Effect of Alpha and Beta Adrenergic Blockade on Epinephrine Induced Pulmonary Insufficiency

J. L. BERK, M.D.,* J. F. HAGEN, B.A.,† R. KOO, M.A.†

From the Department of Surgery, Case Western Reserve University School of Medicine and the Mt. Sinai Hospital of Cleveland, Ohio

Recent studies demonstrated that epinephrine causes significant pulmonary A-V shunting. This study reports the effect of alpha and beta adrenergic blockade on this shunting. Sixty-three anesthetized mongrel dogs were ventilated with a mechanical respirator. Measurements of (1) the pulmonary shunt, (2) cardiac output, (3) mean pulmonary artery, pulmonary capillary wedge and systemic pressures, and (4) pulmonary and systemic vascular resistances were obtained at 5, 15 and 30 minute intervals during the first hour and hourly for 5 hours. Fifteen dogs received no treatment. All others received epinephrine hydrochloride, 2 μg/kg/min for 5 hours. Ten received epinephrine only. Ten were pretreated with propranolol hydrochloride, 250 μg/kg, 12 with phenoxybenzamine, 1 mg/kg, and 16 with phenoxybenzamine and propranolol. Propranolol significantly decreased the epinephrine induced pulmonary shunt at all times and was the most effective drug. Phenoxybenzamine decreased the early shunting, but less than propranolol, and did not decrease the late shunting. Blockade with propranolol and phenoxybenzamine was less effective than propranolol alone. Based on the observed hemodynamic changes it was suggested that beta blockade is effective in reducing epinephrine induced pulmonary insufficiency by favorably altering the flow and distribution of pulmonary blood flow which in turn decreases epinephrine induced ventilation-perfusion inequalities and capillary hypertension both of which result in shunting. Conversely phenoxybenzamine has an unfavorable effect on the pulmonary flow. These studies support previous work in animals and man which showed that beta adrenergic stimulation is important in the pathogenesis of pulmonary insufficiency. Because the amounts of epinephrine used produce blood levels observed in critical illness, these studies add support to a relationship between the increased catecholamine stimulation of critical illness and the associated and often unexplained pulmonary insufficiency.

FOR MORE THAN 75 years the catecholamines have been known to have powerful effects on the heart and systemic circulation, but were thought to have little direct effect on the pulmonary circulation. Most observers believe that pulmonary vasoconstriction can be demonstrated only in special animal preparations, and in the intact animal and man, the increased pulmonary artery pressure and resistance are predominantly, if not exclusively, the result of passive back pressure from the left heart and systemic circulation. Contrary to this view, the authors demonstrated in dogs that an intravenous infusion of epinephrine in amounts that can be produced endogenously in critical illness in man and animals[8-10,12,15,17-19,21] causes significant pulmonary A-V shunting due to a direct effect on the pulmonary microcirculation.[1] These findings added support to a relationship between the increased catecholamine stimulation of critical illness and the associated but often unexplained pulmonary insufficiency.[2-7,11,16,20]

The purpose of this study is to determine the effects of alpha and beta adrenergic blockade on epinephrine induced pulmonary insufficiency.

Methods

Sixty-three healthy, mongrel dogs weighing 15 to 20 kg were fed the afternoon before and permitted water ad lib until the time of surgery and were anesthetized with intravenous pentobarbital sodium, 30 mg/kg. Ventilation was accomplished through a cuffed endotracheal tube by a mechanical ventilator. Oxygenation and ventilation were satisfactory in the supine position in the control group and this position was therefore used in all groups. The animals were sighed every 20 minutes and suctioned as necessary. Non-occlusive catheters were placed in the femoral vein and the aorta, and a Swan-Ganz flow-

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* Professor of Surgery, Case Western Reserve University, School of Medicine, Director of Surgery, Mt. Sinai Hospital, Cleveland, Ohio.

† Research Associates, Department of Surgery, Mt. Sinai Hospital, Cleveland, Ohio.

TABLE 1. *Dose & infusion time of drugs given to each group*

Group	No. Dogs	Drugs		Infusion Volume	Infusion Time
1	15	no treatment			
2	10	epinephrine hydrochloride	2 μg/kg/min	6 ml/kg	5 hr
3	10	propranolol hydrochloride	250 μg/kg	1 ml/kg	15 min
		epinephrine	2 μg/kg/min	6 ml/kg	5 hr
4	12	phenoxybenzamine	1 mg/kg	1 ml/kg	30 min
		epinephrine	2 μg/kg/min	6 ml/kg	5 hr
5	16	phenoxybenzamine	1 mg/kg	1 ml/kg	30 min
		propranolol	250 μg/kg	1 ml/kg	15 min
		epinephrine	2 μg/kg/min	6 ml/kg	5 hr

