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The cardio-toxicity of isoprenaline during hypoxia

J. M. COLLINS, D. G. McDEVITT, R. G. SHANKS AND J. G. SWANTON

Department of Therapeutics and Pharmacology, The Queen's University, Belfast, Northern Ireland

1. The effects of the intravenous injection of isoprenaline on heart rate and arterial pressure has been studied in dogs artificially respired with room air or with 12% oxygen—88% nitrogen.

2. In dogs breathing room air, isoprenaline in doses from 0·02 to 500 μg/kg increased heart rate and reduced arterial pressure. Ventricular fibrillation was produced in one out of three dogs given 250 μg/kg. This was the only dog breathing room air which was killed by isoprenaline.

3. In dogs breathing room air the repeated intravenous injection at 5-min intervals of 2·5 μg/kg increased heart rate and reduced arterial pressure. No ill effects were produced by six doses.

4. In dogs respired with 12% oxygen—88% nitrogen the Pa_{O_2} was reduced from 84 to 38 mm Hg with no changes in Pa_{CO_2}. In these dogs death was produced by doses of isoprenaline which in dogs breathing room air produced normal responses.

5. The fatal dose of isoprenaline (10–50 μg/kg) reduced heart rate and arterial and pulse pressures ; sinus rhythm persisted until arterial pressure was less than 50 mm Hg. Ventricular fibrillation did not occur ; death occurred from cardiac asystole.

6. Death was produced in a similar way in dogs with hypoxaemia by giving four or five doses of isoprenaline (2·5 μg/kg) at 5-min intervals or by two doses of 25 μg/kg.

7. The final reduction in arterial pressure during a fatal response resulted from a reduction in cardiac contractility.

8. These lethal effects of isoprenaline could be prevented by pretreatment with propranolol.

Since the observations of Smith (1966) several reports have been published describing an increase in mortality from asthma (Gandevia, 1968 ; Speizer, Doll & Heaf, 1968). The increase in deaths has been attributed to excessive use of aerosols containing sympathomimetic amines, principally isoprenaline (Speizer, Doll, Heaf & Strang, 1968). In the study of Speizer, Doll, Heaf & Strang (1968) 150 out of 174 patients had been using bronchodilators shortly before death. As isoprenaline administered by inhalation is absorbed rapidly into the blood stream and affects the heart (Chamberlain, 1967), it has been suggested that the deaths in these asthmatic patients may result from sympathomimetic-induced cardiac

arrhythmias—for example ventricular tachycardia or fibrillation (Speizer, Doll, Heaf & Strang, 1968). This is speculation, for detailed studies have not been made in any of these patients. In normal man the intravenous infusion of isoprenaline in small doses (0·8–5·3 μg/min) increases heart rate (Krasnow, Rolett, Yurchak, Hood & Gorlin, 1964); in conscious dogs larger doses (0·4 μg/kg) increase heart rate but do not produce cardiac arrhythmias, (Shanks, unpublished). In anaesthetized cats much larger doses (1 mg/kg) did not cause death (Butterworth, 1963).

In patients with asthma, the tensions of oxygen and carbon dioxide in arterial blood may be altered (Palmer & Diament, 1967; Tai & Read, 1967; Valabhji, 1968). These changes might alter the cardiac actions of isoprenaline and other sympathomimetic amines. The observations described in this paper were made to see if changes in the arterial blood oxygen tension alter the cardiovascular responses to isoprenaline in anaesthetized dogs.

Methods

Observations were made in dogs weighing between 20 and 28 kg and anaesthetized by the subcutaneous injection of morphine sulphate, 0·5 mg/kg, followed 1 hr later by the intravenous injection of pentobarbitone, 20 mg/kg. A cuffed endotracheal tube was inserted and the dogs were artificially respired with room air using a Starling Ideal pump at a rate of 18 strokes/min and stroke of 13 ml./kg body weight. Some dogs were also respired with a mixture of 12% oxygen and 88% nitrogen (British Oxygen Gases Ltd.). Drugs were injected through a catheter in a foreleg vein. Arterial pressure was measured from the left carotid artery by means of a metal cannula leading to a strain gauge (Consolidated Electrodynamics; Type 4-327-L221) attached to a direct writing recorder (Model 8, Devices Ltd.). The electrocardiogram was obtained from needle electrodes inserted into the skin; one lead (I, II or III) was recorded and another used to drive an instantaneous cardiotachometer (Devices Ltd.), the output of which was recorded. All responses were monitored on a four-channel oscilloscope (Airmec). Samples of arterial blood for gas analyses were obtained by means of heparinized syringes from the cannula in the left carotid artery. A sample was taken from all dogs during respiration with room air and before the administration of any drug and from those dogs respired with 12% oxygen—88% nitrogen 5 min after commencement of respiration with this mixture. The P_{CO_2} was measured with the Astrup micro-glass electrode and equilibrating apparatus (Siggaard Andersen, Engel, Jorgensen & Astrup, 1960). P_{O_2} was measured with the Clark electrode supplied and used in conjunction with the Astrup apparatus. In three dogs, left ventricular stroke volume was measured by placing a probe of an electromagnetic flowmeter (M 4000, Statham Instruments, Inc.) around the ascending aorta and recording the output on the Devices recorder at a paper speed of 10 cm/sec.

