Neurohemodynamics of Pulmonary Edema

IV. Effect of Systemic Vasoconstriction and Subsequent Vasodilation on Flow and Pressures in Systemic and Pulmonary Vascular Beds

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The influence of the tone of peripheral blood vessels on pulmonary vascular hemodynamics has been shown to be considerable. That is, sympathetic impulses to the peripheral vascular bed are capable of causing a striking rise in pulmonary vascular pressures even in the absence of pulmonary innervation (1-3) and also of causing a grossly observable increase of pulmonary blood volume (4). Conversely, it was found that blockade of sympathetic impulses to the systemic vascular bed produced a prompt decrease in pulmonary vascular pressures when the latter were initially elevated and also caused a decrease in pulmonary blood volume (1-4).

The data to be presented below were gathered in order to define more completely the hemodynamic changes that occur when the intracisternal injection of ‘fibrin’ is followed by elevations of systemic and pulmonary vascular pressures in the dog.

METHOD

Mongrel dogs of both sexes varying in weight from 10.2 to 20.6 kg. were used. Anesthesia consisted of morphine sulfate, 4 mg/kg., given intramuscularly 30 minutes prior to the intravenous administration of 48 mg/kg. of alpha chloralose and 480 mg/kg. of urethane. When the chest was opened, respiration was maintained by a modified Starling pump.

The intracisternal injection of thrombin and fibrinogen (hereinafter referred to as ‘fibrin’) was made according to a method modified from that of Cameron and De (5) through a 1-cm. longitudinal incision in the atlanto-occipital membrane so that ready egress of fluid occurred and an increase in cerebrospinal fluid pressure was avoided. Three cc. of thrombin and twelve to fifteen cc. of fibrinogen in dilutions as previously described (3) were injected through an indwelling catheter in rapid succession.

Systemic blood flow (cardiac output minus coronary flow) was continuously recorded by a method described in detail elsewhere (6). Briefly, the technique consists of partially removing ribs 3, 4 and 5 on the left and introducing a large bore cannula (fig. 1 A) into the arch of the aorta just distal to the left subclavian artery. After traversing a flowmeter, the blood was conducted through one branch of a Y tube into descending aorta (fig. 1, A’) and through the other branch into the upper part of the body through the brachycephalic artery (fig. 1, B). After this, the left sub-

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clavian artery was either tied off or, rarely, was also cannulated (fig. 1, S). The upper three sets of intercostal vessels were tied off in preparing the aorta for the double cannulation. In this manner left ventricular output minus coronary flow was led through the flowmeter. Thirty-five mg/kg. of Treburon intravenously was the anticoagulant used.\(^2\)

In early experiments aortic flow was recorded with the rotameter of Shipley and Wilson (7). This was later replaced by the Potter\(^3\) electroturbinometer because, among other things, the latter permits the accurate registration of pulsatile flow and there is no need for a buffer bottle. This eliminates blood volume shifts between dog and buffer bottle due to changes in aortic pressure. The characteristics of the Potter electroturbinometer will be described in detail elsewhere (8).

Pressure in the left auricle (or a small lobular pulmonary vein) was obtained by cannulation with a polyvinyl catheter. The catheter for obtaining aortic pressure was placed proximal to the centrally placed aortic cannula (A). Vena cava pressure was obtained through a venous catheter, the tip of which was in the vicinity (2 cm.) of the right auricle. Pulmonary artery pressures were obtained through a Cournand catheter placed by fluoroscopy and checked with pulse tracings. Pressure recording was done with electromanometers (9), the outputs of which were fed into a four-channel, direct-writing recorder. Mean pressures were obtained by electrical integration of the full pulse pressures.

When performed, vagotomy was done bilaterally and low in the neck.

Partial ganglionic blockade was obtained with Ro 2 2222\(^2\) (a trimethylene thiophanium \(d\)-camphor sulfonate), as used by Randall and co-workers (10) in the cat and dog and more recently by us in hypertension and acute pulmonary edema in man (11).

Two and sometimes three ‘standard’ intravenous isotonic saline infusions were given in the half-hour period after the completion of the preparatory procedures. Each of these consisted of 10 cc/kg. body weight given in 1 minute.

