Heart Failure and Pulmonary Edema Produced By Certain Neurologic Stimuli

By ROBERT Paine, M.D., JOHN R. Smith, M.D., Harvey R. BUTCHER, M.D. and FRANK A. Howard, M.D.

Experimental evidence has indicated that the genesis of acute pulmonary edema due to insufficiency of the left ventricular myocardium is dependent upon pulmonary engorgement and rapid filtration of fluid from the capillaries. It has been possible to demonstrate that significant elevation of arterial blood pressure from noxious stimulation of the central nervous system may be poorly tolerated when the myocardium has been previously damaged, so that acute left ventricular failure has occurred. The resulting massive pulmonary edema clearly followed the hemodynamic changes of severe congestion.

Numerous clinical and experimental observations have indicated that acute pulmonary edema occurs from left ventricular insufficiency when cardiac venous inflow and right ventricular function remain adequate. Pulmonary transudation then occurs because of rapid filtration of fluid from the capillaries into the alveolar spaces. On the other hand, the occasional occurrence of fulminating pulmonary edema in patients with injury or other disease of the central nervous system, and unassociated with recognizable heart failure, has raised the question of other mechanisms in the genesis of lung edema. Therefore, many workers have considered the possibility of a "neurogenic" pulmonary edema of reflex origin from cerebrospinal disease and abnormal autonomic function.

The "neurogenic" concept of lung edema formation has been supported by a number of experimental studies. The administration of adrenaline to rabbits has been repeatedly observed to evoke pulmonary edema. Similarly, experimental lead poisoning, large intravenous or intra-arterial blood or saline infusions, hypoglycemia, and injury of the central neural tissues have been shown to provoke pulmonary edema in experimental animals.

Unfortunately, these studies were carried out without critical evaluation of cardiovascular performance during the formation of pulmonary edema, so that the concept of "neurogenic" lung transudation does not appear to be supported by sound experimental evidence.

The neurogenic mechanism of pulmonary edema has been seriously questioned by observers who have studied cardiovascular function in relation to lung congestion and transudation. Paine and his associates demonstrated that fluid exchange in the lungs follows the Starling principles of fluid balance. They showed that, in the course of pulmonary congestion the elevation of capillary pressure in excess of osmotic tension rapidly forced fluid into the alveolar spaces. Conversely, when osmotic tension was sufficiently lowered by the depletion of plasma proteins in a normally functioning circulation, transudation likewise occurred from unopposed normal capillary filtration. These authors were able to provoke pulmonary engorgement and edema by impairing the function of the left ventricular myocardium in various ways. It has also been demonstrated that experimental pulmonary edema accompanying acute heart failure may
be abolished by drugs which improve cardiac function.\textsuperscript{15}

The available evidence, largely summarized by Paine and his co-workers,\textsuperscript{14} suggests that autonomic stimulation of critical degree, or autonomic stimuli arising from injury or other disorders of the central nervous system, may lead to severe derangements of cardiovascular function. If the derangement is such as to overload the left ventricle, pulmonary congestion and edema will ensue. Experiments concerning disorders of cardiovascular performance in relation to aberrant neurologic

mechanisms will be reported in this communication.

**METHODS**

All of the experimental procedures were carried out on dogs under Nembutal anesthesia. Respiration was maintained by a Starling pump attached to a bayonet cannula securely ligated into the trachea. The thorax was opened by longitudinal sternal division, and the preparation was heparinized. Pulmonary arterial pressure was obtained by ligation of a small glass cannula into a branch of the right upper lobar artery with connection by flexible tubing to a conventional mercury manometer. Pulmonary venous tension (as reflected by left atrial tension) was secured by means of a cannula and water manometer attached to the left auricular appendage. Systemic arterial pressure was recorded from one of the femoral arteries using a mercury manom-

eter. Adrenaline was usually administered through the tubing directly into the atrial cavity.

In another group of experiments, acute left ventricular strain was produced by the creation of severe aortic insufficiency by means of valvulotomy. The right common carotid artery was ligated and ligated. A long genitourinary biopsy forceps, with rounded blunt jaws, was then introduced through the artery and into the ascending aorta to the level of the aortic valves. It was not difficult to ascertain the position of the instrument in relation to the valve leaflets, and any one of the cusps could be tightly seized by the blunt jaws and torn from its attachment. It was seldom possible to destroy more than one leaflet of the valve without precipitating immediate and fatal heart failure.

Severe hypertension from injury to the central nervous system was induced by barium sulfate embolism of the brain. For this procedure the right common carotid artery was ligated at its midpoint in the neck; a suspension of 5 per cent barium sulfate in saline was injected through a cannula previously ligated distally into the vessel in cephalic direction. After injection of the suspension, the material was washed into the cephalic circulation with 5 to 8 cc. of whole blood. Embolization of the cephalic circulation was combined with valvulotomy in another series of experiments. Both procedures were readily carried out through the right common carotid vessel.

