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CIRCULATORY CONTROL IN HYPOXIA BY THE SYMPATHETIC NERVES AND ADRENAL MEDULLA

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SUMMARY

1. The effects of severe arterial and primary tissue (carbon monoxide) hypoxia on cardiac output, arterial and right atrial pressures, heart rate and ventilation, have been studied in unanaesthetized normal rabbits, and in animals subjected to adrenalectomy, 'sympathectomy' (guanethidine), adrenalectomy + 'sympathectomy', and section of the carotid sinus and aortic nerves.

2. In both arterial and primary tissue hypoxia the sympathetic nerves play a more important part in the normal circulatory response than the adrenal medullary hormones.

3. Provided one adrenergic effector pathway remains intact, animals with intact chemoreceptors and baroreceptors tolerate both types of hypoxia well. Circulatory control during both types of hypoxia by means of sympathetic nerves alone produces relatively more peripheral vasoconstriction than is observed during reflex control through increased adrenal catecholamine secretion.

4. The occurrence of tonic sympathetic activity in animals with section of carotid sinus and aortic nerves permits maintenance of a high cardiac output during hypoxia but the arterial pressure is low and there is probably less selective distribution of blood flow to the periphery than in animals with normal reflex control.

5. Absence of any adrenergic activity in adrenalectomized and 'sympathectomized' animals results in a gradual fall in cardiac output during prolonged hypoxia, after an initial small rise.

6. The results in guanethidine-treated animals suggest that the sympathetic discharge to the arterial chemoreceptors is a factor sustaining chemoreceptor discharge during prolonged arterial hypoxia.

INTRODUCTION

In the unanaesthetized rabbit, the circulatory effects of arterial hypoxia following inhalation of low oxygen mixtures differ from those of primary tissue hypoxia resulting from inhalation of small concentrations of carbon monoxide in air (Korner & Edwards, 1960*a*; Korner, 1963, 1965*a*). The different response patterns reflect dissimilar modes of reflex circulatory control by the arterial chemoreceptors and baroreceptors in the two types of hypoxia, and are abolished by section of the carotid sinus and aortic nerves (Korner, 1965*a*). In severe arterial hypoxia the arterial chemoreceptors are the main afferent source of excitation of the autonomic nervous system, whilst in primary tissue hypoxia baroreceptor reflexes can account for many of the circulatory effects (Heymans & Neil, 1958; Korner, 1965*a*; Chalmers, Isbister, Korner & Mok, 1965).

Recent experiments in the rabbit with selective α- and β-adrenergic blocking agents have indicated that in moderate arterial hypoxia, with a P_{O_2} of 35–40 mm Hg, there is little increase in orthosympathetic activity. Only during severe hypoxia, with an arterial P_{O_2} below 35 mm Hg, is this activity markedly increased (Chalmers *et al.* 1965). The severity of the stimulus required to evoke increased sympathetic activity probably accounts for some of the conflicting findings concerning the importance of the orthosympathetic system in reflex circulatory control in arterial hypoxia (Harrison, Blalock, Pilcher & Wilson, 1927; Nahas, Mather, Wargo & Adams, 1954; Penna, Soma & Aviado, 1962; Chidsey, Frye, Kahler & Braunwald, 1961; Guyton, 1963). The role of the orthosympathetic system in primary tissue hypoxia induced by carbon monoxide has been less extensively studied than in arterial hypoxia (Korner, 1963, 1965*a*).

The present experiments were undertaken to investigate the role of the sympathetic nerves and of the adrenal medullary hormones in the circulatory response to severe arterial and primary tissue hypoxia. This has been done by comparing the responses of normal rabbits with those of animals subjected, respectively, to adrenalectomy, pharmacological 'sympathectomy' by guanethidine, or to combined adrenalectomy and guanethidine-'sympathectomy' leading to complete interruption of the adrenergic efferent pathways. The effects of hypoxia in the latter group, deprived of its orthosympathetic efferents, have been compared with those obtained in animals with section of the carotid sinus and aortic nerves, where the main afferent pathways for reflex excitation of the autonomic nervous system in both types of hypoxia have been interrupted (Korner, 1965*a*; Chalmers *et al.* 1965).

METHODS

Animals and groups

New Zealand White rabbits, cross-bred with the New Zealand Giant strain (mean weight 2·5 kg; range 2·1–3·4 kg) were used in these experiments. The five groups of animals are illustrated schematically in Fig. 1. Four of these were used to analyse the role of the orthosympathetic effectors, and these were: (1) normal animals with intact orthosympathetic system; (2) adrenalectomized animals; (3) 'sympathetomized' animals following prolonged treatment with guanethidine; (4) animals with interruption of their entire adrenergic effector pathways after combined adrenalectomy and treatment with guanethidine. The fifth group had its orthosympathetic efferent pathways intact, but had been subjected to section of the carotid sinus and aortic nerves. The effects of hypoxia on this group of animals have been reported previously (Korner, 1965*a*).

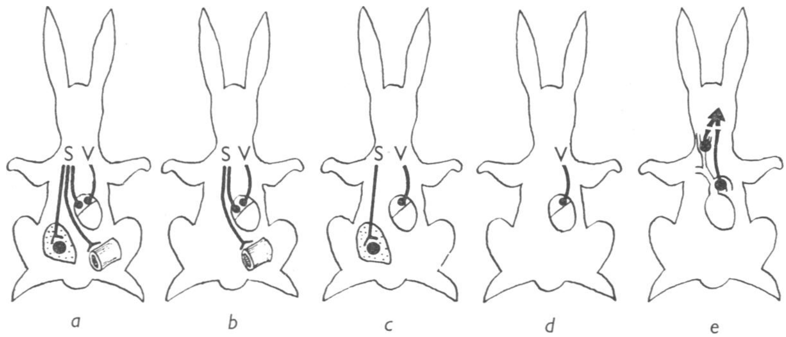

Fig. 1. Schematic representation of different preparations used. S = sympathetic nerves; V = vagus nerve. *a*, normal, *b*, adrenalectomy, *c*, 'sympathectomy', *d*, adrenalectomy + sympathetomy *e*, de-afferented. For detailed description see Methods.

