SUMMARY In anesthetized and vagotomized rats, an intense cerebral compression (CC) by intracranial placement of a space-occupying mass evoked systemic arterial hypertension (SAH), pulmonary venous hypertension (PVH), and pulmonary hemorrhagic edema (PHE) in 2–3 minutes. Observation of the regional weight changes revealed an acute increase in pulmonary blood volume with a decrease in the volume of the systemic vascular beds. With chronically instrumented flow probes, we demonstrated that the overall pattern of imbalance in right and left cardiac outputs was characterized by an immediate fall in aortic flow by 52% accompanying a slower decline in pulmonary arterial flow. In 10 rats with a right heart bypass (venous return to reservoir and constant pulmonary inflow), CC produced severe PVH and PHE associated with SAH, reservoir volume reduction, and no significant change in pulmonary vascular resistance. The increases in left atrial pressure and lung index (lung: body weight x 100) were much greater than those obtained with natural circulation. In 20 left heart-bypassed rats (constant aortic flow either with or without a reservoir between the left atrium and a roller pump), CC induced SAH, whereas no significant changes occurred in the lungs. The lung index was not different from the normal value. The results indicate that neurogenic constriction of the systemic capacitance vessels to favor venous return is not an important hemodynamic event in the centrogenic pulmonary pathology. Pulmonary volume loading leading to pulmonary hypertension and PHE is evoked principally by a dramatic pulmonary hypertension decrease in left ventricular output due to ventricular strain in the face of an intense arteriolar constriction. Circ Res 47: 366–373, 1980

ACUTE FULMINATING pulmonary edema and hemorrhage of neurogenic origin can be associated with various disorders of the central nervous system, such as cerebral compression (CC) (Campbell et al., 1949; Ducker and Simmons, 1968; Ducker et al., 1968; Chen et al., 1973), intracranial injection of chemical irritants (Sarnoff and Sarnoff, 1952; Worthen et al., 1969), preoptic hypothalamic lesions (Maire and Patton, 1956), an ablation of the nucleus tractus solitarius (Doba and Reis, 1973). Sarnoff and associates (Sarnoff and Sarnoff, 1952; Sarnoff and Berglund, 1952) first characterized the neural and hemodynamic mechanisms involved in the pulmonary edema of central nervous origin. They found that activation of the medullary sympathetic mechanism by an intracisternal injection of fibrin evoked striking elevation of systemic arterial pressure (SAP) and pulmonary venous pressure followed by massive pulmonary edema. Since direct sympathetic impulses to the lungs were not essential for the pulmonary damage, they concluded that the pulmonary hypertension and edema were induced by a shift of blood from the systemic vascular beds to the pulmonary circulation as a consequence of systemic vasconstriction. With regard to the pulmonary pathology associated with intracranial compression, early reports (Campbell et al., 1949; Campbell and Visscher, 1949) suggested that the changes were mediated mainly by vagal pathways and the effects of cardiac slowing. However, many investigators (Ducker and Simmons, 1968; Chen et al., 1973; Chen and Chai, 1974) later argued that this type of neurogenic pulmonary change was induced principally by intense sympathetic activation leading to dramatic hemodynamic alterations, a mechanism similar to that induced by an intracisternal injection of fibrin. The concept of hemodynamic crisis in the production of pulmonary hemorrhagic edema was also supported by one of our studies (Chen and Chai, 1974). In that experiment, massive PHE accompanying systemic and pulmonary hypertension was produced by a large intravenous dose of vasoconstrictor agents, such as epinephrine, norepinephrine, angiotensin, and vasopressin. However, the ultimate mechanism of pulmonary volume and pressure loading resulting from systemic vasconstriction remained unresolved.

In previous studies (Chen et al., 1973; Chen and
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A piece of sponge was attached to the end of the metal jugular vein catheter. We used a Grass model 7 bar. After removal of the parietal bones, a plasticine mass (0.2 cm³) was placed first between the parietal bones. A femoral artery was catheterized to measure the SAP with a Statham P23Db transducer. Heart rate (HR) was monitored with a Grass 7P4F tachograph triggered by arterial pulses or ECG signals. The right atrial pressure (RAP) or central venous pressure was monitored with a Statham P23V transducer through a polygraph to display these and the other recordings.

Regional Weighing

To use the method of regional weighing first described by Fell and Rushmer (1961), we made several modifications in the present experiment. In support of the stereotaxic instrument, a head holder was used for head fixation to minimize body displacement during CC. The animal was also paralyzed with intravenous succinylcholine (2 mg/kg) to avoid spontaneous movements and irregular respiration. We placed two scale platforms, one (1.5 cm wide) underlying the thoracic region and the other (4 cm wide) under the abdominal and hindquarters regions. The borders of these scales were 6–7 cm apart. The center of each scale platform was attached to and fixed on top of a Grass FT-10 force-displacement transducer. The latter was situated inside a wooden block and was connected to the Grass polygraph recorder. We calibrated the transducers by placing a known weight on the part of the animal overlying each scale. The experimental design permitted a gross observation of instantaneous distribution of blood volume between body regions above and below the diaphragm.