directed catheter was inserted into a foreleg vein and passed into the pulmonary artery, the location being determined by the oscilloscopic pressure tracing. Pulmonary and systemic pressures were measured by strain gauge manometers and continuously recorded. The zero point of the manometers was set at one half the anterior-posterior diameter of the chest at the fourth interspace. The pulmonary wedge pressure was obtained with the balloon inflated. Cardiac outputs were determined with a densitometer and computer by the dye dilution method using indocyanine green. Simultaneous samples of blood were withdrawn from the pulmonary artery and aorta during at least 4 respiratory cycles. Blood was analyzed for oxygen and carbon dioxide tensions, and pH by the Clark, Severinghaus and pH electrodes, respectively, at 37 C. Hemoglobin concentrations were measured by the cyanmethemoglobin method. Expired gases were collected in a Douglas bag for 5 minute periods and the oxygen and carbon dioxide fractions determined. Oxygen consumption and carbon dioxide production were calculated by the expired gas method and the respiratory quotient was determined. All dogs received intravenous Ouabain, 12.5 μg/kg in divided doses to prevent decreased myocardial contractility and left ventricular failure caused by propranolol.[3,4]

The dogs were randomly divided into 5 groups as indicated in Table 1. Drugs were diluted in normal saline and given by vein using an infusion pump. Group 1 dogs received no drugs. In group 2 epinephrine was infused for 5 hours. In group 3 propranolol was given, steady state values obtained, and epinephrine was begun. In group 4 phenoxybenzamine was infused, steady state values obtained, and epinephrine was begun. In group 5 following the phenoxybenzamine infusion, propranolol was given, steady state values obtained, epinephrine was begun. Measurements were made at 5, 15 and 30 minutes and hourly for 5 hours and included cardiac output and mean pulmonary artery, pulmonary wedge and systemic pressures; P_{O_2}, P_{CO_2}, pH and hemoglobin concentrations of mixed venous and arterial blood. The shunt fraction and pulmonary and systemic resistances were calculated as follows:

The pulmonary arteriovenous shunt was determined by the equation:

$$\frac{\dot{Q}s}{\dot{Q}} \times 100 = \frac{CcO_2 - CaO_2}{CcO_2 - C\bar{v}O_2}$$

where

$\dot{Q}$ = Total pulmonary blood flow
$\dot{Q}s$ = Fraction of pulmonary blood unexposed to alveolar membranes
CaO_2 = Arterial oxygen content (Vol % STPD)
$C\bar{v}O_2$ = Mixed venous oxygen content (Vol % STPD)
CcO_2 = Pulmonary capillary oxygen content (Vol % STPD)

Oxygen content was calculated from the equation:

$$CO_2 = SO_2(1.36 \times Hb) + 0.0031 \times P_{O_2}$$

where

CO_2 = oxygen content (Vol % STPD)
SO_2 = % saturation of hemoglobin
Hb = Hemoglobin concentration (GM %)
P_{O_2} = Partial pressure of oxygen (mm Hg)

The mean alveolar oxygen tension was calculated from the alveolar gas equation:

$$P_{A_{O_2}} = P_{I_{O_2}} - P_{aCO_2}\left(F_{I_{O_2}} + \frac{1 - F_{I_{O_2}}}{R} \right)$$

where

$P_{A_{O_2}}$ = mean alveolar oxygen tension (mm Hg)
$P_{I_{O_2}}$ = moist inspired oxygen tension (mm Hg)
P_{aCO_2} = arterial carbon dioxide tension (mm Hg)
$F_{I_{O_2}}$ = fraction inspired oxygen
R = respiratory quotient

The hemoglobin saturation was determined from standard tables after correcting the P_{O_2} for pH and buffer base.[13]

The calculated arterial and venous oxygen contents were checked periodically by the manometric method of Van Slyke. The pulmonary capillary oxygen content was assumed to be that which the arterial blood would have had if fully equilibrated with mean alveolar gas.

Pulmonary Vascular Resistance

$$PVR = \left(\frac{PAP - PCWP}{CO} \right) 79.9$$

where

PVR = Pulmonary Vascular Resistance (dyne·sec·cm^{-5})
PAP = mean pulmonary artery pressure (mm Hg)
PCWP = mean pulmonary capillary wedge pressure (mm Hg)
CO = cardiac output (L/min)

Systemic Vascular Resistance

$$SVR = \left(\frac{SAP - CVP}{CO} \right) 79.9$$

where

SVR = systemic vascular resistance (dyne·sec·cm^{-5})
SAP = mean systemic arterial pressure (mm Hg)
CVP = central venous pressure (mm Hg)
CO = cardiac output (L/min)

Statistical analyses were by the *t*-test and Duncan's multiple range test.

