EFFECTS OF NOREPINEPHRINE ON HUMAN PULMONARY CIRCULATION

BY

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Received February 9, 1962

The vasoconstrictive action of norepinephrine on the pulmonary vessels has been consistently demonstrated in animals by histological techniques (Patel and Burton, 1957) or by preparations in which pulmonary blood flow could be regulated at will and continuously measured (Rose et al., 1955; Borst, Berglund, and McGregor, 1957; Eliakim and Aviado, 1961); but such techniques are not applicable in man. Pulmonary vasoconstriction following the administration of norepinephrine has not been demonstrated unequivocally in man; although Patel, Lange, and Hecht (1958) reported significant increases of pulmonary vascular resistance during steady-state administration of norepinephrine and interpreted this as indicating pulmonary arteriolar constriction, Fowler et al. (1951) under similar conditions obtained no such increase. Investigating the effect of norepinephrine on the pulmonary circulation in a group of patients with aortic regurgitation, Regan et al. (1959) found no change in pulmonary vascular resistance, whereas an increase was noted in their normal controls. In view of these contradictory reports further investigation of the subject was undertaken.

MATERIAL AND METHODS

The study was carried out in two parts. In 13 subjects (group A) “steady-state” observations of pressures and blood flow in the pulmonary circulation were made before and during infusion of norepinephrine: pulmonary vascular resistance was thus computed. In 9 additional subjects (group B) the moment-to-moment changes of pressure across the pulmonary vascular bed were observed, following a single injection of norepinephrine. While flow, and thus resistance, changes could not be measured by this method, rapid transients that would not be discernible by the “steady-state” method could be observed.

Group A. In this group there were 6 patients with isolated pulmonary stenosis, 1 with atrial septal defect, 3 with small ventricular septal defect, and 2 others, one of whom had been in heart failure three years before after an infundibular resection for the tetralogy of Fallot. There was also one person investigated for a præcordial systolic murmur, in whom no hæmodynamic abnormality was found. All subjects were familiar with the laboratory surroundings and had practised breathing through the mouthpiece of the close-circuit spirometer which measured the oxygen consumption. Right heart catheterization was performed with the subjects mildly sedated and in the post-absorptive state: single lumen, end-hole catheters were introduced from a medial antecubital vein and in each case the diagnostic data were first collected. For the observations control blood samples, oxygen consumption, and pressures were obtained, and this was followed by intravenous administration of norepinephrine at a concentration of 8 μg./ml. in isotonic saline. The rate of administration was adjusted to produce stable systemic hypertension of moderate degree; and the amount thus given

* In receipt of a scholarship from the S. Achilopoulos Foundation, Volos, Greece.

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ranged between 20 and 40 µg./min. in the various patients. As soon as stability was achieved the measurements were repeated.

Analysis of the heparinized blood samples for oxygen was carried out spectrophotometrically with the technique described by Holling et al. (1955). Pressures were measured in mm. Hg from the level of the mid-thorax with electromanometers.* Mean pressures were obtained by electronic integration and were averaged, as were phasic pressures, over three respiratory cycles. Pulmonary and systemic flows were measured by the Fick method and vascular resistances were calculated in dynes/sec./cm.⁻⁵/m.² of body surface area with the following formulae:

Pulmonary vascular resistance =
Mean pulmonary arterial pressure minus mean pulmonary wedged pressure in mm. Hg × 1332
Pulmonary blood flow (ml./sec./m.² of body surface area)

and Systemic vascular resistance =
Mean systemic arterial pressure minus mean right atrial pressure in mm. Hg × 1332
Systemic blood flow (ml./sec./m.² of body surface area)

The significance of the difference between mean results in the control period and during administration of norepinephrine was evaluated by the "t" test.

**Group B.** In this group there were 9 patients with moderate or severe mitral stenosis, which was isolated in 6 and associated with mild regurgitation in 2 and with mild aortic valve disease in 1. Diagnostic right heart catheterization was first performed, and the catheter was left in the proximal right pulmonary artery. The left atrium was then entered by the posterior percutaneous route. Then an injection of norepinephrine in isotonic saline, the amount ranging between 30 and 50 µg. in the various cases, was given in an antecubital or dorsal vein of the hand over a period of 40 seconds, while pulmonary arterial and left atrial mean pressures were continuously recorded at slow paper speed. The systemic pressure was intermittently recorded through an indwelling arterial needle or polyethylene tube. The left atrial needle was removed one and a half minutes from the end of the injection and the procedure thus terminated.

The side-effects of a single or continuous injection of norepinephrine have been described elsewhere (Bousvaros, 1961), and with the dose used in this investigation were not significant. In addition there were no complications of left atrial catheterization.