**RESULTS**

**Effects of Adrenaline on Cardiopulmonary Dynamics.** Nine experiments were performed on nine dogs. Under conditions of opened thorax with positive pressure respiration, mean pulmonary arterial pressure varied in most experiments from 20 to 30 mm. Hg, and left atrial pressure ranged from 10.5 to 16 cm. of water. Control systemic blood pressure was recorded as 95 to 135 mm. Hg mean.

The injection of 0.25 mg. of adrenaline through the left atrial cannula provoked transient hypertension and tachycardia without exception. The hypertension attained or exceeded levels of 230 mm. Hg in all but two instances, and pulmonary venous and arterial pressures were also variably elevated (see table 1). With the exception of two experiments, biopsy of the lung tissue showed no convincing evidence of alveolar transudation on gross or microscopic section.

In two experiments (experiments 25 and 27), pulmonary congestion was clearly evident during the strains imposed by adrenaline. In one,

**Table 1.** *Effects of Epinephrine in Open-Chest Dog Preparations*

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>B.P. Before</th>
<th>B.P. After</th>
<th>P.A. Before</th>
<th>P.A. After</th>
<th>L.A. Before</th>
<th>L.A. After</th>
<th>Rate Before</th>
<th>Rate After</th>
<th>Pulm. Edema</th>
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B. P., P. A. and L. A. represent mean blood pressure, pulmonary arterial pressure and left atrial pressure in mm. Hg or cm. of water. "Before" and "After" indicate before and after 0.25 mg. doses of adrenaline.
experiment 27, the pulmonary arterial pressure was initially elevated. These two preparations responded to adrenaline (0.25 mg.) with marked increases in pulmonary venous and arterial pressures. Pulmonary edema was grossly evident on biopsy, and was confirmed by microscopic study. Dilatation of the heart was observed in the course of the experiment.

The outcome of experiment 33 was of some interest, although it involved a technical error. After control observations and the administration of adrenaline, the atrial cannula was inadvertently loosened so as to allow a free escape of blood from the appendage. Marked hypertension occurred as an adrenaline effect, but increased pulmonary venous pressure was prevented by the rapid run-off of blood from the venous circuit and vascular pressures in the lungs were not elevated. Edema, of course, was not found.

This experimental evidence suggests that only when myocardial function was adequate under the conditions of hypertensive strain was congestion of the lungs absent. When elevation of pulmonary vascular pressures appeared following adrenaline, there were indications of loss of left ventricular output capacity and edema of the lungs occurred. In the latter instances, the causes of myocardial insufficiency invoked by adrenaline were not apparent.

Adrenaline in Dog Preparations with Aortic Insufficiency. Six experiments were performed on six dogs. After control observations of the open-chest preparation were made, aortic valvulotomy was carried out. The establishment of aortic insufficiency was signalized by immediate moderate enlargement of the left ventricle and a conspicuous increase in the force of cardiac contraction. A loud aortic diastolic murmur, frequently associated with a diastolic thrill, was noted over the entire heart. A striking waterhammer pulse invariably occurred. The production of the valvular defect did not materially alter heart rate. However, in four instances mean arterial blood pressure gradually declined to levels of shock; in two, arterial tension was maintained at normal values. In all cases the excursions of the mercury column was augmented. Pulmonary venous and arterial tensions continued within normal range. In spite of the fact that shock occurred in four of the preparations, it was assumed that a sharp elevation of arterial tension, regardless of the control level, might operate as a critically added strain to the previously damaged heart and thus lead to the production of congestion of the lung. This assumption proved to be correct as indicated in table 2.

When circulatory equilibria after aortic regurgitation were assured, 0.25 mg. of adrenaline was administered through the atrial tube. Adrenaline produced a prompt rise of arterial blood pressure in each experiment. However, the blood pressure did not rise to high levels in the animals that were initially in shock. Nevertheless, each preparation exhibited marked pulmonary congestion with edema, manifested by

despite the increase in pulmonary vascular pressures following the strain induced by adrenaline. Conspicuous dilatation of the heart was noted in all instances.

In all of these experiments the administration of adrenaline precipitated pulmonary edema when the hearts had been previously damaged. The presence of vascular collapse did not preclude the occurrence of disastrous failure of the myocardium when the blood pressure was elevated to levels usually considered moderate. Again, pulmonary edema appeared with congestion of the lung tissue.

