Effect of Gram-Negative Endotoxin on Pulmonary Circulation

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A B S T R A C T

KUIDA, HIROSHI, LERNER B. HINSHAW, ROBERT P. GILBERT AND MAURICE B. VISSCHER. Effect of Gram-negative endotoxin on pulmonary circulation. Am. J. Physiol. 192(2): 335-344. 1958.—Effects of endotoxin on the pulmonary hemodynamics of dogs and cats have been studied in intact animals, open chest animals with and without control of cardiac output by an extracorporeal venous reservoir—pump system, and in isolated perfused continuously weighed lungs. Pulmonary artery pressure increased without a rise in left atrial pressure in all preparations following the injection of endotoxin. Pulmonary artery wedge and small pulmonary vein pressures uniformly increased. Total pulmonary vascular, pulmonary arterial and pulmonary venous resistances were calculated in five perfused lungs. The absolute increase in pulmonary venous resistance was greater than in the arterial resistance in four of the five studies and was relatively greater in every instance. There was a consistent increase in lung weight associated with these hemodynamic changes. Analysis of the determinants of lung weight changes has provided evidence to support the conclusion that the pulmonary vascular response to endotoxin administration is characterized predominantly by constriction of pulmonary venules and/or small veins.

PHYSIOLOGICAL disturbances produced in animals by endotoxin have been reviewed by Thomas (1). Included among the toxic manifestations are: “respiratory distress indicated by rapid labored breathing and sometimes blood tinged foam at the nostrils.” Pathologic lesions produced by endotoxin in animals have been summarized by Burrows (2). He mentions “foci of edema, congestion and hemorrhage in the lungs.” Respiratory distress with or without cyanosis is also a frequent manifestation in clinical bacteremic shock (3, 4). Despite these descriptive indices suggesting an abnormality in pulmonary circulation and ventilation, studies of the local, regional and general hemodynamic effects of endotoxin have not included experiments on the pulmonary circulation.

During recent endotoxin studies in this laboratory involving perfusion of isolated kidneys with heart-lung preparations, it was incidentally noted that the administration of endotoxin to the kidney frequently had a deleterious effect on ventilation and right ventricular function of the heart-lung preparation. These observations prompted the present study which deals with the nature and extent of the effect of endotoxin on the pulmonary circulation of dogs and cats.

MATERIALS AND METHODS

General. Endotoxin from E. coli bacteria was used exclusively in this study and was prepared as previously described (5). The ‘crude’ form (a saline suspension of killed E. coli cells) was used in the earlier part of the study. Later experiments were made with the ‘purified’ (Boivin) form which appeared to produce identical responses. Adult animals were used exclusively and were anesthetized.
with pentobarbital sodium (30 mg/kg). Donor blood used in the perfusion experiments was collected in plastic beakers containing heparin (5 mg/100 ml blood) as the anticoagulant. Pressures were measured by means of catheters connected directly to Statham strain gauge manometers. Pressures and lung weight were recorded on a Sanborn Polyviso, and mean pressures were obtained by electrical integration.

The following symbols are used throughout the illustrations:

- **Pressures (mean) in millimeters of mercury**
  - PA = pulmonary artery
  - PAw = pulmonary artery wedge
  - LA = left atrium
  - PVw = small pulmonary vein

- **Resistances in P.R.U. (mm Hg/cc/min. or mm Hg/cc/min/100 gm lung weight)**
  - RT = total pulmonary vascular
  - RA = pulmonary arteriolar
  - RV = pulmonary venous

Resistances were calculated according to the formulas:

\[
RT = \frac{PA - LA}{Q} \\
RA = \frac{PA - PAw}{Q} \\
RV = \frac{PAw - LA}{Q}
\]

where \( Q \) = flow

**Experimental Preparations.** The following experimental preparations were utilized in this study.

1. **Intact or open chest animals.** (A). **INTACT ANIMALS.** A radiopaque cardiac catheter was manipulated under fluoroscopic visualization into the left atrium via the left common carotid artery. Two additional catheters were passed into the pulmonary artery wedge position and the main pulmonary artery via the right external jugular vein.

