Respiratory Responses to Experimental Unilobar Pulmonary Edema

By Frank D. Gray, Jr., M.D., Donald P. Shedd, M.D., and Eiichi Kato, M.D.

The effect of unilobar engorgement and edema in a dog's lung on the effort of breathing was studied by expressing the latter as the velocity of air-flow attained per unit of pressure change across the lung, and as static compliance. Edema of the left lower lobe, produced by shunting blood from the femoral into the pulmonary artery, affected the effort of breathing only at high infusion rates and volumes, otherwise changes in resting (mid) position and respiratory rate kept the effort of breathing constant. Static compliance decreased with infusion, possibly because the infused blood encroached on the air space.

The labored breathing of acute pulmonary edema would logically seem to stem from the excessive fluid pervading and obstructing the pulmonary airways. Engorgement of the pulmonary vessels may contribute to the ventilatory difficulty. Underlying heart and lung disease, a frequent cause in the first place, may also contribute to the dysfunction.

Observations of the intact experimental animal have revealed complex patterns of bronchomotor, hemodynamic, and respiratory functions associated with edema of the lung. These patterns may vary considerably with slight changes in the experimental conditions. In a study of the effect of infusing blood into a single lobe of a dog's lung the lobar tidal air volume uniformly decreased while the vascular blood pressure rose, but the relationship between tidal volume, infusional volume, and vascular pressures was erratic suggesting that multiple factors were involved.

In an attempt to give some quantitative value to the physiologic effects of the variables which could be controlled, a series of experiments was devised in which blood infusion rates were regulated. In addition to measuring tidal volume and vascular pressures, a rough estimation was made of the work of breathing, by calculating the static compliance, and the effort required to inflate the lung during inspiration.

The latter was expressed as the peak air flow velocity attained per centimeter of water pressure drop across the lung from the mouth to the pleural space during inspiration. This velocity-pressure equivalent is not proposed as a precise measure of the work of breathing but merely as a reflection of the result of all the factors which affect the movement of air into the lungs during inspiration influencing the effort required to carry on the active phase of breathing.

Methods

The experiments were carried out on dogs anesthetized with pentobarbital sodium (30 mg./Kg.) using a technic similar to that of an earlier report. A left thoracotomy was performed and the artery, veins, and bronchus of the left lower lobe identified. Snare loop ligatures were prepared and placed around the left lower lobe artery and vein to permit occlusion and release of these from the outside after closure of the chest. Polyethylene cannulas for pressure recording were led into the lobe, one into the artery and one into the vein directed to the lobar side of the respective snare loops. A cannula was inserted through the trachea into the left lower lobe bronchus, and secured by an encircling ligature. After inserting a small metal cannula into the pleural space for pressure measurement, the thoracotomy incision was closed.
The left lower lobe cannula was attached to a small oxygen-filled Krogh spirometer in series with a pneumotachograph, and the remaining lobes were ventilated from an oxygen-filled bell spirometer, again in series with a pneumotachograph. Both spirometers had carbon dioxide absorbing canisters. The lobar artery and vein catheters were connected to the pressure capsules of a Hathaway multichannel blood pressure recording apparatus. The intrapleural and mouth pressures as well as the pneumotachograms were recorded simultaneously on the Hathaway oscillograph.

After determining that the animal was in a steady state by noting no fluctuation in any of the phenomena recorded for 20 to 30 min., ligation of the left lower lobe pulmonary vein and artery was accomplished and infusion into the artery begun. Blood was allowed to flow from the femoral artery via a polyethylene catheter into a plastic bag containing acid-citrate-dextrose* as anticoagulant, thence into the left lower lobe artery at a measured rate.

Except for experiment number 2, the procedure was continued until the left lower lobe tidal volume was reduced to 50 per cent of the starting volume. At the conclusion of the experiment the dog was exsanguinated and an autopsy performed.

