLE 1—PHYSICAL CHARACTERISTICS, VENTILATORY FUNCTION STUDIES, AND BLOOD GAS ANALYSES BEFORE AND AFTER PHLEBOTOMY*

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
<th>V.C. (ml)</th>
<th>Per Cent</th>
<th>R.V. (ml)</th>
<th>Per Cent</th>
<th>FEV/FVC Per Cent</th>
<th>M.V.V. (L/min)</th>
<th>Per Cent</th>
<th>Per Cent N₂ Increase</th>
<th>Pacq mm Hg</th>
<th>Hb</th>
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<tbody>
<tr>
<td>Polycythemia vera</td>
<td></td>
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</tr>
<tr>
<td>H. V.</td>
<td>M</td>
<td>55</td>
<td>64.5</td>
<td>146</td>
<td>3670 (98)</td>
<td>1467</td>
<td>29</td>
<td>81</td>
<td>91</td>
<td>135 (107)</td>
<td>1</td>
<td>94</td>
<td>38</td>
<td>7.395</td>
</tr>
<tr>
<td>D. W.</td>
<td>M</td>
<td>43</td>
<td>68</td>
<td>144</td>
<td>4914 (109)</td>
<td>1616</td>
<td>25</td>
<td>71</td>
<td>96</td>
<td>162 (105)</td>
<td>&lt;1</td>
<td>96</td>
<td>27.5</td>
<td>7.53</td>
</tr>
<tr>
<td>S. L.</td>
<td>M</td>
<td>46</td>
<td>68</td>
<td>154</td>
<td>4164 (94)</td>
<td>895</td>
<td>18</td>
<td>83</td>
<td>94</td>
<td>148 (98)</td>
<td>2</td>
<td>95.3</td>
<td>42.5</td>
<td>7.37</td>
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<tr>
<td>C. W.</td>
<td>M</td>
<td>70</td>
<td>68.75</td>
<td>173</td>
<td>4011 (100)</td>
<td>1835</td>
<td>31</td>
<td>67</td>
<td>82</td>
<td>126 (104)</td>
<td>1</td>
<td>95.8</td>
<td>50.2</td>
<td>7.389</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>(emphysema)</td>
<td>F. B</td>
<td>M</td>
<td>63</td>
<td>68.25</td>
<td>3120 (76)</td>
<td>2502</td>
<td>45</td>
<td>62</td>
<td>81</td>
<td>100 (77)</td>
<td>4</td>
<td>90</td>
<td>39.3</td>
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<tr>
<td>(alv. hypo.)</td>
<td>W. L</td>
<td>M</td>
<td>42</td>
<td>70.75</td>
<td>2906 (73)</td>
<td>1486</td>
<td>34</td>
<td>73</td>
<td>90</td>
<td>66 (40)</td>
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<td>78</td>
<td>60.8</td>
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<tr>
<td>(dif. abnor.)</td>
<td>H. S</td>
<td>M</td>
<td>39</td>
<td>74.5</td>
<td>4638 (86)</td>
<td>1188</td>
<td>20</td>
<td>72</td>
<td>92</td>
<td>184 (104)</td>
<td>3</td>
<td>90.5</td>
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<td>7.444</td>
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<tr>
<td>(chr. bron.)</td>
<td>M. L</td>
<td>F</td>
<td>45</td>
<td>59</td>
<td>1926 (73)</td>
<td>991</td>
<td>34</td>
<td>47</td>
<td>74</td>
<td>50</td>
<td>1</td>
<td>92.3</td>
<td>41.5</td>
<td>7.378</td>
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<tr>
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<td></td>
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</tr>
<tr>
<td>(emphysema and chr. bron.)</td>
<td>E. L</td>
<td>M</td>
<td>64</td>
<td>65.5</td>
<td>1486 (40)</td>
<td>2850</td>
<td>66</td>
<td>48</td>
<td>91</td>
<td>39 (33)</td>
<td>6</td>
<td>96</td>
<td>54</td>
<td>7.42</td>
</tr>
</tbody>
</table>