   (B). **OPEN CHEST ANIMALS.** The chest was opened through a longitudinal sternal splitting incision. Artificial respiration was carried out by a constant pressure respirator connected to a tracheal cannula. Polyethylene catheters were placed in: a) the left atrium via the left atrial appendage, b) the pulmonary artery, and c) the pulmonary artery wedge position via the main pulmonary artery.

   Aortic pressure was measured in both groups through a polyethylene catheter inserted into the femoral artery. Lethal doses of endotoxin (15 mg/kg of ‘crude’ or 5 mg/kg of ‘purified’) were injected intravenously.

2. **Controlled cardiac output.** The experimental preparation used to obtain a constant cardiac output in an open-chest animal without bypassing any part of the circulation has been described previously (6). In essence, it consists of draining the cavae through separate canulae (with the azygous vein ligated) into an external venous reservoir and pumping the blood back into the right atrium at a constant rate by means of a constant output pump (Sigmamotor Co., Middleport, N. Y.). Pressures were obtained as in IB, and similar doses of endotoxin were used.

3. **Isolated perfused weighed lung.** The chest of the animal from which the lung was to be obtained was opened under artificial respiration by splitting the sternum longitudinally. Five to ten minutes after the administration of heparin (5 mg/kg), the azygous vein and both venae cavae were ligated, and the heart, lungs and thoracic segments of the aorta and esophagus were removed without interrupting ventilation. The perfusion cannula, which had been filled to its tip with blood, was inserted and tied into the main pulmonary artery. In earlier preparations, the pericardium, both ventricles and the right atrium were dissected off and the left atrium drained at near zero pressure. In later experiments the left atrial pressure was controlled by ligating the ascending aorta and fixing a large glass cannula into the apex of the left ventricle. The opening of the cannula could then be adjusted to obtain the desired hydrostatic level. The lung was placed on a perforated plastic plate which was suspended from one end of the balance beam of a strain gauge weighing device previously described (7). Venous drainage was collected in a funnel under the plastic plate and returned to the arterial reservoir by a second pump. Perfusion was begun usually after an interruption of no longer than 2–3 minutes. The perfusion rate of a particular experiment was determined by gradually increasing the arterial pump to the highest flow rate that did not result in a progressive gain in lung weight.

Thirteen of the perfusions were carried out.
with a pump-oxygenator system (8), and four with a venous reservoir-pump system. The latter consisted simply of collecting the drainage from the lung in a reservoir and pumping it back into the pulmonary artery. When the oxygenator was used, ventilation could either be maintained or discontinued; in its absence, however, ventilation was required to maintain oxygenation.

Pulmonary artery pressure was measured through a needle inserted into tubing and advanced to the tip of the arterial cannula. Left atrial pressure was measured through a catheter inserted directly or via the drainage cannula into the left atrium. Pulmonary artery wedge pressure was measured in five experiments through a no. 7 F cardiac catheter inserted directly into the main pulmonary artery and wedged out in the periphery. Pressure in a small pulmonary vein was measured in seven experiments by passing a fine polyethylene catheter (1.2 mm o.d.) out into a peripheral vein via the left atrium. If this catheter was advanced until it became wedged, a pressure identical to that in the pulmonary artery was recorded, while if it was withdrawn by minute increments, a range of pressures could be obtained between pulmonary arterial and left atrial.

### Table 1. Effect of Endotoxin on Pulmonary Hemodynamics in Animals with Lungs in Situ

<table>
<thead>
<tr>
<th>Exp. No., Species</th>
<th>Control</th>
<th>After endotoxin*</th>
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<tbody>
<tr>
<td></td>
<td>Pressure, mm Hg</td>
<td>Percentage Increase in PA</td>
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<td>PA</td>
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### Group I. Cardiac Inflow uncontrolled

<table>
<thead>
<tr>
<th>Exp. No., Species</th>
<th>Flow, cc/min</th>
<th>Control</th>
<th>After Endotoxin*</th>
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<tbody>
<tr>
<td></td>
<td>Pressure, mm Hg</td>
<td>RT</td>
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#### Group II. Cardiac inflow maintained constant

Total pulmonary vascular resistance in mm Hg/cc/min.

* Data after the administration of endotoxin were taken at the peak of the pulmonary response except for the aortic pressures which were the lowest levels reached.

influence on the wedge pressure of increasing left atrial pressure, or of increasing pulmonary artery pressure by occluding a contralateral branch of the pulmonary artery.