Operative procedures

Preparation of the animals. Thermistor catheters were inserted into the upper abdominal aorta, as described previously (Korner, 1965*b*), at a preliminary operation under sodium pentobarbitone anaesthesia (Veterinary Nembutal, Abbott, initial dose 30–40 mg/kg I.V., supplemented as required). The animals used in the subsequent experiments had all rapidly regained their normal activity and were eating and drinking. On the day of the experiment fine polyvinylchloride (PVC) catheters were inserted into the central ear artery and the right atrium, whilst a light metal tracheotomy tube was introduced into the trachea, using local infiltration anaesthesia (0·5 % lignocaine HCl) of the skin of the ear and neck (Edwards, Korner & Thornburn, 1959; Korner, 1965*b*). The incisions were closed after further infiltration of the skin edges with local anaesthetic.

Adrenalectomy. Adrenalectomy was carried out in two stages, and in later experiments in a one-stage operation, under sodium pentobarbitone anaesthesia. The operative details of adrenalectomy in the rabbit are described elsewhere (White, 1965). When the two-stage procedure was employed, the right adrenal gland was completely excised 2–3 weeks before the second stage operation. Two hours before commencing the second operation the animals received 2 mg cortisone acetate (Merck, Sharp and Dohme, Pty. Ltd.), 3 mg deoxycorticosterone acetate (British Pharmaceuticals Pty. Ltd.) and 20 mg oxytetracycline (Pfizer Pty. Ltd.), all intramuscularly (I.M.) At the operation the left adrenal gland was removed, and the aortic thermistor implanted in the usual way. On the first post-operative day the animals received 2 mg cortisone acetate, and 2 mg deoxycorticosterone acetate, followed by a daily maintenance regime of 1 mg cortisone acetate and 2 mg deoxycorticosterone acetate. Oxytetracycline was given at a dose of 20 mg/day I.M. for the first two post-operative days. The rabbits received food and water *ad libitum*, and remained in good condition with normal serum electrolyte and blood urea values (White, 1965). Experiments were carried out 3–5 days after the operation.

Administration of guanethidine

After implanting the aortic thermistor, a fine PVC catheter was left indwelling in the right atrium (Korner, 1965*b*). The animals were given one daily dose of 12·5 mg/kg of guanethidine (Ismelin, Ciba) I.V. from the first post-operative day for 7–14 days. Following each injection the catheter was filled with concentrated heparin solution (5000 i.u./ml.). After 2–3 days of treatment the animals exhibited ptosis, nasal stuffiness and some diarrhoea, but continued to eat and drink normally, and to maintain their body weight. In adrenalectomized animals the administration of guanethidine started 3–5 days after the second operation. Apart from the usual side effects ascribable to guanethidine these animals also remained in good condition, with normal serum electrolytes and blood urea values.

In the doses used, guanethidine renders sympathetically innervated effector structures including the heart, arterial and venous system, unresponsive to sympathetic nerve stimulation (Maxwell, Plummer, Schneider, Povalski & Daniel, 1960; McCubbin, Kaneko & Page, 1961; Gaffney, Bryant & Braunwald, 1962). The drug depletes the sympathetic nerve endings of their noradrenaline stores, but has little effect on the catecholamine content of the adrenal medulla and central nervous system (Maxwell *et al.* 1960; Cass, Kuntzman & Brodie, 1960; Cass & Spriggs, 1962; Athos, McHugh, Fineberg & Hilton, 1962; Abercrombie & Davies, 1963).

Owing to some doubts regarding a possible vagal blocking action by guanethidine (see Results), the effects of graded electrical stimulation of the peripheral end of the sectioned cervical vagus nerve on heart rate and arterial pressure were examined in two anaesthetized rabbits (sodium pentobarbitone), before and after administration of a single dose of guanethidine, and in two animals treated with guanethidine for seven and fourteen days.

Measurement of cardiac output, blood pressure and heart rate

Cardiac output was measured by the thermodilution method, as described previously (Fegler, 1954; Korner, 1965*b*). Ear artery and right atrial pressures were recorded using a Statham P 23 AC strain gauge, a Grass 5 P 1 pre-amplifier, and a Grass Model 5 Polygraph. The zero reference plane for arterial and right atrial pressure measurements was an arbitrary plane 5 cm above the floor of the rabbit box. Mean pressures were obtained by electronic damping, and heart rates were obtained by counting from the arterial pressure record.

Administration of gas mixtures, blood gas and pH measurements

In each experiment the animals inhaled 8 % O_2 in N_2 (8 % O_2), or 0·2 % CO + 21 % O_2 in N_2 (0·2 % CO). The gases were freshly prepared from cylinders of air, N_2 and 0·5 % CO in air and administered through the respiratory valve—polythene bag assembly described previously (Edwards *et al.* 1959). Expired air was collected for 30 sec after each cardiac output measurement, and the ventilation expressed as l./min of dry gas at s.t.p. Arterial blood was collected anaerobically during the control and test periods, and the O_2 content, CO_2 content, O_2 capacity, pH, P_{CO_2} and P_{O_2} were measured, or calculated, as described previously (Korner, 1965*a*).

Following completion of the minor operative procedures on the day of the experiment the rabbit was placed inside a large rabbit box, where it sat comfortably without restraint. Recording commenced 1 hr after placing the animal into the box. In each animal two experiments were carried out, and the effects of inhaling both 8 % O_2 and 0·2 % CO were examined. Each experiment consisted of a control period (breathing room air), a test period (breathing test gas) and a recovery period (breathing room air). There was an interval of 60–90 min between the two experiments, and the order of testing the two gas mixtures was alternated from animal to animal.

