Neurohemodynamics of Pulmonary Edema

II. The Role of Sympathetic Pathways in the Elevation of Pulmonary and Systemic Vascular Pressures following the Intracisternal Injection of Fibrin

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The authors criticize the concept of "neurogenic pulmonary edema" as resulting from an increase in pulmonary capillary permeability mediated by nerve impulses to those vessels. They show that one of the methods used to produce "neurogenic pulmonary edema" markedly elevates systemic and pulmonary vascular pressures, the latter to levels high enough to produce pulmonary edema. Vagotomy and/or upper thoracic sympathectomy do not prevent the elevation of pulmonary vascular pressures. Blockade of the sympathetic innervation to the systemic vascular bed lowers the systemic vascular pressures and brings the pulmonary vascular pressures back to normal. The control of pulmonary vascular pressures by sympathetic impulses to the systemic vascular bed is demonstrated.

The concept of neurogenic pulmonary edema, which relates central nervous injury, irritation, or stimulation to the pulmonary edema state, has suffered somewhat from a lack of observation of those phenomena concurrently going on in the cardiovascular system.

As a result the view has become widespread that the pulmonary edema state results from an increase in pulmonary capillary permeability mediated by nerve impulses, independent of that hemodynamic change which might readily be expected to produce pulmonary edema, namely, an increase in pulmonary capillary pressure.

One notable exception to the foregoing has been the recent study of Campbell, Haddy, Adams and Visscher,1 in which these authors demonstrated that increased intracranial pressure produced acute pulmonary edema which was preceded by a rise in both pulmonary arterial and venous pressures. This was not, however, accompanied by arterial hypertension, but instead by bradycardia and a lowered cardiac output. The pathway was demonstrated to be vagal.

In 1949, Cameron and De,2,3 in attempting to produce chronic hydrocephalus in the rabbit, injected a combination of thrombin and fibrinogen into the cisterna magna of the rabbit. The rabbit promptly developed massive, overwhelming, lethal pulmonary edema. The authors felt that this occurred as a result of increased pulmonary capillary permeability resulting from nerve impulses, primarily vagal. These phenomena seemed worthy of closer hemodynamic scrutiny, especially with regard to those pressure changes occurring in the pulmonary vascular bed. Accordingly, the following study was undertaken.

The integration of this work with other pulmonary edema research by previous investigators will not be done here but will be attempted in a subsequent communication.

Method

Eighteen rabbits weighing from 1.6 to 2.9 Kg. were used, and the anesthetic was a 25 per cent solution of urethane given intravenously in doses of 4 cc. per Kilogram. Ninety mongrel dogs weighing from 10.5 to 20.5 Kg. were anesthetized with morphine sulfate 4 mg. per Kilogram, chloralose 48 mg. per Kilogram, and urethane 480 mg. per Kilogram. The morphine sulfate was given intramuscularly 30 minutes prior to the intravenous administration of the latter two agents, which were then given slowly as a mixed warm solution. The results of experiments on these dogs will form the basis of a

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Aided by a research grant from the National Heart Institute, United States Public Health Service.

Circulation, Volume VI, July 1952
Spinal anesthesia was administered through previously placed subarachnoid catheter according to the method of Co Tu. When total spinal anesthesia was desired, 5 cc. of a 4 per cent solution of procaine hydrochloride were rapidly injected.

In rabbits the atlanto-occipital membrane was visualized and 0.2 to 0.3 cc. thrombin and 1.0 to 2.0 cc. fibrinogen were injected through a needle in rapid succession. One rabbit received only the fibrinogen. In the early dog experiments a similar technic was employed, using 3.0 cc. thrombin and 10 to 13 cc. fibrinogen. The solutions were made up by dissolving 0.12 Gm. thrombin (500 units) in 5 cc. isotonic saline and by dissolving 0.4 Gm. fibrinogen in 15 cc. isotonic saline. The combined injection will hereinafter be referred to as fibrin. In later dog experiments the atlanto-occipital membrane was opened widely (1.5 cm.) and the solutions simply sprayed over the dorsal aspect of the medulla with a catheter pointing towards the tentorium. This permitted ready egress of fluid and prevented a rise in cerebrospinal fluid pressure.