### Results

Experimental data have been divided into three groups on the basis of the experimental preparations. The results in each group will be presented separately.

**Group I. Cardiac Inflow Uncontrolled (5 Dogs, 4 Cats).** Two of the dogs were intact and the remaining animals were open chest preparations. Aortic pressure fell to low levels in all but one cat experiment. Pulmonary artery pressure consistently increased while left atrial pressure remained essentially constant. These
changes are summarized in table I. A distinct difference was noted in the temporal sequence of events between dogs and cats. This difference is demonstrated in figure 1 where it is evident that the fall in aortic pressure in the dog clearly precedes the rise in pulmonary artery pressure, whereas in the cat, systemic hypotension occurs after the pressure in the pulmonary artery has reached a peak. Satisfactory pulmonary artery wedge pressures were obtained in only three of the preparations, but in each instance increased significantly. There was always a delay period between the intravenous injection of endotoxin and the onset of the pulmonary vascular response, despite the fact that the endotoxin reached the lungs within a few seconds. This delay period was quite variable, ranging from 5 to 90 seconds.

Coincident with the pulmonary vascular response, an alteration was noted in the ventilation of the lungs. This was particularly striking in the experiments in which the hemodynamic response was marked. It was characterized by failure of the lungs to collapse during the expiratory phase, and with a diminished tidal exchange when using a constant pressure respirator. It was frequently necessary to increase the pressure of the respirator by several centimeters of water to achieve adequate ventilation. The use of a constant volume (Starling) respirator in one case was associated with a marked increase (100%) in inspiratory intratracheal pressure, and therefore, in airway resistance.

Group II. Controlled Cardiac Inflow (5 Dogs, 1 Cat). The increases in pulmonary artery pressure in these animals were similar to those in group I. Since the flow rates used in these studies were below the physiologic range, quantitative comparison of the groups is difficult. However, with a known and constant flow, it is possible to calculate the increase in pulmonary vascular resistance following the injection of endotoxin. The absolute increments in pressures and resistances are presented in table I. The relative increase in resistance averaged 165% of control values (range 79–260%). Shock did not develop in these animals because cardiac output was artificially maintained.

Group III. Perfused Isolated Weighed Lung (11 Dog Lung and 6 Cat Lung Perfusions). The flow rates used to perfuse the isolated lungs were also below the normal range, but the control pulmonary artery pressures were reasonably physiological, ranging
from 11.5 to 23 mm Hg (average 16). There was, however, a wide variation in control resistances ranging from 0.014 to 0.123 mm Hg/cc/min/100 gm lung in dog lungs and 0.070-0.215 in cat lungs. Whether or not the lungs were ventilated had no effect on the pulmonary vascular response to endotoxin.

The record of an experiment in which a satisfactory pulmonary artery wedge pressure was obtained is shown in figure 2. The typical response to the injection of endotoxin was characterized by a delay period following which there was a progressive increase in both pulmonary artery and pulmonary artery wedge pressure and a concomitant gain in lung weight. The most dramatic changes were noted in a cat lung in which the pulmonary artery pressure rose to 200 mm Hg and the lung gained 130 gm in weight. Excluding this one exceptional result, the gain in lung weight averaged 8% of the weight of the lung (drained of blood) at the termination of the experiment with a range of 0% (in one cat lung) to 23%. Small pulmonary vein pressure regularly increased in the seven experiments in which it was measured. Left atrial pressure could not change in these experiments because of drainage at a constant hydrostatic level and a constant blood flow rate.

Calculated total and segmental control resistances and those at the peak of the endotoxin response in the experiments with wedge pressure measurements are presented in figure 3. The increase in total resistance averaged 91% of control values, and is the result of increments in both arteriolar and venous components except in one case in which the arteriolar resistance decreased 6%. The absolute increase in arteriolar resistance was somewhat greater than in venous resistance in only one of the five experiments. The relative increase in venous resistance, however, was consistently greater, averaging 197% compared with an average increase of 43% in arteriolar resistance.

