Brit. J. Pharmacol. (1953), **8**, 98.

THE EFFECT OF ADRENALINE AND NORADRENALINE INFUSIONS ON RESPIRATION IN MAN

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(RECEIVED SEPTEMBER 30, 1952)

During the course of investigations on the cardiovascular responses to intravenous infusions of adrenaline and noradrenaline in man an increase in the rate and depth of the respiration was frequently observed, especially during the first few minutes of the infusion period. This was usually accompanied by a feeling of tightness in the chest.

The stimulating action of small doses of adrenaline on the respiration in unanaesthetized man (Tompkins, Sturgis, and Wearn, 1919; Lyman, Nicholls, and McCann, 1923; Cori and Buchwald, 1930; Courtice, Douglas, and Priestley, 1939) and animals (Boothby and Sandiford, 1923) and in anaesthetized animals (Nice, Rock, and Courtright, 1914; Nice and Neill, 1924; Wright, 1930) is well known. Reale, Kappert, Skoglund, and Sutton (1950) reported an increased rate and depth of respiration with intravenous noradrenaline in man, but a direct comparison of the effects of the two drugs on the respiration does not appear to have been made.

In the present investigation the influence of adrenaline and noradrenaline on the respiratory pattern and gaseous exchange was examined in the conscious human subject.

METHODS

The subjects were examined two to three hours after a light breakfast. The laboratory was temperature-controlled at 20–23° C., and the subject lay on a couch with face-mask and stethograph in position for at least 30 minutes before any observations were made.

The experiments were divided into two groups. In the first, records were made of the respiratory pattern while the oxygen consumption was determined during intravenous infusions of adrenaline and noradrenaline. Records of the forearm blood flow were made at the same time to correlate the respiratory changes with the cardiovascular responses to the infused drugs. In the second group of experiments the changes in alveolar CO_2% were recorded in addition to the respiratory movements.

The rubber face-mask covered only the nose and was carefully fitted to avoid leaks. It was used in preference to a mouth-piece because it was more comfortable and interfered to a minimal extent with the resting pattern of respiration. Tracings of the rate and depth of respiration were obtained with a float-recorder connected to two stethographs, one around the chest and the other around the abdomen (Shepherd, 1951; Dornhorst and Leathart, 1952). Forearm blood flow was measured with a venous occlusion plethysmograph filled with water at 33–35° C. (Barcroft and Edholm, 1945). The intravenous infusions were maintained at a rate of 4 ml./min. by means of a mechanically driven syringe. During a 10-minute control period 0.9% NaCl (with ascorbic acid 0.001%) was infused and blood flow records obtained at half-minute intervals; adrenaline (*l*-adrenaline tartrate, B.D.H.) or noradrenaline ("Levophed," Bayer) made up in this solution was then infused for 10 minutes at a rate of 10 μg. or 20 μg./min. The ascorbic acid saline solution was then resumed for 10 minutes.

In the first group of experiments the expired air was collected in Douglas bags, one five-minute sample being taken before, two during, and one after the drug infusion. The volume of each of the samples was measured and the CO_2% and O_2% determined with a Scholander gas analysis apparatus; the oxygen consumption during each period was calculated and expressed as ml. used per minute. The estimations were accurate to $\pm 10\%$.

In the second group of experiments the alveolar air was collected continually by means of a sampler modified from that described by Rhan and Otis (1949). The last 10 ml. of each expiration was drawn through an infra-red CO_2 analyser by an air-pump; the sampling was controlled by a valve, operated by an electro-magnetic relay device, which was triggered by an inspiratory valve in the nose-piece. The samples were therefore of end-expired air, but during quiet breathing in these experiments the CO_2% values were very close to those obtained by the Haldane-Priestley sampling of alveolar air. Readings on the analyser were taken every 10 seconds and corrected for the slow loss in sensitivity of the instrument throughout the experimental period.

