THE CATECHOLAMINES IN THE PULMONARY ARTERIAL PRESSOR 
RESPONSE TO ACUTE HYPOXIA *

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A moderate reduction in the oxygen content of inspired air elicits an increase in the pulmonary arterial pressure in animals and man (1–5). It has been suggested that the catecholamines may be involved in this pressor response (6, 7). However, it is uncertain if this hypothesis applies to the effects of tolerable levels of hypoxia in man, since the experimental evidence for enhanced adrenal activity derives exclusively from observations made during severe hypoxia and asphyxia in animals (8–17).

The present study attempted to assess the role of the catecholamines in effecting the pulmonary arterial pressor response to acute hypoxia in man. To supplement these observations on man, experiments were performed on reserpinized dogs to determine whether the pulmonary arterial pressor response to acute hypoxia persists after depleting the pulmonary vascular nerve endings of norepinephrine.

MATERIALS AND METHODS

Subjects

Twenty-two subjects were studied in the unanesthetized, postabsorptive, "basal" state. All of these subjects were either entirely normal or else had small, circumscribed pulmonary lesions. Their ages ranged from 14 to 54 years.

Three other subjects were studied during the course of thoracotomy. Two had discrete pulmonary neoplasms; the other had a discrete, small mediastinal tumor. Their ages were 22, 24, and 59 years, respectively.

Five dogs were used for the part of the study designed to deplete pulmonary vascular nerve endings of norepinephrine.

Methods

For convenience in presentation, the study has been subdivided into four parts.

Part I. Preliminary observations were made on 9 subjects. These consisted of a comparison of the concentrations of epinephrine and norepinephrine in systemic arterial blood prior to and during 15 minutes of breathing 11 per cent oxygen in nitrogen. The results of these studies are included in Table 1 (Subjects TM to DG).

Part II. More extensive observations were made on 13 other subjects. The right heart was catheterized in each of these subjects with a double-lumen catheter. The brachial artery was cannulated with a Cournand needle. Open circuits were used to administer specific inspired mixtures and to collect expired gas. Each study consisted of four consecutive periods: 1) control, 2) acute hypoxia, 3) infusion of norepinephrine, and 4) acute hypoxia during the infusion of norepinephrine. Between periods, the subject was disconnected from the open circuit for 15 to 30 minutes of relaxation and ambient air breathing.

Control, ambient air (period 1): Ten to 15 minutes after the completion of right heart catheterization and brachial arterial cannulation, a period of ambient air breathing was begun; the open-circuit system consisted of a mouthpiece, a three-way, low dead space valve, and a Tissot gasometer. After 15 minutes of breathing ambient air, the expired air was collected for 2 minutes. During the middle minute of the gas collection, samples of mixed venous and peripheral arterial blood were withdrawn simultaneously for the determination of the gaseous composition, pH, and concentration of catecholamines.

Acute hypoxia (period 2): During this period, a mixture of 11 per cent oxygen in nitrogen was substituted for ambient air. This inspired mixture was breathed for 16 minutes. During the last 2 minutes, expired gas and blood samples were collected as in the preceding period.

Infusion of norepinephrine (period 3): The third period involved the intravenous administration of norepinephrine in saline. The initial rate of infusion was 4 to 6 μg per minute; it was increased every 3 to 5 minutes until the pulmonary arterial blood pressure reached the
level which had occurred spontaneously during acute hypoxia. The final rate of infusion was different for each subject; it ranged from 12 to 67 \( \mu g \) per minute. This rate of infusion was continued for 10 minutes to achieve a constant blood level of norepinephrine (18). During the final 2 minutes of the infusion, blood and gas samples were withdrawn as during the previous periods.