DISCUSSION

The characteristic pulmonary hypertension that develops as a response to the administration of endotoxin in intact or open chest animals (group I) although variable in magnitude is usually moderate, and does not appear to be the usual major factor in producing fatal shock in dogs. In our total experience with the administration of endotoxin to the dog, severe pulmonary hypertension accompanied by gross pulmonary edema, right heart failure and sudden death has been exceedingly rare. On the other hand, in cats such manifestations occur within a few minutes after endotoxin injection. There is a possible explanation for this species difference.

It was demonstrated in a previous study in this laboratory (6) that systemic hypotension in dogs produced by endotoxin is largely a consequence of a reduction in cardiac output, as total peripheral resistance does not change significantly. It was further demonstrated that the decreased cardiac flow was due to a diminution of venous return resulting from pooling of blood in the hepatic and portal beds. The observation of a considerable lag between the fall in aortic pressure and the rise in pulmonary artery pressure in the dog indicates that pulmonary blood flow is already reduced by the time the pulmonary response occurs. This would serve as a ‘protective’ mechanism as far as the lungs are concerned, preventing potentially greater pulmonary hypertension. That such a mechanism does not operate in the cat has been demonstrated in a separate study (manuscript in preparation) wherein the amount of early vascular pooling in the liver...
and gut of cats was found to be far less than that which occurs in dogs. Thus if cardiac output of the cat is less affected by endotoxin, the difference in the temporal relationships (fig. 1) and the greater incidence of gross pulmonary edema may be explained. On this basis the pulmonary response assumes a much more significant role in the over-all picture of endotoxin shock in the cat.

The pulmonary arterial pressure rise in the intact animal is suggestive of an increase in resistance to flow through the pulmonary bed. By maintaining constancy of cardiac filling rate, as in the experiments in group II, it became possible to quantitate the change in total pulmonary vascular resistance. The measurements show that in five dogs the average values increased by 158% at the peak of the pulmonary response. An effect of such magnitude is obviously not negligible, even though it may be masked by other actions in the intact dog. It is not known whether man resembles the cat or the dog in regard to visceral pooling with agents having effects like bacterial endotoxin. However, the occurrence of pulmonary symptoms in some types of anaphylactoid reactions suggests that lung circulation changes deserve investigation in such states.

**Hemodynamic Mechanism of the Increase in Pulmonary Resistance.** The increase in total pulmonary vascular resistance observed in the constant cardiac output experiments could be the result of an increase in arterial resistance resulting from constriction of the pulmonary arterioles. This could not, however, explain the observation of the development of gross pulmonary edema in some animals following the administration of endotoxin. Such a phenomenon is explicable, according to current views as to the main determinants of lung edema formation (9), only by a disturbance of the hydrostatic-osmotic pressure relationships in the pulmonary capillaries or by an increase in capillary membrane permeability to protein.
Assuming that no change occurs in the osmotic pressure of the perfusate under the conditions of these experiments, edema would have to be due to either an increase in hydrostatic pressure or in capillary permeability. The fact that left atrial pressure remained essentially constant in all experiments effectively eliminates the possibility that left ventricular failure could be a factor in increasing capillary hydrostatic pressure, but does not rule out the possibility that it could be due to pulmonary venous constriction. To assess this possibility, it was of importance to estimate changes in pulmonary capillary pressure.

Pulmonary artery wedge pressure affords the closest available approximation to pulmonary capillary pressure, and was therefore measured in the isolated perfused lung experiments (fig. 3). Supporting information was obtained in numerous measurements of pressures in small pulmonary veins (<2 mm bore) which invariably showed a rise after administration of endotoxin, indicating an increase in resistance to flow in the veins of intermediate bore. This observation is considered to be of importance in showing that the artery wedge pressure changes were due to venous segment resistance alterations and not to artifacts. The additional observation that the pressure in the larger pulmonary veins did not change while large alterations occurred in the smaller veins indicates that the constriction is more or less localized in the region of the venules and small veins. Although the responses in the several experiments were variable in magnitude, the results show that on the average calculated pulmonary venous resistance accounted for a greater portion of the increase in total resistance than did arterial resistance. The moment-to-moment changes in pressures, lung weight and calculated resistances in two experiments are plotted in figure 4. It is evident that in both experi-

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**Fig. 4. Lower panel: replot of records of PA, PA, and LA pressures in two isolated perfused lung experiments. Abscissa, time in minutes. 5 mg of endotoxin was injected at zero time. Middle panel: observed changes in lung weight. The weight of the trimmed lung drained of blood is given. Upper panel: moment-to-moment changes in calculated resistances \( R_T \), \( R_A \) and \( R_V \) expressed in mm Hg/cc/min/100 gm lung weight showing the predominant increase in venous resistance in both experiments. The flow rate used in each experiment is given.**
ments the increase in venous resistance was absolutely and relatively greater than in arterial resistance.