Because of the difficulty in separating the elastic recoil factor and variable amounts of active expiratory effort from resistive factors, the expiratory phase of the respiratory cycle was not studied, and only the inspiratory phase in which elastic recoil and resistive factors are additive will be described. The peak velocity of air flow was measured as the highest point of the pneumotachograph curve. Usually this turned out to be a plateau of several tenths of a second duration, and the differences between intrapleural and mouth pressures during that period were averaged. From these data the peak velocity imparted to air flow in centimeters per second for each centimeter of water pressure drop across the lung was calculated at regular intervals. Hereafter this value will be referred to as the velocity-pressure equivalent. The velocity-pressure equivalent increases as the work of breathing decreases. Compliance was expressed as the inspired tidal volume divided by the pressure difference between points of no flow, or ml./cm. water.

At the beginning of each experiment observations were recorded every 2 to 4 min. In those experiments extending over more than 10 min,

---

*Seventy-five milliliters of acid citrate dextrose solution (U.S.P. formula A, containing 16.8 mEq.) was used for each 500 ml. of blood. The composition of this anticoagulant is: sodium citrate, 22.6 Gm.; citric acid, 7.4 Gm.; dextrose, 24.5 Gm.; water to make 1,000 ml.
RESULTS

Experiment 1: Pulmonary Vein Occlusion, Patent Pulmonary Artery, No Blood Infused into Left Lower Lobe. The purpose was to observe the effect of pulmonary venous occlusion alone, since it was felt that some sequestration of blood would occur. Figure 1A demonstrates the prompt rise in left lower lobe intravascular pressures following ligation, and the gradual decrease in left lower lobe tidal volume to the 50 per cent level. During this period there was a slight rise in respiratory rate and in the velocity-pressure equivalent. Only the compliance of the control lobe was significantly altered, and it increased.

Experiment 2: No Vessels Ligated, Blood Infused at 22 ml. per min. (Fig. 1B). Again the left lower lobe intravascular pressures rose, but even after 45 min. of infusion the left lower lobe tidal volume fell only 28 per cent. Of course no blood was being sequestered in the lobe since the venous outflow was patent. The respiratory rate was nearly constant. There was a slight rise in the velocity-pressure equivalent in both control and infused lobes, and compliance fell in the latter.

Experiments 3 and 4: Both Pulmonary Artery and Vein of Left Lower Lobe Ligated, Blood Infused at 9 and 12 ml. per min. Respectively. In both experiments the left lower lobe vascular pressures rose promptly (table 1), and the tidal volumes decreased to 50 per cent or lower. The control tidal volumes and the respiratory rates remained almost constant, and the velocity-pressure equivalent increased in the control lobes of both lungs, remained constant in the infused lobe of experiment 3 but decreased in the infused lobe of experiment 4. Compliance fell in both infused lobes but dropped in the con-

Fig. 2. A. Experiment 6. B. Experiment 8.
### Table 1.—Measurements Before and After Unilateral Pulmonary Edema