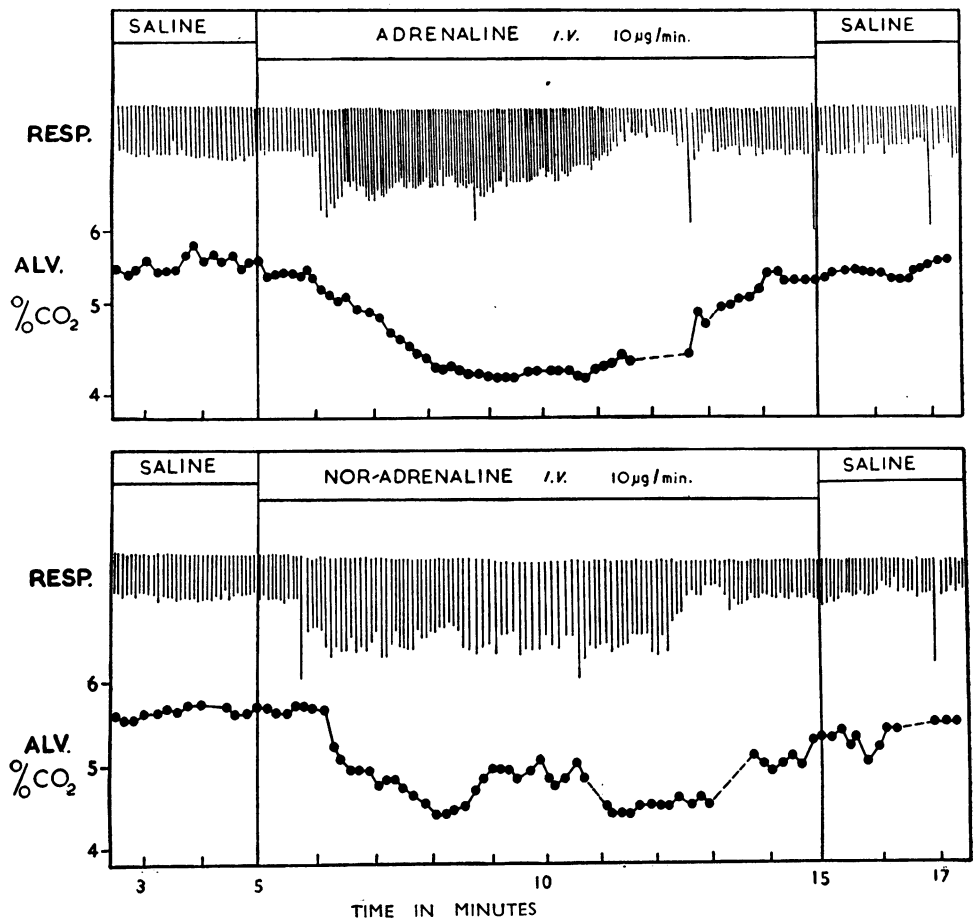

FIG. 1.—Stethograph records and alveolar air CO_2 % during intravenous infusions of adrenaline and noradrenaline, at the rate of 10 µg./min. for 10 min., in subject R.W.

RESULTS

Fig. 1 shows two stethograph records, one taken during adrenaline and the other during noradrenaline infusion. In both there is a marked increase in tidal volume, and there is an increase in respiratory rate with adrenaline. The increase in rate was not present in every experiment, but an increase in depth was always found with both drugs. The increase in tidal volume was often preceded by a few sighing inspirations, and was greatest during the first five minutes of the infusion. The transient shallow respiration which follows the hyperpnoea in these two records was observed in about one-third of the subjects.

Fig. 2 shows the average of six experiments with adrenaline and six with noradrenaline in which the respiration rate, respiratory minute volume, and oxygen consumption are compared together with measurements of the forearm blood flow. The blood flow was recorded, as it gave an objective measure of the subject's response to the drug infused. The response to adrenaline followed the normal pattern (Allen, Barcroft, and Edholm, 1946) with an initial transient vasodilatation followed by a sustained increase in flow ; noradrenaline often produced a small transient increase in flow at the beginning of the infusion, but there was no sustained vasodilatation.

The average increase in respiratory rate was small with both adrenaline and noradrenaline, but the minute volume was always conspicuously increased. This increase in minute volume was greatest during the first five minutes of the infusion, and was larger with adrenaline than with noradrenaline.

These changes in respiratory pattern were accompanied by alterations in the respiratory exchange. Adrenaline increased the oxygen con-