Results

The mean values of all groups for the parameters described below, together with the standard error of the mean and statistically significant changes, are listed in Tables 2–7.

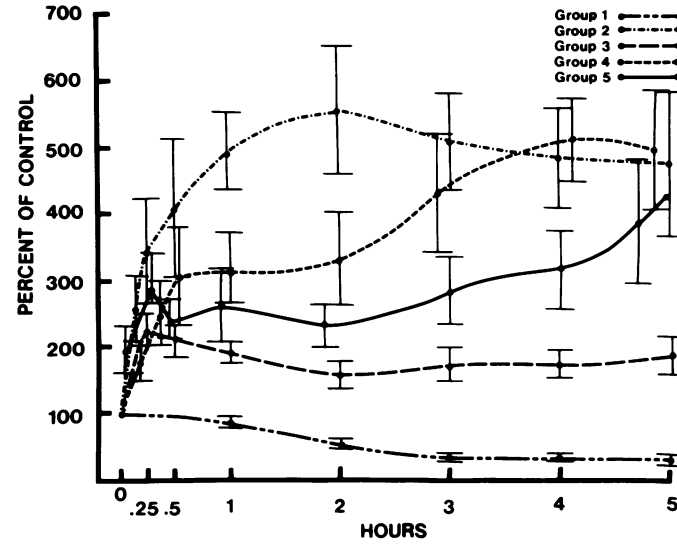

FIG. 1. Comparison of mean per cent of control changes of the pulmonary shunt of groups 1–5. Vertical lines represent SEM.

Pulmonary shunt: (Table 2) In groups 3 and 5 during the baseline period, the shunt decreased significantly* after propranolol, and these values were significantly lower than the control shunts in groups 1, 2 and 4. Statistical comparisons of the per cent of control values of the shunt among the 5 groups (Fig. 1) were as follows: Group 1 was significantly different from groups 2, 3, 4 and 5 for 5 hours. Group 2 was significantly different from group 3 for all 5 hours; from group 4 at 1 and 2 hours; and from group 5 at 1, 2, 3 and 4 hours. Group 3 was significantly different from group 4 at 1, 2, 3, 4 and 5 hours;

* The word "significant" as used in describing the results means a statistically significant difference, $P < 0.025$.

TABLE 2. *% Shunt* $\left(\frac{\dot{Q}s}{\dot{Q}} \times 100 \right)$

Group	N	Control	Minutes			Hours				
			5	15	30	1	2	3	4	5
1	15	10.0 ± 1.2				8.6 ± 1.5	5.1* ± 1.1	4.1* ± 1.1	3.3* ± 0.7	2.7* ± 0.8
2	10	8.8 ± 1.8	16.7* ± 2.5	21.2* ± 2.8	22.0* ± 2.0	36.4* ± 3.6	37.7* ± 3.6	36.8* ± 4.2	35.0* ± 4.2	33.5* ± 5.8
3	10	5.3 ± 0.5	9.3* ± 1.5	11.3* ± 1.4	10.6* ± 1.4	10.3* ± 1.3	8.0* ± 1.0	8.3* ± 1.2	9.2* ± 1.0	10.5* ± 1.5
4	12	8.8 ± 0.9	14.8* ± 2.2	19.1* ± 2.7	22.5* ± 3.3	23.4* ± 3.0	24.1* ± 3.2	30.7* ± 4.7	34.1* ± 5.6	33.0* ± 5.4
5	16	5.7 ± 0.6	9.7* ± 1.3	12.2* ± 1.3	11.7* ± 1.4	11.2* ± 1.3	11.4* ± 1.9	14.3* ± 3.4	12.0* ± 2.1	15.8* ± 3.5

* Statistically significant change from control, $P < 0.025$.

TABLE 3. *Cardiac Output (ml/kg)*

Group	N	Control	Minutes			Hours				
			5	15	30	1	2	3	4	5
1	15	223.6 ± 26.5				174.0 ± 19.2	129.8* ± 14.7	106.0* ± 9.9	96.0* ± 8.8	87.0* ± 9.3
2	10	151.6 ± 14.4	215.2* ± 17.6	236.5* ± 17.8	245.4* ± 16.2	240.5* ± 19.0	212.3* ± 11.4	136.5* ± 15.1	113.6* ± 10.0	96.9* ± 10.9
3	10	128.2 ± 12.5	144.7 ± 14.6	172.4* ± 17.2	138.0 ± 15.0	116.8 ± 11.8	71.1* ± 7.4	53.5* ± 3.6	55.0* ± 5.9	51.8* ± 7.5
4	12	158.0 ± 12.9	235.9* ± 19.9	274.7* ± 29.0	272.5* ± 33.1	242.4* ± 24.5	234.8* ± 15.2	232.7* ± 16.5	251.5* ± 21.3	226.8* ± 20.5
5	16	111.0 ± 6.0	174.8* ± 11.7	210.8* ± 16.7	208.5* ± 14.2	180.1* ± 10.2	157.2* ± 14.9	150.7* ± 11.0	150.2* ± 14.3	157.4* ± 19.5