**Acute hypoxia during the infusion of norepinephrine (period 4):** Between the third and fourth periods, the infusion of norepinephrine was continued. In 5 of the subjects, the rate of infusion was unchanged (20 to 67 \( \mu g \) per minute); in the other 8, the rate of infusion was gradually reduced until the pulmonary arterial pressure returned to the preinfusion level (final rates of infusion from 4 to 20 \( \mu g \) per minute). In each instance, the infusion rate was kept constant for 10 minutes before the subject began to breathe the hypoxic inspired mixture (as in period 2). The duration of the hypoxic period, as well as the times of sampling both expired gas and blood, was the same as in the previous periods.

Blood pressures were recorded every 4 minutes during the first two periods and continuously during the last two periods. The recording system consisted of Statham strain gauges as pressure transducers and an oscilloscopic recording apparatus (Electronics for Medicine). The usual criteria were applied for adequacy of the pulmonary wedge pressure (19). Pulmonary vascular resistance was calculated as the ratio of pulmonary arterial minus pulmonary wedge pressure to the cardiac output. The systemic vascular resistance was calculated as the ratio of the brachial arterial mean blood pressure to the cardiac output.

The expired gases collected during each period were used to calculate the rates of oxygen uptake and the respiratory exchange ratios. The cardiac output was calculated by the Fick principle for oxygen in all subjects. In 5 of these (MA, CB, RS, JK, and TW), cardiac output and “central blood volume” were also determined by the Stewart-Hamilton principle immediately prior to the end of each period; for this purpose, indocyanine green dye was injected into the pulmonary artery, and brachial arterial blood was withdrawn at a constant rate through a densitometer (Colson) for the inscription of the dye dilution curve by the oscilloscopic recorder (20-22).

The oxygen content and capacity of blood were determined volumetrically, in duplicate, by the method of Van Slyke and Neill (23). The pH of blood was determined using a McInnes-Belcher glass electrode. The oxygen and carbon dioxide content of expired gas were determined in duplicate using a micro-Scholander gas analyzer (24).

The concentrations of epinephrine and norepinephrine in plasma were determined fluorometrically by the trihydroxyindole procedure of Cohen and Goldenberg (25). This method is sensitive to changes of 0.2 \( \mu g \) per L of blood.

**Part III.** Three other subjects were studied during open thoracotomy. Needles were placed in the pulmonary artery, the left atrium, and the aorta; blood pressures were recorded prior to, during, and after, a single rapid injection of 0.4 or 0.8 \( \mu g \) of norepinephrine into the exposed pulmonary artery. Although open thoracotomy undoubtedly produces considerable derangements in the circulation, the simultaneous registration of these blood pressures in the course of a single circulation provides a

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**TABLE 1**

<table>
<thead>
<tr>
<th>Systemic arterial ( O_2 ) saturation</th>
<th>Pulmonary arterial mean pressure</th>
<th>Epinephrine†</th>
<th>Norepinephrine†</th>
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<td>Hypoxia</td>
<td>Air</td>
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<tr>
<td>----------------------------------------</td>
<td>---------------------------------</td>
<td>-------------</td>
<td>----------------</td>
</tr>
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<td>TM</td>
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<tr>
<td>DG</td>
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<td>82</td>
<td>0.18</td>
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<tr>
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</tr>
<tr>
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<td>97</td>
<td>71</td>
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</tr>
<tr>
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</tr>
<tr>
<td>TA</td>
<td>99</td>
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</tr>
<tr>
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<td>0.25</td>
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<tr>
<td>CB</td>
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<td>Mean</td>
<td>98</td>
<td>72</td>
<td>0.20</td>
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</table>

* Acute hypoxia was induced by the breathing of 11 per cent oxygen in air.
† Concentration in systemic arterial blood.
measure of sequential changes in resistance. To record these blood pressures, the needles were connected by way of vinyl plastic tubing (26) to the Statham gauges and the electronic recorder.

Part IV. Reserpine (2.5 to 4.0 mg per kg) was administered intramuscularly to each of 5 dogs, 18 to 36 hours before they were tested with acute hypoxia. At the time of study, small quantities of pentobarbital (Nembutal) were injected intravenously to induce a state of light anesthesia. Respiration was accomplished by means of an intermittent positive pressure respirator (Bird) connected to the dog by way of an endotracheal tube. As in the human studies, an open circuit was used to deliver either ambient air or a mixture of 11 per cent oxygen in nitrogen, and expired air was collected in a Tissot gasometer. The sequence of the hemodynamic measurements was identical with that described above for periods 1 and 2 of the studies on man.