Systemic vascular resistance was calculated according to the formula of Green and co-workers (12) and expressed in P.R.U. The same formula was used for pul-

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\(^2\) The Ro 2-2222 (Arfonad) used in this study was supplied by Dr. Elmer L. Sevringhaus, Hoff- man-La Roche, Inc., Nutley, N. J.

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monary vascular resistance. It will be recognized that inasmuch as the flow being measured was cardiac output minus coronary flow, the calculations are in error by the amount of coronary flow in each instance. The induced hemodynamic changes were of such a magnitude that the errors due to changes in coronary flow could be largely neglected.

What shall be called the external left ventricular work per minute was calculated by multiplying the aortic pressure minus left auricle pressure in millimeters of Hg X \( 0.0136 \times 1.06 \times \) systemic blood flow. This was then expressed in kilogram meters (kg. m.).
The values listed below were taken within 30 seconds prior to the injections of 'fibrin,' Ro 2-2222, or phlebotomy, and between 1 and 2 minutes after the injections. The 200-cc. phlebotomies required between 2 and 4 minutes, and the values listed were taken within 1 minute after the phlebotomies were completed.

RESULTS

Forty technically successful experiments were performed on twenty dogs and form the basis of this report. These included hemodynamic observations on the effect of the intracisternal injection of fibrin, on the subsequent effect of Ro 2-2222 after the fibrin, on the effect of phlebotomy after fibrin, and finally on the differential effect of systemic vasodilation first without and then with a decrease in peripheral vascular resistance. The data are presented in tables 1 to 5 and are summarized below.

Hemodynamic Changes Following Intracisternal Injection of Fibrin (Group IA, B and C. Table 1). All 20 dogs showed a marked tachycardia and a striking aortic hypertension, the values for which are listed in Table 1. Eighteen of the twenty dogs (groups IA and B) had an average rise in peripheral vascular resistance of 94 per cent. The other two dogs had a fall of 8 per cent (group IC), and their hypertension was due only to an increased systemic blood flow. Vena cava pressure rose 3 mm. Hg or more in 16 of the 20 dogs, and in the remaining 4 it rose from 0.3 to 1.4 mm. Hg. In the 18 dogs in which a rise in systemic resistance occurred (groups IA and B), left auricle pressure rose 21 mm. Hg from an average of 6.0 to an average of 27.0 mm. Hg. In the other 2 dogs, the only 2 of the 20 which did not show evidence of systemic vasoconstriction (group IC), the average left auricle pressure did not rise. Of the 18 dogs which had an increase of peripheral resistance after fibrin, 12 had a decrease in sys-
temic blood flow averaging 25 per cent (group IA). See figure 2. The other 6 had an average increase in systemic flow of 11 per cent (group IB) with an over-all decrease in blood flow of 13 per cent for the 18 dogs that developed an increased systemic resistance (groups IA and B). In the two dogs of the third group (IC) where neither peripheral resistance nor left auricle pressure rose, flow was markedly elevated, that is an average of 82 per cent.

The average ‘prefibrin’ systemic blood flow for the 20 dogs (group I) was 115 cc/kg/minute. This indicates that in spite of the extensive surgery required, heparinization, and the open chest, the dogs studied were in a reasonably good circulatory state.

Comparison of Effect of Intracisternal Fibrin on Pulmonary and Systemic Vascular Resistances (Table 2). In 3 of the 20 dogs studied, mean pulmonary arterial pressures were also recorded. In these dogs, therefore, pulmonary as well as peripheral vascular resistances could be calculated. The data are listed in table 2 and show that

| Table 2. Comparison of effect of intracisternal fibrin on pulmonary and peripheral vascular resistance¹ |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | P. ART.         | L. AUR.         | FLOW            | PULMONARY R.U.  | PERIPHERAL R.U. |
| t68²            | 18.0 22.0       | 8.0 14.0        | 2.32 2.06       | .0043 .0039     | .058 .108 +86   |
| 113²            | 23.5 28.7       | 2.2 17.7        | 2.53 1.79       | .0084 .0061     | .075 .139 +85   |
| 99³             | 23.0 25.0       | 7.0 9.0         | 1.54 1.52       | .0104 .0105     | .115 .153 +33   |
| Av.             | 21.5 25.2       | 5.7 13.6        | 2.13 1.79       | .0077 .0068     | .083 .133 +68¹  |

¹ Dog weight and systemic vascular pressures may be seen in table 1. ² No vagotomy. ³ Vagotomy. ⁴ Average calculated from the sum of the individual percentage changes, not from the average values.

while systemic resistance rose an average of 68 per cent, pulmonary vascular resistance did not rise but rather fell 12 per cent. See figure 2.