Effects of Embolic Injury of the Brain. The previous observations indicated that severe sympathetic stimulation may cause myocardial failure, especially when the heart muscle has been previously injured. Therefore, it seemed logical to study some of the cardiovascular

### Table 2.—Effects of Adrenaline on Animals Previously Subjected to Aortic Valvulotomy, and with Aortic Insufficiency

<table>
<thead>
<tr>
<th>Exper. No.</th>
<th>B. P. Before</th>
<th>B. P. After</th>
<th>P. A. Before</th>
<th>P. A. After</th>
<th>L. A. Before</th>
<th>L. A. After</th>
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<td>74</td>
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<td>210</td>
<td>20</td>
<td>55</td>
<td>15</td>
<td>80</td>
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</table>

Symbols as in table 1.
effects of abnormal autonomic stimuli from injury of the central nervous system.

Six experiments were carried out on six dogs as described under "Methods." When control observations were completed, 0.5 cc. of 5 per cent barium sulfate suspension was injected cephalad into the right common carotid artery and washed in with whole blood. The injection was followed immediately by a mild, evanescent tonic convulsion and subsequent relaxation of the animal. In all instances there was a prompt rise of arterial blood pressure and the occurrence of bradycardia, with a moderate decrease of heart rate. The hypertensive reaction was transient in each case, and both the hypertension and bradycardia invariably subsided in 6 to 10 minutes. Actual elevations of blood pressure were less extreme than from 0.25 mg. doses of adrenaline, and in all instances attained mean levels of 165 to 230 mm. Hg. Pulmonary venous and arterial pressures were not significantly changed with the exception of one experiment where pulmonary venous tension rose from 8.5 to 32 cm. of water and mean pulmonary arterial pressure increased from 24 to 32 mm. Hg. Minimal edema was thought to be present on section of the lung. Lung biopsies from the remaining uncongested lungs showed no transudation.

Production of Marked Pulmonary Congestion in Animals with Aortic Valvulotomy and Cephalic Embolization. These observations were carried out on six animals. As in the preceding cases, these preparations exhibited slight cardiac dilatation following valvulotomy, together with waterhammer pulse and the other manifestations of aortic regurgitation. Arterial blood pressure declined to shock level in one of these animals; normal arterial tension was sustained after valvulotomy in the remainder. Pulmonary vascular pressures were likewise within normal limits following the creation of the valve defect. Without exception, these animals showed violent circulatory changes during particulate embolism of the cephalic vessels (cf. table 3). In all of the cases, with the augmentation of arterial tension (and depression of heart rate), there was striking dilatation of the myocardium and a sharp elevation of the left atrial pressure. Left atrial distension was followed almost simultaneously by pulmonary arterial hypertension. The lungs became turgid and voluminous and large rhonchi were audible some distance away. Biopsy of the lung showed intense transudation. The overwhelming heart failure was tolerated only briefly as shock and death quickly ensued. It should be emphasized that under the conditions of myocardial strain imposed by aortic valvulotomy, the function of a number of these hearts deteriorated under moderate increases of blood pressure. It would appear that the degree of hypertension necessary to impose the critical point of myocardial overload might vary depending upon the severity of strain from aortic insufficiency and upon other possible conditions intrinsic to the heart muscle.

**Table 3.—Effects of Cerebral Embolism on Animals Previously Valvulomized and with Aortic Regurgitation**

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>B.P. Before</th>
<th>B.P. After</th>
<th>P.A. Before</th>
<th>P.A. After</th>
<th>L.A. Before</th>
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<th>Rate After</th>
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<td>221</td>
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<td>13.5</td>
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<td>168</td>
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</table>

Symbols same as table 1.

From the data offered in these experiments, it would appear that the genesis of pulmonary edema is referable to incomplete function of the left ventricular myocardium which involves failure of optimum removal of pulmonary venous blood. Under these conditions, continued adequate performance of the right ventricle, together with an abundant venous return to the heart, lead to pulmonary engorgement and severe alveolar transudation resulting from rapid capillary filtration.11 Regarding the present study, the evidence suggests that the heart may be greatly burdened from the hypertension induced by adrenaline, but that heart failure does not always occur. However, when the heart was previously damaged by the creation of (acute) aortic insufficiency, the superimposi-
tion of hypertension and marked tachycardia from epinephrine became intolerable with resultant breakdown of cardiac function and induction of congestion and edema of the lungs.