*Upper figures are values before and lower figures after phlebotomy.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Red Cell Mass ml./Kg.</th>
<th>Plasma Volume ml./Kg.</th>
<th>Blood Volume ml./Kg.</th>
<th>PCV Per Cent Observed</th>
<th>D&lt;sub&gt;150&lt;/sub&gt; Per Cent Predicted</th>
<th>Blood Withdrawn (ml.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycythemia vera</td>
<td></td>
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<tr>
<td>H.V.</td>
<td>2931</td>
<td>44.1</td>
<td>3783</td>
<td>57.0</td>
<td>6714</td>
<td>101.1</td>
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<tr>
<td>D.W.</td>
<td>2189</td>
<td>33.7</td>
<td>2597</td>
<td>39.9</td>
<td>4786</td>
<td>73.6</td>
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<tr>
<td>S.L.</td>
<td>2911</td>
<td>42.1</td>
<td>3881</td>
<td>56.2</td>
<td>6792</td>
<td>98.2</td>
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<tr>
<td>C.W.</td>
<td>3259</td>
<td>42.4</td>
<td>3337</td>
<td>43.5</td>
<td>6596</td>
<td>85.9</td>
</tr>
<tr>
<td>Secondary polycythemia</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(emphysema)</td>
<td>F.B.</td>
<td>2602</td>
<td>32.3</td>
<td>2524</td>
<td>31.6</td>
<td>5126</td>
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<tr>
<td>(alveolar hypoventilation)</td>
<td>W.L.</td>
<td>2988</td>
<td>36.8</td>
<td>4334</td>
<td>44.0</td>
<td>7958</td>
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<td>(diffusion abnormality)</td>
<td>H.S.</td>
<td>3513</td>
<td>33.7</td>
<td>3335</td>
<td>36.2</td>
<td>6538</td>
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<tr>
<td>Polycythemia, unclassified</td>
<td>(chronic bronchitis)</td>
<td>M.L.</td>
<td>1806</td>
<td>32.3</td>
<td>2528</td>
<td>45.1</td>
</tr>
<tr>
<td>Relative polycythemia</td>
<td>(emphysema and chronic bronchitis)</td>
<td>E.L.</td>
<td>2334</td>
<td>30.8</td>
<td>2766</td>
<td>36.4</td>
</tr>
</tbody>
</table>

*Upper figures are values before and lower figures after phlebotomy*
DLCO was measured by a modification of the breath holding method using an inspired gas mixture of approximately 0.1 per cent CO and 13 per cent He in air. Breath-holding times ranged from 9 to 11.25 seconds and alveolar volumes for each set of determinations varied less than 400 ml. for each subject except for one variation of 580 ml. and another of 622 ml. Two to five determinations of the DLCO were performed on each patient before and after phlebotomy. Normal values were derived from the prediction formulae of Burrows and co-workers.

**Results**

**Pulmonary Function Studies.** Table 1 lists the diagnoses, ventilatory function studies and arterial blood gases of all patients before and after phlebotomy. Figure 1 summarizes the pulmonary physiologic characteristics of the polycythemia groups before phlebotomy. Pulmonary function was normal in all patients with polycythemia vera. Studies after phlebotomy in all patients revealed no significant changes that could be attributed to reducing the red cell mass or hemoglobin concentration.

**Hematologic Studies.** Pre- and post-phlebotomy measurements of red cell mass, plasma volume, total blood volume, packed cell volume, as well as the total volume of blood removed, are included in Table 2 and summarized in Fig. 2.

Subjects with absolute polycythemia initially had an increased red cell mass of greater than 2 S.D. above mean normal values. The mean red cell mass of the polycythemia vera subjects was 158 per cent of normal before and 119 per cent after phlebotomy while the average packed cell volume was 58.3 per cent and 45.8 per cent respectively. In the secondary polycythemia group, the mean pre-phlebotomy red cell mass was 129 per cent of normal and the post-phlebotomy red cell mass 91 per cent. The mean packed cell volume fell from 57 per cent to 46.3 per cent after venesection. Although the red cell mass in the patient considered to have relative polycythemia was 117 per cent of normal, this represents an increase of less than 2 S.D. above the mean of normal values.

A tendency toward a post-phlebotomy expansion of plasma volume resulted in variable changes in the total blood volume.

In eight subjects, the total amount of blood removed was 1,000 to 1,500 ml. withdrawn over a three to 16-day period. Thirty-five hundred ml. of blood was withdrawn from one subject over a 13-day period. The average time lapse between the termination of phlebotomies and the completion of all post-phlebotomy pulmonary and hematologic studies was 11.7 days. Post-phlebotomy blood volume studies could not be obtained on the subject with unclassified absolute polycythemia.

**Pulmonary Diffusing Capacity.** With the exception of one subject with secondary polycythemia and pulmonary emphysema, phlebotomy resulted in a significant fall in DLCO in all subjects. Figure 3 illustrates the relationship between the packed cell volume and DLCO before and after phlebotomy. Individual values for DLCO are listed in Table 2.

The mean DLCO for the entire group was 93 per cent of predicted before and fell to 71 per cent after phlebotomy. The mean for polycythemia vera patients was 123 per cent before and 93.8 per cent after phlebotomy. The secondary polycythemia group had a mean pre-phlebotomy value of 56 per cent of predicted which fell to 43.9 per cent with venesection.

The smallest decrease in DLCO after phlebotomy occurred in a patient with polycythemia vera, but was found to be significant (p<.01).