* Statistically significant change from control, $P < 0.025$.

and from group 5 at 4 and 5 hours. Groups 4 and 5 were not significantly different for 5 hours.

Cardiac Output (Table 3): In groups 3 and 5 the cardiac outputs decreased significantly after propranolol and were then less than the control cardiac outputs in groups 1, 2 and 4, with a significant difference between groups 1 and 3; and groups 1, 2, 4 and 5. A statistical comparison of the per cent of control values of the cardiac output among all groups (Fig. 2) showed that groups 1 and 3 were not significantly different for the entire period and that both were significantly less than groups 4 and 5 for the entire period and group 2 for the first 2 hours. There was no significant difference between groups 2, 4 and 5 during the first 2 hours, but thereafter groups 4 and 5 remained elevated and were not significantly different from each other but were significantly different from group 2 which gradually decreased becoming not significantly different from groups 1 and 3 at 4 and 5 hours.

Mean Pulmonary Pressure (Table 4): A statistical comparison of the per cent of control values (Fig. 3) showed group 2 to be significantly elevated above all groups for the entire period. There were no significant differences among the other groups.

Mean Pulmonary Artery Wedge Pressure (Table 5): In all groups there were either no significant changes or a fall in the wedge pressure except in group 3 at 5 and 15 minutes and in group 5 at 5 minutes when there were significant increases. It should be noted that many raw values were low or negative. This was attributed to the method of setting the zero point of the manometer in mongrel dogs with varying chest shapes. The changes are accurate and valid for determining resistance, but per cent of control changes are not meaningful and were not calculated.

Pulmonary Vascular Resistance (Table 6): The control resistance in group 3 was higher than that of groups 1, 2, 4 and 5 all significant except group 5.

A statistical comparison of the per cent of control values showed that group 1 was significantly less than group 2 at 4 and 5 hours; significantly less than group 3 at 1, 2 and 4 hours; and significantly greater than groups 4 and 5 at 5 hours. Group 2 was less (not significant) than group 3 at 1,

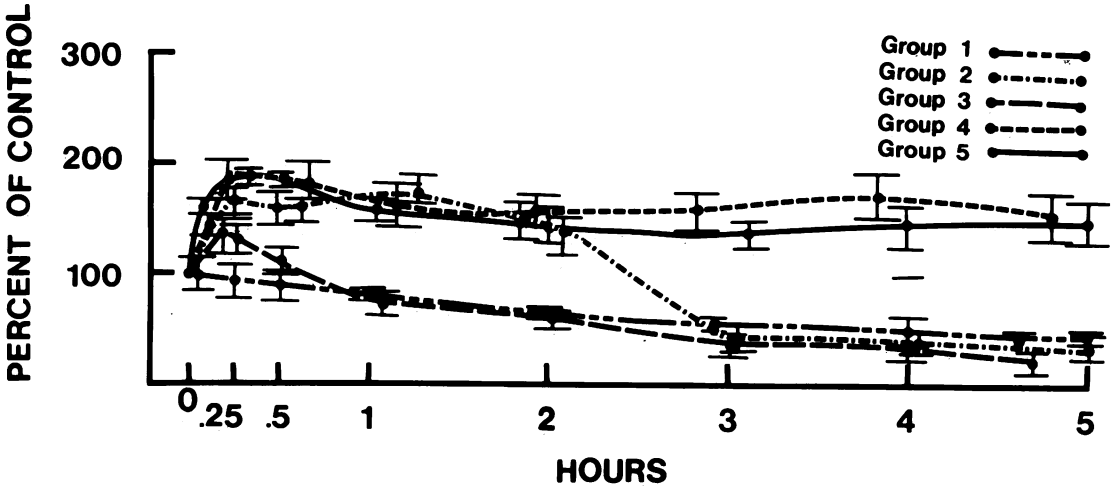

FIG. 2. Comparison of mean per cent of control changes of the cardiac output of groups 1–5. Vertical lines represent SEM.