Isoprenaline was used as the sulphate, but the doses quoted in the text, are expressed in terms of the base.

Results

The mean values of Pa_{O_2} and Pa_{CO_2} from all the dogs during respiration with room air and from those respired with 12% oxygen—88% nitrogen are given in Table 1. Respiration with the hypoxic mixture reduced Pa_{O_2} without changing Pa_{CO_2}.

Responses to increasing doses of isoprenaline

The changes in heart rate and arterial pressure produced by the intravenous injection of a series of increasing doses of isoprenaline (0·5 to 100 μg/kg) were determined in six dogs. There was an interval of 5–10 min between each dose. The averaged results are given in Table 2. Isoprenaline increased heart rate and reduced arterial pressure (Fig. 1a); the changes were greatest with isoprenaline 2·5–10·0 μg/kg. Larger doses produced more prolonged and slightly smaller heart rate responses. The reduction in the latter may have resulted from the gradual increase in resting heart rate that occurred. In some dogs occasional ventricular ectopic beats occurred after the injection of isoprenaline; their incidence was not related to the dose of isoprenaline. All animals survived the largest dose of isoprenaline (Table 5A). The effects of a series of increasing doses of isoprenaline (0·02 to 500 μg/kg) was studied in another three dogs. The responses were similar to those obtained in the first group of six dogs. Ventricular fibrillation occurred in one of these three dogs after the administration of isoprenaline 250 μg/kg. The remaining two dogs survived 500 μg/kg.

Respiration with 12% oxygen—88% nitrogen

After administration of the series of increasing doses of isoprenaline 0·5 to 100·0 μg/kg in five dogs respired with room air, respiration with 12% oxygen—88% nitrogen was started. Five minutes later the intravenous administration of the same series of increasing doses of isoprenaline was commenced. The changes in heart rate and arterial pressure produced by isoprenaline 0·5 and 2·5 μg/kg are reported in Table 3A and were less than occurred when the same doses were given during respiration with room air (Table 2). In three of these five dogs the responses to isoprenaline 10·0 μg/kg were different from those obtained when they breathed room air. The normal decrease in arterial pressure was not followed by a return to the resting level but continued to fall so that within 2 min it was less than 50 mm Hg (Fig. 1b). There was also a striking reduction in pulse pressure. After an initial increase, heart rate declined to the resting level for 60–90 sec and then fell

TABLE 1. *Mean values* (±SEM) *for* Pa_{O_2} *and* Pa_{CO_2} *in anaesthetized dogs during respiration with room air and with* 12% *oxygen*–88% *nitrogen*

	No. of dogs	Pa_{O_2} (mm Hg)	Pa_{CO_2} (mm Hg)
Room air	30	84·0±4·1	44·8±1·7
12% oxygen–88% nitrogen	26	38·0±2·1	44·7±2·5

TABLE 2. *Average changes* (±SEM) *in heart rate, systolic and diastolic pressure produced by intravenous injection of isoprenaline in six dogs respired with room air*

		Dose of isoprenaline (μg/kg)					
		0·5	2·5	10·0	25·0	50·0	100·0
Heart rate (beats/min)	R	190 ±12·6	204±11·5	200 ±11·3	208± 8·7	212±10·6	222 ±13·0
	I	+67·5± 6·4	+82± 6·6	+81·7± 8·8	+71± 6·0	+63± 4·9	+62·5± 5·7
Systolic pressure (mm Hg)	R	202 ±15·2	220±22·9	211 ±17·9	203±13·7	201±12·6	193 ±12·8
	I	−47 ±10·0	−56± 6·4	−67 ±10·9	−74± 7·2	−74± 6·2	−78 ± 5·3
Diastolic pressure (mm Hg)	R	165 ±14·5	182±26·4	171 ±15·6	154± 8·9	151± 7·4	145 ± 7·1
	I	−65 ±14·9	−91± 5·2	−106 ± 7·2	−103± 5·1	−99± 5·5	−97 ± 4·9