When the preparatory maneuvers had been completed, a positive displacement pump was used to accomplish the intravenous infusion of 10 cc. per Kilogram of isotonic saline in one minute. Either one, two, or occasionally three such “standard” infusions were given in the 30-minute period prior to the injection of fibrin. Prior to the intracisternal injection of fibrin, these infusions were never observed to elevate pulmonary venous pressure more than 2 mm. Hg. For purposes of comparison, in some experiments this “standard” infusion was given one or more times after the intracisternal injection and again after ganglionic blockade.

RESULTS

Observations in the Rabbit

1. Response of the Rabbit to the Intracisternal Injection of Fibrin. The response of the rabbit to the intracisternal injection of fibrin was as previously described. A generalized rigor, usually opisthotonus, defecation and urination, and a variable respiratory pattern ranging from apnea to intense tachypnea and hyperpnea occurred. When apnea occurred, positive pressure breathing was applied until the death of the rabbit. Frequently, pink froth and fluid poured out of the tracheal cannula or, in those instances where positive pressure breathing was used, through the escape hole in the tracheal cannula just prior to or following death. The latter occurred in from 2.5 to 35 minutes following the intracisternal injection. The lungs of the rabbits at postmortem examination were

* Supplies of this compound were made available through the generosity of Dr. Elmer L. Sevringhaus of Hoffmann-La Roche, Inc., Nutley, N. J. This agent has been given the name Arfonad.
as described by Cameron and De²,³ and as previously shown.⁴ Pulmonary edema, varying in intensity from moderate to severe, occurred visualizing the left auricle and its response to the intracisternal injection of fibrin. Figure 1 shows photographs taken just before and 70 and 105

![Fig. 1. Rabbit heart seen through left thoracotomy incision and incised pericardium. Rabbit is on its right side with head to the left in each picture. A. 10 seconds prior to injection. Left auricle is in systole. B. 70 seconds after intracisternal injection of 0.3 cc. thrombin and 3.0 cc. fibrinogen in rapid succession. Note enlargement of left auricle. C. 105 seconds after injection. Auricle almost covers the ventricles. Auricular pulsations were hardly visible in the grossly distended left auricle shown in C.]

![Fig. 2. Pressure tracings from left auricle and right carotid artery of rabbit. Pressure in millimeters of mercury at the left. Solid lines are electrically integrated (mean) pressures; others are full pressures in this and subsequent illustrations. 1 mm. (each fine vertical line) = 1 second. Intracisternal injection of 0.3 cc. thrombin at first arrow and 3.0 cc. of fibrinogen at second arrow.]

in all but one of the rabbits. A systematic hemodynamic study was not made in the rabbit, but several findings were of interest. When a left thoracotomy incision and opening of the pericardium was performed, it was possible to seconds after the fibrin injection. It can be seen that significant enlargement of the left auricle occurred. The left ventricle also appeared to enlarge in this and other experiments, but was not as readily photographed. One rabbit receiving an intracisternal injection of fibrinogen alone without preliminary thrombin also developed acute pulmonary edema which was as pronounced and more rapidly lethal (2.5 minutes) than the average rabbit receiving both agents.

2. Response of Left Auricular and Carotid Arterial Pressures. Following the intracisternal injection of fibrin, a rise in carotid arterial and left auricular pressure developed in the four rabbits in which these pressures were measured (fig. 2).

Observations in the Dog

Characteristically, following the intracisternal injection of fibrin, there was a sharp elevation of arterial pressure and, more or less simultaneously, a rise in pulmonary artery,
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“capillary,” and venous pressures. This was accompanied by a transient motor and respiratory response similar to, but less marked than, that seen in the rabbit. Central systemic venous pressure rose either slightly (3 mm. Hg) or markedly (30 mm. Hg). When an elevation of pulmonary vascular pressures did occur, it usually reached a peak sometime within the first minute and then either remained elevated, fell slightly to a sustained plateau, or returned to control levels in about five minutes. In the latter case, they could be readily re-elevated frequently as: (a) more experience with the injection technic was obtained, and (b) the open atlanto-occipital membrane technic described above was used, and (c) two or occasionally three “standard” infusions rather than one were given prior to intracisternal fibrin injection.

