Experimental Studies on the Acute Pulmonary Edema (Part II)

THE ROLE OF THE VENOUS RETURN IN THE PATHOGENESIS OF ADRENALIN PULMONARY EDEMA

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In the previous report the author analysed the relationship between the incidence of pulmonary edema and the change in the femoral artery pressure and suggested that the pulmonary edema took place on the input side of the heart when the load on the heart is increased beyond a critical limit, the load being thrown on the heart when it tries to pump blood into a system of high blood pressure. In this report the author studied the relationship between the adrenalin pulmonary edema and venous return. The pulmonary edema is prevented from taking place by a variety of means, i. e., the ligation of a unilateral femoral vein, pulmonary arteriolar blockade by lycopodium spores and the bleeding. This fact indicates that the incidence of a relative increase in the venous return over output is an important trigger mechanism of the adrenalin pulmonary edema.

At the same time it was suggested that the mobilization of depot blood was a cause of this relative increase in the venous return.

IN THE previous report the author studied the relationship between the systemic artery blood pressure and the incidence of the pulmonary edema; it was suggested that the heart had a limited ability to sustain loads and that the systemic blood pressure could be elevated only up to a certain plateau level no matter how much adrenalin may be given. It was suggested that the pulmonary edema set in on the input side of the heart when the left heart is driven to pump blood beyond its critical limit as regards the load. Since the heart operates in compliance with Starling's law of the heart, the heart tries to dispose of an increased input load by increasing its residual volume during diastole and increasing the venous pressure. Hemodynamically speaking, such an increase in the input load must be essentially a relative increase in the venous return over the output from the left heart. Since the blood is in a continuous circulation, the returning blood is just the "output" blood on the other end of the same circle; why,

then, should there occur an imbalance between the rate of output and that of the venous return?

It was shown in this laboratory by Ike¹⁾ and Odake²⁾ that the adrenalin pulmonary edema was prevented from taking place by ligating a systemic vein; the bloodless phlebotomy³⁾ and bleeding are the recognized conventional therapeutic means in the treatment of the pulmonary edema.

In order to evaluate the effect of reducing the venous return on the adrenalin pulmonary edema in detail the author performed a series of experiments; this paper aims to describe these experiments and discuss the significance of the venous return in the pathogenesis of the pulmonary edema.

METHODS

About 160 albino rats (Whistar strain) weighing from 100 to 200 grams and treated in different ways, i. e., with the ligation of a large vein, the blockade of the pulmonary arterioles or bleeding, have been examined for the response to the intra-

venous injection of 0.5 mg/kg of adrenalin, a dose which was the minimum necessary amount to induce a lethal pulmonary edema in normal albino rats (c.f. Table I); they were examined in terms of the mortality rate and lung-body ratio (lungs weight/body weight $\times 100$) and for the histopathological findings of the lungs. The femoral artery pressure and electrocardiograms were recorded in large-sized albino rats (weighing about 200 grams) in the same way as in the preceding report.

The reduction of the venous return was achieved in the following ways:

(1) Ligation of a large systemic vein:

In un-anesthetized albino rats a unilateral femoral vein was ligated by a method described by Ike¹³ immediately after the intravenous injection of adrenalin.

(2) The blockade of pulmonary arterioles:

In un-anesthetized albino rats 0.5 cc or 1.0 cc of 1% lycopodium spore suspension in physiological saline solution was injected into the femoral vein; adrenalin was injected intravenously about 10 minutes later.

(3) Bleeding:

Animals were anesthetized by the intraperitoneal injection of urethane (in dose of 1 g/kg) and studied in different groups as follows: (a) Prior to adrenalin injection, about 5% to 60% of the total estimated blood volume of albino rat was withdrawn by suction as quickly as possible, and adrenalin was injected about 10 minutes later. This group of animals served to estimate the necessary degree of bleeding for the procedure to be of any preventive value. (b) All animals were bled in amounts corresponding to 10% of the estimated total blood volume but the rate of the bleeding was either rapid or slow, and adrenalin was injected intravenously at the end of about 10 minutes after

bleeding; this group served to estimate the influence of the rate of bleeding. (c) Animals were bled up to 10% of the total estimated blood volume but adrenalin was injected intravenously at different points of time after the bleeding, i.e., at the end of 10 minutes, 2 hours and 5 hours; this group of animals served to estimate the time factor, i.e., the lapse of time between the bleeding and adrenalin injection. For the estimation of the total blood volume of albino rats the author relied on the values given by Everett, Simmons & Lasher⁴³, i.e., 55.6 μ l/g for male and 53.1 μ l/g for female.

