Diffuse Bilateral Pulmonary Edema Associated with Unilobar Miliary Pulmonary Embolization in the Dog

By DONALD SINGER, M.D., CHARLES HESSER, M.D., RUTH PICK, M.D. AND LOUIS N. KATZ, M.D.

Unilobar injection of starch solution produced pulmonary infarction at the site of injection and diffuse bilateral pulmonary edema. The predominantly or entirely unilobar distribution of the embolizing material was established by histologic methods and by a technic using whole lung lobe suspension stained with Lugol's solution. Evidence is presented suggesting that the pulmonary edema in the nonembolized lobes is attributable to neural or neurohumoral mechanisms.

In the course of studies since 1938 attention has been drawn to the marked disproportion between the part of the pulmonary vascular bed directly affected by multiple small emboli and the extraordinary severity of the sequelae encountered. For references see Katz. The disparity has led us, as well as others, to the hypothesis that neural or neurohumoral mechanisms are involved in the sequence of events following embolization.

More recently, our studies have focused on the pulmonary edema noted after miliary embolism. This was stimulated by the observation that unilobar starch injection will frequently lead to severe bilateral edema, particularly if the embolization also results in the production of a localized confluent infarct in the injected lobe.

Basic to the evaluation of these observations on pulmonary edema is an adequate demonstration of the localization of the embolizing starch granules to the injected lobe. Previous methods employed by us were based on histologic evaluation of random samples prepared from each lobe. In this report a method is described which gives a more comprehensive picture of the starch content in the injected and uninjected lobes. Comparison of the two methods was made in each of several animals to check on the reliability of the histologic random sample technic in assessing the over-all starch distribution.

In the course of these recent studies, observations were also made on the nature of the pulmonary infarction produced by the starch and its role in the pathogenesis of the bilateral pulmonary edema. Also checked were the possibilities: (1) of transfer of the starch via the systemic circulation to the part of the lungs not primarily injected, and (2) of the pulmonary edema on the contralateral side arising from edema fluid via the airways from the embolized lung. An attempt was further made to determine how much bilaterally injected starch was necessary to cause pulmonary edema in the absence of confluent infarction. In the course of such injections evidence of laminar flow was clearly demonstrated.

Materials and Methods

Sixteen dogs were trained, and the essential surgery was done under local procaine anesthesia around the incision site. Thirty-seven dogs were anesthetized with sodium pentobarbital (intravenous 25 mg./Kg.), additional pentobarbital being given as necessary to maintain a satisfactory level of anesthesia. Embolization was produced by an aqueous or saline suspension of starch (1 to 5 per cent concentration and 10 to 50 μ diameter particle size). Three animals were injected with 10 per cent NaOH in varying amounts. The others were injected with starch via a no. 9 Cournand type catheter in the left pulmonary artery wedge position, the main pulmonary artery or the left lower branch, or the right ventricle or atrium.

In order to eliminate the possibility of airway spread of the edema fluid a no. 24 Foley urethral...
catheter was employed to block the right main bronchus just beyond the carina in 4 animals. It was inserted into the trachea through the tracheotomy tube prior to embolization under fluoroscopic control; the Foley bag being rinsed with a Diodrast solution. A tank containing 95 per cent O₂ under positive pressure was used to aerate this side of the lung, the remainder was aerated by room air. The position of the catheter and the adequacy of the bronchial obstruction were confirmed at autopsy.

Animals were sacrificed 1 hour after embolization. The heart, lungs and tracheobronchial tree in each case were examined macroscopically for the presence of pulmonary infarction, atelectasis and edema, and the position of the catheter tip(s). Edema was graded as follows: 4 +, parenchyma grossly waterlogged, spontaneous runoff of fluid on section, and tracheobronchial tree filled with foam and fluid; 3 +, no spontaneous runoff of fluid on section, but considerable outpouring after minimal manipulation of the cut surfaces and tracheobronchial tree usually as in 4 +; 2 +, only a small runoff of fluid on minimal manipulation of cut surface; 1 +, only minimal amounts of fluid and foam can be expressed from the cut parenchyma, and small amounts may be seen escaping from the orifices of the small bronchi on compressing the surrounding lung tissue.