1. The Development of Acute Pulmonary Edema in the Dog after the Intracisternal Fibrin Injection. Since the study was concerned with hemodynamic observations and the effect of systemic vasodilation on pulmonary vascular pressures, only two dogs which developed elevated left auricular pressures after the fibrin were left untreated. These showed generalized pulmonary edema at postmortem examination.

2. Effect of Intracisternal Fibrin on the Arterial and Venous Pressures of the Pulmonary and Systemic Vascular Beds. Figure 3A shows the hypertension that developed in vena cava, pulmonary artery, left auricle, and femoral artery following the intracisternal injection of fibrin. The initial period of bradycardia was replaced by tachycardia. It was assumed that pulmonary capillary pressure would be slightly higher than left auricular pressure, or, in this case...

![Fig. 3. Pressure tracings from vena cava, pulmonary artery, left auricle and femoral artery of dog. A fibrin injection 11 minutes previously had been only partially successful in producing hypertension. Solid lines = electrically integrated (mean) pressures; other lines, full pulse pressures. Chart speed is 2.5 mm. per second except for brief portion in A where speed is 25 mm. per second. A. Intracisternal injection of 3 cc. thrombin at first arrow and 11 cc. fibrinogen at second arrow. B. Starts four minutes after end of A. 0.04 mg. per kilogram Ro 2-2222 given intravenously at arrow. Note return of vena cava, pulmonary artery, and pulmonary venous pressures to normal levels with only slight fall of femoral arterial pressure.](http://circ.ahajournals.org/DownloadedFrom)
instance, more than 70 mm. Hg. It is noteworthy that the mean pressure gradient between femoral artery and thoracic vena cava was markedly widened, whereas the pressure gradient between pulmonary artery and vein was hardly altered following the fibrin injection. The highest left auricular pressure obtained after the fibrin injection is shown in figure 3. In those dogs in which a significant pulmonary vascular hypertension developed, the post-fibrin increment of pulmonary venous pressure varied between 10 and 64 mm. Hg.

3. Effect of the Autonomic Blocking Agent, Ro 2-2222, on Elevated Pulmonary and Systemic Vascular Pressures. Since the pathways were suspected of being autonomic, an autonomic blocking agent was used to ascertain whether the elevated pulmonary vascular pressures could be lowered by ganglionic blockade. Figure 3B is a record from the same experiment as shown in Figure 3A and starts four minutes after the end of that tracing. Vena cava, pulmonary artery, and pulmonary venous pressures promptly fell to control levels after the intravenous injection of 0.05 mg. per kilogram of Ro 2-2222. It is important to note that the return to normal levels of central venous and pulmonary vascular pressures occurred simultaneously with a relatively slight fall in systemic arterial pressure. In all instances where elevated pulmonary arterial and venous pressures developed after the intracisternal injection of fibrin, the administration of Ro 2-2222 was followed by a fall of these pressures to control levels or below.

4. Effect of Vagotomy on Elevated Left Auricular Pressure. It was important to find out if the causal pathway was vagal (fig. 4). Following the intracisternal fibrin injection and the development of arterial hypertension and tachycardia, left auricular pressure rose from a control level of 11 mm. Hg to 51 mm. Hg. This then gradually fell to the sustained plateau of 30 mm. Hg as seen at the beginning of the tracing in figure 4. Bilateral cervical vagotomy was followed by a further slight elevation of left auricular pressure. Partial ganglionic block-

![Figure 4. Pressure tracings from left auricle and femoral artery of dog. Chart speed = 1 mm. per second. 3 cc. thrombin and 11 cc. fibrinogen given into cisterna magna previously (see text). Vagus nerves cut at first arrow. 0.04 per kilogram Ro 2-2222 given intravenously at second arrow.](http://circ.ahajournals.org/)

ade with Ro 2-2222 then produced a slight fall of arterial pressure and a prompt return of left auricular pressure to the control level. Bilateral cervical vagotomy was performed either prior to or during the elevation of pulmonary venous pressure resulting from the intracisternal injection of fibrin in 20 dogs. Prior vagotomy did not protect against the elevation of pulmonary venous pressure. Vagotomy performed during the period of elevated pulmonary venous pressure either did not change this value or, as happened more frequently, caused a further elevation.