It must be pointed out, however, that a lack of change in calculated arterial resistance as shown in figure 4 cannot be construed as proof of an absence of a change in arterial vasomotor tone. Haddy and Campbell (10), and Borst et al. (11) have shown in different types of experiments that passive increases in capillary pressure brought about by increasing left atrial pressure or by changing airway resistance are associated with a decrease in calculated total pulmonary vascular resistance. This effect was substantiated in the present studies by the simple experiment of increasing the hydrostatic level of left atrial drainage. Calculated total, arterial, and venous resistances all decreased. The important thing to note is that in the absence of a change in vascular tone, arterial resistance actually decreases as a response to an increased distending pressure. In view of these considerations, if the response to endotoxin was exclusively one of venous constriction, all other changes being passive, the calculated arterial resistance should decrease. The fact that it even remains constant, therefore, must be taken as evidence of an increase in arterial vascular tone. Thus it must be concluded that the hemodynamic response to endotoxin is characterized by both arterial and venular and/or small vein constriction, but that the venous component usually predominates. It may be noted that the effects herein reported occurred in the passively collapsed lung as well as when the lung was ventilated by periodic positive pressure inflation. This point may be important in eliminating the possibility that the vascular effect might be due to a remote influence of bronchoconstriction since moderate bronchoconstriction can alter intra-alveolar pressure only in the ventilated lung. Furthermore, it may be pointed out that increased intra-alveolar pressure would be expected to raise arterial segment rather than venous segment resistance.

Mechanism and Significance of Lung Weight Changes. The gain in lung weight which uniformly occurs following the injection of endotoxin can be due to an increase in intravascular volume, to an increase in extravascular fluid resulting from filtration, or to a combination of both factors. Furthermore, intravascular volume expansion could occur at any or all segments of the pulmonary vascular bed. Visscher, Haddy and Stephens (9) have pointed out that of the various immediate determinants in the genesis of pulmonary edema, pulmonary capillary pressure is probably the most generally important. They listed the direct determinants which produce an increase in capillary pressure (assuming a change in only one variable at a time): pulmonary arteriolar dilatation, pulmonary venular constriction, and increase in left atrial pressure. The hemodynamic evidence in the present studies of pulmonary venular constriction thus provides a basis for the development of lung edema. However, it also offers a mechanism for an increase in intravascular volume of vessels proximal to the constriction, particularly of the capillaries. The fact that arterial constriction of variable magnitude is occurring concomitantly obviously complicates the analysis of changes in segmental volumes.

The weight of the lung is a composite of the sum of weights of the tissue cells, the blood in the arteries (Bₐ), capillaries (Bₐ) and veins (Bᵥ), the extracellular tissue fluid (TF), and extravasated blood (Bₑ). The tissue cell component can probably be assumed to be constant over the times of our experiments, consequently changes may be assumed to be due to alterations in blood volume in the above four blood compartments, and in tissue fluid.

\[
\Delta W = \Delta B_a + \Delta B_v + \Delta B_v + \Delta B_e + \Delta TF \quad (i)
\]

Bₐ, Bᵥ, and Bₑ will be determined by the intravascular pressures and the elasticity characters of the several compartments at any time. Bₑ and TF will depend upon time rates of accumulation or removal of fluid in the relevant compartments. If there is an increase in venous segment resistance it can be expected that both Bₑ and TF will increase, because in a constant flow situation the pressure in the capillaries will rise. This will result in a rise in the arterial segment pressures and therefore a distention of arterial vessels, if there were no simultaneous change in arterial segment elasticity. Actually the measurements following endotoxin administration indicate either no change or a rise in arterial segment resistance, which is incompatible with the assumption of no change in
arterial segment elasticity. The resistance would fall with increased pressure due to vessel diameter increase with elevated intraluminal pressure. The changes in $B_a$ can be expected to depend upon changes in the capillary pressure ($P_c$). Assuming that capillaries have a volume that is linearly related to pressure one can say that $\Delta B_a = k \Delta P_c$, where $k$ is a vessel volume elasticity coefficient. One can then ascertain what proportion of the total weight change ($\Delta W$) could be due to changes in $P_c$ following endotoxin administration.