<table>
<thead>
<tr>
<th>Exper. no. &amp; type</th>
<th>Period*</th>
<th>Mean pressure, mm. Hg.</th>
<th>Resp. rate</th>
<th>Tidal vol. ml</th>
<th>Velocity-pressure equivalent</th>
<th>Compliance (ml/cm. Hg)</th>
<th>Resting neg intrapleural press. (cm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PA</td>
<td>PV</td>
<td>Control</td>
<td>LLL</td>
<td>Control</td>
<td>LLL</td>
</tr>
<tr>
<td>1</td>
<td>a</td>
<td>17</td>
<td>7</td>
<td>34</td>
<td>220</td>
<td>40</td>
<td>35.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b</td>
<td>16</td>
<td>7</td>
<td>33</td>
<td>220</td>
<td>40</td>
</tr>
<tr>
<td>PV ocl.</td>
<td>4</td>
<td>31</td>
<td>22</td>
<td>38</td>
<td>220</td>
<td>35</td>
<td>35.0</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>31</td>
<td>24</td>
<td>42</td>
<td>210</td>
<td>30</td>
<td>35.0</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>31</td>
<td>24</td>
<td>46</td>
<td>200</td>
<td>20</td>
<td>35.0</td>
</tr>
<tr>
<td>2</td>
<td>a</td>
<td>22</td>
<td>5</td>
<td>32</td>
<td>235</td>
<td>92</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b</td>
<td>20</td>
<td>4</td>
<td>32</td>
<td>235</td>
<td>90</td>
</tr>
<tr>
<td>Inf. at 22 ml./min.</td>
<td>3</td>
<td>26</td>
<td>12</td>
<td>33</td>
<td>270</td>
<td>90</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>38</td>
<td>24</td>
<td>320</td>
<td>90</td>
<td>18.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>38</td>
<td>23</td>
<td>320</td>
<td>87</td>
<td>19.0</td>
</tr>
<tr>
<td>22 ml./min.</td>
<td>22</td>
<td>37</td>
<td>19</td>
<td>39</td>
<td>310</td>
<td>82</td>
<td>18.0</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>30</td>
<td>13</td>
<td>40</td>
<td>305</td>
<td>74</td>
<td>17.5</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>24</td>
<td>11</td>
<td>42</td>
<td>300</td>
<td>66</td>
<td>17.0</td>
</tr>
<tr>
<td>PA, PV ocl.</td>
<td>3</td>
<td>a</td>
<td>2</td>
<td>70</td>
<td>365</td>
<td>45</td>
<td>12.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b</td>
<td>2</td>
<td>73</td>
<td>365</td>
<td>45</td>
<td>13.0</td>
</tr>
<tr>
<td>Inf. at 9 ml./min.</td>
<td>3</td>
<td>25</td>
<td>70</td>
<td>365</td>
<td>40</td>
<td>16.0</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>a</td>
<td>30</td>
<td>69</td>
<td>365</td>
<td>38</td>
<td>17.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b</td>
<td>30</td>
<td>69</td>
<td>325</td>
<td>22</td>
<td>18.0</td>
</tr>
<tr>
<td>12 ml./min.</td>
<td>4</td>
<td>a</td>
<td>20</td>
<td>10</td>
<td>40</td>
<td>220</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b</td>
<td>18</td>
<td>10</td>
<td>41</td>
<td>220</td>
<td>56</td>
</tr>
<tr>
<td>Inf. at 12 ml./min.</td>
<td>3</td>
<td>30</td>
<td>20</td>
<td>50</td>
<td>250</td>
<td>53</td>
<td>27.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>33</td>
<td>27</td>
<td>53</td>
<td>285</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>33</td>
<td>27</td>
<td>55</td>
<td>300</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>34</td>
<td>29</td>
<td>53</td>
<td>300</td>
<td>20</td>
<td>33.5</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>34</td>
<td>29</td>
<td>50</td>
<td>285</td>
<td>5</td>
<td>33.5</td>
</tr>
<tr>
<td>PA, PV ocl.</td>
<td>5</td>
<td>a</td>
<td>12</td>
<td>4</td>
<td>35</td>
<td>200</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b</td>
<td>10</td>
<td>4</td>
<td>35</td>
<td>200</td>
<td>50</td>
</tr>
<tr>
<td>Inf. at 13 ml./min.</td>
<td>3</td>
<td>18</td>
<td>10</td>
<td>35</td>
<td>240</td>
<td>33</td>
<td>17.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>26</td>
<td>18</td>
<td>35</td>
<td>200</td>
<td>0</td>
</tr>
<tr>
<td>13 ml./min.</td>
<td>6</td>
<td>a</td>
<td>24</td>
<td>17</td>
<td>30</td>
<td>200</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b</td>
<td>25</td>
<td>17</td>
<td>30</td>
<td>200</td>
<td>46</td>
</tr>
<tr>
<td>Inf. at 20 ml./min.</td>
<td>4</td>
<td>34</td>
<td>23</td>
<td>37</td>
<td>200</td>
<td>35</td>
<td>39.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>43</td>
<td>32</td>
<td>37</td>
<td>200</td>
<td>24</td>
</tr>
<tr>
<td>23.5 ml./min.</td>
<td>10</td>
<td>48</td>
<td>37</td>
<td>36</td>
<td>220</td>
<td>18</td>
<td>35.0</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>70</td>
<td>52</td>
<td>33</td>
<td>280</td>
<td>10</td>
<td>25.0</td>
</tr>
<tr>
<td>PA, PV ocl.</td>
<td>7</td>
<td>a</td>
<td>16</td>
<td>5</td>
<td>20</td>
<td>360</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b</td>
<td>15</td>
<td>5</td>
<td>21</td>
<td>370</td>
<td>65</td>
</tr>
<tr>
<td>Inf. at 23.5 ml./min.</td>
<td>4</td>
<td>50</td>
<td>9</td>
<td>46</td>
<td>325</td>
<td>54</td>
<td>25.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>58</td>
<td>19</td>
<td>60</td>
<td>325</td>
<td>45</td>
</tr>
</tbody>
</table>