RESULTS

1) The effect of ligating a unilateral femoral vein on the incidence of adrenalin pulmonary edema

As is shown in Table II the ligation of a unilateral femoral vein clearly blocked the adrenalin pulmonary edema. Histopathologically, too, there was no obvious sign of pulmonary edema or hemorrhage in cases of survival.

As is clear from Fig. 1, even with the unilateral ligation of the femoral vein the intravenous

Fig. 1. Changes of blood pressure and cardiac rate following the intravenous injection of adrenalin in the rat subjected to the ligation of the femoral vein. (Note) Ligation ($\uparrow$) and release ($\downarrow$) of the femoral vein.

TABLE I MORTALITY AND LUNG-BODY RATIO AFTER THE INTRAVENOUS INJECTION OF ADRENALIN TO ANESTHETIZED RATS WITH THE INTRAPERITONEAL INJECTION OF URETHANE

Dose of Adrenalin (mg/kg)	Urethane 1.0 g/kg	Number of Cases	Average Body Weight (g)	Mortality (%)	Lung-Body Ratio
Normal Control		25	125	0	0.78 ± 0.12
0.3	Given	10	127	10	1.25 ± 0.37
0.5	Not Given	10	133	100	2.65 ± 0.28
	Given	10	112	90	2.27 ± 0.45
1.0	Given	8	124	100	2.66 ± 0.18

TABLE II EFFECT OF LIGATION OF THE FEMORAL VEIN ON ADRENALIN PULMONARY EDEMA

Procedure	Number of Cases	Average Body Weight (g)	Mortality (%)	Lung-Body Ratio
Control	10	133	100	2.65 ± 0.28
Ligation of Femoral Vein	10	135	20	1.30 ± 0.50

injection of adrenalin caused the femoral artery pressure to be elevated markedly associated with reflex bradycardia just as it was the case in the control group. With ligation, however, the duration of the blood pressure rise was somewhat shorter than in the control group.

2) The effect of the pulmonary arteriolar blockade on the incidence of adrenalin pulmonary edema

Animals became dyspneic immediately after the infusion of lycopodium spores. With 1.0 cc suspension 3 animals developed dyspnea, cyanosis and convulsion of four limbs and died 4-8 minutes after the injection. In all other animals the dyspnea was of short duration and normal breathing was restored soon. Parenthetically these 3 fatal cases were autopsied together with 3 cases of survival; no case showed any sign of pulmonary edema.

As is shown in Table III, while adrenalin pulmonary edema nearly failed to be blocked with 0.5 cc of lycopodium suspension, it was clearly blocked or alleviated with 1.0 cc of the suspension. Histologically, too, the signs of pulmonary edema and hemorrhage were milder in the lycopodium group, i.e., 2 cases of survival receiving 0.5 cc suspension and all cases receiving 1.0 cc suspension, than in the control group. Most lung fields were practically free from pulmonary edema and hemorrhage, although limited lung fields showed marked signs of the change even when pulmonary edema could be prevented clinically.

Lycopodium spores were found to have obstructed the pulmonary arterioles throughout the entire lungs. Where such an obstruction was complete, the pulmonary edema was successfully

blocked.

Where the section showed pictures of marked pulmonary edema and hemorrhage lycopodium spores were not found in large numbers. In the sections of the liver, spleen and kidneys no lycopodium spores were found.

3) The effect of bleeding on the incidence of adrenalin pulmonary edema

As is clear from Table IV, a rapid bleeding obviously blocked the adrenalin pulmonary edema. With removal of only 5% of the total estimated blood volume (0.33 cc on the average) the incidence of adrenalin pulmonary edema was markedly reduced. With removal of more than 30% of the total blood volume adrenalin pulmonary edema was blocked completely. Where more than 40% was removal, 4 animals died in the course of the observation, presumably because of the hemorrhagic shock. In such cases there was no sign of pulmonary edema or hemorrhage.