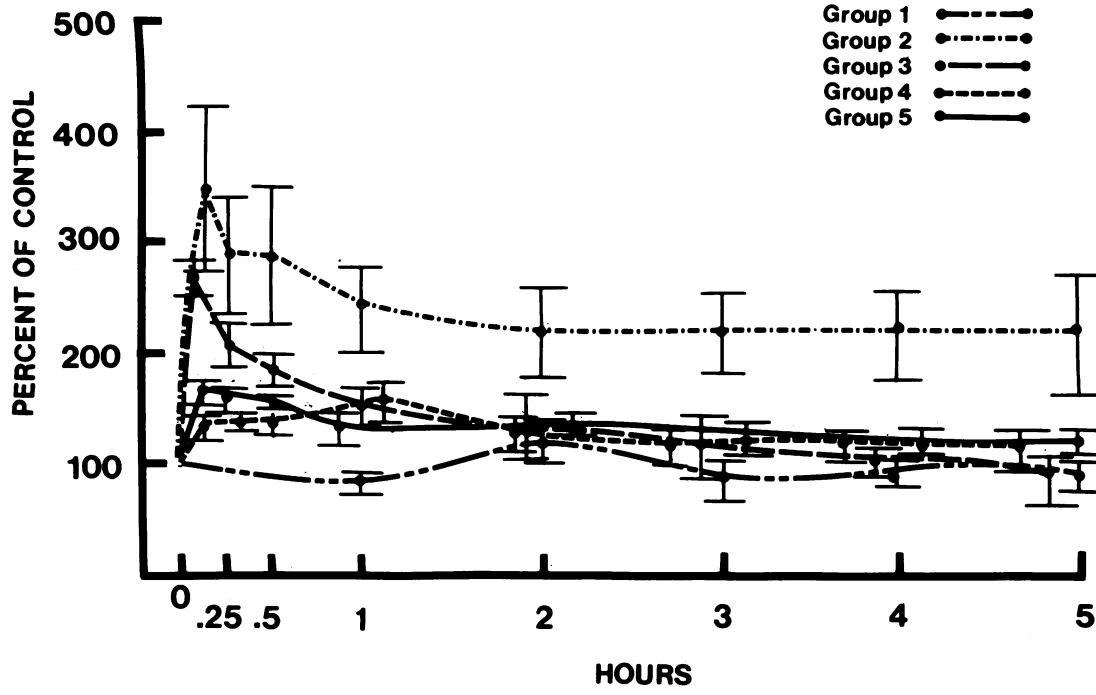

FIG. 3. Comparison of mean per cent of control changes of the pulmonary artery pressure of groups 1–5. Vertical lines represent SEM.

2 and 3 hours; was significantly greater than group 3 at 4 and 5 hours; and was significantly greater than groups 4 and 5 at 2, 3, 4 and 5 hours. Group 3 was significantly greater than groups 4 and 5 at all times. There was no significant difference between groups 4 and 5 (Fig. 4).

Systemic Vascular Resistance (Table 7): The control value of the resistance in group 3 was significantly higher than the other groups. A statistical comparison of the per cent of control values (Fig. 5) showed group 1 to be significantly greater than groups 4 and 5 at all times; greater than group 2 at all times, significant at 1 hour; and less than group 3 at all times, significant at 2 and 3 hours. Group 3 was significantly greater than groups 2, 4 and 5 at all times and groups 4 and 5 were not significantly different from each other at any time.

Discussion

Previous studies demonstrated that epinephrine in physiological amounts causes significant pulmonary arteriovenous shunting.[1] Based on sequential hemodynamic and pathological findings, the authors suggested that epinephrine causes a non-uniform change in the pre-capillary resistance with vasoconstriction in some areas and vasodilatation in others, resulting in a redistribution of the increased pulmonary blood flow, which in turn causes ventilation-perfusion inequalities and shunting. That vasoconstriction can occur in some areas of the lung and vasodilatation in others is supported by the work of Lehr[14] who noted a remarkable redistribution of the pulmonary blood flow in rabbits with vasoconstriction in some areas

TABLE 4. *Mean Pulmonary Artery Pressure (mm Hg)*

Group	N	Control	Minutes			Hours				
			5	15	30	1	2	3	4	5
1	6	10.3 ± 2.2				8.0 ± 1.0	8.2 ± 1.1	7.5 ± 1.2	6.6 ± 1.2	7.5 ± 0.7
2	10	7.7 ± 1.4	18.5* ± 0.8	16.3* ± 1.1	14.0* ± 1.8	13.8* ± 0.7	13.0* ± 1.1	13.2* ± 1.0	12.4* ± 1.0	12.3* ± 1.3
3	9	9.5 ± 0.6	25.2* ± 2.3	18.3* ± 1.8	16.3* ± 1.7	13.4* ± 1.9	11.7 ± 2.0	9.9 ± 1.9	9.8 ± 1.2	8.2 ± 1.8
4	12	9.2 ± 0.8	12.3* ± 1.2	12.8* ± 1.3	12.5* ± 1.3	11.9* ± 1.0	11.2 ± 1.0	9.9 ± 1.1	10.3 ± 1.1	10.0 ± 1.3
5	16	7.3 ± 0.6	11.2* ± 1.0	10.8* ± 0.9	11.1* ± 0.8	9.8* ± 0.8	9.9* ± 0.9	8.9 ± 1.0	8.7 ± 1.0	7.4 ± 0.9