* Periods: a = Control, b = Infusion at; occl. = occlusion.
Experiments 5 and 6: Both Pulmonary Artery and Vein of Left Lower Lobe Occluded, Blood Perfused at 13 and 20 ml. per min. Respectively. As in all of the other experiments, the intravascular pressures rose at once (table 1 and fig. 2A). The respiratory rate remained constant. The control tidal volume remained constant in experiment 5 and rose slightly in experiment 6, whereas the left lower lobe tidal volume decreased steeply in both. The velocity-pressure equivalents dropped almost as sharply as the tidal volumes of the left lower lobes in both experiments, but remained constant in the control lobes of experiment 5 and decreased moderately in the control lobes of experiment 6. Compliance was constant in both control lungs, and dropped in both infused lobes.

Experiments 7, 8, and 9: Both Pulmonary Artery and Vein of Left Lower Lobe Ligated, Blood Infused into Lobe at 23.5, 19, and 16 ml. per min. respectively. Again the lobar intravascular pressures rose and the left lower lobe tidal volumes fell to 50 per cent or below while control tidal volumes remained unchanged or rose slightly (table 1 and fig. 2B). In all three the respiratory rate rose to very high levels. The velocity-pressure equivalents remained almost constant for the left lower lobes in experiments 8 and 9, dropping slightly in the infused lobe of experiment 7 and in the control lobe of both 7 and 9. Compliance decreased in both control and infused lobes of all 3 experiments.

Pathologic Studies. All of the lobes in which infusion was carried out after the pulmonary artery and vein had been occluded were grossly large, heavy, and dark red in color. They showed no tendency to collapse, and blood ran freely from the cut surfaces. The control lobes were grossly normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal. Microscopically the infused lobes showed vascular engorgement with homogeneous pink staining material filling the alveoli and bronchial passages. The control lobes also had scattered areas of vascular engorgement, but were generally normal.

### Table 1—(Cont.)

<table>
<thead>
<tr>
<th>Exper. no. &amp; type</th>
<th>Period</th>
<th>Mean pressure, mm. Hg</th>
<th>Resp. rate</th>
<th>Tidal vol. ml.</th>
<th>Velocity-pressure equivalent</th>
<th>Compliance (ml/cm Hg)</th>
<th>Resting neg. intrapleural pres. (cm. H2O)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PA</td>
<td>PV</td>
<td>Control</td>
<td>LLL</td>
<td>Control</td>
<td>LLL</td>
</tr>
<tr>
<td>8 PA, PV occl.</td>
<td>a</td>
<td>10</td>
<td>2</td>
<td>105</td>
<td>45</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>10</td>
<td>3</td>
<td>105</td>
<td>45</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>32</td>
<td>23</td>
<td>135</td>
<td>42</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>I f. at 19 ml./min.</td>
<td>7</td>
<td>34</td>
<td>23</td>
<td>135</td>
<td>37</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>31</td>
<td>22</td>
<td>145</td>
<td>29</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>39</td>
<td>23</td>
<td>150</td>
<td>16</td>
<td>32</td>
<td>14</td>
</tr>
<tr>
<td>9 PA, PV occl.</td>
<td>a</td>
<td>10</td>
<td>2</td>
<td>120</td>
<td>30</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>10</td>
<td>3</td>
<td>120</td>
<td>30</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>32</td>
<td>23</td>
<td>135</td>
<td>28</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Inf. at 16 ml./min.</td>
<td>7</td>
<td>24</td>
<td>25</td>
<td>120</td>
<td>27</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>20</td>
<td>10</td>
<td>80</td>
<td>20</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>20</td>
<td>11</td>
<td>100</td>
<td>22</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>36</td>
<td>11</td>
<td>100</td>
<td>14</td>
<td>17</td>
<td>8</td>
</tr>
</tbody>
</table>