Hemodynamic Changes Induced by Systemic Vasodilation With Ro 2-2222 After the Intracisternal Injection of Fibrin (Table 3). After the intracisternal injection of fibrin had produced the type of hemodynamic changes shown in tables 1A and B, Ro 2-2222 was administered in doses of 0.04 to 0.05 mg/kg, intravenously. In five of the nine dogs left auricle pressure fell spontaneously somewhat from its ‘post-fibrin’ elevation and was re-established to a high, steady level by means of a saline infusion of 10 cc/kg, before the injection of Ro 2-2222. These data are listed in table 3. Vena cava pressure fell from an average of 8.2 to 4.5 mm. Hg, left auricle pressure fell from an average of 29.1 to 7.9 mm. Hg, and mean aortic pressure fell from an average of 252 to 158 mm. Hg. Peripheral vascular resistance fell an average of 48 per cent, and systemic blood flow rose an average of 34 per cent. The average weight of the dogs in this group was 16.8 kg. Figure 3 shows a tracing from one such experiment.

Hemodynamic Effects of a 200-cc. Phlebotomy After Elevation of Left Auricle Pressure by Intracisternal Fibrin. (Table 4). A 200-cc. phlebotomy was performed in four dogs after the intracisternal injection of fibrin had produced elevated left auricle pressures. The phlebotomy data are listed in table 4. Vena cava pressure fell
from an average of 12.4 to 4.7 mm. Hg, left auricle pressure fell from an average of 29.0 to 6.8 mm. Hg, aortic pressure fell from an average of 279/150 to 239/136 mm. Hg. Systemic blood flow fell 26 per cent. The average weight of this group was 16.1 kg. On a weight basis this would be comparable to a phlebotomy of 620 cc. in a 50-kg. patient. Figure 4 shows the hemodynamic changes before and after fibrin and then after subsequent phlebotomy.

Comparison of Hemodynamic Effects of Systemic Vasodilation Without and With Decreased Systemic Resistance on Blood Flow and Left Auricle Pressure (Table 5). There are two apparent physical consequences of generalized systemic vasoconstriction: first, an increased resistance to blood flow and secondly, a diminution of the blood volume in the constricted vessels. In the experiments listed in table 5, the physiological consequences of these two physical sequelae were studied.

| TABLE 3. HEMODYNAMIC CHANGES INDUCED BY VASODILATION WITH RO 2-2222 AFTER INTRACISTERNAL INJECTION OF FIBRIN (GROUP III) |
|---|---|---|---|---|
| EXPER. NO. | WT. | V.C. | L. AUR. (P.V.) | AORTA | SYSTEMIC FLOW | P.R.U. |
| | kg. | mm. Hg | mm. Hg | mm. Hg | | |
| 94 | 14.0 | 6.6 | 5.5 | 40.5 | 12.0 | 235 | 180 | .93 | 1.50 | 161 |
| 112 | 18.0 | 2.9 | 1.8 | 17.7 | 2.2 | 252 | 200 | 1.79 | 2.71 | +51 |
| 68 | 14.0 | 2.9 | 3.7 | 49.0 | 7.0 | 270 | 145 | 1.45 | 2.15 | +48 |
| 48 | 10.7 | 16.0 | 7.5 | 38.5 | 8.0 | 240 | 100 | 1.75 | 2.52 | +44 |
| 50 | 10.5 | 9.5 | 7.0 | 30.0 | 14.0 | 170 | 85 | .90 | 1.40 | +41 |
| 89 | 15.1 | 11.8 | 6.6 | 25.0 | 8.5 | 225 | 140 | 2.10 | 2.64 | +21 |
| 71 | 30.6 | 3.7 | 1.5 | 21.0 | 8.0 | 230 | 160 | 2.01 | 2.40 | +18 |
| 111 | 16.0 | 8.2 | 3.9 | 21.0 | 7.0 | 255 | 220 | 2.60 | 3.05 | +17 |
| 77 | 19.5 | 12.5 | 5.9 | 19.0 | 4.0 | 198 | 135 | 5.24 | 5.45 | +6 |
| Av. | 10.8 | 8.2 | 4.5 | 29.1 | 7.0 | 232 | 158 | 1.89 | 2.42 | +34 |

1 Estimated from systolic and diastolic pressures. 2 Average calculated from the sum of the individual percentage changes, not from the average values.