Tissue blocks were taken from the infarcted area, from the midportion of the left lower lobe along its vertebral border and from the corresponding area of the right lower lobe. Hematoxylin-eosin stained sections were examined for congestion, edema, atelectasis, or necrosis, but especially as to the number of starch granules per section, and their distribution within the pulmonary vasculature. The number of starch granules found are reported as follows: (a) small amount, 1 to 10 granules/slide; (b) moderate amount, 10 to 25; (c) large amount, 25+ (in no instance was this less than 50).

In order to provide a check on this essentially random sample technic of estimating lobar starch distribution the following procedure was devised and used in 27 dogs and the results compared with that obtained from the method described. Each lung lobe was separated from its attachments, weighed, cut up into small pieces, and ground in a Waring type blender with Ringer's solution (3 ml./Gm. of tissue) until a fine uniform suspension was obtained. Care was taken to avoid overheating. The suspension was allowed to stand for 30 min. and then 0.1 ml. aliquotes were pipetted onto a glass slide, and an equal amount of Lugol's solution added. Two preparations were made from each of the lobar suspensions. A gross estimate of the number of clearly defined, purple stained starch granules was made by scanning the slides under low power. Then, the number of granules were counted in 10 fields, examined under magnification of 100 fold.

Occasional kidney sections were examined microscopically for starch granules. In addition, arterial blood samples were occasionally examined immediately after embolization for the same purpose.

RESULTS

Determination of Lobar Starch Distribution. The starch distribution was found to be primarily a function of the site of injection. In the 10 animals receiving 1 Gm. in the left pulmonary arterial wedge position (table 4) there was an overwhelming localization of the starch on the injected side. The contralateral lung showed few, and in some instances, no granules. The starch was most commonly found in the capillaries, but was also seen in clumps in the arterioles. Injection of the same amount of embolizing material into a branch of the left pulmonary artery produced a similar unilobar spread in 19 of 24 animals. Five dogs (dog 7, table 4) showed an essentially bilateral distribution of the starch with large numbers of granules in the several lobes, as did all of those injected into the right ventricle (and right atrium). The generalized bilateral distribution could not have been achieved by passage through the systemic circulation and back to the lungs since no starch was found in the kidneys or systemic blood examined. Thus, it is clear that unilateral starch embolization can be attained by injection into the wedge position, and in many instances, by injecting into a branch of the pulmonary artery.

The validity of this deduction was verified by the experiments in which the microscopic estimate of starch localization was checked, simultaneously, with the method based on starch counts of aliquot portions of suspensions of whole lobes. Typical results are shown in table 4. The parallelism of the results with the two methods of counting starch granules is striking.

An incidental observation of some importance was made, namely that the distribution of starch granules among the several lung lobes did not approach equality except when the injection was made into the right atrium.* This suggests lack of complete

* In the case of the right atrial injection the starch was evenly distributed to the several lung lobes, the count being on the average 336, and the differences 78.
mixing of starch injected into the right ventricle, and confirms the presence of laminar flow in the pulmonary arterial tree. The importance of this result as a limiting factor to the interpretation of the presently popular dye-dilution technics is evident.

Production of Confluent Pulmonary Infarction by Localized Starch Injection. It has been reported that experimental pulmonary infarction is infrequently produced in healthy animals without pre-existing congestion of the pulmonary circulation. Contrary to these reports, we have been able to produce confluent, raised, usually well-demarcated hemorrhagic lung infarct in 10 of 11 dogs embolized via the left pulmonary wedge position, and in 17 of 24 injected via a branch of the left pulmonary artery (table 1). Only 2 such infarcts resulted in 14 dogs in which varying amounts of starch were injected into the right ventricle or atrium (table 2).

The infarcted areas were roughly pyramidal or circular in outline, about 3 X 3 to 4 cm. in size, and usually located in the apex of the injected lung lobe. However, other locations in the injected lobe, such as the diaphragmatic surface, were occasionally seen. Histologically, the infarcts were of the incomplete variety, with capillary congestion and intra-alveolar hemorrhage, but without necrosis. Capillary, and, less commonly, smaller arteriolar thrombi were seen in the infarcted area. The peri-infarction tissue showed varying degrees of congestion and atelectasis. There was no significant difference in the incidence of lung infarction between animals prepared under local and general anesthesia.