Measurement of Aortic Flow and Pulmonary Arterial Flow

Rats were instrumented chronically under sterile conditions, artificial ventilation, and pentobarbital anesthesia. A midline thoracotomy was performed through the sternum. An electromagnetic flow transducer (Biotronex BL-6020 to 6035, 2.0 to 3.5-mm i.d.) was placed around the ascending aorta in one group of rats and around the pulmonary artery in another group. A 21-gauge polyethylene tube was inserted into the left atrial appendage to measure the left atrial pressure (LAP) or pulmonary venous pressure in some rats. After the operation, penicillin was given to prevent infection, and the cannula was flushed with heparinized saline to avoid clotting. Sixteen rats (six with aortic flow probes and 10 with pulmonary arterial flow probes) were selected to enter the acute experiment approximately 7 days after surgery. The selection was based on their food intake, general activity, and response to provocation. Blood flow was measured with a Biotronex BL-613 flowmeter. Calibration was done after the experiment by passing blood through the flow transducer at a constant rate (Kumazawa et al., 1969; Doba and Reis, 1973). The LAP was monitored with a Statham P23Db transducer.

Right and Left Heart Bypass

We used a roller pump (American Optical model 16450), an extracorporeal reservoir, and tubing to control the right or left cardiac output in rats under artificial ventilation and after a right or left thoracotomy (2–3 ribs were removed). The bypass per-
fusion system was primed with heparinized blood from donor rats. For the right heart bypass, short pieces of polyethylene tubing were used to cannulate the right atrium (13 gauge) through the atrial appendage, and the pulmonary artery (16 gauge) through the right ventricle. The pulmonary arterial cannula was connected to the outflow side of the pump with Teflon tubing (1/16-inch i.d., 1/8-inch o.d.). A short piece (3 cm) of large bore Silastic tubing was connected to the right atrial cannula to divert venous return into a reservoir, from which blood was pumped to the pulmonary artery at a constant flow rate. The latter was set to maintain SAP close to the level existing before the bypass procedure. Despite frequent failures, a satisfactory preparation was achieved in 10 rats. Adequacy of left ventricular function was verified by observing a constant LAP and a prompt rise in arterial pressure upon a temporary increase in pump flow rate. Pulmonary arterial perfusion pressure (PAP) was measured from the pump outflow tubing via a side outlet near the pulmonary artery. Two types of left heart bypass were performed in a total of 20 rats to keep a constant aortic flow. In one type, blood was drained from the left atrium to a reservoir and was pumped back to the aorta through a carotid and a femoral artery. In the other type, blood was pumped directly from the left atrium into the aorta without passing through a reservoir. LAP was measured via a side outlet near the atrium. The flow rate was adjusted to maintain a prebypass level of arterial pressure which was measured from the other femoral artery. Blood volume inside the reservoir was monitored with a Statham P23V transducer that was connected to the reservoir bottom. Before CC, the reservoir volume and other parameters remained constant for at least 5 minutes. For comparison, CC was done in control experiments (natural circulation) approximately 30 minutes after open-chest surgery. In the bypass preparations, the pulmonary and systemic vascular resistances (PVR and SVR) were calculated from the PAP, LAP, SAP, RAP, and perfusion flow (Q):

\[ PVR = \frac{(PAP - LAP)}{Q} \]  
\[ SVR = \frac{(SAP - RAP)}{Q} \]  

**Examination of the Lungs**

At the end of the experiment, the trachea was clamped. The lungs were excised and examined grossly. They were rinsed with saline, freed from fatty tissue, lightly blotted with filter paper, and then weighed. The lung index, which denotes the lung weight-to-body weight ratio \( \times 100 \), was calculated to compare the degrees of PHE (Maire and Patton, 1956; Chen et al., 1973; Doba and Reis, 1973; Chen and Chai, 1974). The normal lung index was thereby obtained in 20 rats killed by an intraperitoneal overdose of pentobarbital. The wet-to-dry lung weight ratio, which is a measure of excess fluid in the lungs, was used to assess PHE pulmonary edema (Guyton and Lindsey, 1959). However, this measurement did not appear to be a good index for comparing the degree of pulmonary damage produced by an intense CC, because the primary change was hemorrhage instead of edema (fluid filtration) (Chen et al., 1973).

The data were expressed as means \( \pm \) sd. For statistical evaluation, we used unpaired or paired t-tests to make comparisons between groups and the analysis of variance test for comparisons among groups. A probability \( (P) \) value of less than 0.05 was considered significant.