A screw clamp was tightened on the tubing conducting blood from the arch of the aorta (fig. 1A) to a point where the pressure drop (and therefore the resistance) across the clamped part of the 'aorta' was 80 to 90 per cent of the pressure drop (resistance) in the whole systemic circulation. This clamp, by lowering the pressure in the carotid sinus, induced a reflex systemic vasoconstriction. Two of the four dogs had also previously been given fibrin. These values are under columns 1. Under columns 2 are the values obtained with the aortic screw clamp still in place and the systemic resistance therefore almost unchanged but with blood vessels holding a larger volume of blood because of dilation induced by the injection of Ro 2-2222. Under columns 3 are the values after decreasing the systemic resistance by removing the aortic screw clamp.

The time elapsed from columns 1 to 3 was between 2 and 3.5 minutes.

It will be seen that systemic vasodilation without much change in systemic resistance lowered left auricle pressure from an average of 24.6 to 9.4 mm. Hg, but flow did not increase (changes from columns 1 to 2). When the screw clamp was released (changes from columns 2 to 3), that is to say, little further vasodilation but a great decrease in resistance, flow rose markedly (82%), but left auricle pressure fell...
only another 2.4 mm Hg. The changes thus obtained would seem to relate the restriction of flow to the high systemic resistance, whereas the elevated left auricle pressures (high pulmonary blood volume) were apparently related to the decrease in systemic blood volume.

**Effect of Intracisternal Fibrin on External Left Ventricular Work per Minute and per Liter of Systemic Blood Flow.** Further calculations from the average values for group 1A and B reveal that a) before the fibrin, external left ventricular work was an average of 4.07 kg m/minute for a systemic blood flow of 1.91 liters/minute or 2.13 kg m/liter of blood pumped and b) after fibrin, external left ventricular work was 5.12 kg m for a flow of 1.64 liters/minute or 3.12 kg m/liter of blood pumped, an increase of 47 per cent in the external work expended to pump each liter of blood after the fibrin.

**Fig. 3. V. C., VENA CAVA. P. V., pulmonary vein. A, aorta. C. O., systemic blood flow (rotameter). Ro 2-2222 (Arfonad), 0.045 mg/kg. given at arrow. Dog weight 16.7 kg. Note rise in flow which accompanies fall in all pressures after the Ro 2-2222.**

**Effect of Ro 2-2222 on External Left Ventricular Work per Minute and per Liter of Systemic Blood Flow.** Similar calculations from the average values of the nine dogs in table 3 reveal that a) after the fibrin (before the Ro 2-2222 was given) external left ventricular work was 5.50 kg m/minute for a systemic blood flow of 1.88 liters/minute or 3.02 kg m/liter of blood pumped, b) after the Ro 2-2222 was given, external left ventricular work was 5.23 kg m for a systemic blood flow of 2.42 liters/minute or 2.16 kg m/liter of blood pumped, a decrease of 26 per cent in the external work expended to pump each liter of blood after the Ro 2-2222.

**Hemodynamic Effects of Intracisternal Fibrin During Total Spinal Anesthesia.** It seemed worth while to ascertain whether the fibrin injection did indeed exert its hemodynamic effects via neuronal pathways or, by a mechanical effect, caused the liberation of humoral substances elaborated by the central nervous system (13). To that end, the usual fibrin injection was made into the cisterna magna of a dog previously subjected to a total spinal anesthesia with procaine according to the technique of Co Tui and co-workers (14). In this dog tendon reflexes, respiration and the response to bilateral common carotid artery occlusion were absent following the induction of the spinal block. The fibrin injection evoked a motor response of the head, but
no alteration was observed in either the pulse rate, vena cava, pulmonary artery, pulmonary capillary, or femoral artery pressures.

