Epinephrine-Induced Pulmonary Edema in Crosscirculated Animals*

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Summary

Blood with epinephrine was infused into crosscirculated dogs and comparison was made between animals receiving the infusion only in their heads, only in their trunks, or in their entire circulation.

The procedure was invariably followed by pulmonary edema in all experimental animals.

Left ventricular systolic pressure elevations and increases of the dp/dt of this chamber were similar in all animals irrespective of the area infused. Left ventricular end-diastolic pressure elevations also occurred in all animals but were greater in the "trunk dogs" than in the "head dogs" or the "whole dogs".

These results suggest that both neurogenic stimuli and circulating catecholamines (either injected or secreted under the influence of nerve stimulation) contribute to the chain of events leading to formation of pulmonary edema.

Additional Indexing Words:
Heart failure Neurogenic pulmonary edema Left ventricular compliance

Previous experiments1) in this laboratory showed that injection of blood with massive doses of epinephrine was followed in the dog by acute, severe pulmonary edema. They also showed that this acute episode was invariably accompanied by a dramatic elevation of left ventricular end-diastolic pressure, which, percentwise, was greater than that of the systolic pressure, and by an increase of left ventricular dp/dt. The present experiments, based on cross-circulation between 2 or 3 animals, were devised in order to clarify the part played by the central nervous system in the sequence of events that leads to this type of experimental edema of the lungs.

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MATERIAL AND METHOD

Two different experimental preparations were employed.

(1) In 2 experiments, crosscirculation between 2 dogs was established in the following manner. Two adult mongrel dogs were anesthetized with morphine (5 mg./Kg.) and chloralose (100 mg./Kg.) in 1 experiment and only chloralose (150 mg./Kg.) in the other. The carotid arteries, jugular veins, and vagi were exposed bilaterally through a medial neck incision. The neck muscles were exposed, ligated, and cut. The vertebral arteries and veins were exposed bilaterally via a superior mediastinal approach. A tracheotomy was performed and a tracheal tube inserted. A No. 7 Goodale-Lubin catheter was advanced into the left ventricular cavity via the left carotid, and connected to a Statham P23Db transducer. A circular metal clamp was positioned around the dogs' necks so that the exposed vessels and nerves remained above it. Both animals received 10 mg./Kg. of heparin. Each animal then received an infusion of 77 ml./Kg. of blood from a donor dog. The venous and arterial vessels were then cannulated (Fig. 1) connecting the trunk of dog B with the head of dog A, and the trunk of dog A with the head of dog B, respectively. The neck clamps were then maximally tightened to cut off any residual blood flow. Epinephrine (1.1 mg./Kg.—calculation based on the combined weights of both dogs) was injected at an initial rate of 0.52 mg./min. at first, and at 1.31 mg./min. during the last third of the experimental period into the cannula carrying venous blood into the trunk of dog B, thus circulating first in the trunk of this dog and then in the head of dog A (Fig. 1).

(2) In 4 additional experiments, crosscirculation between 3 dogs was established as follows. Three adult mongrel dogs were anesthetized with morphine sulphate (3 mg./Kg.) and chloralose (100 mg./Kg.). Dog B was prepared in the

Fig. 1. Scheme of crosscirculation between 2 dogs.
same manner as the dogs in experiments type 1 and the cardiac catheter was placed either in the left ventricular cavity (2 experiments) or the left atrium (2 experiments).

In 3 experiments, both carotid arteries and jugular veins were exposed in dog A, and a No. 7 Goodale-Lubin catheter was advanced into the aorta via the left femoral artery. The proximal segments of both carotid arteries and jugular veins were cannulated and connected to the distal (cephalic) segments of the respective vessels of dog B. In 1 experiment, the femoral arteries and veins were exposed and used to perfuse the head of dog B while the left carotid artery was used to record systemic pressure. In all experiments the animals were heparinized (10 mg./Kg.).

In dog C one carotid artery and one jugular vein were exposed. A catheter was advanced via a femoral artery into the left atrium (2 experiments) or left ventricle (2 experiments). The distal (cephalic) end of the jugular vein was cannulated and connected to the central end of a jugular of dog B. The distal (cephalic) end of a carotid was cannulated and connected to the central end of a carotid of dog B (Fig. 2).

Epinephrine (1.1 mg./Kg., dose based on combined weights of dogs B and C) was injected into the venous cannula going from dog C into dog B. Therefore, epinephrine, after mixing with venous blood, was distributed to the trunk of dog B and to one carotid of dog C in equal concentration, then recirculated into the trunk of dog C.