**Results**

**Regional Weight Changes**

In 10 vagotomized rats, an intense CC evoked acute increases in SAP and HR. Concomitantly, the regional weight changes (AWT) consisted of an increase in thoracic weight and a decrease in weight of the abdomen-hindquarters regions. The changes reached a maximum of 4–6 g above or below the baseline within 20 seconds after CC. Despite a terminal decline in SAP and HR about 3 minutes after CC, the weight changes stayed around the plateau level (Fig. 1). At approximately the end of the hypertensive plateau, pink-tinged frothy fluid came out from the tracheal tube. Postmortem, the lungs showed dark-red discoloration and were swollen and globular in appearance. The pathological changes in the lungs have been described in detail elsewhere (Chen et al., 1973). The lung weight was about three times the normal value (lung index
of 1.62 ± 0.24 comparable with the normal value of 0.55 ± 0.08). The early phase of thoracic weight increase was probably the result of intravascular blood redistribution. With the development of PHE, most of the weight changes became irreversible because of blood extravasation in the lungs.

Imbalance in Right and Left Cardiac Outputs

Pulmonary arterial flow was measured in 10 rats, and aortic flow in another six rats with chronically instrumented flow probes. LAP was recorded through chronically implanted catheters in eight of the 16 rats. Since we observed little variation in the time course of changes in SAP, HR, RAP, and LAP, these changes were averaged at different times after CC (Fig. 2). The individual and average changes in systemic flow (ΔQ) were expressed as the percentage increase or decrease from the baseline. The latter were 76 ± 8 ml/min for pulmonary arterial flow and 70 ± 11 ml/min for aortic flow. Accompanying the profound rises in SAP and LAP within 40 seconds after CC, the aortic flow decreased dramatically to 45–58% below the baseline. During the first 10 seconds, the pulmonary arterial flow transiently increased by 4–23.2% in four rats, whereas it decreased by 1.6–7.2% in another six rats. Thereafter, the pulmonary arterial flow declined gradually in all animals, reaching an average of −44.5% at 40 seconds. As shown in Figure 2, the overall pattern of imbalance in systemic flows was characterized by a fast fall in aortic flow associated with a slower decrease in pulmonary arterial flow. In this series of experiments, the value of the lung index was 1.58 ± 0.18.

Right and Left Heart Bypass

Severe PHE was observed after CC in 10 rats with a right heart bypass. In this preparation with a constant flow perfusion to the pulmonary circulation, the hemodynamic responses to CC included rises in SAP, PAP, and LAP with a decrease in reservoir volume (Fig. 3). In 20 rats with the left

![Figure 2](image-url)
Hemodynamic responses to CC in 10 vagotomized rats with a right heart bypass. ARRV, the change in right reservoir blood volume. With the venous return bypassed through a reservoir and a constant pulmonary arterial inflow, CC causes acute rises in SAP, PAP, and LAP and a decrease in reservoir blood volume. The increase in LAP is slightly greater than the increase in PAP, reflecting a small decrease in pulmonary pressure gradient or PVR.

In Table 1, we compare the maximal changes in SAP, LAP, and lung index in the various groups of animals. Although systemic arterial hypertension was greatest in the left heart bypass group, the value of the lung index was not different from that of the normal lungs (groups 4 and 5 vs. group 1). In addition, the rise in LAP (4.6 ± 1.2 mm Hg) observed in the left heart bypass group without a reservoir was much lower than that in the control experiments with natural circulation (41.2 ± 7.1 mm Hg). In contrast, the values of ΔLAP and lung index in the right heart bypass group were much higher than those obtained in the control experiments (group 3 vs. group 2).

The changes in PVR and SVR were calculated at 20 seconds after CC (Table 2); at that time, the cardiovascular response usually had reached a maximum. In 10 animals with a right heart bypass the PVR increased in only three rats, whereas it decreased in the other seven rats. The average change was a decrease by −0.06 ± 0.09 mm Hg·min/ml from the control of 0.24 ± 0.06 mm Hg·min/ml (Table 2). The change was, however, not statistically significant. In the left heart bypass preparation, the SVR was consistently elevated to 292% of the control (Table 2).