**DISCUSSION**

The above data constitute an attempt to attack the various factors involved in the genesis of acute hypertensive pulmonary edema. The fact that 18 of the 20 dogs exhibited tachycardia, elevation of systemic and pulmonary vascular pressures, and a restriction of systemic blood flow relative to the elevated ventricular filling pressures establishes a similarity between the experimental syndrome produced by the fibrin and acute pulmonary edema in the hypertensive patient.

**Welch Hypothesis.** In view of the above data it seems appropriate to re-examine the Welch hypothesis (15) of 'left ventricular failure' in the genesis of acute pulmonary edema. It is not possible from the above data to detract from the importance of the concept which relates the resistance which a failing left ventricle faces with the occurrence and intensity of pulmonary congestion. For, as may be seen in table 1, left auricle pressure rose in the 18 dogs which developed increased systemic resistance but not in the other 2 dogs in which the resistance was not elevated; and it was certainly true that in those 18 dogs the work required to pump each liter of blood was markedly increased after the increase of systemic resistance.

On the other hand, the concept of a left ventricle having an excessive resistance to face does not entirely explain the hypertensive pulmonary edema syndrome observed for the following reasons. First, it will be noted that 6 of the 20 dogs receiving fibrin exhibited marked elevations of left auricle pressure even while systemic blood flow increased (group IB). Secondly, dilation of the systemic vascular bed in dogs (table 5) in which systemic resistance was maintained at a high level resulted in a marked lowering of pulmonary capillary pressures. Thirdly, the extent to which pulmonary capillary pressure will rise after total aortic occlusion has been directly correlated with the tone of the systemic blood vessels (3). The tone of the systemic blood vessels therefore seems to be of importance in producing elevated pulmonary capillary pressures not only by increasing the systemic resistance but also by reducing the volume of blood in the systemic vascular bed, this volume decrement being shifted into an area of lower constrictor potential, namely the lungs. The integrated schema embracing both of these factors is shown in figure 5. This schema does not
include whatever alterations may occur in pulmonary capillary permeability. It will be seen that the increased resistance or 'Welch' component relates largely to the restriction of systemic blood flow, whereas the elevated pulmonary vessel pressures are mostly related to shift of blood from periphery to lung.

Mechanism of Elevation of Pulmonary Vascular Pressures. It may be argued that the elevation of pulmonary vascular pressures after fibrin was produced by pulmonary vasoconstriction. That this is not so has been demonstrated by 1) the data in table 2 which showed that an increase in pulmonary vascular resistance did not occur and 2) previous experiments in which complete pulmonary denervation prior to the fibrin injection did not prevent the subsequent pulmonary vascular hypertension (3).

The relationship of pulmonary blood volume to pulmonary vascular pressures has been the subject of a separate report (16). These studies revealed that at low pressures a substantial increase in volume produced only slight elevations of pressure, whereas at high pressures the same volume increment greatly increased the pressure. More recently, in vivo studies (4) demonstrated that systemic vasoconstriction was accompanied by a striking increase of pulmonary blood volume as well as an elevation of left auricle pressure and that these were always quantitatively related. Those experiments also confirm the above interpretation, namely that the pulmonary vascular hypertension occurring after fibrin cannot be explained on the basis of pulmonary vasoconstriction.

Comparison of Effects of Phlebotomy and Systemic Vasodilation. The above-
mentioned studies further revealed that for any given increase or decrease of total blood volume, the changes induced in pulmonary blood volume and pulmonary vascular pressures were much more pronounced during systemic vasoconstriction than during vasodilation. The phlebotomy experiments in this study (table 4) were all done in dogs with induced systemic vasoconstriction. This fact along with the nature of the pressure-volume relationship of the pulmonary vascular bed (16) accounts for the pronounced effect of phlebotomy on left auricle pressure. It is apparent, therefore, that the withdrawal of blood from the systemic venous bed exerted its effect mainly by reducing the pulmonary blood volume.