Statham P23Db transducers were connected to all catheters for pressure recordings. Lead II of the ECG was also recorded. A tracing of the first derivative (dp/dt) of left ventricular pressure, i.e. of the rate of change of pressure, was recorded by linear differentiation of the pressure signal to 50 cycles/sec. using an RC analog computer. Both photographic and direct writer transcriptions of these parameters were obtained in each experiment.

At the end of each experiment, the dogs were sacrificed with i.v. nembutal, the lungs and trachea were removed, weighed, and examined for evidence of pulmonary
edema (foam in the trachea, foam exuding from parenchymal cut). The lung/body weight indices were then determined according to the formula:

\[
\frac{\text{wet lung weight (Gm.)}}{\text{body weight (Kg. x 10)}} = \text{L/B index}
\]

In our experience, an index of 0.8 is normal, an index of 1.0 is evidence of congestion, and an index above 1.2 is definite evidence of edema. Indices between 1.3 and 4 usually correlate with the amount of foam in the trachea.

Results

The results of the experiments are presented in Table I.

The first type of experiment was based on crosscirculation between 2 dogs, so that one animal would receive blood and epinephrine only in the cerebral circulation (dog A=head dog) while the other would receive it in the circulation of the body (heart, lungs, systemic vessels) but not in the cerebral circulation (dog B=trunk dog). The systolic pressure of the left ventricle rose in both animals to an equivalent degree. The end-diastolic pressure of the left ventricle rose in both animals but far more in the “trunk dogs” (72 and 80 mm.Hg, respectively) than in the “head dogs” (40 and 44 mm.Hg, respectively). The dp/dt of the left ventricular pressure rose in all dogs reaching from 2 to 3 times the control values. Pulmonary edema occurred in both the “head dogs” and the “trunk dogs”; its severity varied in the two sets of experiments being higher in the “trunk dog” (L/B index=1.8) than in the “head dog” (L/B index=1.16) in experiment 1, and the opposite in experiment 2, where the L/B index of the “head dog” was 2.44 in contrast with 1.54 in the “trunk dog”.

The second type of experiment was based on crosscirculation between 3 dogs, so that dog C would receive blood and epinephrine both in the trunk and the head (“whole dog”) while dog B would receive it only in the trunk (“trunk

Table I.

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>LVSP</th>
<th>LVEDP</th>
<th>LV dp/dt</th>
<th>L/B Index</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Maximum</td>
<td>Control</td>
<td>Maximum</td>
</tr>
<tr>
<td>1</td>
<td>A*</td>
<td>144</td>
<td>224</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>B**</td>
<td>116</td>
<td>256</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>A*</td>
<td>146</td>
<td>240</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>B**</td>
<td>148</td>
<td>232</td>
<td>0</td>
</tr>
</tbody>
</table>

* Head Dog; ** Trunk Dog
Series II: Crosscirculations between Three Dogs

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>LVSP Control</th>
<th>LVSP Maximum</th>
<th>LVEDP Control</th>
<th>LVEDP Maximum</th>
<th>LV dp/dt Control</th>
<th>LV dp/dt Maximum</th>
<th>L/B Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>C*</td>
<td>120</td>
<td>312</td>
<td>0</td>
<td>40</td>
<td>10</td>
<td>30</td>
<td>1.3</td>
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<tr>
<td>B**</td>
<td>116</td>
<td>248</td>
<td>0</td>
<td>32</td>
<td>12</td>
<td>19</td>
<td>1.8</td>
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<tr>
<td>C*</td>
<td>176</td>
<td>280</td>
<td>0</td>
<td>40</td>
<td>6</td>
<td>13</td>
<td>1.17</td>
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<tr>
<td>B**</td>
<td>148</td>
<td>288</td>
<td>0</td>
<td>56</td>
<td></td>
<td></td>
<td>1.16</td>
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<tr>
<td>L/B Index</td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Left Atrial Pressure Control</th>
<th>Left Atrial Pressure Maximum</th>
<th>L/B Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>C*</td>
<td>2/0</td>
<td>30/14</td>
<td>1.2</td>
</tr>
<tr>
<td>B**</td>
<td>4/0</td>
<td>60/28</td>
<td>1.6</td>
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<tr>
<td>C*</td>
<td>0 (mean)</td>
<td>44 (mean)</td>
<td>2.4</td>
</tr>
<tr>
<td>B**</td>
<td>-2 (mean)</td>
<td>4 (mean)</td>
<td>1.2</td>
</tr>
</tbody>
</table>

* Whole Dog; ** Trunk Dog

dog A); dog A would supply blood to the head of dog B.