5. Effect of Preliminary Bilateral Removal of the Sympathetic Chain from the Stellate to the Fifth Thoracic Ganglion. The possible role of sympathetic impulses directly to the lung itself
was investigated by making the fibrin injection in dogs from which the sympathetic chains from the stellate through the fifth thoracic ganglia on both sides had been removed intact. This type of experiment was carried out in four dogs, and elevations of pulmonary vascular pressures were obtained in all of them, although the average rise was about one-third less than in those with intact sympathetic ganglions.

6. Effect of Bilateral Upper Thoracic Sympathectomy and Midcervical and Upper Thoracic Vagotomy and Bilateral Phrenicectomy. Professor I. de Burgh Daly was kind enough to consider this material. He suggested that the above combination of denervation procedures would strengthen somewhat the position in regard to complete pulmonary denervation and his suggested type of denervation was done in one dog. The intracisternal injection of fibrin was followed in one minute by a rise of vena cava pressure from 4 to 9 mm. Hg, of pulmonary artery pressure from 18 to 38 mm. Hg, of pulmonary “capillary” pressure from 9 to 31 mm. Hg, and of femoral artery pressure from 145/95 to 295/180 mm. Hg.

7. Effect of “Standard” Infusion on Pulmonary Venous Pressure before and after Intracisternal Fibrin and after Partial Ganglionic Blockade. It was thought worthwhile to ascertain the effect of a “standard” infusion on pulmonary venous pressure before, during, and after the induction of peripheral vasoconstriction in a dog from which the pulmonary sympathetic had been removed. Figure 5 shows the record of dog 38, in which a bilateral upper thoracic sympathectomy had been performed as described above. Prior to the injection of fibrin, a standard intravenous infusion (10 cc. normal saline per kilogram in one minute) had little effect on pulmonary venous pressure, that is, a rise of 1 mm. Hg. After the fibrin injection pulmonary venous pressure was 21 mm. Hg (start of fig. 5.4). At that time a “standard” infusion caused a marked rise in pulmonary venous pressure, that is, from 20 to 42 mm. Hg (between first and second arrows). At the third arrow a bilateral cervical vagotomy was done and was followed promptly by a further significant rise of pulmonary venous pressure. Partial blockade of the remaining intact ganglia (those which supply the splanchnic bed

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**Fig. 5.** Pressure tracings from vena cava, pulmonary vein, and femoral artery of dog from which the sympathetic ganglia had been removed on both sides from the stellate through the fifth ganglion. Chart speed = 1 mm. per second. Prior to the intracisternal injection of thrombin and fibrinogen a “standard” saline infusion elevated pulmonary venous pressure 1 mm. Hg. The injection of thrombin and fibrinogen elevated pulmonary venous pressure from 5 to 21 mm. Hg as seen at the beginning of A. A “standard” saline infusion was administered between the first and second arrows in A. The vagus nerves were cut at the third arrow and at the fourth arrow 0.05 mg. per kilogram Ro 2-2222 was given intravenously. B starts 14 minutes after end of A. A “standard” saline infusion was given between the first and second arrows.
and vascular areas from D-6 and below) was followed by a prompt fall to normal levels of the elevated pulmonary venous pressure. Fourteen minutes later (fig. 5B) while the dog was still partially under the influence of the ganglionic blockade, the effect on pulmonary venous pressure of another "standard" infusion was similar to that obtained prior to intracisternal fibrin, namely, a negligible rise. The same result was obtained with Ro 2-2222. It was, however, more gradual in onset. This time factor was presumably related to the slower development of the subarachnoid chemical sympathectomy.

9. Effect of Curare Administered Prior to the Intracisternal Fibrin. Because it was thought that the diffuse motor activity that follows the intracisternal injection of fibrin might play a role in this phenomenon, curarization with de-

![Fig. 6. Pressure tracings from vena cava, pulmonary artery, left auricle and root of aorta in dog. Chart speed = 1 mm. per second. Signal at the bottom. Vagus nerves cut. Aortic occlusion at the beginning of each signal and release at the end. A, B, C, D, and E are six minutes apart. Two minutes after each aortic occlusion, 0.5 per cent of dog's weight of isotonic saline given. Ro 2-2222, 0.05 mg. per kilogram, given intravenously two minutes prior to B.](http://circ.ahajournals.org/ARCH-26011/S1.png)
tion with decamethonium did not lower previously elevated pulmonary vascular pressures.