Discussion

Pulmonary hypertension and PHE can be induced after hemodynamic alterations associated with generalized vasoconstriction either of neurogenic origin (Sarnoff and Sarnoff, 1952; Sarnoff and Berglund, 1952; Chen et al., 1973; Doba and Reis, 1973) or caused by pharmacological intervention (Chen and Chai, 1974). In the present investigation, a method of regional weighing allowed us to observe that an intense CC produced an acute increase of blood volume in the thoracic region and an accompanying decrease in areas below the diaphragm. It has been hypothesized that an accumulation of blood in the lungs is the result of a shift of blood from high constrictor area (systemic circulation) to an area of low constrictor potential (pulmonary circulation) (Sarnoff and Sarnoff, 1952; Sarnoff and Berglund, 1952; Chen and Chai, 1974). The results of the present study appear to modify this concept and explain the mechanism of transfer in blood volume between the pulmonary and systemic circulation. The pulmonary volume and pressure loading after CC or perhaps other neurogenic disorders is initiated principally by a profound decrease in left cardiac output. An increased venous return subsequent to a reduction in the systemic vascular
TABLE 1 Comparison of the Maximal Changes in SAP, LAP, and Lung Index in Various Groups of Vagotomized Rats after CC

<table>
<thead>
<tr>
<th>Group Description</th>
<th>n</th>
<th>Increase of SAP (mm Hg)</th>
<th>Increase of LAP (mm Hg)</th>
<th>Lung index</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Normal lungs (without CC)</td>
<td>20</td>
<td>93.6 ± 14.1</td>
<td>62.6 ± 6.5</td>
<td>0.56 ± 0.08</td>
</tr>
<tr>
<td>(2) Control (open chest, natural circulation)</td>
<td>10</td>
<td>128.8 ± 13.8</td>
<td>2.24 ± 0.28</td>
<td>0.54 ± 0.07</td>
</tr>
<tr>
<td>(3) Right heart bypass (via a reservoir)</td>
<td>10</td>
<td>194.2 ± 20.4</td>
<td>4.6 ± 1.2</td>
<td>0.54 ± 0.07</td>
</tr>
<tr>
<td>(4) Left heart bypass (via a reservoir)</td>
<td>10</td>
<td>192.6 ± 19.8</td>
<td>0.52 ± 0.09</td>
<td>0.54 ± 0.07</td>
</tr>
</tbody>
</table>

P values

<table>
<thead>
<tr>
<th>vs. (1)</th>
<th>vs. (2)</th>
<th>vs. (3)</th>
<th>vs. (4)</th>
<th>vs. (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&gt;0.2</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&gt;0.2</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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Values are means ± SD.

capacity is not important for the genesis of the centrogenic pulmonary pathology.

It has been well documented that arteriolar constriction and increased peripheral resistance are the major hemodynamic events involved in the Cushing pressor response to CC (Cushing, 1901; Brown, 1956; Ducker and Simmons, 1968; Ducker et al., 1968; Chen et al., 1973). Cardiac output may rise or fall, depending on the degree of intracranial hypertension (Ducker et al., 1968; Brashear and Ross, 1970).

There is little information with respect to the effect of CC on the venous capacitance vessels or the systemic vascular capacity. In response to a moderate intracranial compression, vasomotor tone in the intestine (Brown, 1956) and venous return through both venae cavae (Rodbard and Stone, 1954) have been shown to increase. To produce an accumulation of blood in the lungs, the pulmonary inflow must exceed the outflow for a period of time. In the present study, we illustrate that the overall pattern of imbalance in right and left cardiac outputs is characterized by an immediate and profound fall in aortic flow accompanying a slower decline in pulmonary arterial flow. A transient rise of pulmonary inflow by about 20% was observed in only three of the 10 rats (Fig. 2). The dramatic decrease in cardiac output in the face of intense systemic vasoconstriction is probably the result of left ventricular overload secondary to tremendous increase in total peripheral resistance (Guyton et al., 1973; Doba and Reis, 1973; Dampney et al., 1979). The imbalance in both sides of the heart and the transfer of blood into the pulmonary circulation can be initiated by acute left ventricular failure without a simultaneous and equal weakening of the right heart (Lindsey et al., 1957) and can be independent of a neurogenic reduction in the systemic vascular capacity (Guyton et al., 1973). In contrast to a marked increase in SVR, the PVR is affected slightly after CC (Table 2). This factor may enable the right heart to pump more blood into the pulmonary circuit as the left heart fails to pump adequate flow out of the lungs. However, at this point, we cannot preclude the possible involvement of an active constriction of systemic capacitance vessels until we examine the results obtained in the heart bypass studies.

The relative importance of changes in pulmonary inflow...
transmural pressure (Carlill and Duke, 1956; Lloyd and Schneider, 1969) that outweighs active pulmonary vasoconstriction, if any. However, we do not mean to suggest that direct sympathetic impulses to the lungs have entirely no effect on the rise of pulmonary vascular pressures in the face of passive volume loading. Under some circumstances, sympathetic effects on the pulmonary circulation may cause a significant decrease in distensibility or capacity, despite no change in resistance (Ingram et al., 1968; Aarseth et al., 1971). It is possible that an active pulmonary vasomotor reaction may not affect the resistive property, but it may alter the pressure-volume characteristics and thereby exaggerate the degree of pulmonary hypertension and pathology. Such a contention cannot be concluded from the data of the present experiments.

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