In each experiment one control and one test blood sample were obtained. Approximately thirty sets of measurements of cardiac output, arterial, and right atrial pressures, heart rate and ventilation were made; 2–4 values of each of the latter parameters were obtained for each animal during each of the selected time intervals shown in Figs. 2–4, 6 and 7, and these were averaged in each animal for each time interval. The timing of the various measurements was similar in all experiments, so that the mean values for each time interval could be determined for animals receiving similar treatment. The standard error of the mean of each parameter has been estimated by analysis of variance (Mather, 1949) from the error mean square (EMS) after subtracting 'between animals' and 'between times' sums of squares from the total sum of squares. In a group of n similarly treated animals the S.E. of the mean for each time interval is $(\mathrm{EMS}/n)^{\frac{1}{2}}$, and is represented graphically by the symbol on the left hand side of each parameter in Figs. 2–4, 6 and 7. The S.E. of the difference between the means of any two time intervals is $(2\,\mathrm{EMS}/n)^{\frac{1}{2}}$.

RESULTS

Resting values in animals with varying degrees of orthosympathetic control

The initial resting values of the various parameters in the four groups of rabbits with differing degrees of orthosympathetic control, but intact carotid sinus and aortic nerves, are summarized in Table 1. The values for heart rate, cardiac output and arterial pressure were similar in normal and adrenalectomized animals. Following treatment with guanethidine there was significant reduction in heart rate and arterial pressure, but not in cardiac output. After combined adrenalectomy and guanethidine-'sympathectomy' the blood pressure was reduced further and the cardiac output was now about 20% below the values observed in the control group. The significance of this fall in output is, however, uncertain, in view of the lower mean body weight in this group of animals. The above findings indicate that in the rabbit, as in other species, tonic orthosympathetic effects on the resting circulation are mediated by the sympathetic nerves rather than by the adrenal medullary hormones (Celander, 1954; Folkow, Löfving & Mellander, 1956).

Effects of arterial hypoxia

Inhalation of 8% O_2 resulted in similar marked reduction in arterial P_{O_2} in normal, adrenalectomized, and guanethidine-'sympathectomized' rabbits, but in the group with combined adrenalectomy plus guanethidine-'sympathectomy' the reduction in arterial P_{O_2} was somewhat smaller (Table 2).

The effects on ventilation were similar in normal and adrenalectomized animals (Fig. 2). The ventilation rose to a maximum during the first 10–15 min hypoxia and the increase was well sustained, subsiding by less than 10% of the maximum value. In the two groups of animals treated with guanethidine, the respiratory response differed from the above pattern (Fig. 2). During the early part of hypoxia the rise in ventilation was similar to that of normal rabbits, but subsequently the response was

TABLE 1. Resting circulatory and respiratory measurements obtained during the initial control period in four groups of rabbits: normal, adrenalectomized, guanethidine-treated, adrenalectomized and guanethidine-treated. In each animal the results were based on six to eight measurements of each parameter except the blood analyses, where only one measurement per animal was obtained. The number in brackets after each group is the number of rabbits used

	Normal (5)		Adrenalectomy (7)		Guanethidine (6)		Adrenalectomy and guanethidine (3)	
	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
Body weight (kg)	2·43	±0·08	2·47	±0·09	2·58	±0·18	2·13	±0·04
Cardiac output (ml./min)	637	±41	612	±56	598	±40	519	±43
Heart rate (beats/min)	264	±8·1	273	±14·7	191	±8·6	178	±4·5
Art. pressure (mm Hg)	97	±3·8	90	±4·2	83	±4·0	75	±1·2
Rt. atrial pressure (mm Hg)	−2·6	±0·6	−1·2	±0·9	−1·5	±0·7	−0·5	±0·3
Ventilation (l./min)	1·33	±0·16	1·14	±0·11	1·39	±0·13	1·19	±0·32
Art. saturation (%)	96	±0·4	96	±0·8	96	±0·7	96	±0·6
Art. P_{CO_2} (mm Hg)	30	±5·3	37	±2·5	30	±1·6	38	±2·0
pH	7·45	±0·02	7·41	±0·04	7·48	±0·02	7·47	±0·11

TABLE 2. Changes in arterial blood composition during inhalation of low O_2 and CO mixtures in the various groups. The number in brackets after each group is the number of rabbits used. C = control period breathing room air; T = test period breathing test mixture; S.E. Δ = S.E. of difference calculated as within animal comparisons

	Art. P_{CO_2} (mm. Hg)			Art. pH			Art. saturation* (%)			Art. P_{O_2} (mm. Hg)	
	C	T	S.E. Δ	C	T	S.E. Δ	C	T	S.E. Δ	T	S.E.
Low O_2											
Normal (5)	31	13	±4·4	7·44	7·65	±0·012	96	55	±2·4	25	±1·3
Adrenalectomy (4)	39	19	±3·7	7·42	7·64	±0·034	95	59	±3·7	27	±2·7
Guanethidine (4)	29	14	±2·6	7·47	7·69	±0·023	96	56	±0·9	25	±1·1
Adrenalectomy + guanethidine (3)	34	18	±1·0	7·48	7·64	±0·082	97	60	±1·9	32	±0·9
De-afferented (5)†	34	26	±3·0	7·46	7·46	±0·082	93	48	±3·5	27	±2·4
Carbon monoxide											
Normal (4)	27	27	±1·2	7·44	7·39	±0·024	97	56	±1·7	—	—
Adrenalectomy (6)	32	30	±2·8	7·45	7·44	±0·018	97	54	±3·3	—	—
Guanethidine (3)	32	26	±2·7	7·46	7·45	±0·010	95	59	±1·2	—	—
Adrenalectomy + guanethidine (2)	38	33	±0·1	7·42	7·37	±0·023	96	60	±1·6	—	—
Deafferented (3)†	27	22	±2·2	7·55	7·48	±0·055	98	54	±3·2	—	—

* In animals breathing 0·2 % CO in air art. saturation = $(HbO_2)/HbO_2+HbCO+Hb)$.