10. Effect of Total Aortic Occlusion on Pulmonary Vascular Pressures before and during Ganglionic Blockade. Another type of experiment, in addition to those cited above, was performed with the hope of throwing some light on the role of changes in peripheral vascular blood volume as well as changes in peripheral vascular resistance when peripheral vasoc

Just what occurs locally when the medulla is bathed in fibrin is not readily apparent. There is evidence to support the view that this is a nonspecific irritative or locally stimulating phenomenon, since Jarisch and associates\textsuperscript{11} reported that veratrine introduced into the cisterna magna of rabbits also produced pulmonary edema. This was confirmed by Horst and co-workers.\textsuperscript{12}

In other experiments not described above intracisternal protoveratrine was also followed by marked elevations of pulmonary vascular pressures but not as immediate in onset. Further evidence that the clotting process is not essential to this phenomenon is also indicated by the rapidity with which the changes develop and, also, by the observation that fibrinogen alone produced acute pulmonary edema in the one rabbit to which it was given.

In view of the striking changes in heart rate and systemic and pulmonary arterial and venous pressures, it seems that some pronounced stimulation, either direct or indirect, is being brought to bear upon the cardiovascular regulatory centers of the brain. This is about as far as our understanding of this part of the sequence goes.

Since bilateral cervical vagotomy neither prevents the rise in pulmonary vascular pressures nor lowers elevated pressures when done after the fibrin injection, vagal impulses do not appear to play a causative role in the production of these elevated pressures in the dog. In the majority of instances when vagotomy was performed after the elevation of pulmonary vascular pressures, it was followed by a further rise indicating that vagal activity was, if anything, conferring a partial protective effect.

It is well to emphasize the basic difference between the experimental syndrome described above and that used by Campbell, Haddy, Adams and Vischer.\textsuperscript{1} These authors observed that increasing intracranial pressure by the inflation of a subdural balloon over the dog's cerebrum was followed by a moderate elevation of pulmonary arterial and venous pressures and eventually pulmonary edema. However, systemic arterial pressure either fell or remained at control levels and the pulse rate was slowed. Vagal blockade with atropine returned pul-
monary vascular pressures to normal, elevated cardiac output, and averted the development of pulmonary edema. There is a reasonably satisfying comparison to be made between the experimental syndrome produced by these authors and that which is seen clinically in the postoperative neurosurgical patient or one with brain injury from other causes.

The experimental pulmonary edema syndrome, which has been the subject of this communication, more closely resembles the cardiovascular type of pulmonary edema, since it is accompanied by hypertension, tachycardia, and markedly elevated pulmonary arterial and venous pressures. As will also be seen from a subsequent communication, cardiac output is restricted in relation to the rise in left auricle pressure. It may be argued that the hypertension seen in these experiments is more severe than that seen clinically and that the conditions are “unphysiologic.” It should be remembered, however, that the experimental syndrome described in the above experiments is one in which an attempt was made to produce a cardiovascular type of pulmonary edema in an organism with a normal heart. Clinical pulmonary edema of the cardiovascular type generally occurs in an organism in which disease has significantly diminished the work capacity of the heart as a pump. The diseased human heart may reasonably be expected to fail at a lower challenge threshold than that of the normal dog.

The elevation of pulmonary vascular pressures apparently does not depend upon the integrity of the sympathetic nerve supply to the lung, since these pressures rose with intracisternal fibrin even after a bilateral upper thoracic sympathectomy had been performed. The combined denervation procedure suggested by Prof. I. de Burgh Daly likewise did not prevent the elevation of pulmonary vascular pressures following intracisternal fibrin. The average elevation of pulmonary venous pressure was less than that seen in dogs with intact sympathetic ganglia. It must be remembered, however, that the sympathectomy performed also deprived a significant portion of the peripheral vascular bed of the possibility of participating in the constrictor response.