RESULTS

1. Measurement of the concentrations of epinephrine and norepinephrine in arterial and mixed venous blood during hypoxia. In the upper portion of Table I are listed the arterial blood concentrations of epinephrine and norepinephrine in 16 normal subjects during ambient air breathing and during hypoxia. Values for the pulmonary arterial mean blood pressures are also indicated for 7 subjects (EB to MH). As may be seen, the arterial oxygen saturation decreased in each subject during hypoxia. During ambient air breathing, the average oxygen saturation for the group was 98 per cent (range, 96 to 100 per cent); during hypoxia, the average saturation fell to 72 per cent. In each of the seven subjects in whom pulmonary arterial pressure was measured, the decrease in systemic arterial oxygen saturation was associated with an increase in pulmonary arterial mean blood pressure; the average increase was 53 per cent. However, despite these changes in peripheral arterial oxygen saturation and in pulmonary arterial pressure during hypoxia, there was no statistically significant change (p > 0.1) in the concentration either of epinephrine or of norepinephrine in the peripheral arterial blood.

The relationship between the concentrations of catecholamines in arterial blood and in mixed venous blood drawn simultaneously is shown for five subjects in Table II. The test periods when the comparisons were made are indicated in the second column. It may be seen that there was no arteriovenous difference for norepinephrine greater than 0.2 µg per L in any of the subjects. In only one of the five subjects (MH) was the arteriovenous difference for epinephrine greater than 0.2 µg per L (0.32 µg per L).

2. Duplication of the pulmonary arterial hypertension observed during hypoxia by the infusion of norepinephrine. The rates at which norepinephrine had to be infused during ambient air breathing in order to duplicate the level of pulmonary arterial pressure which occurred during acute hypoxia are listed for each subject in Table III (period 3). It may be seen that the rates varied from subject to subject, and ranged from 12 to 67 µg per minute (0.17 to 1.4 µg per minute per kg). In 8 of the 13 subjects, peripheral arterial blood samples were drawn after a stable level of pulmonary hypertension had persisted for 8 to 10 minutes. As shown in Table III, the concentrations of norepinephrine in these samples ranged from 1.6 to 5.8 µg per L. These levels of circulating norepinephrine, which were required to duplicate the hypoxic increase in pulmonary arterial pressure, were from 13 to 22 times higher than the levels of norepinephrine which occurred spontaneously in the same subjects during acute hypoxia (period 2).

3. Comparison of the ventilatory and circulatory effects of acute hypoxia and of norepinephrine in the same subjects. Table III also lists the ventilatory and circulatory measurements obtained from each subject during the four consecutive test periods. In this section, only the measurements of the first three test periods (e.g. control, hypoxia, and infusion of norepinephrine) will be compared; for convenience, the final period will be considered separately.
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<th>Conc. in blood</th>
<th>SaO2</th>
<th>A-V</th>
<th>VO2</th>
<th>CO</th>
<th>HR</th>
<th>PA</th>
<th>P</th>
<th>BA</th>
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<td>24</td>
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<td>99</td>
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<td>5.7</td>
<td>86</td>
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<tr>
<td>1.69 m²</td>
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<td>12</td>
<td>2.40</td>
<td>71</td>
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**TABLE III**

**Effects of acute hypoxia and of norepinephrine on pulmonary and systemic hemodynamics**

*Values are given as mean ± SD.*
## TABLE III—(Continued)

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<tr>
<th>Subj., Wt, Age, Sex, BSA</th>
<th>Fio₂</th>
<th>Norepinephrine Rate of infusion in blood</th>
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<th>HR</th>
<th>PA s</th>
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<th>m</th>
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<th>d</th>
<th>m</th>
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<td>%</td>
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<td>mm Hg</td>
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<td>0.85</td>
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<td>97</td>
<td>5.0</td>
<td>0.85</td>
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<td>20</td>
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<td>97</td>
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<td>0.85</td>
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</table>