† Data of animals with section of carotid sinus and aortic nerves from Korner (1965*a*).

less well sustained especially in the 'sympathectomy' group, and fell by about 20–30% of the maximum. In both the guanethidine-treated groups the ventilation also recovered more rapidly following hypoxia, usually falling below the initial control values immediately after resumption of air-breathing (Fig. 2).

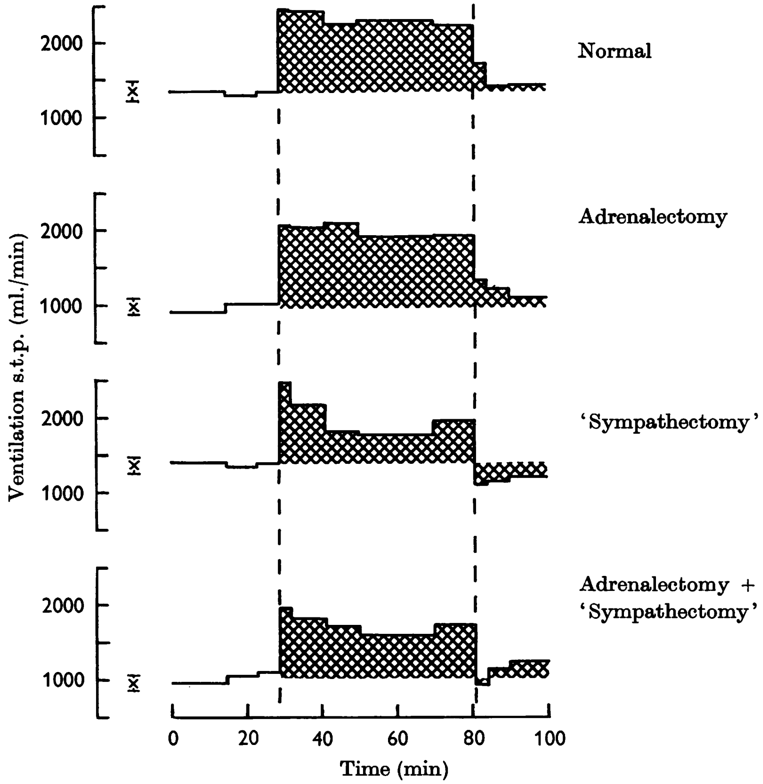

Fig. 2. Mean effects of breathing 8% O_2 on the ventilation (ml./min s.t.p.) in rabbits (from above down): five normal; four adrenalectomized; four guanethidine 'sympathectomized'; three adrenalectomized and guanethidine-'sympathethectomized'; Animals breathed test mixture between vertical interrupted lines, room air at other times. Hatching denotes deviation of the test and recovery values from the initial control values. Symbol on left: cross indicates mean initial control value, with S.E. of mean of a single time interval above and below cross.

The circulatory findings in the normal animals differed slightly from those observed previously (Korner, 1965*a*), possibly owing to the greater reduction in arterial P_{O_2} in the present experiments. The effects during the early phase of hypoxia consisted of bradycardia, a rise in arterial pressure and a transient reduction in cardiac output (Fig. 3, left panels), in agreement with previous observations. The duration of bradycardia was, however, less prolonged, the heart rate rising significantly above initial control values in four out of five animals during the 'steady state'. The cardiac output also increased more rapidly from its initial minimum, with an 'overshoot' of about 10 % of the initial control value, followed by a return to this level.

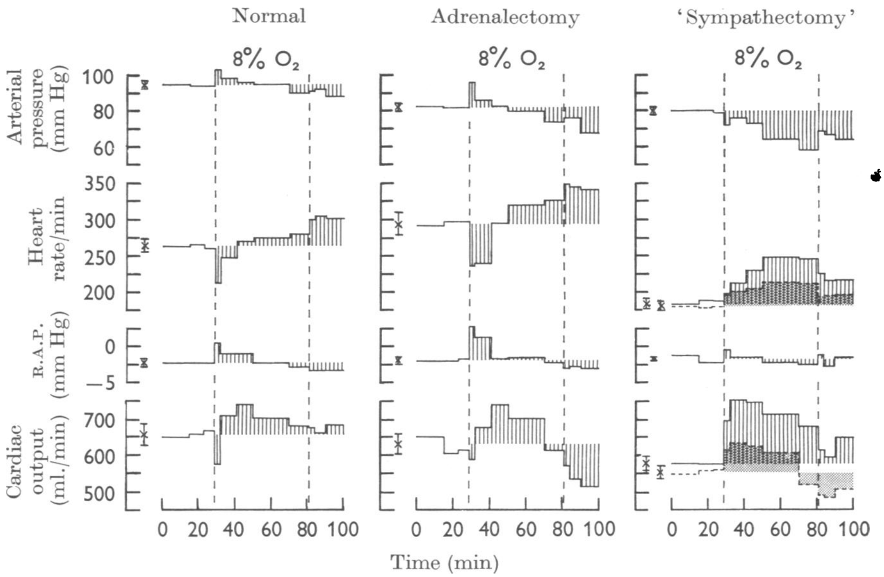

Fig. 3. Mean effects of breathing 8 % O_2 on arterial pressure (mm Hg); heart rate (beats/min); right atrial pressure (R.A.P. mm Hg) and cardiac output (ml./min) in five normal (*left panels*), four adrenalectomized (*middle panels*) and four guanethidine-'sympathectomized' rabbits (*right panels*). The dotted values for heart rate and cardiac output superimposed on the results of the guanethidine-'sympathectomized' group are the results from three adrenalectomized and guanethidine-'sympathectomized' animals (see Fig. 4). Notation as in Fig. 2.