It is appropriate to compare the effect of phlebotomy with the effect of systemic vasodilation in the presence of elevated pulmonary vascular pressures. The two groups of dogs were of comparable body weight. Phlebotomy and systemic vasodilation both lowered left auricle pressure to a comparable extent. However, after phlebotomy,

**Table 5. Effect of Peripheral Vasodilation with and without Decreased Systemic Resistance on Flow and Left Auricle Pressure**

<table>
<thead>
<tr>
<th>EXPER. NO.</th>
<th>WT.</th>
<th>L. AUR.</th>
<th>AORTA</th>
<th>SYSTEMIC FLOW</th>
<th>P.R.U.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kg</td>
<td>mm. Hg</td>
<td>mm. Hg</td>
<td>1/min</td>
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<tr>
<td>91</td>
<td>15.0</td>
<td>18.0</td>
<td>10.0</td>
<td>8.0</td>
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<tr>
<td>94</td>
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<td>97</td>
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<td>10.0</td>
<td>8.5</td>
<td>235</td>
</tr>
<tr>
<td>83</td>
<td>20.2</td>
<td>38.0</td>
<td>6.5</td>
<td>6.5</td>
<td>295</td>
</tr>
<tr>
<td>Av.</td>
<td>16.0</td>
<td>24.6</td>
<td>0.4</td>
<td>7.0</td>
<td>264</td>
</tr>
</tbody>
</table>


systemic blood flow fell 26 per cent, whereas after systemic vasodilation systemic blood flow rose 34 per cent.

The external work required of the left ventricle to pump each liter of blood was not greatly diminished by phlebotomy, whereas with systemic vasodilation this reduction was substantial. From both a theoretical and a practical point of view it would seem reasonable to use as a therapeutic measure a clinical maneuver which simultaneously and immediately reduces pulmonary blood volume and also lowers systemic resistance, especially in a patient whose cardiac output is critically low. This would also conserve hemoglobin and serum protein, a matter of practical importance to the patient who is subjected to repeated attacks of pulmonary edema.

**Changes in Pulmonary Capillary Permeability.** Many investigators have postulated that, among other things, reflexes acting over autonomic pathways may alter pulmonary capillary permeability, thereby producing pulmonary edema (5, 17, 26). Measurements of left auricle pressure were, however, not made. The authors do not deny the possibility of alteration in pulmonary capillary permeability but evidence concerning its occurrence is inconclusive in the absence of observed data on left auricle or pulmonary capillary pressures.

**General Considerations.** It is of course advisable to avoid drastic reductions in arterial pressure in hypertensive patients especially if extensive organic vascular
disease is present, largely out of consideration for the tissues supplied by the cerebral, coronary and renal arteries. It has been shown elsewhere (3) that only slight to moderate systemic vasodilation is required to produce a striking lowering of pulmonary vascular pressures when these are initially high. This approach also postulates the availability of an agent for clinical use with which a predictable and desirable degree of peripheral vasodilation can be achieved. Ro 2-2222 (Arfonad) appears to meet these specifications (11).

**Previous Investigations With Vasodilator Agents.** Brunton (27) attributed the salutary effect of amyl nitrite on angina pectoris to systemic vasodilation and the “fall of blood pressure (which) eases the heart at once when this organ is unable to overcome the resistance which is opposed to it.” Goodman and Gilman (28) suggested that nitroglycerin may be useful in the therapy of acute pulmonary edema because of peripheral pooling. Burton (29) noted that his cardiac patients fared better in labor if spinal anesthesia were used. Sarnoff and Farr (30) administered spinal anesthesia as the sole therapeutic measure with conspicuous success in four patients in acute pulmonary edema. Hingson (31) stated that peripheral vasodilation with caudal anesthesia was more effective in controlling acute lung edema than morphine, digitalis or oxygen. Bryce-Smith and co-workers (32) have reported similar results.

Mokotoff and Ross (33), while studying the effect of spinal anesthesia on renal ischemia during congestive heart failure, noted “that several of the patients who were dyspneic and orthopneic before spinal anesthesia could lie flat with no apparent discomfort while the clearance studies under anesthesia were completed.” Johnson (34), in a recent study using the blue dye technique for estimating pulmonary blood volume in man, observed that systemic vasodilation with spinal anesthesia resulted in a 25 per cent decrease in pulmonary blood volume and that this change could be reversed by placing the patient in the head-down position.

Frisk and co-workers (35) obtained suggestive data that tetraethylammonium shifted blood from lungs to systemic vessels, and this drug has been used in the study of congestive failure by Relman and Epstein (36), Hilden (37) and Hayward (38). Werkö et al. (39) came to similar conclusions using hexamethonium bromide.