* a, b are control studies at least 20 min. apart; numerals refer to minutes after occlusion; PA, pulmonary artery; PV, pulmonary vein; occl., occluded; Inf. at — ml./min., rate of infusion into PA of LLL; Control, all lobes except the left lower lobe; LLL, left lower lobe.
Blood pH, electrolyte concentration, and arterial oxygen saturation were observed and found constant during the course of the experiments, and no experiments were accepted in which these values were abnormal. Since the animal breathed pure oxygen throughout, the high arterial oxygen saturation cannot, of course, be taken as an indication of normal ventilation.

During every experiment except the first in which no blood was infused, the resting intrapleural pressure became less negative as the experiment progressed. This was, no doubt, due to the effect of the volume of blood added to the intrathoracic space, rather than to a lower mid-position of the lung.

**DISCUSSION**

Lobar tidal volume decreases when a large volume of blood is sequestered in a single lobe of a dog's lung, probably because of simple mechanical encroachment upon the air space by the blood-engorged pulmonary capillaries. In an earlier report this phenomenon has been shown to occur in the presence of a rise in intravascular pressure but the relationship is not linear. This is not surprising because the infused volume has three escape routes: bronchial veins, lymphatics, and across the capillary membrane into alveoli. The bronchial arteries form a potential source of increased pressure and volume. In all experiments the lobar tidal volume decreased, even in those in which the combination of occlusion and perfusion was not present (experiments 1 and 2), suggesting that a rise in intravascular pressure may, in itself, contribute to a diminished tidal volume.

In general, a low static compliance implies high tissue resistance and elastic factors, whereas a low velocity-pressure equivalent might also reflect a high airway resistance. If compliance increases or remains constant, a decrease in the velocity-pressure equivalent must reflect an increase in the airway resistance.

The change in the velocity-pressure equivalent corresponded in degree to the marked drop in tidal volume in only 2 of the 9 experiments in spite of the enormous changes that must occur in a single lobe of a dog's lung when up to 500 ml. of blood are infused after occluding the venous drainage, hence one must conclude that a very effective mechanism exists for maintaining a free airway. Apparently under certain critical conditions, present in experiments 5 and 6, and possibly related to infusion rate, these homeostatic mechanisms break down and the effort needed to impart normal velocity to air flow increases. Since in all but the first experiment the static compliance of the infused lobe fell, the preservation of the velocity-pressure equivalent must be an airway phenomenon.

The drop in compliance of the infused lobes might reflect diminished air space because of simple encroachment upon the air space by the infused blood. A smaller air volume is associated with lower compliance since the latter is influenced by the surface area against which a pressure differential is exerted. This may explain, in part, the decreased compliance and increased work of breathing noted by Marshall, McIroy and Christie and by Christie and Meakins in congestive heart failure.

Static compliance changes were roughly parallel with the velocity-pressure equivalent in the control lobes of all experiments except 7, 8, and 9, where compliance fell and the velocity-pressure equivalent remained constant. The hyperventilation seen in these experiments probably resulted in distention beyond the elastic limits of the lung, leading to dilatation of the bronchial airways and a very great elastic recoil force.

The increased static compliance observed in the control lobes of experiments 1, 2, 4, 5, and 6, probably coincided with a rise in resting volume, still within the elastic limits of the lung tissue.

The rise in intravascular pressures must represent, in part, the mechanical effect of filling an isolated vascular segment the drainage of which has been occluded. It is of interest that the pressures rose rapidly during the initial phase, then, in some of the experiments (3, 4, and 8), reached a plateau in.
UNILOBAR PULMONARY EDEMA

spite of continued infusion to very high total blood volumes. Several possible explanations present themselves. Possibly fluid is lost rapidly into the airways by transudation or capillary wall rupture after the intravascular pressure reaches a critical point, or new vascular areas open to absorb the additional volume. The phenomenon might also represent a decrease in vascular tone occurring when the pressure reaches a high level. One might also speculate that the bronchial veins become increasingly important at high pressure levels thus allowing a large flow from the pulmonary vessels into the azygous system.