**RESULTS**

**Group A.** A summary of the changes in the systemic circulation produced by norepinephrine is given in Table I. Similar findings have been consistently described in the past (Goldenberg et al., 1948; Barnett et al., 1950; and Fowler et al., 1951).

The data on the pulmonary circulation are shown in Fig. 1. During administration of norepinephrine considerable elevation of pulmonary wedged and pulmonary arterial pressure developed,

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**TABLE I**

**SUMMARY OF CHANGES IN SYSTEMIC CIRCULATION IN GROUP A UNDER INFLUENCE OF NOREPINEPHRINE**

<table>
<thead>
<tr>
<th></th>
<th>Control (average ± SD)</th>
<th>With norepinephrine</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean systemic arterial pressure (mm. Hg)</td>
<td>85±8.2</td>
<td>126±11.5</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm. Hg)</td>
<td>5.9±3.5</td>
<td>10.8±3.4</td>
<td>0.001&lt;p&lt;0.01</td>
</tr>
<tr>
<td>Systemic blood flow (l./min./m.² body surface area)</td>
<td>3.6±2.6</td>
<td>3.1±2.5</td>
<td>0.02&lt;p&lt;0.05</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes/sec./cm.⁻⁵/m.² body surface area)</td>
<td>1792±351</td>
<td>2902±396</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>84±16</td>
<td>70±9</td>
<td>0.02&lt;p&lt;0.05</td>
</tr>
</tbody>
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* New Electronic Products, London.
but neither the pressure gradient between these two, nor the pulmonary blood flow, were significantly affected. There was considerable variability in the individual change of pulmonary vascular resistance; a small increase was noted in most cases, which (the group taken as a whole) was not statistically significant.

**Group B.** The values of mean pulmonary arterial and left atrial pressure in each of these patients, before and at 20-second intervals from the beginning of the injection of norepinephrine, are shown in Fig. 2. The pulmonary arterial pressure increased in all 9 within 20 seconds. There was also a rise in the left atrial pressure in 8 patients, which followed 20 to 40 seconds after the increase in pulmonary arterial pressure in Cases I to VI but occurred simultaneously with the latter in Cases VII and IX. In three (Cases V, VI, and VII) left atrial pressure was reduced coincidentally with the early rise of pressure in the pulmonary artery; this reduction was more pronounced and prolonged in Case VII in whom left atrial pressure did not eventually exceed the control value.

The gradient between mean pulmonary arterial and left atrial pressure was initially augmented in Cases I to VII. This was due to the early rise of pulmonary arterial pressure in Cases I to IV and to both pulmonary arterial pressure rise and left atrial pressure fall in Cases V, VI, and VII. The subsequent steep rise in left atrial pressure resulted in a reduction of this gradient and, at the time of peak systemic pressor response, its mean change was not significant (1 mm. Hg±2.8). Since that moment may be considered as corresponding with the time of flow and pressure estimation in the "steady-state" method, at which stage pulmonary blood flow was not significantly modified, pulmonary vascular resistance in group B as a whole was presumably unchanged by norepinephrine. As seen in Fig. 2 there was no qualitative or quantitative difference in the response of the three patients with additional lesions (Cases II, V, and VIII).

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Fig. 1.—Changes in the pulmonary circulation in group A during continuous intravenous infusion of norepinephrine.

In each section the control figures are on the left and those during norepinephrine infusion are on the right. PA\textsuperscript{m}: mean pulmonary arterial pressure. PW\textsubscript{w}: mean pulmonary wedged pressure. PF: pulmonary blood flow. PVR: pulmonary vascular resistance. NE: during administration of norepinephrine.
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Mean systemic arterial pressure increased by 25 to 45 per cent in all these patients and returned to control levels within three to four minutes. The rise of systemic pressure was evident within 30 seconds of the start of the injection: as it was not continuously registered, the exact time relation of the onset of pressure rise in the systemic and pulmonary artery could not be ascertained. The heart rate was not significantly modified in the 7 patients who had atrial fibrillation, but a small reduction was noted in Cases I and VIII who were in sinus rhythm 20 to 30 seconds from the beginning of the injection.