**Discussion**

Roughton and Forster have shown that the diffusing capacity of the lungs for CO is determined by the diffusion characteristics of the alveolar capillary membrane and by the actual rate of CO uptake by the red cells in the pulmonary capillaries.
This is expressed in terms of resistances by the equation:

\[
\frac{1}{D_L} = \frac{1}{D_m} + \frac{1}{\theta V_c}
\]

1/Dₗ is the total resistance to diffusion. 1/Dₘ is the resistance to diffusion by the alveolar capillary membrane, which consists of the alveolar epithelium, the interstitial fluid, the capillary endothelium and the intracapillary plasma.

θ is the product of (1) the rate at which CO displaces O₂ in the hemoglobin molecule and (2) the hemoglobin concentration in the capillary. V_c is the pulmonary capillary volume. It is evident that a significant change in any of these four factors would result in a corresponding change in the total diffusing capacity.

With regard to Dₘ, there is no reason to suspect that polycythemia vera alters the character of the alveolar capillary membrane. It is quite likely that the subjects with other types of polycythemia, all of whom had either low diffusing capacities or other abnormalities of pulmonary function, had impaired membrane diffusion. However, phlebotomy alone would not be expected to alter membrane resistance to diffusion in either group. In our patients this is further suggested by the fact that ventilatory function studies did not change significantly after venesection in any patient.

The component of θ which consists of the rate at which CO displaces O₂ in the hemoglobin molecule should not be abnormal since no characteristic defects in the red cells or in the hemoglobin molecule have been demonstrated in polycythemic patients. Reduction of red cell mass and hemoglobin concentration would not be expected to influence this molecular chemical process.

Hemoglobin concentration is obviously a factor and may be the sole factor accounting for supernormal diffusing capacities in polycythemia vera and in the reduction of DLCO following phlebotomy in all types of polycythemia. The relationship between hemoglobin concentration and diffusing capacity holds true generally for high or low diffusing capacities before the hemoglobin concentration is reduced by phlebotomy. Further, Rankin, McNeill and Forster have observed this same relationship between hemoglobin concentration and diffusing capacity in anemia patients before and after transfusion.

The fourth variable that could influence the diffusing capacity in polycythemia before and after phlebotomy is the volume of blood in the pulmonary capillaries. The only method currently available for estimating the V_c is calculation from the previous equation when DLCO is measured at different oxygen tensions. Using this technique, Burgess and Bishop found low capillary volumes in polycythemia vera subjects and suggested that this was the result of thromboses in the small pulmonary vessels. However, their values for V_c were variable and in some instances extremely low. Because the status of the pulmonary capillary volume in polycythemia remains uncertain, further investigation is indicated.

**Summary**

Observations on the diffusing capacity before and after phlebotomy have been made in nine subjects with various polycythemic states. As a group, subjects with untreated polycythemia vera have high diffusing capacities. Phlebotomy results in reduction of the diffusing capacity in all types of polycythemia. Our results show that the diffusing capacity of the lungs for carbon monoxide varies directly with hemoglobin concentration. This relationship between the diffusing capacity and hemoglobin concentration is independent of the level of DLCO before phlebotomy.

**Resumé**

L’auteur a étudié la capacité de diffusion avant et après phlébotomie chez neuf sujets atteints de différentes formes de polyglobulies. Dans l’ensemble les sujets atteints de polyglobulie vraie non traitée ont des capacités de diffusion élevées. La phlébotomie provoque la réduction de la capacité de diffusion dans tous les types de polyglobulies. Les résultats rapportés montrent que la capacité de diffusion des poumons pour
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l'oxyde de carbone varie directement avec la concentration d'hémoglobine. Ce rapport entre capacité de diffusion et concentration de l'hémoglobine est indépendant du taux de diffusion de l'oxyde de carbone avant phlébotomie.

ZUSAMMENFASSUNG


REFERENCES


For reprints, please write Dr. Hans Weill, 1430 Tulane Avenue, New Orleans.

RUPTURED CHORDAE TENDINEAE

Fifteen cases of severe mitral regurgitation secondary to ruptured chordae tendineae have been reviewed, eight of whom underwent open-heart surgery. Three patients are living at this time with two being markedly improved.

Progressive deterioration within the year following onset of difficulty or sudden worsening of previous cardiac symptoms characterized the usual clinical course. The aortal systolic murmur, always loud, was conspicuously harsh and radiated to the base of the heart, simulating aortic stenosis when the mural cusp was ruptured. Although strongly suggesting the diagnosis, the sudden onset of an aortal systolic murmur could be documented in only three instances. The presence of a small left atrium radiographically with tall left atrial "v" waves and marked reflux of contrast material into a paradoxically pulsating left atrium also pointed to the correct diagnosis.