The systolic pressures of the left ventricle rose in both "whole" and "trunk" dogs (experiments 1 and 2) to very high levels. The left atrial pressures rose in both the "whole dog" and the "trunk dog" in experiment 3, only in the "whole dog" in experiment 4.

The end-diastolic pressure of the left ventricle (or the mean pressure of the left atrium) rose in all animals (except trunk dog of experiment 4). The ratios of these pressure elevations were higher in the majority of experiments (1, 2, and 4) in the "whole dogs" as compared to the "trunk dogs" with the exception of experiment 3 where this relationship was reversed. The dp/dt of the left ventricular pressure rose in both dogs of each set of the 3 experiments where it was measured (experiments 1, 2 and 3). Pulmonary edema occurred in all pairs of animals but varied because it was lower (experiments 1 and 3), higher (experiment 4), or equivalent (experiment 3) in the "whole dog" as compared to the "trunk dog". It is remarkable, though puzzling, that the severity of edema, as indicated by the lungs/body weight indices did not always correlate with the degree of elevation of left ventricular end-diastolic or left atrial mean pressure.

**Discussion**

Previous experiments\(^{2}\) had described a standard method for inducing pulmonary edema (P.E.) in the dog, based on rapid injection of blood with
large doses of epinephrine. In the course of such experiments, it was noticed that, prior to the onset of P.E., two phenomena constantly appeared, a marked elevation of the left ventricular end-diastolic pressure (LVEDP) to levels of 70 or 80 mm Hg, and a marked increase of the left ventricular dp/dt. This was interpreted as evidence of a change of compliance of the left ventricular wall which, in the presence of a high venous return, was followed by pressure elevation in the pulmonary capillary bed, and then by transudation.

The part played by either circulating epinephrine or adrenergic nerve impulses reaching the left ventricular wall had already been studied by injecting blood with epinephrine either into the left carotid artery toward the brain or intravenously.1) LVEDP rose less with intravenous infusion. That nerve impulses played a role seemed demonstrated by the fact that both LVEDP elevation and pulmonary edema were less constant and less severe when the heart was denervated*.

In the present study, an attempt was made to differentiate between the CNS-mediated and the direct effect of an infusion of blood and epinephrine in the pathogenesis of pulmonary edema.

Experiments in crosscirculated dogs showed that the infusion of blood with epinephrine causes an elevation of the LVEDP, an increase of LV dp/dt, and pulmonary edema *both when it acts only on the heart and systemic vessels (trunk dog) and when it acts only on the cerebral vessels (head dog).* In the latter, peripheral vasoconstriction, caused by sympathetic discharge and probably reinforced by adrenal secretion, may well cause overloading of the left ventricle. A modification of the left ventricular wall compliance could thus occur, even in the absence of cardiac nerves stimulation.

Subsequent experiments compared crosscirculated dogs in which the epinephrine did or did not act on the cerebral vessels. Even though elevation of LVEDP (or left atrial mean pressure) were higher in the "whose dogs" (3 out of 4 experiments), the severity of pulmonary edema varied in the various experiments between the 2 dogs of each series (the third dog acted merely as a donor).

Elevation of the LVEDP (or LA mean pressure) was greater in the majority of the "trunk dogs" (experiment 1B and 2B of series I; 1B, 2B and 3B of series II) than in the "head dogs" (experiment 1A, 2A) and than in 1 out of 2 "whole dogs" (experiment 4A). This might lead to the conclusion that central stimuli decrease the effect of catecholamines on the left ventricle. However, in the comparison between "whole dogs" and "trunk dogs" only 1 out of 2 experiments showed this trend. In the comparison between "head

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* Surgical denervation has been shown to be frequently followed by incomplete biological denervation.9)
dogs” and “trunk dogs”, it should be pointed out that action of the injected catecholamines on the brain alone was able to produce the result, even though no direct effect of them was exerted on the heart. It is highly possible, however, that catecholamines, secreted under the influence of nerve stimuli, were also involved.

Experiments with crosscirculation and injection of blood with epinephrine had been previously conducted by Kováč.3) The finding of an elevated left atrial pressure was explained as the result of left ventricular failure. The present series of experiments confirms the elevation of left atrial pressure in both animals of a series submitted to crosscirculation and injected with blood and epinephrine; it shows that this elevation is caused by elevation of left ventricular end-diastolic pressure; it also reveals that such an increase, occurring at a time of maximal increase of contractility (as evidenced by an increase of the dp/dt), is not related to left ventricular failure but to a particular modification of left ventricular compliance. The latter seems to be caused by either circulating catecholamines, nerve impulses, or both.

REFERENCES