The circulatory findings during hypoxia in adrenalectomized rabbits were closely similar to those observed in the normal group (Fig. 3, middle panels). During recovery there were minor differences in the response of the two groups, with greater reduction in arterial pressure and cardiac output in adrenalectomized animals.

In animals 'sympathectomized' with guanethidine, reflex orthosympathetic activity can be increased only through increased liberation of adrenal medullary hormones, consisting, in the rabbit, mainly of adrenaline acting on hypersensitive effector structures (Goodall, 1951, Hökfelt, 1951; Shepherd & West, 1952; Trendelenburg, 1963). The circulatory response differed considerably from normal. During the early phase of hypoxia there was tachycardia, a small regular fall in blood pressure, and a marked immediate rise in cardiac output (Fig. 3, right panels). The blood pressure was further reduced and the heart rate increased during the 'steady-state'. Comparison of these changes with those observed in rabbits with combined adrenalectomy plus guanethidine-'sympathectomy' suggests that about half the increase in heart rate and cardiac output is due to increased adrenal catecholamine secretion (Fig. 3, right panels, stippled hatching, and Fig. 4, left panels).

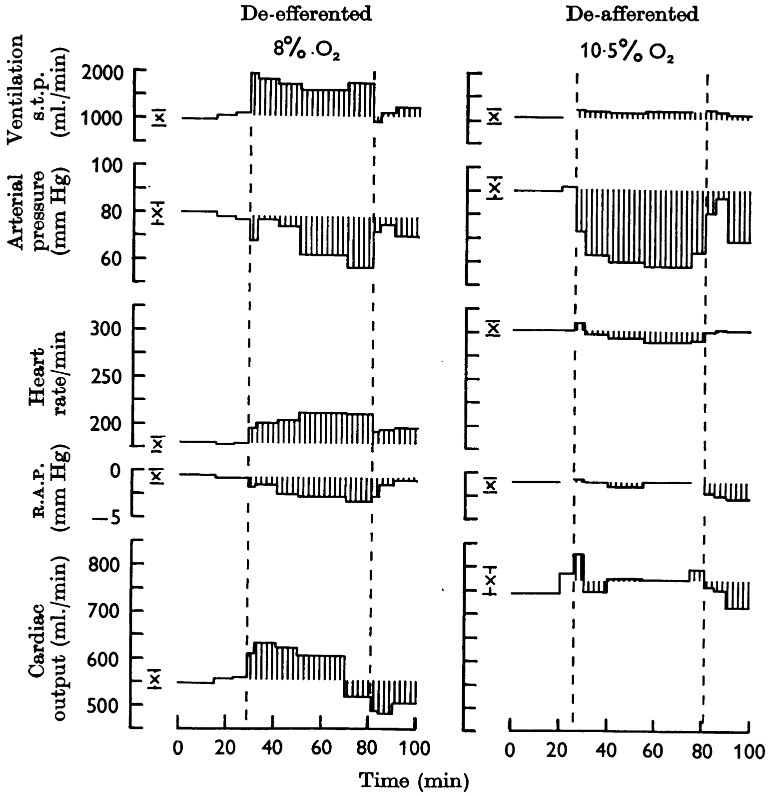

Fig. 4. *Left* (de-efferented). Mean effects of breathing 8 % O_2 on ventilation (ml./min s.t.p.), arterial pressure (mm Hg), heart rate (beats/min), right atrial pressure (mm Hg) and cardiac output (ml./min) in three adrenalectomized and guanethidine-'sympathectomized' rabbits. Notation as in Fig. 2. *Right* (de-afferented). Mean effects on above parameters of similar reduction in arterial P_{O_2} resulting from inhalation of 10·5 % O_2 in five animals with section of carotid sinus and aortic nerves.

In the latter animals with complete interruption of adrenergic efferents the arterial pressure fell by about the same amount as in animals subjected only to guanethidine-'sympathectomy'. The small increase in heart rate is probably the result of baroreceptor-mediated reduction in vagal activity, since it is not observed in animals with section of the carotid sinus and aortic nerves (Fig. 4). The initial small increase in cardiac output was not sustained throughout the test period, falling below initial control values after about 30–40 min hypoxia. In all experiments there was significant reduction in the right atrial pressure (Fig. 4, left panels).

It is of interest to contrast these effects in de-efferented animals, with the results obtained in rabbits with section of the carotid sinus and aortic nerves (Korner, 1965*a*; Fig. 4, right panels). In the de-afferented animals the initial control values for heart rate, cardiac output and arterial pressure are increased, reflecting greater tonic orthosympathetic activity after nerve section (Heymans & Neil, 1958; Korner, 1965*b*). During hypoxia the blood pressure fell more rapidly than in the de-efferented group, but the final blood pressure levels were similar in both groups. The high initial cardiac output, and heart rates, were well sustained throughout hypoxia,

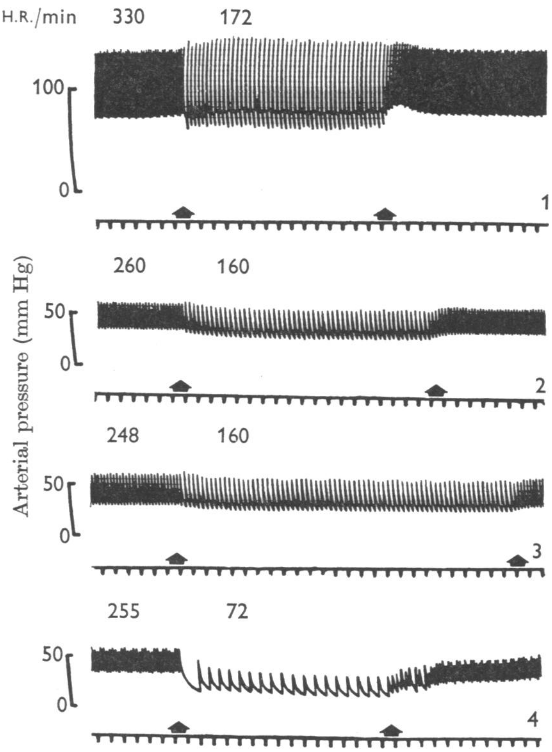

Fig. 5. (1–3) Records of blood pressure and heart rate obtained in the course of stimulating peripheral end of r. cervical vagus (between arrows) with rectangular 3 V pulses, 500 μsec duration, at 20 c/s: (1) before, (2) 10 min after, and (3) 2 hr after injection of 12·5 mg/kg guanethidine I.V.