* Fio₂ = fraction of oxygen in the inspired gas mixture; SaO₂ = arterial oxygen saturation; Ve = minute ventilation; BTPS = respiratory exchange ratio of expired air; V̇O₂ = oxygen uptake, STPD; CO = cardiac output; HR = heart rate; PA = pulmonary arterial pressure, systolic (a), diastolic (d), mean (m); P = "wedge" = Pulmonary arterial "wedge" pressure; PVR = pulmonary vascular resistance; BA = brachial arterial pressure, systolic (a), diastolic (d), and mean (m); SVR = systemic vascular resistance.

† Periods: 1 = control; 2 = acute hypoxia; 3 = infusion of norepinephrine; 4 = acute hypoxia during infusion of norepinephrine.
During the control period, the minute ventilation averaged 4.3 L per minute per m² of body surface area, and increased by approximately 10 per cent during hypoxia and norepinephrine infusion, respectively. The respiratory exchange ratios were 1.0 or less throughout each of the periods. In all subjects but one (MA), the respiratory exchange ratio during the hypoxic period differed from control by 0.13 or less. In Subject MA, the inordinate increase of 0.24 in the respiratory exchange ratio, as well as the 10 per cent decrease in oxygen uptake, raised the prospect that his value for cardiac output during hypoxia might be artificially low (3). However, independent determinations of the cardiac output by the Stewart-Hamilton dye dilution method in Subject MA and in four others (CB, RS, JK, and TW) during each of the three periods provided values which did not differ from the corresponding Fick values by more than 12 per cent. Because of this close agreement, the values obtained by the dye dilution method are not included in the table.

The average cardiac output by the Fick method during the control period was 6.8 L per minute. In Subject CU, the control cardiac output was unusually high (5.8 L per minute per m² of body surface area); this high level persisted, without apparent reason, throughout the test periods. During hypoxia, cardiac output increased in 9 of the 13 subjects, with an average increase for the group of 19 per cent. During the infusion of norepinephrine, the average cardiac output was 7 per cent less than control.

During hypoxia, the heart rate increased in each subject, averaging 15 beats more per minute than during the control period. The corresponding changes in stroke volume were slight and inconsistent in direction (−17 to +12 ml). During the infusion of norepinephrine, the heart rate decreased in 10 of the 13 subjects, averaging approximately 15 beats less per minute than during the control period. The stroke volumes either remained unchanged or increased: in 8 of the 13 subjects, the increments in stroke volume were 5 ml or less; in the other 5, the increments ranged from 8 to 30 ml.

The changes in pulmonary arterial and wedge pressures, and in pulmonary vascular resistance are presented in detail in Table III and summarized for each of the three periods in Figure 1. The figure illustrates that, according to plan, approximately equal levels of pulmonary arterial pressure were achieved during periods 2 (hypoxia) and 3 (norepinephrine). However, these two periods are strikingly different with respect to both the pulmonary wedge pressures and calculated resistance. In contrast to the unchanged wedge pressure and the increased resistance during hypoxia, the wedge pressure increased (by 4 to 13 mm Hg) and the resistance remained unchanged during the infusion of norepinephrine: on the average, the pulmonary vascular resistance rose from 0.06 ± 0.02 mm Hg per ml per second during ambient air breathing to 0.14 ± 0.04 mm Hg per ml per second during hypoxia; it reverted to control values (0.06 ± 0.03 mm Hg per ml per second) during the infusion of norepinephrine.