* Statistically significant change from control, $P < 0.025$.

TABLE 5. *Pulmonary Artery Wedge Pressure (mm Hg)*

Group	N	Control	Minutes			Hours				
			5	15	30	1	2	3	4	5
1	15	1.50 ± 1.92				−1.0 ± 0.87	−1.42 ± 0.93	−1.33 ± 1.54	−2.25 ± 1.60	−2.32 ± 1.85
2	10	−1.20 ± 0.68	1.80 ± 1.90	0.30 ± 1.40	−2.31 ± 0.89	−2.00 ± 0.95	−2.00 ± 0.50	−2.80 ± 0.47	−3.00 ± 1.07	−3.81* ± 0.53
3	10	1.38 ± 0.68	15.69* ± 3.37	6.31* ± 1.70	5.50 ± 2.32	0.11 ± 1.17	−1.13* ± 1.15	−1.13* ± 1.39	−2.36* ± 1.84	−4.33* ± 1.17
4	12	0.63 ± 0.52	1.50 ± 0.88	0.14 ± 0.82	0.67 ± 0.79	−0.25 ± 0.65	−1.55* ± 0.09	−3.10* ± 0.82	−3.06* ± 0.90	−3.56* ± 1.35
5	16	0.20 ± 0.63	2.10* ± 0.84	1.02 ± 0.75	0.69 ± 0.89	−0.30 ± 0.66	−1.19 ± 0.70	−2.53 ± 0.54	−2.53* ± 0.85	−2.50* ± 1.15

* Statistically significant change from control, $P < 0.025$.

and vasodilatation in others in response to a variety of experimental stimuli.

It was further suggested that the sustained capillary hypertension transmitted from the pulmonary artery through the dilated areas set off a vicious cycle and caused the observed sequential formation of interstitial edema, alveolar edema, alveolar collapse, hemorrhage, pneumonia and hyaline membrane, the final picture being that of shock lung.

The present studies have shown that beta blockade with propranolol significantly decreases the epinephrine induced pulmonary insufficiency for the entire period. Early in the period, propranolol very likely is effective by decreasing both the cardiac output and the pulmonary vasodilatation, the latter suggested by the increased total pulmonary resistance occurring with a decreased cardiac output. Both changes can be expected to decrease the epinephrine induced redistribution of the pulmonary blood flow, thereby decreasing the flow and pressure in the dilated areas. The decreased flow decreases the ventilation-perfusion inequalities and the early shunting. The decreased pressure in the dilated areas will diminish the formation of interstitial edema and the subsequent pathological changes causing the late shunting. Preliminary pathological studies have shown this. Further, in the propranolol treated group after 3 hours the pulmonary vascular resistance remained at approximately 200 per cent of control while the resistance in the epinephrine treated group progressively increased to above 400 per cent of control at 5 hours. The difference can be explained by the progressive pathological changes that occurred in the epinephrine group which do not seem to occur in the propranolol group.

It is pertinent to note that the hemodynamic changes, i.e., decreased shunt, decreased cardiac output, and increased pulmonary vascular resistance, in the baseline period of groups 3 and 5 following propranolol were in the same direction but much smaller than the changes in the propranolol treated dogs after epinephrine. These observations suggest that in the resting state there is a balance between pulmonary vasoconstriction and vasodilatation resulting in minimal but finite ventilation-perfusion inequalities and shunting, and that beta blockade decreases the shunt by altering this balance by the same hemodynamic mechanisms as the dogs receiving propranolol and epinephrine but less in degree.