From flow data to be presented elsewhere, it will be clear, as might be anticipated, that the elevation of systemic arterial pressure is largely the result of increased peripheral vascular resistance. Further evidence that centrally mediated nerve impulses to the lung are not an important factor in the rise of pulmonary vascular pressures will be found in the fact that the pulmonary vascular resistance is not elevated following the intracisternal fibrin. In any case, it would be difficult to hold pulmonary vasoconstriction responsible for the marked elevations of left auricular pressure observed above.

The administration of a “standard” infusion uniformly produced a significant rise in pulmonary venous pressure after peripheral vasoconstriction had been induced by intracisternal fibrin. Contrariwise, the same infusion had little or no effect on pulmonary vascular pressures if it was administered either prior to the intracisternal fibrin or after pulmonary vascular pressures had been returned to normal by means of ganglionic blockade.

Of considerable interest in the interpretation of the above data is the fact that pulmonary vascular pressures may be elevated by impulses travelling over sympathetic fibers to the peripheral vascular bed, and conversely, they may be returned to normal by sympathetic blockade of the peripheral vascular bed. This relationship may help to reconcile in some measure the opposing views of those who do and those who do not believe that there is significant nervous control of the volume and pressure of the blood in the pulmonary vascular bed.

It was clear from gross observation of the left auricle (fig. 1) and pulmonary veins as well as consideration of the pressure elevations in the pulmonary vascular bed that a marked increase in the volume of blood between the pulmonic and mitral valves takes place after medullary stimulation with fibrin. That there is a striking increase in peripheral vascular resistance and apparent left ventricular failure will be shown in a subsequent publication. However, to consider this the complete explanation of the observed phenomena would be an oversimplification of the problem, for generalized peripheral vasoconstriction, in addition to
increasing peripheral vascular resistance, also decreases the volume of blood which can be held in the peripheral vascular bed. This extra volume of blood must then be shifted to some other area, presumably to a vascular bed with little or no constrictor potential, the lung.

As seen in figure 6A when the aorta was occluded for 30 seconds, left auricular pressure rose sharply. During the period of aortic occlusion it is to be expected that the low pressure in the carotid sinuses induced peripheral vasoconstriction. In figure 6B, two minutes after ganglionic blockade, aortic occlusion resulted in a much smaller elevation of left auricular pressure. As the ganglionic blockade wore off, the rise in left auricular pressure gradually regained its previous level (fig. 6C, D, and E). Leaving aside the effect of Ro 2-2222 on the coronary vessels, it is reasonable to assume that the aortic occlusion produced a similar impedance effect whenever it was applied. With constrictor impulses to the peripheral vascular bed intact, left auricular pressure rose sharply, and when these were blocked, the rise was much less pronounced. It would seem that peripheral vasoconstriction should be thought of as producing a blood shift from periphery to lung as well as increasing the resistance against which the left ventricle works, insofar as the effect on pulmonary capillary pressure is concerned. This has recently been confirmed in other studies utilizing a technic for the continuous registration of changes in pulmonary blood volume.12

The therapeutic implications of the principle of peripheral vasodilation in the management of acute pulmonary edema are apparent, especially in view of previous data from patients in acute pulmonary edema who were treated with spinal anesthesia.14 That a significant lowering of pulmonary venous pressure can be achieved with only a slight lowering of arterial pressure gives rise to the hope that this principle may prove useful in the treatment of the pulmonary edema accompanying coronary insufficiency as well as that accompanying hypertension. Moreover, closer scrutiny of the above figures reveals that left auricular or pulmonary venous pressure began to fall at a time when systemic arterial pressure had fallen hardly at all. Theoretically, at least, if it is possible to adjust the degree of peripheral vasodilation delicately, it should be possible to diminish significantly elevated pulmonary venous pressures with only a slight fall in arterial pressure. Preliminary clinical results with Ro 2-2222 suggest that delicate adjustment of peripheral vascular resistance is possible.15

The authors are keenly aware of the pitfalls to be encountered in the casual application of Starling's law to the patient or intact animal with acute heart failure. And yet, even taking into account the fact that there may be a whole "family" of curves instead of a single curve to express the relationship between end diastolic pressure and stroke work, it seems reasonable to conclude that in at least some of the experiments shown above, the left ventricle was working at a more advantageous point on the Starling curve after peripheral vasodilation had produced a lowering of left auricular pressure.