**DISCUSSION**

Pulmonary vascular resistance, being the ratio of the pressure gradient across the pulmonary vascular bed to the flow, is according to Poiseuille’s law inversely related to the fourth power of the radius. The limitations in applying this law (which describes the flow of a simple liquid through a straight, smooth-walled, non-distensible, circular tube) to a biological system have been clearly reviewed by Lilienthal and Riley (1954). Provided these limitations are recognized, an increase of pulmonary vascular resistance may be cautiously interpreted as indicating a decrease in vascular geometry, in other words vasoconstriction, and a reduction in resistance may be interpreted as representing an increase in vessel calibre or vasodilatation. The words vasoconstriction and vasodilatation will, hereafter, be used in this sense and not as indicating changes in distensibility or vascular tone. Vascular tone, being the force of contraction of the smooth muscle in the vessel wall, is related to the level of transmural (intravascular minus extravascular) pressure, and its changes may help in determining whether the response of vascular cross-section to a certain stimulus is active or passive. Thus an increase in pulmonary vascular resistance associated with higher transmural pressure (i.e. tone) implies active vasoconstriction, whereas vasoconstriction accompanied by reduced tone is more difficult to interpret and may well be passive secondary to the decrease in transmural pressure and/or changes of flow. Similarly a decrease in pulmonary vascular resistance associated with a reduction in vascular tone may be considered as active vasodilatation, whereas a fall in resistance with a coincident rise in transmural pressure probably represents passive vasodilatation, most often secondary to the distending effect of the elevated transmural pressure. These points have

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FIG. 2.—Pulmonary arterial and left atrial mean pressures in group B at 20-second intervals from the onset of a single intravenous injection of norepinephrine. The injection lasted from 0 to 40 seconds and the values at 0 time represent the control figures. The patients are indicated with latin numbers (I to IX). For Cases I to VIII the pressure scale is on the left of the figure and for Case IX the scale is on the right. The dotted lines represent the gradient between pulmonary arterial (PA) and left atrial (LA) pressure.
been given extensive consideration in recent articles (Burton, 1959; Blount and Grover, 1960; Swan and MacLean, 1960; Moret, Pattay, and Megevand, 1961).

In the present study administration of norepinephrine produced a considerable rise of pulmonary arterial and pulmonary wedge pressure in group A, and of pulmonary arterial and left atrial (with one exception) pressure in group B. As norepinephrine is unlikely to have induced a rise in extravascular pressure, the difference between intraluminal and perivascular pressure, i.e. the transmural pressure, must have increased. Absence of a significant increase in pulmonary vascular resistance on the other hand would suggest that there was no vasoconstriction in response to norepinephrine. However, one ought to consider that a rise of left atrial and pulmonary arterial pressure produces a fall in resistance by passive distension of the pulmonary vessels. This has been shown convincingly in animals (Carlill and Duke, 1956; Borst et al., 1956; Piiper, 1957) and has also been confirmed in man by observations of the reverse phenomenon, i.e. an increase in pulmonary vascular resistance following the fall of left atrial pressure, immediately after surgical splitting of a stenotic mitral valve (Richman, Long, and Rapaport, 1960). Reflex pulmonary vasodilatation has also been observed secondary to stimulation of carotid and aortic baroceptors (Daly and Daly, 1959; Gersmeyer, 1961). In the presence of raised left atrial, pulmonary wedged, pulmonary arterial, and systemic arterial pressures one would expect a reduction in pulmonary vascular resistance. As this did not happen in our cases, it may be concluded that there was coincident and equivalent increase in resistance which, in the presence of higher transmural pressure, should be interpreted as active vasoconstriction by direct action of norepinephrine on the vessel wall. A similar interpretation may be given to the findings of Fowler et al. (1951). However, considerable doubt remains as to the validity of this conclusion in view of potential errors in calculated pulmonary vascular resistance. The limited accuracy of such values is well recognized (Shepherd and Wood, 1959; Blount and Grover, 1960; Lee, 1960) and may account, wholly or in part, for the contradictory conclusions of the studies mentioned in the introduction. This applies particularly to the data of Patel et al. (1958), in over half of whose cases pulmonary wedged pressure was not recorded during administration of norepinephrine but was indirectly estimated from a regression line relating increments of wedged pressure to those of systemic arterial pressure in the remaining subjects, in whom these parameters and their response to norepinephrine were measured. Errors may also have been responsible for the variability of the individual change of pulmonary vascular resistance in group A, in contrast to the consistent and uniform increase in systemic vascular resistance. This variability appeared irrespective of diagnosis and cannot be explained on the basis of the heterogeneity of the patients studied.