As is shown in Table V, for an equivalent amount of blood loss, the rate of the bleeding did not influence the effectiveness of the procedure. Allowing a long time to intervene between the bleeding and intravenous injection of adrenalin somewhat reduced the effectiveness of the bleeding.

As to the change in the femoral artery pressure due to bleeding, the pressure was markedly lowered upon removal of 20-30% of the total blood volume, as shown in Fig. 2; the recovery was very slow and the femoral artery pressure was not quickly restored to its initial value. The quicker the bleeding or the larger the amount removed, the greater the degree of the blood pressure fall.

TABLE III EFFECT OF PULMONARY EMBOLISATION PRODUCED BY LYCOPODIUM SPORES (ONE PER CENT SUSPENSION) ON ADRENALIN PULMONARY EDEMA

<i>Dose of Lycopodium (cc)</i>	<i>Number of Cases</i>	<i>Average Body Weight (g)</i>	<i>Mortality (%)</i>	<i>Lung-Body Ratio</i>
Control	10	133	100	2.65 ± 0.28
0.5	10	143	80	2.46 ± 0.61
1.0	7	165	28.6	1.40 ± 0.32

TABLE IV EFFECT OF RAPID BLEEDING OF VARIOUS AMOUNTS OF BLOOD ON ADRENALIN PULMONARY EDEMA

<i>Volume of Blood Withdrawn %</i>	<i>Average cc</i>	<i>Number of Cases</i>	<i>Average Body Weight (g)</i>	<i>Mortality (%)</i>	<i>Lung-Body Ratio</i>
Control		10	112	90	2.27 ± 0.45
5	0.33	5	125	0	1.25 ± 0.26
10	0.65	10	120	0	1.01 ± 0.25
20	1.41	10	131	0	0.92 ± 0.16
30	1.88	5	115	0	0.82 ± 0.18
40	2.43	2	109	100	0.94 ± 0.05
50	2.89	2	104	50	0.78 ± 0.22
60	3.36	2	103	50	0.64 ± 0.08

TABLE V EFFECT OF BLEEDING DONE SLOWLY OR RAPIDLY, OR AT THE VARIOUS PERIOD OF TIME BEFORE ADRENALIN ON ADRENALIN PULMONARY EDEMA. (NOTE) IN ANY CASES TEN PER CENT OF THE ESTIMATED TOTAL BLOOD VOLUME WAS WITHDRAWN

Rapidity of Bleeding	Lapse of Time between Bleeding and Adrenalin Injection	Number of Cases	Average Body Weight (g)	Mortality (%)	Lung-Body Ratio
Control		10	112	90	2.27 ± 0.45
Rapid	10 min.	10	120	0	1.10 ± 0.25
Rapid	2 hrs.	5	138	0	1.14 ± 0.13
Rapid	5 hrs.	5	148	20	1.41 ± 0.39
Slow	10 min.	5	120	0	1.10 ± 0.18

Upon the intravenous injection of adrenalin the femoral artery pressure became elevated with the same markedness as in the control group, except in cases bled rapidly where the blood pressure prior to the adrenalin injection was extremely low. In increment and percentage increase in the blood pressure the group of bleeding exceeded that of control animals, but the duration of the rise was shorter in the bleeding group than in the control group. All these cases showed no obvious signs of pulmonary edema on autopsy.

The change in cardiac rate was analysed in 7 cases where 10 to 30% of the total estimated blood volume was removed rapidly. Immediately after bleeding it was increased slightly in 2 cases, decreased in 2 cases and unchanged in 3 cases; before adrenalin injection it was decreased in 4 cases and unchanged in 3 cases. The injection of adrenalin was followed by outbursts of A-V block, ventricular extrasystoles as it was the case with the control group; there were marked reflex brady-

cardia and arrhythmia. In 7 cases studied the percentage decrease in cardiac rate was $54.6 \pm 6.4\%$ on the average, a value practically the same with that of the control group, $54.2 \pm 6.3\%$ (average of 5 cases). As is shown in Fig. 3 the observed percentage decrease in cardiac rate was independent of the amount of blood loss, although

Fig. 3. Adrenalin bradycardia after the bleeding. L/B: Lung-body ratio.