TABLE 6. *Pulmonary Vascular Resistance (dynes sec/cm^5)*

Group	N	Control	Minutes			Hours				
			5	15	30	1	2	3	4	5
1	6	200.9 ± 40.1				179.7 ± 31.3	261.3 ± 73.1	280.1 ± 57.2	278.0 ± 79.9	346.4* ± 63.2
2	10	219.5 ± 47.1	439.1* ± 94.0	324.8* ± 52.8	263.6* ± 28.7	312.0* ± 35.4	409.9* ± 42.1	519.8* ± 60.3	509.1* ± 67.8	619.9* ± 64.0
3	9	355.1 ± 43.4	749.3* ± 87.0	580.8 ± 161.8	641.7* ± 154.9	590.3* ± 118.5	753.3* ± 100.3	832.4* ± 157.8	930.1* ± 153.8	937.7* ± 177.4
4	12	261.2 ± 29.5	230.0 ± 28.4	210.5 ± 25.5	208.2 ± 25.2	232.1 ± 32.7	210.7 ± 26.3	244.1 ± 44.3	187.0 ± 30.5	193.2 ± 28.0
5	16	286.3 ± 31.9	280.4 ± 31.5	239.3 ± 31.2	233.8 ± 24.3	239.1 ± 25.9	278.6 ± 32.0	244.4 ± 26.4	272.0 ± 44.5	249.6 ± 37.3

* Statistically significant change from control, $P < 0.025$.

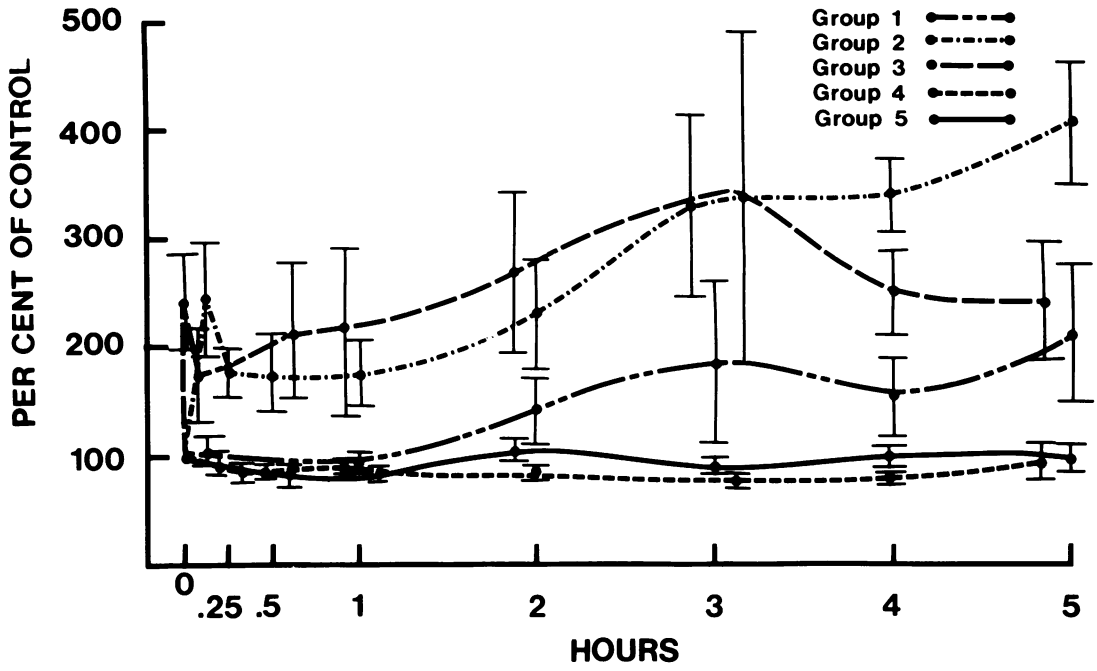

FIG. 4. Comparison of mean per cent of control changes of the pulmonary vascular resistance of groups 1–5. Vertical lines represent SEM.

The small but significant increase in the shunt in group 3 probably was due to incomplete beta blockade as suggested by the increased heart rate and cardiac output.

In the group treated with phenoxybenzamine, the alpha blockade of epinephrine induced vasoconstriction will result in increased vasodilatation in the pulmonary vascular bed. The beta effect of epinephrine which causes vasodilatation, will be unchanged or even increased. (There is evidence that alpha blockade releases catecholamines from alpha receptor sites making more available for stimulation of the beta receptors.) The low pulmonary vascular resistance is consistent with this degree of vasodilatation. Early, however, the shunting would be less than that resulting from epinephrine alone because the increased flow and pressure in the individual capillaries would be less because the increased cardiac output is distributed over a much larger capillary bed, as opposed to the group receiving epinephrine alone in which the increased pulmonary blood flow is redistributed from the constricted bed to the smaller dilated bed. In the epinephrine group the cardiac output begins to fall at 3 hours while in the group receiving phenoxybenzamine and epinephrine, it remains elevated for the entire period and very likely continues to contribute to ventilation-perfusion inequalities and shunting. In addition, most probably the sustained capillary pressure contributes to interstitial edema formation and subsequent pathological changes which can explain the progressive pulmonary insufficiency. Pathological studies are necessary to confirm this.