The intriguing observations of Wasserman (22) that massage of the carotid sinus may be an effective measure in acute pulmonary edema was attributed by that author to the resulting reflex effects on the capillary permeability of the lung. In view of the above data it is to be suspected that induced reflex systemic vasodilation caused the relief. Inadvertent occlusion of the common carotid artery just below the

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**Fig. 5. Hemodynamic Effects** of systemic vasoconstriction (left) and hemodynamic effects of systemic vasodilation in the presence of a high L.A. pressure (right). See text.
sinus, rather than massage of the sinus itself might, however, be hazardous. One of us (S. J. S.) is acquainted with three patients with recent coronary infarcts who frequently went into attacks of acute pulmonary edema within minutes after straining at stool. Straining at stool is a close approximation of the Valsalva maneuver, the striking pressor effects of which have been shown to be mediated over sympathetic pathways causing systemic vasoconstriction (40). The reader is also referred to the reviews of Luisada (21), Henneman (41), Lombardo and Harrison (42), and the early writings of Hope (43).

Little has been said about which portion of the systemic vascular bed is most important to a consideration of the data presented above. It has been stated that the physiologic consequences of ‘systemic vasoconstriction’ are an increase in resistance and a decrease in systemic blood volume resulting in a transfer of blood to the lung. On an a priori basis it is to be expected that the resistance changes are attributable largely to arteriolar activity, whereas the blood volume shift is largely due to changes in the veins and venules. The reasoning behind the former seems obvious. The rationale for the latter is rather more complicated. It may, however, be understood from the review of Landis and Hortonstine (44) on the functional significance of the veins and also from the work of Gollwitzer-Meier (45) who held that there is simultaneous and quantitatively similar activity of arterioles and veins whenever vasomotor impulses act on the systemic vascular bed.

Finally, and perhaps of greatest fundamental importance, the conclusion seems unavoidable that nervous impulses originating in the medulla and traversing sympathetic pathways to systemic blood vessels can exert a profound effect on the pressure and volume of the blood in the lung.

**Summary and Conclusions**

Stimulation of medullary centers by the intracisternal injection of ‘fibrin’ produced systemic and pulmonary arterial and venous hypertension and a 94 per cent average increase in peripheral vascular resistance in 18 of the 20 dogs studied. In 12 of the 18 dogs peripheral vascular resistance rose 107 per cent, and flow fell 25 per cent. In the other six, resistance rose 66 per cent while flow rose 11 per cent. In both groups, whether flow rose or fell, left auricle pressure rose significantly, 22.4 mm. Hg in the former and 18.3 mm. Hg in the latter. Two of the twenty dogs did not develop an increase of peripheral vascular resistance, even though aortic hypertension was marked. These were the only two in which left auricle pressure did not rise. Pulmonary vascular resistance did not rise in the three dogs so studied. The effect of partial ganglionic blockade with Ro 2-2222 after fibrin in the nine dogs so studied was to lower peripheral vascular resistance 48 per cent, lower left auricle pressure 21.2 mm. Hg from 29.1 to 7.9 mm. Hg, and increase systemic flow 34 per cent. The effect of a 200-cc. phlebotomy in four dogs after fibrin was to lower left auricle pressure from 29.0 to 6.8 mm. Hg and decrease systemic flow 26 per cent. External left ventricular work after fibrin was increased 48 per cent per liter of blood pumped. The administration of Ro 2-2222 after fibrin then decreased external left ventricular work by 25 per cent per liter of blood pumped. The Welch hypothesis of ‘left ventricular failure’ does not completely explain acute hypertensive pulmonary edema. A high resistance to left ventricular output will cause a markedly elevated pulmonary capillary pressure only if systemic blood vessels by their constriction shift blood into the lung. Conversely, the same resistance to left ventricular output will not cause marked elevation of pulmonary capillary pressure if the peripheral vascular bed is dilated. It is concluded, therefore, that both physical components of systemic
vasoconstriction, not simply the increased resistance component, contribute to the genesis of hypertensive pulmonary edema.

On the basis of the above data, systemic vasodilation with a moderate depressor effect should both diminish the work required for the left ventricle to pump each liter of blood, decrease pulmonary blood volume and pressure by peripheral pooling, and elevate cardiac output. The clinical results obtained thus far suggest that this principle may have a place in the therapeutic armamentarium for this syndrome.

REFERENCES