More significant evidence for occurrence of pulmonary vasoconstriction with norepinephrine was obtained in the second part of this study by continuous recording of pressure in the pulmonary artery and the left atrium. Thus in seven of the nine patients in group B, within 20 seconds of the onset of norepinephrine injection, an increase in pulmonary arterial pressure occurred without a coincident rise in left atrial pressure. This could not have resulted from changes of intrathoracic pressure since these would influence both left atrial and pulmonary arterial pressure alike and so would not alter the driving pressure across the pulmonary vascular bed (Fowler, 1960). Neither can increase of bronchomotor tone be implicated since norepinephrine produces slight bronchial dilatation (Luduena et al., 1949). Changes of flow in the diminutive precapillary anastomoses between the bronchial and the pulmonary vascular network are most unlikely to cause the initial rise of pressure in the pulmonary artery. Furthermore the results of the elegant animal experiments by Martinez et al. (1961) and Aramendia, de Letona, and Aviado (1962) suggested that the flow from the pulmonary artery into the bronchial veins via anastomotic channels was not reduced by norepinephrine. Finally, whether an increase of blood flow could have been the cause of the early rise of pulmonary arterial pressure should be examined. Although cardiac output during steady-state norepinephrine administration is unchanged or slightly decreased, as shown here and by others (Goldenberg et al., 1948; Fowler et al., 1951; Tuckman and Finnerty, 1959), a brief initial increase of pulmonary flow, observed in some animal experiments (Daly and Luck, 1959), cannot be
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would have resulted in a rise of left atrial pressure. Therefore, active pulmonary vasoconstriction remains the only possible explanation for the early rise in pressure in the pulmonary artery of these seven patients.

Similar observations in dogs have been published (Bartorelli et al., 1954; Rose et al., 1962). The latter authors monitored several parameters and detected a rise in pulmonary arterial pressure after intravenous injection of norepinephrine before any effects on the systemic circuit were apparent.

A fall in left atrial pressure in three patients in group B was seen almost simultaneously with the early rise of pulmonary arterial pressure. In view of its early appearance this may best be explained by a temporary decrease in pulmonary venous flow, which represents a known effect of the vasoconstrictive properties of norepinephrine (Rose et al., 1955; Borst et al., 1957). These three patients had the higher resting levels of pulmonary vascular resistance, which in mitral stenosis is due in large measure to functional vasoconstriction (Wood et al., 1957), and they could conceivably have exhibited greater responsiveness to norepinephrine. Such increased responsiveness may have averted a rise of left atrial pressure in Case VII, in whom the resting values were critically high.

Despite evident limitations, the method used in group B proved superior to the steady-state method, in that the conclusions were not based on the interpretation of changes in pulmonary vascular resistance, the values of which are often of limited accuracy. Furthermore a dissociation of the primary effect of norepinephrine on the vessel wall from the opposing effect of a rise in transmural pressure was succeeded, owing to a short time lag, in the onset of a rise in left atrial pressure. The brevity of this stage and the present inability to measure blood flow continuously, at the inflow and outflow of the pulmonary circulation, constitute significant shortcomings in the method that limit its wider application.

The average increase of mean pulmonary arterial pressure in six patients with pure pulmonary stenosis was 58.5 per cent above control levels, compared with 59.4 per cent in the remainder of the patients in group A. Thus, a failure of pulmonary arterial pressure to rise in cases of pulmonary stenosis, under the influence of norepinephrine, as found by Duff, Sandler and Verel (1960), was not observed in this study.

SUMMARY

The effect of norepinephrine on the pulmonary vessels was investigated in 21 patients and 1 normal subject. In 13, pulmonary vascular resistance was measured during intravenous injection of the amine: a small increase over control figures was found, but was not statistically significant. It was thought that the coincident rise of pulmonary wedge pressure, by producing passive dilatation of the pulmonary vessels, obscured any vasoconstrictive action of norepinephrine. This and the potential errors in calculated pulmonary vascular resistance cast doubts on the appropriateness of this approach. Therefore, the response of pulmonary arterial and left atrial pressures, recorded continuously, to a single intravenous injection of norepinephrine, was observed in 9 patients with pure or predominant mitral stenosis. In the majority of these patients the pulmonary arterial pressure rose, preceding by 20 to 40 seconds a rise in left atrial pressure. Reasons in support of the conclusion that this early widening of the gradients between pulmonary arterial and left atrial pressures probably represented a manifestation of vasoconstriction produced by norepinephrine were discussed.

I wish to express my gratitude to Dr. Charles Baker and to Dr. Dennis Deuchar for permission to study and report upon their patients, to Dr. Alan Johnson for his invaluable contribution during the investigation and for the statistical analysis of the results, and to Dr. Maurice McGregor for helpful suggestions during the preparation of the manuscript.
ADDENDUM

Since the present article was submitted for publication Goldring et al. (1962) reported that administration of norepinephrine in 3 subjects produced an earlier rise of pressure in the left atrium than in the pulmonary or systemic artery. The discrepancy between these observations and those of the present study is not easy to explain and may have been due to the following differences in their experimental protocol: (a) the subjects were investigated during thoracotomy, (b) the injection of norepinephrine was made into the pulmonary artery, and (c) the dose used was 0.8 μg., i.e. 25 to 50 times smaller than the amount used in the present study.

REFERENCES