Fig. 2. Effect of adrenalin on the blood pressure after the rapid bleeding (upper) and the slow bleeding (lower). L/B: Lung-body ratio.

reflex bradycardia subsided earlier and more completely in the bleeding group than in the control group. On autopsy all these animals showed no marked signs of pulmonary edema or hemorrhage.

DISCUSSION

It was shown in this experiment on albino rats that the ligation of a unilateral femoral vein or the pulmonary arteriolar blockade by lycopodium spores prevented the adrenalin pulmonary edema from taking place. Since a common effect of both procedures was that they reduced the amount of blood presented to the pulmonary capillaries, this reduction appears to be responsible for the preventive effect observed. It was shown by Otake²⁾ that the ligation of a femoral vein reduced the venous return both mechanically and reflexly; according to Sakaguchi⁵⁾ and Daley et al.⁶⁾ the lycopodium spores do not pass the pulmonary capillaries but occlude the pulmonary arterioles, a fact which forces us to accept that the preventive effect on pulmonary edema was due to the direct effect of the lycopodium spores blocking the inflow into the pulmonary arterioles. This point was well borne out by the histological examination of pulmonary tissues of the animals in which the pulmonary edema was successfully prevented. Where lycopodium spores markedly obstructed the arterioles, sections of the tissue were completely free from signs of pulmonary edema.

Now that the adrenalin pulmonary edema was successfully prevented by a reduction of the venous return (i. e., reduction in the pulmonary inflow) or by the direct blockade to the inflow at the point of the pulmonary arterioles, it is obvious that the venous return has an important bearing on the genesis of adrenalin pulmonary edema. Next, we must ask how an increase in the venous return over output is brought about. Obviously, if the rate of the left ventricular output equals that of venous return, there should be no increase in venous return over output; that is to say, if the systemic vascular bed serves simply as an inert trough to let the blood through, no relative increase in venous return over output can take place. Where there is actually a

relative increase in venous return, one must accept that the peripheral blood vessel is no longer a passive trough but an active element regulating the venous return. In other words the injection of adrenalin must have acted on the point of the blood-depot mobilization. If this is the true state of affairs it is predictable, and it is indeed the case, that any change causing a reduction in the depot-blood volume acts preventively on the adrenalin pulmonary edema.

Since the depot blood is mobilized by bleeding, as was found by Inō⁷⁾ in this laboratory, the bleeding obviously reduces the amount of available depot-blood. Thus the experiment on bleeding was essentially a test of a thesis: the depot-blood has an active bearing on the incidence of adrenalin pulmonary edema. It was found by this author that the bleeding had a preventive effect on the adrenalin pulmonary edema. It may be concluded from this that the mobilization of the depot-blood by adrenalin is an important trigger of adrenalin pulmonary edema, since a mobilization obviously results in a relative increase in the venous return over output. It appears it is this relative increase in the venous return that drives the left ventricle to pump blood beyond its critical limit as regards the tolerable load, as reported in the previous paper. The fact that the blockade of the venous return resulted in a shortening of the duration of the systemic hypertension in comparison with what was seen in the control group also suggests that this relative increase in the venous return over output was a cause of the sustained elevation of the systemic blood pressure.

SUMMARY

On about 160 albino rats the relationship between the incidence of adrenalin pulmonary edema and venous return was studied and the results were as follows:

- 1) The adrenalin pulmonary edema was prevented from taking place by the following procedures: (a) the ligation of a unilateral femoral vein, (b) blockade of the pulmonary arterioles with lycopodium spores (c) bleed-

ing.

2) This fact indicates that an important trigger of the adrenalin pulmonary edema is a relative increase in the venous return over left ventricular output; the mobilization of the depot-blood is presumably the cause of this relative increase.

3) It was suggested that this relative increase in venous return drives the left heart to pump blood beyond its critical limit as regards the tolerable load, thus leading to the adrenalin pulmonary edema.

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