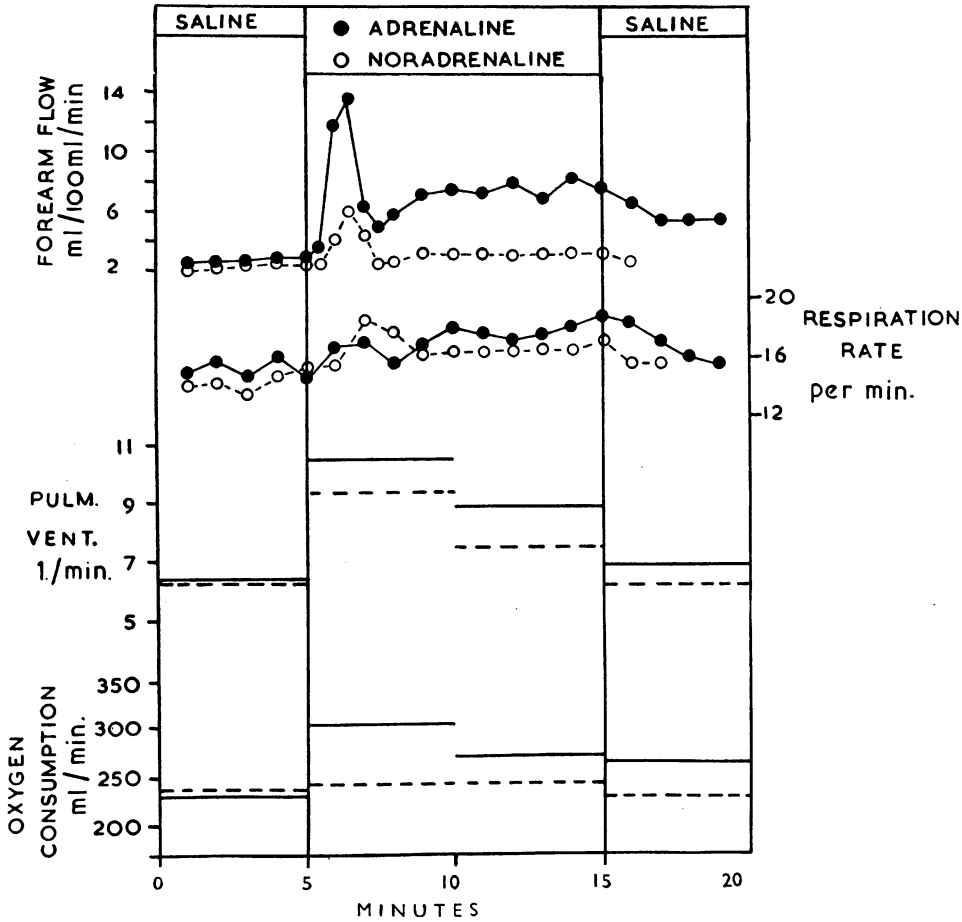

FIG. 2.—A comparison of the influence of adrenaline and noradrenaline, given as continuous intravenous infusion at the rate of 20 μg./min. for 10 min., on forearm blood flow, respiratory rate, pulmonary ventilation, and oxygen consumption in man. The values are the average of six experiments with adrenaline and six with noradrenaline.

sumption by an average of 32% during the first five minutes of the infusion (Table I). The increase was not so marked during the second five-minute period; in four of the subjects there was a fall towards the resting value, while in two the increase was maintained. The effect of noradrenaline on the oxygen consumption was variable; three subjects showed an increase comparable with that found with adrenaline, one a fall, and two no change, during the first five minutes. In one subject only was there a definite increase in oxygen consumption during the second five-minute period.

In the second group of experiments the alveolar air was sampled in 10 subjects during adrenaline infusions. A fall in the CO_2% was recorded in seven of these; it remained unaltered in three. A fall in the alveolar CO_2% was also observed in five out of six subjects receiving noradrenaline infusions. This fall in alveolar CO_2 started during the second minute of the infusions, and the minimum value was reached between the fourth and fifth minute. The alveolar CO_2 rose gradually during the second five-minute period of the infusion, and was frequently at the resting level during the last minute of the infusion. Fig. 1 shows the alveolar CO_2 figures which were obtained at the same time as the stethograph records for subject R. W. The values cannot be regarded as absolute due to the lag in the galvanometer of the infrared analyser.

DISCUSSION

The observed stimulation of respiration by adrenaline in man is in keeping with the results of Tompkins, Sturgis, and Wearn (1919), Lyman, Nicholls, and McCann (1923), and Courtice, Douglas, and Priestley (1939), who gave compara-

TABLE I

A COMPARISON OF THE STIMULATING ACTION OF INTRAVENOUS ADRENALINE AND NORADRENALINE ON THE PULMONARY VENTILATION AND OXYGEN CONSUMPTION DURING THE FIRST (A) AND SECOND (B) FIVE-MINUTE PERIODS OF INFUSION. THE VALUES ARE EXPRESSED AS % CHANGE FROM THE RESTING VALUES