(4) Record of blood pressure and heart rate obtained during stimulation of peripheral end of r. cervical vagus with pulses of 13 V, 1 msec duration at 50 c/s in another rabbit after Fig. (7) days' treatment with guanethidine (12·5 mg/kg/day).

Figures above each tracing indicate heart rate before and after vagal stimulation. Time marker, 1 sec.

and the right atrial pressure was maintained. During the 'steady-state', the cardiac output was thus about 50% greater in the de-afferented than in de-efferented rabbits, although reflex increase in orthosympathetic activity during hypoxia has been abolished in both groups (cf. Chalmers *et al.* 1965).

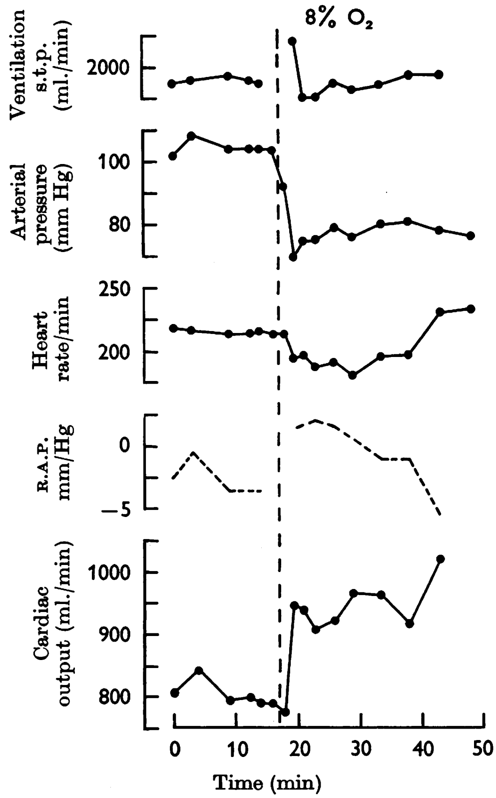

Fig. 6. Circulatory and respiratory effects of extreme arterial hypoxia (art. P_{O_2} 20 mm Hg) obtained in one guanethidine-'sympathectomized' rabbit. Further description in text.

The absence of bradycardia from the early circulatory response of both groups of animals treated with guanethidine was unexpected, since in the rabbit this effect is largely mediated by the vagus following strong arterial chemoreceptor stimulation (Korner & Edwards, 1960*b*). Electrical stimulation of the cardiac end of the cervical vagus readily produced bradycardia in anaesthetized animals treated with guanethidine (Fig. 5). Absence of bradycardia was thus not the result of inability of the heart to respond to vagal stimulation. During hypoxia bradycardia was observed in only one animal treated with guanethidine (Fig. 6). In this animal the ventilation

TABLE 3. Mean ventilation (l./min. of dry expired gas at s.t.p.) during selected time intervals during the control, test and recovery periods in various groups of animals breathing 0·2 % CO. The S.E. of the mean of each time interval has been calculated by analysis of variance as described in Methods. The number in brackets after each group is the number of rabbits used

	Control (air)			Test (0·2 % CO)					Recovery (air)			S.E. of mean
Time from start (min) ...	−15	−23	−28	−32	−41	−50	−70	−80	−84	−90	−100	
Group												
Normal (4)	1·11	1·24	1·17	1·12	1·14	1·25	1·30	1·65	1·67	1·66	1·72	±0·11
Adrenalectomy (6)	1·16	1·07	1·09	1·03	1·00	1·21	1·14	1·15	1·14	1·07	1·05	±0·13
Guanethidine (3)	1·10	1·32	1·21	1·42	1·48	1·39	1·23	1·54	1·45	1·44	1·33	±0·19
Adrenalectomy and guanethidine (2)	1·32	1·24	1·39	1·32	1·19	1·41	1·71	—	1·69	1·15	0·94	±0·16

did not increase during hypoxia, resulting in extreme reduction in the arterial P_{O_2} to 20 mm Hg, together with slight, transient bradycardia before termination of the experiment.

Effects of primary tissue hypoxia

Inhalation of 0·2 % CO induced similar changes in the blood gas and pH measurements of all groups (Table 2). Changes in ventilation were minimal in all groups, except in adrenalectomized rabbits treated with guanethidine, in which the ventilation increased significantly after 20 min hypoxia (Table 3).