The occurrence of hypertension following cerebral damage from particulate embolism is of some interest. Many years ago, Cushing published his well-known observation that cerebral compression provoked a rise of systemic blood pressure of a magnitude sufficient to overcome the loss of cerebrovascular irrigation from the external force of compression. The work implied that cerebral ischemia may be directly concerned in the elevation of blood pressure following cephalic trauma or failure of vascular function. Houssay and Molinelli suggested that injury (piqüre) of the floor of the fourth ventricle may result in hypertension by inciting a reflex discharge of epinephrine. Years later, Dixon and Heller demonstrated that the injection of kaolin in the region of the medulla oblongata produced a rise of intraventricular tension with resultant elevation of systemic blood pressure. This study again affirmed the observations of Cushing. Similarly, other workers noted that damage to the medulla by fibrin mixtures regularly invoked hypertension, although increased intracranial pressure was said not to occur. A number of investigators have recorded transient hypertension resulting from stimulation of the cerebral cortex and from ischemia of the central nervous system. Taylor and Page were able to induce hypertension in dogs for varying periods by a variety of injurious stimuli to the brain, including ischemia and intense diathermic heat localized about the brain stem. The work of Villaret and his associates is likewise of interest. They embolized the cerebrovascular system with particulate matter and observed the occurrence of hypertension, and frequent bradycardia, from the insult. In our experiments, comparable effects from miliary cerebral embolization were evident. The particulate matter was presumably widely disseminated throughout the cerebrovascularature, and the assumption is made that multiple foci of cerebral ischemia may lead to hypertension from stimulation of central autonomic centers.

As with the experiments employing adrenalin, the hypertension from cerebral injury may be equally pernicious when the load is thrown upon the damaged heart. It was noted again that, under hypertensive strain, pulmonary congestion did not occur unless there were indications of myocardial insufficiency and augmentation of vascular pressures of the lungs. The drastic, moderate, or even slight elevations of blood pressure appeared to be sufficient in the presence of aortic regurgitation to cause severe cardiovascular strain. Nevertheless, it is also possible that the sudden bradycardia occurring in some experiments from neural damage was also instrumental in diminishing left ventricular output, and flooding the lungs. In experimental animals, pulmonary edema has been shown to occur following extreme cardiac slowing and death from acetylcholine, and observations on the controlled circulation have likewise demonstrated striking restrictions of cardiac output from marked diminution of heart rate. Presumably, if abrupt bradycardia occurs with continuing optimum venous return of blood to the right ventricle, the resulting fall of minute output and ensuing impedance of escape of pulmonary venous blood may enhance vascular congestion of the lungs.

A consideration of even greater importance is the mechanism by which venous blood is made available to the right ventricle, in the face of diminishing stroke output of the left ventricle. Under the conditions of these experiments and those reported before the faltering of left ventricular function, brought about by any means, resulted in pulmonary congestion because of the probable abundant venous return and right ventricular competence. The availability of venous blood in heart failure has been explained on the basis of increased blood volume or by increased venous constriction occurring as a part of a general augmentation in vascular resistance. However, it has been exceedingly difficult to achieve salt and water retention in the dog, as the animal appears to have an efficacious mechanism for excess sodium elimination. Also these experiments were of such brief duration that retention of water could scarcely occur. Therefore, it seems improbable that water retention and a consequent increase in blood volume are concerned in the
continuation of high venous return in these experiments. Although the alternative hypothesis of increased venous constriction as a means of hastening the flow of capillary-venular blood has not been proved, it seems to explain most readily the carriage of blood from arteries to veins in the face of a falling left ventricular output.

The data secured from these experiments, as well as from others previously quoted, appears to warrant the conclusion that certain stresses may lead to cardiovascular failure through neurogenic mechanisms. When heart failure occurs from these stresses, the resulting pulmonary edema is cardiogenic. The data do not permit the assumption that direct neurogenic effects upon the lungs are concerned in the pathogenesis of pulmonary edema.

SUMMARY

A resume of the experimental evidence concerning the mechanism of pulmonary edema from heart failure has been presented. The concept best supported by the evidence indicates that pulmonary edema results from engorge ment of the lungs and rapid capillary filtration of fluid as a result of left ventricular insufficiency. The hypothesis that direct neural effects upon the pulmonary vasculature may cause pulmonary edema was examined as follows:

In open-chest preparations of dogs, systemic arterial pressure together with pulmonary venous and arterial pressures were measured by appropriate manometry. The administration of adrenaline or embolization of the cerebral circulation by barium sulfate crystals provoked transient severe hypertension, with tachycardia and bradycardia respectively. Evidence was obtained that normal heart muscle may withstand the hypertensive strain thus produced, since in most preparations the pulmonary vascular pressures were not sufficiently altered to cause pulmonary transudation. In occasional seemingly normal animals, the hypertension from these procedures produced functional staggering of the left ventricle, and when subsequent elevation of pulmonary vascular tensions occurred, alveolar transudation resulted. When the hearts of animals had been previously damaged by aortic valvulotomy so as to cause aortic insufficiency, the vascular strains imposed by epinephrine or by miliary cerebral ischemia regularly caused left ventricular failure. The subsequent events of myocardial dilatation, and augmentation of pulmonary vascular pressure and intense edema of the lungs were invariably outspoken. No evidence was obtained that direct neurogenic effects upon the lungs were concerned in the formation of pulmonary transudation.

It is concluded from these experiments that although stresses against the damaged myocardium may be of neurogenic character, the generation of pulmonary edema is due to a cardiogenic mechanism.

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