Several other observations not listed in Table III are relevant to the interpretation of these data: 1) continuous records of pulmonary vascular pressures during the infusion of norepinephrine showed that the increase in pulmonary arterial pressure either accompanied or followed the increase in wedge pressure but never preceded it; 2) in the
four subjects in whom measurements of right ventricular end-diastolic pressures were obtained during all three periods (EB, MH, TA, and CU), these pressures were found to remain unchanged during hypoxia (of the order of 1 to 2 mm Hg) and to increase during the infusion of norepinephrine (the highest value for end-diastolic pressure, 8 mm Hg, occurred in Subject CU, who received the most rapid infusion of norepinephrine); and 3) in the five subjects in whom the central blood volume was measured (MA, CB, RS, JK, and TW), the values during hypoxia and during the infusion of norepinephrine did not vary significantly (± 15 per cent) from control.

The effects of hypoxia and of norepinephrine on the systemic circulation appear in the final columns of Table III. During hypoxia, the systemic arterial pressure and the systemic vascular resistance remained unchanged despite the increase in pulmonary vascular resistance. On the other hand, during the infusion of norepinephrine, the systemic arterial pressure and systemic vascular resistance increased even though the pulmonary vascular resistance remained unchanged.

4. The effect of the combination of acute hypoxia and the infusion of norepinephrine on the pulmonary circulation. The respiratory and circulatory responses of each subject to acute hypoxia during the infusion of norepinephrine (period 4) are listed in Table III for comparison with the responses during acute hypoxia per se (period 2). The subjects are divided into two groups according to the rates of infusion: a slow rate of infusion (4 to 20 µg per minute) increased the level of circulating norepinephrine without increasing pulmonary arterial pressure (Subjects EB to CU); a more rapid rate (20 to 67 µg per minute) increased the pulmonary arterial pressure to the levels of period 3 (Subjects TL to TW). Despite these variations in the rate of infusion, the levels of the minute ventilation, respiratory exchange ratios, and peripheral arterial oxygenation of period 4 were similar to those of period 2.

In Figure 2, the pulmonary vascular pressure and resistance during periods 2 and 4 are com-

![Figure 2](image-url)
pared. The left half of this figure is concerned with the effects of the slow infusion rates (4 to 20 
mg per minute), and the right half with the effects of the rapid infusion rates (20 to 67 mg per min-
ute). It may be seen that the slow infusion of norepinephrine did not modify the pulmonary vas-
cular response to acute hypoxia. On the other hand, during the rapid infusion of norepinephrine, 
the increase in pulmonary arterial pressure ex-
ceeded that which occurred during acute hypoxia per se. However, because of the concomitant in-
crease in pulmonary wedge pressure, the value for pulmonary vascular resistance did not exceed 
that which obtained during acute hypoxia per se.

5. The effect of a single injection of norepineph-
rine directly into the pulmonary artery in open-
chested subjects. Figure 3 illustrates the sequence of changes in blood pressure recorded simultane-
ously from the pulmonary artery, the left atrium, 
and the aorta, before and after an injection of norepinephrine directly into the exposed pulmo-
nary artery of a human subject during thoracot-
omy. It may be seen that the first increase in pressure occurred in the left atrium 2.5 seconds 
after the injection; this was followed by an increase in aortic pressure 6 seconds after the injection.

The pulmonary arterial pressure was the last to increase, 11 seconds after injection.

6. The effect of depleting the lungs of norepi-
 nephrine on the pulmonary pressor response to 
hypoxia in dogs. Figure 4 compares the changes in the cardiac output and pulmonary arterial mean 
pressure of five reserpinized dogs during acute hypoxia with the changes observed in four other nonreserpinized dogs previously studied in this laboratory in the same way (27). It may be seen 
that the pulmonary arterial pressor response ob-
served during hypoxia in the reserpinized dogs was 
the same as the response of the control dogs.

DISCUSSION

The results of these observations on man indicate 
that circulating epinephrine and norepinephrine 
are not involved in the pulmonary arterial pressor 
response to acute hypoxia of moderate degree. 
This conclusion is based on several lines of evi-
dence: 1) the concentrations of these catechol-
amines in blood during acute hypoxia do not ex-
ceed the concentrations during ambient air breathing; 2) the levels of circulating norepinephrine 
which must be reached during ambient air breathing in order to duplicate the pulmonary hyperten-
sion of acute hypoxia are far in excess of those 
which occur spontaneously during acute hypoxia; 
3) circulating norepinephrine seems to elicit pul-
monary hypertension by a different mechanism 
from that which operates during acute hypoxia; 
and 4) an increase in the level of the circulating norepinephrine that is insufficient to raise the pul-
monary wedge pressure does not augment the pul-
monary arterial pressor response to acute hypoxia.