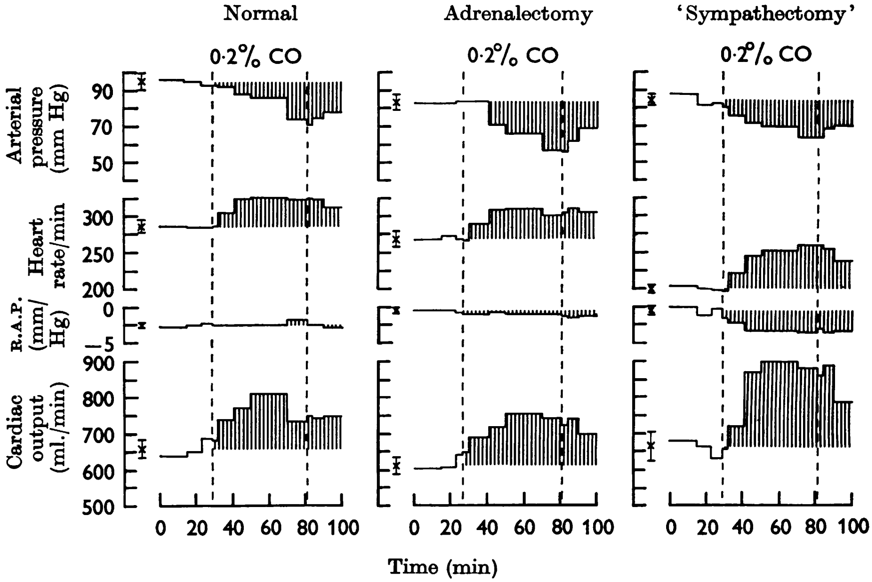

Fig. 7. Mean effects of breathing 0·2 % CO on arterial pressure (mm Hg), heart rate (beats/min), right atrial pressure (R.A.P. mm Hg) and cardiac output (ml./min) in four normal (*left panel*), six adrenalectomized (*middle panel*), and three guanethidine-'sympathectomized' rabbits (*right panel*). Notation as in Fig. 2.

The circulatory effects of inhalation of 0·2 % CO in normal rabbits consisted of an increase in heart rate and cardiac output, and a fall in arterial pressure (Fig. 7, left panels), in agreement with previous findings (Korner, 1965*a*). This response was not significantly modified by adrenalectomy (Fig. 7, middle panels). After guanethidine-'sympathectomy' the changes were again qualitatively similar (Fig. 7, right panels). However, the changes in heart rate and cardiac output in 'sympathectomized' rabbits were larger than normal in relation to the initial control values, and there was also significant reduction in right atrial pressure.

After combined adrenalectomy and guanethidine-'sympathectomy', the rise in heart rate and cardiac output was significantly smaller than after guanethidine-'sympathectomy' alone, indicating that the effects in the latter animals were the result of increased adrenal catecholamine secretion (Fig. 6, right panel; Fig. 8, left panel). Furthermore, after adrenalectomy plus drug-'sympathectomy' there was a more pronounced fall in arterial pressure.

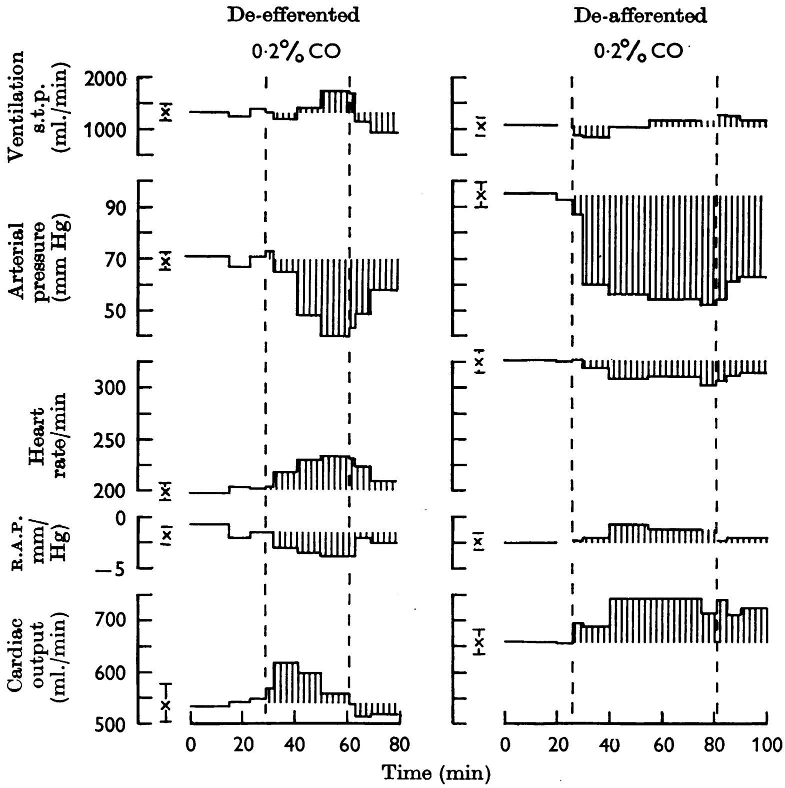

Fig. 8. *Left* (de-efferented). Mean effects of breathing 0·2 % CO on ventilation (ml./min s.t.p.), arterial pressure (mm Hg), heart rate (beats/min), right atrial pressure (mm Hg) and cardiac output (ml./min) in two adrenalectomized and guanethidine-'sympathectomized' rabbits. Notation as in Fig. 2.

Right (de-afferented). Mean effects on above parameters of breathing 0·2 % CO in three rabbits with section of the carotid sinus and aortic nerves.

Comparison of the results in the de-efferented animals with those obtained in rabbits with section of the carotid sinus and aortic nerves indicates that in both preparations there was a marked fall in arterial pressure during hypoxia with somewhat lower absolute pressure values observed in de-efferented rabbits. The rise in heart rate observed in rabbits with interrupted adrenergic pathways was not observed after aortic nerve section, suggesting that it was of carotid sinus and baroreceptor origin and mediated through the vagus. In contrast to the transient slight increase in cardiac output and fall in right atrial pressure during inhalation of 0·2% CO in de-efferented animals, the cardiac output increased above its initially elevated value in the de-afferented rabbits and this was associated with a rise in right atrial pressure (Fig. 8, right panels). As in arterial hypoxia, the cardiac output is thus about 50% higher in the de-afferented animals during primary tissue hypoxia than in rabbits with complete interruption of their adrenergic efferent pathways.