Horst and co-workers12 using intracisternal veratrine found that the development of pulmonary edema in the rabbit was prevented by the prior administration of the hydrogenated derivatives of ergotamine. Cruchaud and Vermeil16 using intracisternal fibrin in rabbits found that the pulmonary edema was prevented by Dibenamine in three rabbits and by dihydroergotamine in five. Neither group measured left auricular or pulmonary venous pressures but their data suggested that the sympathoadrenal system was in some way involved.

In experiments not described above Ro 2-2222 did not prevent the pressor response to epinephrine and also did not lower arterial pressure which was previously elevated by epinephrine. This makes it unlikely that endogenously secreted epinephrine was a decisive factor either in the elevation of pulmonary vascular pressures or in their return to normal with ganglionic blockade. It does not, however, preclude the possibility that endogenously secreted epinephrine may have contributed to the over-all response.

Lastly, the authors are obliged to justify the use of a new term in connection with acute pulmonary edema. The term "neurogenic pulmonary edema" has been used by many authors to convey a variety of meanings. In the minds
of some it represents an influence on pulmonary capillary permeability in the absence of an increase in pulmonary capillary pressure. In the view of others it represents any pulmonary edema in which nerve impulses have a primary causal role without special consideration of whether or not they cause a significant elevation of pulmonary capillary pressure. In recent years the authors have come to feel that its usefulness as a means of explicit communication is far outweighed by the confusion it engenders.

It was thought that a more causally specific term would be helpful. The phrase “neurohemodynamic pulmonary edema” has been found useful in our laboratory and is herewith defined.

**Neurohemodynamic pulmonary edema** is that state wherein an increase in the rate of transfer of fluid from pulmonary capillary to the extravascular space of the lung is brought about by an increase in pulmonary capillary pressure, which in turn is brought about either directly or indirectly by nerve impulses.

**Summary and Conclusions**

1. The intracisternal injection of thrombin and fibrinogen (fibrin) is followed by stimulation of the cardiovascular centers. This produces an elevation of pulmonary and systemic arterial and venous pressures in the dog and carotid and left auricular pressures in the rabbit. It also produces a grossly observable increase in the blood volume of the left auricle and pulmonary veins.

2. Bilateral vagotomy prior to the fibrin injection does not prevent this elevation, nor does intercurrent vagotomy lower the elevated pulmonary vascular pressures in the dog.

3. Bilateral upper thoracic sympathectomy (stellate to fifth thoracic ganglion) performed prior to the fibrin injection does not prevent the elevation of pulmonary vascular pressures, nor does total pulmonary denervation.

4. Elevated pulmonary vascular pressures return to normal promptly after ganglionic blockade with Ro 2-2222.

5. It is felt that nerve impulses causing peripheral vasoconstriction can create a substantial increase in the volume and pressure of blood in the pulmonary vascular bed. Conversely, effective blockade of these impulses can reverse these phenomena.

6. It is noteworthy that only a small decrease in peripheral arterial pressure may be required to return markedly elevated pulmonary vascular pressures to normal.

7. On a theoretic basis peripheral vasodilation, by lowering left auricular pressure from markedly elevated levels, alters hemodynamics in such a way that the left ventricle works at a more advantageous point on Starling’s curve.

8. The intravenous infusion of 10 cc. of isotonic saline per kilogram in one minute has little effect on pulmonary venous pressure (<2 mm. Hg) in the normal anesthetized dog. In the presence of marked peripheral vasoconstriction, however, a similar infusion produces striking elevations of pulmonary venous pressure.

9. The shift of blood from periphery to lung is probably not only a matter of left ventricular failure but also dependent in part upon the fact that a vascular bed of high constrictor potential (systemic) can shift blood into an area of low constrictor potential (pulmonary) and thereby elevate the pressure in the latter. Conversely, peripheral vasodilation can shift blood from lung to periphery.

10. The use of the term “neurogenic pulmonary edema” has, in the authors’ opinion, ceased to be a useful means of explicit communication. The suggestion is made that it be discarded in favor of what, under appropriate circumstances, is felt to be a more meaningful term, namely, “neurohemodynamic pulmonary edema.” A definition of this term has been suggested.

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Circulation. 1952;6:51-62
doi: 10.1161/01.CIR.6.1.51

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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