The leveling off of the pressure is probably not the result of sudden shift of blood volume into the pulmonary veins subsequent to the drop in pulmonary vascular resistance which occurs at high pulmonary vascular pressures since the pulmonary venous pressure rose pari passu with the pulmonary artery pressure in the present experiments. The surprising rise in pulmonary artery and vein pressure in experiment 1 in which only pulmonary venous ligation was carried out suggests that a reflex mechanism is responsible. In this experiment (fig. 1A) in which there was no infusion, if the rise in pressure were entirely passive, one would not expect the pulmonary artery and vein pressures to rise above the base-line pulmonary artery pressure.

An increase in the resting lung volume (functional residual capacity) subsequent to greater inspiratory effort is known to increase the vascular capacity of the lung, and bronchomotor tone itself has been implicated in vascular phenomena. When a sufficient amount of excess blood has entered the lobe, it seems likely that pressure-sensitive nerve endings are stimulated to produce increased inspiratory effort and higher resting lung volumes, thereby increasing vascular capacity and maintaining a constant intravascular pressure in the face of further increments of filling.

The plateau phenomenon did not occur when the velocity-pressure equivalent dropped (experiments 5, 6), suggesting that the rapid rate of infusion utilized in these experiments elicited a different reflex mechanism. If, instead of reflex inspiratory effort, there were in these experiments an increase in bronchomotor tone which has been implicated by Rodbard in the regulation of pulmonary vascular phenomena, the continuing rise in pulmonary vascular pressure as well as the drop in the velocity-pressure equivalent could be explained readily. At slower infusion rates this reflex phenomenon might be dominated by the inspiratory effort reflex. An attractive alternative, that the drop in velocity-pressure equivalent is merely the result of edema fluid in the bronchiolar and bronchial air passages, is not supported by the observation that the airways in all experiments were filled with edema fluid at autopsy, whereas only experiments 5 and 6 showed this ventilatory phenomenon.

Another reflex phenomenon appeared in those experiments (7—9) in which very rapid infusion rates were maintained. Here the respiratory rate rose to unusual heights. The fact that values for the velocity-pressure equivalents remained constant probably reflects the obligatory rise in resting lung volume incidental to the rapid respiratory rate. With greater resting volume the bronchi dilate, reducing airway resistance.

The possibility that the increased respiratory rate, by virtue of a "pumping" action, increased lymph drainage thus clearing the airways of edema fluid must be considered in this regard. No attempt was made to estimate lymph flow.

Obviously reflexes cannot be demonstrated by the technics of the present experiments which can only indicate some of the possibilities. However, these experiments do show that although tidal volume is sacrificed whenever large amounts of blood enter the lung (even in experiment 2 in which no sequestration occurred) the effort of breathing as reflected in the pressure needed to impart a given velocity to air flow was impaired only within a narrow range of infusion rates.
be no change in effort. If the postulated reflexes do, in fact, exist, they might serve well to limit some aspects of acute pulmonary edema.

The air flow and intravascular blood pressure phenomena of a single lobe of a dog's lung into the pulmonary artery of which large amounts of blood are infused after occlusion of both pulmonary artery and vein are, in part, simple physical readjustments. This mechanical concept is inadequate, however, to explain all of the observations made in the course of such experiments. Other hemodynamic factors including bronchial vein flow and lymph drainage are probably important. A group of reflexes involving changes in the degree of inflation of the lung, respiratory rate, and possibly bronchomotor tone can be evoked to explain consistently all of the phenomena observed in this series of experiments. The rate of filling of the vascular structures may determine the dominating reflex.

The present type of experiments can only give an over-all view of these very complex physiologic mechanisms. They suggest that neurogenic reflexes and hemodynamic patterns play interdependent roles as has been reported frequently. Other studies have shown the influence of the lung innervation in protecting against acute pulmonary edema. Further experiments utilizing nerve section and blocking agents, and measuring flow in bronchial veins and lymph channels must be carried out for confirmation.