The injection of 10 per cent NaOH into the pulmonary arterial wedge position also resulted in the production of confluent lung infarction (table 3). When 0.5 ml. of NaOH was used, the infarct was grossly identical with that seen after starch injection, except for a darker color. Histologically, lung infarct produced by NaOH differed from that produced by the starch in that the former showed massive necrosis of the pulmonary parenchyma.

This gives a rough estimate of the accuracy of this method.

### Table 1.—Results of Unilobar* Starch Injection into Left Pulmonary Arterial Wedge Position (LPAW) and Left Pulmonary Artery (LPA)

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of dogs</th>
<th>Number of dogs with pulmonary infarcts</th>
<th>Number of dogs with diffuse bilateral pulmonary edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPAW</td>
<td>10</td>
<td>9 (90%)</td>
<td>15 (79%)</td>
</tr>
<tr>
<td>LPA</td>
<td>19</td>
<td>17 (89%)</td>
<td>2 (10%)</td>
</tr>
</tbody>
</table>

* Dogs with bilateral distribution of starch are excluded from this table.
† Edema was mild (1+ to 2+).
‡ In 3 of these dogs this bilateral edema occurred despite the continuous occlusion of the right main bronchus by a Foley bag.

### Table 2.—Results of Starch Injection into Right Ventricle

<table>
<thead>
<tr>
<th>Amount of starch injected (Gm.)</th>
<th>Number of dogs</th>
<th>Number of dogs with pulmonary infarcts</th>
<th>Number of dogs with diffuse bilateral pulmonary edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>2*</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* These dogs died 5 and 7 min., respectively, after embolization.
† Edema was mild throughout (1+ to 2+).

Production of Bilateral Pulmonary Edema by Localized Miliary Pulmonary Embolization and Its Relationship to Presence of Confluent Pulmonary Infarction. The development of marked diffuse, bilateral pulmonary edema of severe degree subsequent to unilobar embolization with starch, previously described by us, is confirmed by our present studies (table 1). Bilateral pulmonary edema occurred in almost all instances in which a confluent pulmonary infarct developed (24 of 26 animals in table 1). It was most severe, usually 4+, in the infarcted area and in the remainder of the injected lobe, and somewhat less so in the other lobes (3+—4+).* In three instances in which unilobar starch distribution did not

* Diffuse pulmonary edema was also seen in 5 animals developing confluent pulmonary infarction in the presence of bilateral starch distribution (table 2)
UNILOBAR PULMONARY EMBOLIZATION AND PULMONARY EDEMA

Table 3.—Results of Injection of 10 Per Cent NaOH (0.5 to 2.5 ml.) into Left Pulmonary Arterial Wedge Position

<table>
<thead>
<tr>
<th>Number of dogs</th>
<th>Number of dogs with pulmonary infarcts</th>
<th>Number of dogs with diffuse bilateral pulmonary edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>3*</td>
<td>3</td>
<td>3†</td>
</tr>
</tbody>
</table>

* One dog had the right main bronchus occluded prior to and during the procedure.
† The edema was massive throughout (4+).

Table 4.—Distribution of Starch after Injection of 1 Gm. into Left Pulmonary Arterial Wedge Position as Determined by: (1) Histologic Estimation of Selected Sections and (2) Count of Particles in Aliquots of Whole Lobe Suspensions

<table>
<thead>
<tr>
<th>Dog no</th>
<th>Histologic technic on lower lung lobe</th>
<th>Suspension technic on lower lung lobe*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>S†</td>
</tr>
<tr>
<td>30</td>
<td>L</td>
<td>0</td>
</tr>
<tr>
<td>31</td>
<td>L</td>
<td>0</td>
</tr>
<tr>
<td>32</td>
<td>L</td>
<td>S</td>
</tr>
<tr>
<td>27</td>
<td>L</td>
<td>0</td>
</tr>
<tr>
<td>28</td>
<td>L</td>
<td>0</td>
</tr>
<tr>
<td>29†</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>5§</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>6§</td>
<td>L</td>
<td>S</td>
</tr>
<tr>
<td>7§</td>
<td>L</td>
<td>L</td>
</tr>
</tbody>
</table>

* Values represent number of granules in 10 medium power (X100) fields. In dogs 1 and 2 the exact number was not recorded.
† Only 1 or 2 granules seen in entire count.
§ Three Gm. starch injected.
§ Starch injected into left pulmonary artery.
M, medium amount; L, large amount; S, small amount.