DISCUSSION

Role of the orthosympathetic system in hypoxia

The present experiments suggest that the sympathetic nerves play a more important role than the adrenal medullary hormones in the normal circulatory response to arterial hypoxia, since this is unaffected by adrenalectomy but is extensively modified by pharmacological 'sympathectomy' with guanethidine. This is in accord with the demonstration of only a small increase in circulating catecholamine levels during severe arterial hypoxia (Baugh, Cornett & Hatcher, 1959; Fowler, Shabetai & Holmes, 1961; Fukuda & Kobayashi, 1961; Malmejac, 1964). The present findings indicate that in animals in which sympathetic nerves are the sole reflex adrenergic effector pathway there is an increase in total peripheral resistance during arterial hypoxia suggestive of peripheral vasoconstriction, whilst in animals depending only on adrenal catecholamines the total peripheral resistance falls. This is most clearly seen during the early phase of arterial hypoxia in which there is a rise in arterial pressure and fall in cardiac output in adrenalectomized animals (TPR 165% of control), but a fall in arterial pressure and marked increase in cardiac output in 'sympathectomized' animals (TPR 76% of control). The rise in cardiac output in the latter group is largely the result of myocardial stimulation by adrenal catecholamine secretion, since the response is much attenuated in the group of adrenalectomized plus 'sympathectomized' animals. The present experiments suggest that in early arterial hypoxia there is probably less *uniform* distribution of peripheral blood flow (with preferential perfusion of some regions at the expense of others) as a result of increased neural activity than occurs after increased secretion of adrenal hormones (cf. Krogh, 1929; Korner, 1963). The above differences between adrenalectomized and 'sympathectomized' animals are still present during the 'steady state', but are much less marked. At this time the cardiac output is similar in both groups (as well as in normal animals) but there is greater reduction in systemic vascular resistance in 'sympathectomized' rabbits than in the other groups.

In primary tissue hypoxia the response of the adrenalectomized animal resembles more closely that of normal rabbits than the response of the 'sympathectomized' groups. This is consistent with the view that neural activity plays a more important role in the circulatory response than the adrenal medullary hormones. However, the results of Fukuda & Kobayashi (1961) suggest that the latter are secreted in greater amounts in this type of hypoxia than in arterial hypoxia.

The circulatory findings in primary tissue hypoxia are suggestive of over-all peripheral vasodilatation, with a rise in cardiac output and fall in arterial pressure occurring in normal, adrenalectomized and 'sympathectomized' rabbits. There are, however, quantitative differences in the circulatory response of the three groups, with the greatest rise in cardiac output and fall in systemic resistance observed in 'sympathectomized' animals. In primary tissue hypoxia, as in arterial hypoxia, increased sympathetic nerve activity thus has *relatively* greater constrictor effects on the peripheral vessels than increased secretion of adrenal catecholamines.

The cardiac output values observed in both types of hypoxia are approximately similar in animals with reflex orthosympathetic control through at least one adrenergic effector, to those found in animals with section of the carotid sinus and aortic nerves. In these de-afferented animals reflex control of the circulation in hypoxia is largely abolished, although tonic sympathetic activity is present (Heymans & Neil, 1958; Korner, 1965*a*, *b*; Chalmers *et al.* 1965). Since the de-afferented animal has a much lower arterial pressure during hypoxia than rabbits with some reflex circulatory control, it seems probable that the cerebral circulation would be less adequately perfused in the former animal as a result of more widespread arteriolar dilatation and less selective distribution of blood flow. However, maintenance of tonic sympathetic activity to the heart and veins does allow the de-afferented animal to have a cardiac output during hypoxia 50% above that found in de-efferented rabbits with complete abolition of orthosympathetic activity. In the latter the cardiac output falls gradually during hypoxia after a small initial rise, probably as a result of progressive venodilatation. This is suggested by the gradual fall in the right atrial pressure in these animals. The de-efferented animal has similar problems of distribution of blood flow to the de-afferented rabbit, but seems less able to maintain its already relatively low cardiac output during prolonged hypoxia. As a result its tissue oxygen supply to all parts of the body is probably inadequate.

Sympathetic nerves and bradycardia

The complete absence of bradycardia during arterial hypoxia in the two groups of guanethidine-treated animals calls for comment. Three factors could explain the reduced fall in heart rate. First, reduction in bradycardia would be expected since potentiation by baroreceptor reflexes of the effects of chemoreceptor stimulation on heart rate is abolished or reversed owing to the fall in blood pressure (Euler & Liljestrand, 1943; Heymans & Neil, 1958; Downing & Siegel, 1963; Chalmers *et al.* 1965). In addition, the chronotropic effects of adrenaline acting on a hypersensitive pacemaker in the guanethidine-'sympathectomized' rabbits could outweigh the effects of increased vagal activity, converting it into a tachycardia, and could account for the relatively slower increase in heart rate than in cardiac output in this group. This factor would obviously not be operative in animals subjected to combined adrenalectomy and guanethidine.

A third factor which could explain the absence of bradycardia is a possible smaller increase in arterial chemoreceptor discharge for a given reduction in arterial P_{O_2}. This is suggested by the less sustained increase in ventilation during severe hypoxia. This type of respiratory response is observed in normal animals during milder degrees of arterial hypoxia, and presumably less arterial chemoreceptor activity in the absence of central respiratory depression (Korner, 1965*a*). In the present experiments extreme reduction in aterial P_{O_2} was necessary to evoke bradycardia reflexly, though it could be readily produced by direct vagal stimulation. The findings suggest that in the normal animal increased sympathetic activity is a factor sustaining the chemoreceptor discharge during prolonged severe arterial hypoxia. This could be accomplished by reduction in carotid blood flow (Floyd & Neil, 1952; Daly, Lambertsen & Schweitzer, 1954; Eyzaguirre & Lewin, 1961), or by modulation of chemoreceptor activity in the same way as demonstrated for certain mechanoreceptors (Loewenstein, 1956; Hunt, 1960; Paintal, 1965).

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