These observations on the circulating catechola-
mines do not exclude the possibility that the release of norepinephrine at intrapulmonary vascular 
nerve endings may be involved (28). However, 
the present study also suggests that this prospect 
is unlikely, since the administration of reserpin 
to dogs, in doses larger than those conventionally 
used to deplete canine tissues of norepinephrine 
(29), did not prevent or blunt the rise in pulmo-
nary arterial pressure during acute hypoxia. This 
failure of reserpine to modify the pulmonary ar-
terial pressor response is consistent with the 
persistence of this response in man in the face of
surgical sympathectomy (30, 31) and “chemical” denervation (32).

It is generally agreed that acute hypoxia elicits pulmonary hypertension by inducing pulmonary vasoconstriction (3, 33). There is less unanimity concerning the mechanism by which the infusion of norepinephrine elevates pulmonary arterial pressure: on the one hand there is evidence that “back pressure” from the left heart is involved (34–37); on the other there is evidence that pulmonary vascular resistance increases (35, 38–41). The present study indicates that in intact man the “back pressure” effect predominates. The evidence for this view is of several different types: 1) after the injection of norepinephrine into the exposed pulmonary artery during open thoracotomy, the increase in left atrial and aortic pressures preceded the increase in pulmonary arterial pressure; 2) during the infusion of norepinephrine, the increase in pulmonary arterial pressure either accompanied or followed the increase in pulmonary wedge pressure but never preceded it; and 3) the infusion of norepinephrine during acute hypoxia (i.e., when pulmonary vasoconstriction presumably exists) failed to elicit any further increase in pulmonary vascular resistance.

These studies do not indicate the precise mechanisms by which norepinephrine increases the pulmonary wedge pressure. In particular, the failure of norepinephrine to decrease consistently the calculated pulmonary vascular resistance (42) raises the prospect that norepinephrine elicits a combination of pulmonary vasoconstriction and “back pressure.” However, the sequence of changes in left atrial and aortic pressures after the injection of norepinephrine into the pulmonary artery suggests that a direct effect of norepinephrine on left atrial muscle is primarily involved. This hypothesis is consistent with the positive inotropic effect of norepinephrine on isolated cardiac muscle (43).

SUMMARY

1. The role of circulating catecholamines in the pulmonary arterial pressor response to acute hypoxia of moderate degree was investigated in 25 human subjects. Supplementary observations on five dogs concerned the role of norepinephrine contained in pulmonary nerve endings.

2. Acute hypoxia was not associated with an increase in the levels of circulating epinephrine or norepinephrine.

3. During ambient air breathing, the levels of circulating norepinephrine had to be increased at least 13 times above control levels in order to duplicate the pulmonary arterial pressor response to acute hypoxia.

4. In intact man the infusion of norepinephrine elicited pulmonary arterial hypertension by a mechanism different from that of acute hypoxia: the pressor response to acute hypoxia arose from an increased pulmonary vascular resistance to perfusion; the pressor response to norepinephrine originated primarily in “back pressure” from the left heart (i.e., without an increase in pulmonary vascular resistance).

5. Levels of circulating norepinephrine that were insufficient to increase the pulmonary wedge pressure did not exaggerate the pulmonary arterial pressor response to acute hypoxia.
6. Depletion of the pulmonary vascular nerve endings of norepinephrine by reserpine in dogs did not prevent the usual pulmonary arterial pressor response to acute hypoxia.

7. The present study provides no evidence for a role of either epinephrine or norepinephrine in the pulmonary arterial pressor response to acute hypoxia of moderate degree.

REFERENCES