Drug	Subject	% Increase Pul. Vent.		% Change O_2 Cons.	
		A	B	A	B
Adrenaline 20 μg./min.	J.A.	153	87	+51	+33
	M.Y.	44	8	+24	−6
	R.L.	51	31	+28	+27
	R.B.	54	44	+15	+35
	P.B.	121	87	+56	+3
	R.P.	13	7	+19	+13
	Average:	73	44	+32	+18
Noradrenaline 20 μg./min.	S.B.	59	22	+21	+9
	R.W.	40	13	+31	—
	R.B.	39	13	+2	+13
	J.A.	42	18	+16	−12
	P.B.	70	19	0	+7
	R.P.	44	40	−23	+3
	Average:	49	21	+8	+4

tively small doses by injection. Cori and Buchwald (1930) used continuous intravenous infusions, and found a slight increase of the respiration rate with doses one-tenth of the value of those used in the present investigation ; no record of the minute volume was given. Courtice, Douglas, and Priestley attributed their response to lactic acid production, and this may account for some of the respiratory effects with adrenaline seen by other workers. However, the rapid and abrupt onset of the respiratory responses to both adrenaline and noradrenaline described in this paper must be independent of lactic acid production : Bearn, Billing, and Sherlock (1951) showed that the blood lactate was not significantly raised until 10 minutes after the beginning of a continuous infusion of adrenaline of the same size as in the present experiments, and with noradrenaline there was no lactic acid production. The " adrenaline apnoea " seen in the anaesthetized animal is due to the large pressor response produced by the big doses of adrenaline used ; the stimulating action of adrenaline in the anaesthetized animal was observed by Wright (1930) when the blood pressure rise was prevented by a compensator. Small doses of adrenaline were found by Boothby and Sandiford (1923) to stimulate the respiration in unanaesthetized dogs ; Nice, Rock, and Courtright (1914) and Nice and Neill (1924) obtained similar results in anaesthetized dogs, cats, and rabbits.

The time relationships of the respiratory responses to the beginning of the infusion were the same for adrenaline and noradrenaline. The pattern was characterized firstly by the abrupt onset of the hyperpnoea which was maintained, though not at the original level, throughout the first five minutes ; and secondly by the diminished extent of the responses during the second five minutes of the infusion. The onset of the increased rate and depth of respiration, accompanied by the fall in alveolar CO_2%, occurred 1 to 1½ minutes after the beginning of the infusion, corresponding in time with the initial changes in forearm blood flow. The initial changes in heart rate and in arterial blood pressure caused by adrenaline and noradrenaline infusions begin at the same time (Allen *et al.*, 1946 ; Barcroft and Konzett, 1949). It is of some interest that all of these responses to adrenaline and noradrenaline, both respiratory and cardiovascular, are at their maximum between the second and the fifth minute of infusion, while they tend to diminish during the second five-minute period, though remaining above their resting levels.

The increased oxygen consumption produced by adrenaline in every subject confirms the frequently observed calorigenic effect of this hormone. The inconsistent calorigenic response to equivalent doses of noradrenaline is in keeping with the results of Reale, Kappert, Skoglund, and Sutton (1950) ; Bearn, Billing, and Sherlock (1951) also showed that noradrenaline had only a small effect on splanchnic oxygen consumption. *In vitro* Sutherland (1950) found that noradrenaline was less effective than adrenaline in releasing glucose from glycogen in tissue slices. The fact that the average increase in the minute volume with noradrenaline was 75% of that with the same dose of adrenaline indicates that the increased oxygen consumption in these experiments cannot be attributed solely to increased activity of the respiratory muscles. The difference between the metabolic effects of adrenaline and noradrenaline also suggests that the stimulation of respiration, observed to approximately the same degree in both, is not due to any general increase in metabolism.

The fall in alveolar CO_2 also observed by Lyman, Nicholls, and McCann (1923) can be attributed to the increase in minute volume, for both are at their maximum during the first five minutes of the infusion period. As with all other respiratory stimulants, with the exception of CO_2 itself, the stimulation of respiration by adrenaline and noradrenaline proceeds in spite of the diminished alveolar CO_2 tension which may fall as low as 32 mm. Hg. This low CO_2 tension may be responsible for the short period of shallow respiration sometimes seen during the latter part of the infusion.

SUMMARY

1. In the normal human subject both adrenaline and noradrenaline stimulate the respiration to a comparable degree when given intravenously at the rate of 10–20 μg./min.

2. There is an increase in tidal volume, an increase in respiratory minute volume, and accompanying this a fall in the alveolar CO_2%. The respiratory rate was usually, but not always, increased

3. The respiratory responses to both adrenaline and noradrenaline are characterized firstly by the abrupt onset of the hyperpnoea, and secondly by the gradual diminution of the response throughout the infusion period.

4. The adrenaline infusions increased the oxygen consumption by an average of 32%, while noradrenaline caused no consistent change. It is suggested, therefore, that the hyperventilation produced by adrenaline and noradrenaline is independent of any general increase in metabolic rate.

We wish to thank Professor H. Barcroft for advice and encouragement. We are also indebted to Dr. A. C. Dornhorst for advice, to the students and colleagues who acted as subjects, and to Mr. G. T. Hales for technical assistance. Part of the expenses were defrayed from an M.R.C. grant to Professor Barcroft.

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