The possibility of significant aspiration of edema fluid from the injected lobe into the remainder of the lung as a cause for the edema in the latter was tested in 3 dogs by occluding the right main bronchus. In 2 starch was injected in the left pulmonary artery wedge position (table 1); in the third NaOH was injected to produce the infarct. All developed a confluent infarct and severe bilateral edema (table 1). In each instance, the bronchus was found tightly occluded by the Foley bag and the contralateral edema present was comparable to the other animals without such airway obstruction. Aspiration of edema fluid is thus excluded as a possible cause of the bilateral pulmonary edema.

DISCUSSION

Pulmonary edema has been among the least discussed of the sequelae of miliary pulmonary embolization. Its bilateral occurrence after unilobar starch embolization, especially when made into the pulmonary arterial wedge position, with the development of a localized confluent infarct at the site of injection, has been previously reported by us.2 Pretreatment of the animals with a variety of antihistaminic and antihistaminic compounds often results in marked diminution or complete suspension of edema formation in the noninjected lobes, with little if any effect on that of the injected lobe.4

The accumulated data from our studies were interpreted as supporting a dual mechanism of starch action as regards the edema formation: (a) a local action on the site surrounding the parenchyma and vasculature producing the infarction, and (b) a distant action, involving some neural or neurohumoral mechanism, responsible for the edema in the remainder of the lung.4

Basic to this formulation are two assumptions: (1) that the injected starch is entirely, or at least overwhelmingly, localized to the injection site—which was demonstrated—and that (2) the number of granules found in the other lobes is not sufficient to produce the edema by any direct action of their own.

Although injection into the artery of a lung lobe or its wedge position did indeed produce...
an overwhelmingly unilobar starch distribution, varying numbers of granules were almost always seen in the nonembolized lobes. In order to ascertain the role of this disseminated starch in the generalized pulmonary edema formation, starch was injected into the right ventricle. It was found that the same amount of starch which when introduced into the pulmonary artery or its more peripheral radicles produced both localized pulmonary infarction and diffuse pulmonary edema, did neither when introduced into the right ventricle. Yet the starch count of the contralateral lung lobes was much higher in the latter than in the former situation. From these results it is concluded that the small amount of starch found in the noninjected lung lobes of unilobarly injected animals could not account for the development of the massive edema in these lobes. Other mechanisms, i.e., neuro or neurohumoral, have to be invoked to account for the phenomena observed.

It required a three to fourfold increase in the amount of starch injected into the right ventricle to lead to bilateral edema in the absence of confluent pulmonary infarction. As table 5 shows the starch granule counts under these circumstances throughout the lungs were of the order of magnitude seen in the injected lobe with pulmonary infarction (and associated bilateral edema). The cause of the edema in the bilaterally injected starch may in this instance be due to disseminated multiple minute lung infarcts (behaving similarly to a localized larger confluent infarct in the unilobar preparation).

These experiments confirm our earlier studies as regards the great facility with which pulmonary infarcts may be produced by the unilobar injection of bland starch emboli. This is at variance with the reports of the majority of investigators who concluded that this is not feasible in the presence of a normal pulmonary circulation. Their work suggests that some pre-existent block to the normal circulation is necessary.

The association of localized pulmonary infarction with generalized pulmonary edema formation poses the question of a possible role of the infarction as the trigger mechanism for distant edema formation. This is emphasized by the absence in some animals of generalized edema when confluent pulmonary infarction did not occur despite a large preponderance of granules in the injected lung lobe. The role of the infarction in the pathogenesis of the massive bilateral edema was supported by the comparable results obtained from the local intra-arterial injection of 10 per cent NaOH.

The 2 dogs demonstrating unilobar location of starch, bilateral pulmonary edema but no confluent pulmonary infarction, suggest that the processes giving rise to infarction rather than the lesion per se, are involved in the edema formation. However, in one of these animals there was indirect evidence suggesting left heart failure.