In Figure 4A one notes that with an increase in $P_A w$ (which is for this purpose assumed to equal or be directly related to $P_c$) of 11 mm Hg, there is an increase of 39 gm in the weight of the lungs at 4 minutes after endotoxin. Thus the approximate volume elasticity coefficient factor for the capillary bed in this lung is 3.5 cc/mm Hg, if the foregoing assumptions are valid. Since the volume of the capillary bed is not known, further refinements in calculations are not warranted. This is obviously a minimum value for $\Delta B_a$ because it is scarcely conceivable that $B_a$ and $B_v$ did not fall, since decreases in vessel bore are the mechanisms producing increases in $R_a$ and $R_v$.

It is to be noted, however, that the $P_A w$ ($P_c$) falls much more with time after reaching a maximum. This can only be interpreted, on the basis of the present reasoning, that as time progresses factors other than $B_c$ in equation 1 enter into the process. Very likely TF is the major additional factor, although $B_p$ is not ruled out, nor are further changes in $B_a$ and $B_v$. With the fall from their maxima in the values for $R_a$ and $R_v$, it is to be expected that $B_a$ and $B_v$ would rise.

This type of calculation has been made for each experiment with endotoxin and also with some other agents which result in lung weight changes associated with hemodynamic alterations. In each case so far tested the qualitative results are in harmony with the conclusion that any agents which raise $R_a$ increase lung weight, and vice versa. Furthermore, when $R_a$ rises without a rise in $R_v$, the lung weight falls, as it should be expected to do from a decrease in arterial segment volume (12).

The demonstration of the capacity of the pulmonary venous system to participate in hemodynamic reactions under appropriate stim-

ul-i is not unique to this investigation. Previous studies in this field have been made by Smith (13), Hall (14), and Nisell (15). A recent report by Aviado and Schmidt (16) on the pathogenesis of alloxan induced pulmonary edema deserves particular mention. Based on evidence provided by continuous recording of perfusion reservoir volume and of radiation to the lung surface from $P^32$-tagged red cells, the authors were able to deduce that alloxan caused an initial increase in arterial segment resistance followed subsequently by venous constriction which resulted eventually in lung edema. Our conclusions with regard to the response of the pulmonary veins based on somewhat more direct evidence are, therefore, similar to theirs.

**Mechanisms of the Effect of Endotoxin on Pulmonary Vessels.** The fundamental mechanism by which endotoxin exerts its effect on the vessels of the lung remains unknown. Evidence has been accumulated, however, which sheds some light on this problem.

The consistent delay in all experiments between the first circulation of endotoxin through the lung and the onset of the pulmonary response suggests that the effect may not be produced by endotoxin itself acting directly upon the smooth muscle, but rather through the liberation of some agent or agents in the blood. It may be noted that when blood substitutes such as dextran or gelatin solution are substituted for blood as the perfusate endotoxin does not produce a response in the isolated lung (manuscript in preparation). These studies also argue against a direct effect of endotoxin on capillary permeability. The increase in airway resistance (bronchoconstriction) which occurs concomitantly with the pulmonary vascular response suggests that the intermediary substance or substances have generalized smooth muscle activity. The qualitative effects of histamine (12) and large doses of serotonin are similar to those of endotoxin. However, it is unlikely that histamine release can account for the actions of endotoxin, at least in the absence of other processes. The release of an amount of histamine sufficient to produce the pulmonary response would be expected to produce a marked reduction in systemic peripheral resistance. The fact that this has not been observed (6) means either that histamine is not involved, or that if it is, its effects on the systemic arteries are
neutralized by a pressor substance. We have also made an isolated observation in a perfused lung wherein after repeated administration of smaller doses a 500-μg dose of histamine failed to elicit a pulmonary response and yet a subsequent standard dose of endotoxin produced significant alterations in vascular resistance.

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REFERENCES