SUMMARY

Pulmonary vascular pressures, respiratory rates, tidal volume, static compliance and the effort required to impart a given velocity to air flow (velocity-pressure equivalent) were studied in the sequestered left lower lobe and the remaining lobes of the lung in 9 dogs. In 7 the left lower lobe pulmonary artery and vein were occluded, and blood shunted from the femoral artery into the lobar pulmonary artery. In 1 only the pulmonary vein was occluded and no blood was infused; and in 1 other no occlusion was performed, and only infusion into the lobar pulmonary artery was carried out.

In the sequestered left lower lobe the pulmonary vascular pressure rose regularly, and the tidal volume fell. The respiratory rate was variable as was the velocity-pressure equivalent. An increased respiratory rate appeared to prevent inordinate increases in effort needed to impart velocity to air flow. At low infusion rates, similarly, there was no increase in effort, although tidal volume diminished.

Conclusions are not warranted beyond a simple description of events, but nervous reflexes and possible changes in bronchial vein and lymphatic flow are suggested by the data.

ACKNOWLEDGMENT

The authors are indebted to Mr. Armand Negri for his assistance in the surgical procedures, and to Misses Nina Gambina, Susie Miranda, and Adrienne Audette for performing the laboratory analyses involved in this study.
pro impartir velocitate al fluxo de aere. Sim-
ilemente, un lente progresso del infusion non
esseva associate con ulle augraento del effortio
ben que le volumine del aere currente se re-
duceva.

A parte le simple description del evenimen-
tos nulle conclusiones es justificate. Tamen,
le datos pare suggerer le presentia de reflexos
nervose e possibilemente le occurrentia de
alterationes in le fluxo del vena bronchial e
in le fluxo lymphatic.

REFERENCES

shallow breathing from pulmonary conges-
tion and edema. J. Exper. Med. 49: 531,
1929.

2. Henneman, P. H.: Acute pulmonary edema
with special reference to experimental
studies. New England J. Med. 235: 590,
619, 1946.


4. Drinker, C. K.: The Clinical Physiology of
the Lungs. Springfield, Ill., Charles C
Thomas, 1954.

5. Aviado, D. M., Jr., and Schmidt, C. F.: Re-
flexes from stretch receptors in blood
vessels, heart and lungs. Physiol. Rev. 35:

G.: The physiology and pharmacology of

7. Sherr, D. P., and Gray, F. D., Jr.: Experi-
mental unilobar pulmonary edema. Yale

8. —, Alley, R. D., and Lindskog, G. E.: Ob-
servations on the hemodynamics of bron-
chial-pulmonary vascular communications. J.

9. Williams, M. H., Jr., and Towbin, E. J.: Magni-
ture and time of development of the
collateral circulation to the lung after oc-
clusion of the left pulmonary artery.

intrapleural pressure in congestive heart

11. Marshall, R., McIlroy, M. B., and Christi-
, R. V.: The work of breathing in mitral

12. Williams, M. H., Jr.: Relationships between
pulmonary artery pressure and blood flow
in the dog lung. Am. J. Physiol. 179: 243,
1954.

13. Borey, H. G., McGregor, M., Whittenber-
er, J. L., and Berglund, E.: Influence of pul-
monary arterial and left atrial pressures on
pulmonary vascular resistance. Circulation
Research 4: 393, 1956.

blood flow and distention on the capacity
of intrapulmonary vessels. Am. J. Physiol.

factor in the regulation of the pulmonary

hemodynamics of pulmonary edema. II. The
role of sympathetic pathways in the eleva-
tion of pulmonary and systemic vascular
pressures following the intracisternal injec-

17. Ferguson, D. J., and Berkas, E. M.: Effect
of lung denervation on pulmonary hyperten-
sion and edema. Circulation Research 5:
310, 1957.


19. Farber, S.: Neuropathie pulmonary edema:
Further observations. Arch. Path. 30: 180,
1940.
Respiratory Responses to Experimental Unilobar Pulmonary Edema
FRANK D. GRAY, JR., DONALD P. SHEDD and EIICHI KATO

Circ Res. 1958;6:507-515
doi: 10.1161/01.RES.6.4.507
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1958 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/6/4/507