The possibility that the edema in the noninjected lobes might have arisen in the infarcted lobe and aspirated during the postembolic tachypnea from the latter into the former, there in turn to incite further transudation by a direct irritant action, was excluded by the observation that obstruction of the main bronchus of the contralateral lung did not diminish the intensity of edema formation in the noninjected lung lobes.

**SUMMARY**

Injection of starch granules into a lobar branch of the pulmonary artery, or into the arterial wedge position, produces an overwhelming localization of the particles to the injected lobe. Such unilobar miliary embolization, in almost all instances, results in a confluent pulmonary infarct and bilateral edema of severe degree. In those animals that did not develop a pulmonary infarct the edema in the noninjected lobes was minimal or absent. Comparable results were achieved by the intravascular injection of NaOH into the arterial wedge position of one lung lobe.

It is concluded, therefore, that the edema in the noninjected lung lobes is attributable to the operation of a neural or neurohumoral
mechanism, perhaps triggered by the infarct and any substances released within it.

Aspiration of edema fluid via the airways as a cause of bilateral pulmonary edema was excluded by airway obstruction of the bronchus to noninjected lung lobes.

Injection of starch into the right ventricle, in an amount similar to that injected into a lung lobe vessel (1 Gm.), with distribution of large numbers of starch granules to all lobes, produced neither pulmonary infarction nor edema. Therefore, the relatively few starch granules that are found in the noninjected lobes when a lung lobe is embolized are of little or no importance in the production of the disseminated lung edema.

It requires a three to fourfold increase in the amount of starch injected in the right ventricle to lead to bilateral pulmonary edema. In these cases, the starch granule count approaches that in the lobe directly injected with the smaller quantities of starch. The cause of the disseminated pulmonary edema with these large amounts of starch may be the development of multiple minute pulmonary infarcts which operate in the same manner as the confluent infarct does.

These experiments offer a further demonstration of the well-known phenomenon of laminar flow.

**SUMMARIO IN INTERLINGUA**

Le injection de granulos de amylo in le branca lobar del arteria pulmonar o in le position del cuneo arterial produce un localisation massive del particulas in le lobo recipiente le injection. Iste type de unilobar embolisation miliari resulta in quasi omne casos in confluent infarcimento pulmonar e in grades sever de edema bilateral. In le animales que non dissevloppava infarcimento pulmonar le edema del lobo non recipiente le injection esseva minimal o absente. Resultatos comparabile eseva effectuate per le injection intravascular de NaOH in le position del cuneo arterial de un lobo pulmonar.

Per consequente il esseva conclude que le edema in le non-injicite lobos pulmonar es attribuibile al action de un mechanismo neural o neuro-humoral, possiblemente initiate per le infarcimento e le un o le altere substantia generate in illo.

Le possibilitate que le bilateral edema pulmonar esseva cause per aspiration de fluido via le canales aeree esseva excludite per le obstruction del broncho serviente le non-injicite lobos pulmonar.

Le injection de amylo in le ventriculo dextere in quantitates simile a illos injicite in un vaso de lobo pulmonar (1 g)—con distribution de grande numeros de granulos de amylo in omne lobos pulmonar—produceva ni infarcimento pulmonar ni edema. Per consequente, le relativamente pauc numero numero de amylo que es trovate in le non-injicite lobos quando un lobo pulmonar es embolizate ha minor o nulle importantia in le production del disseminate edema pulmonar.

Es requirite un triple o quadruple augmento del quantitate de amylo injicite in le ventriculo dextere pro effectuar bilateral edema pulmonar. In tal casos, le numeration del granulos de amylo attinge quasi le total trovate in lobos pulmonar subjicite a injectiones directe del plus basse quantitate de amylo. Le causa del disseminate edema pulmonar que es observate post injectiones de iste grande quantitates de amylo es possibilemente le disveloppamento de multiple minuscule infarcimentos pulmonar que age exactamente como le unic infarcimento confluent.

Iste experimentos presenta un demonstration additional del ben-cognoscite phenomeno de fluxo laminar.

**REFERENCES**

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