In the group treated with alpha and beta blockade, the shunt, cardiac output and pulmonary artery

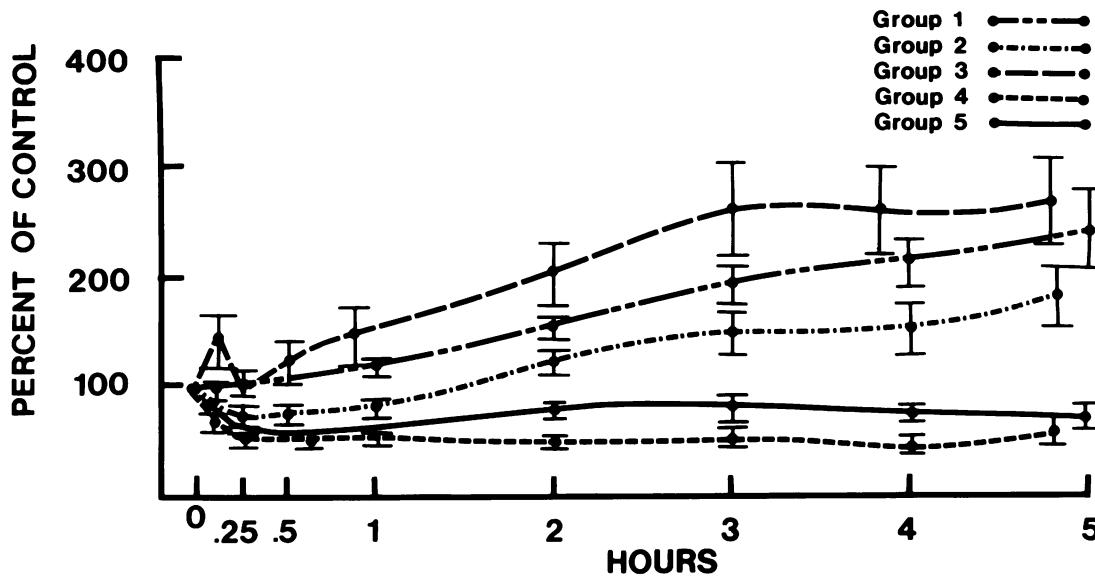

FIG. 5. Comparison of mean per cent of control changes of the systemic vascular resistance of groups 1–5. Vertical lines represent SEM.

TABLE 7. *Systemic Vascular Resistance (dynes·sec/cm⁵)*

Group	N	Control	Minutes 5	Minutes 15	Minutes 30	Hours 1	Hours 2	Hours 3	Hours 4	Hours 5
1	15	3797 ± 487				4278 ± 474	5511* ± 598	6819* ± 955	6981* ± 870	7251* ± 803
2	10	3984 ± 422	3934 ± 703	2990 ± 401	2542* ± 300	3276 ± 509	4951 ± 709	5844* ± 944	5962* ± 1024	7166* ± 1252
3	10	5743 ± 643	7858 ± 1651	5719 ± 958	6714 ± 1007	7812 ± 1265	10282* ± 1564	13332* ± 1581	13261* ± 3029	15686* ± 3483
4	12	2956 ± 225	1955* ± 225	1433* ± 236	1475* ± 192	1628* ± 244	1485* ± 255	1616* ± 360	1417* ± 206	1650* ± 259
5	16	4469 ± 344	3889 ± 404	2977* ± 429	2670* ± 270	2918* ± 303	3565* ± 415	3344* ± 379	3305* ± 453	3032* ± 308

* Statistically significant change from control, $P < 0.025$.

pressure were less and the pulmonary vascular resistance was greater for the entire period than the group receiving alpha blockade alone, but none of the changes were significant. More studies may show a significant difference.

That the systemic vascular resistance was less in the epinephrine group than the control group is consistent with the known peripheral vasodilatory effect of small doses of epinephrine. Also the observation that the systemic vascular resistance in the propranolol group was greater than that of the control or epinephrine groups is consistent with the effect of beta blockade, i.e., less vasodilatation increases the resistance at the same cardiac output.

It is concluded that propranolol significantly decreases epinephrine induced pulmonary insufficiency for the entire period. Phenoxybenzamine decreases the early shunting but less than propranolol and does not decrease the late shunting. Blockade with propranolol and phenoxybenzamine is less effective than propranolol alone. These results support previous studies in animals and man[2–8,16,20] which suggest that beta adrenergic stimulation is important in the pathogenesis of the pulmonary insufficiency associated with critical illness, and that beta blockade is beneficial.

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