R, Resting value; I, maximum change produced by isoprenaline.

rapidly to a rate of 40–50/min (Fig. 1b). The electrocardiogram showed that sinus rhythm persisted until arterial pressure was less than 50 mm Hg when either a slow A-V nodal rhythm or irregular ventricular ectopic beats occurred; the rate of these beats gradually decreased until cardiac asystole and death occurred. Two of the five dogs had normal responses to isoprenaline, 10 μg/kg, but one had a similar fatal response after 25·0 μg/kg and the other after 50·0 μg/kg. These results are summarized in Table 5A.

As the doses of isoprenaline given to these animals when they were respired with room air may have influenced the responses that occurred when the drug was given during hypoxia, observations were made in four dogs which were respired with room air for 10–15 min, changed to the hypoxic mixture for 5 min and then given increasing doses of isoprenaline. The changes in heart rate and arterial pressure

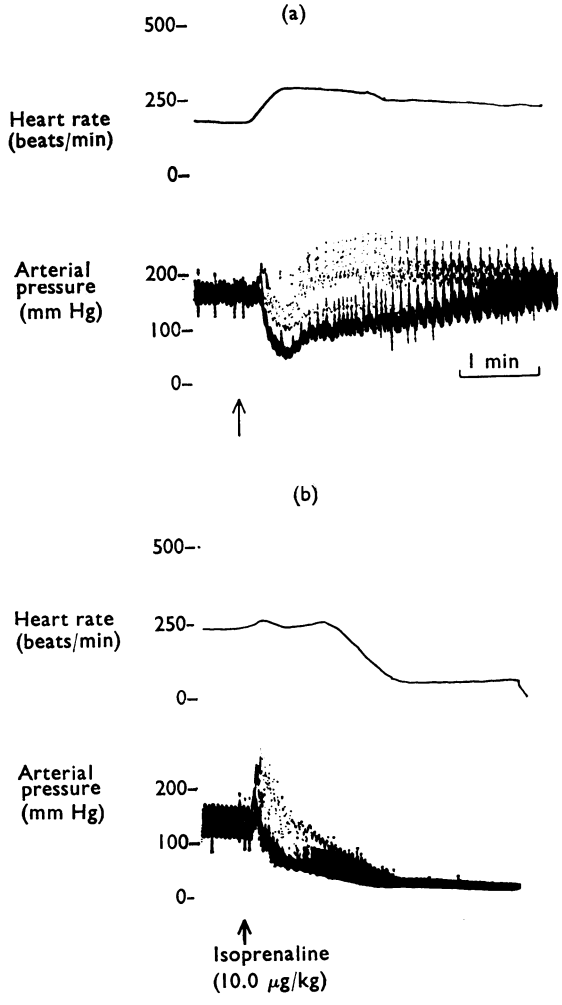

FIG. 1. Records of heart rate and arterial pressure in an anaesthetized dog. Responses to the intravenous injection of isoprenaline, 10 μg/kg, during respiration with room air (a, top panel) and later with 12% oxygen—88% nitrogen (b, lower panel).

TABLE 3. *Average changes (±SEM) in heart rate, systolic and diastolic pressure produced by intravenous injection of isoprenaline in dogs respired with 12% oxygen–88% nitrogen*

		A		B	
Dose of isoprenaline (μg/kg)		0·5	2·5	0·5	2·5
Number of dogs		5	5	4	4
Heart rate (beats/min)	R	198±20·2	196±22·3	225± 8·7	238±10·8
	I	+18±10·0	+45±13·1	+97± 8·5*	+98±10·1*
Systolic pressure (mm Hg)	R	232±15·8	225±17·1	224±10·2	242±13·5
	I	−8±26·8	−41± 8·9	−59± 4·3	−94±11·7*
Diastolic pressure (mm Hg)	R	153±10·0	154±11·8	178± 5·9	164± 9·8
	I	−14±14·0	−35±21·0	−92± 5·2*	−92± 5·7

A, Followed isoprenaline administrations during respiration with room air.
B, No previous dose of isoprenaline.
* $P<0·05$ for comparison of responses in groups A and B. Where no asterisk is shown, $P>0·05$ for comparison of responses in groups A and B.
R, Resting value; I, maximum change produced by isoprenaline.

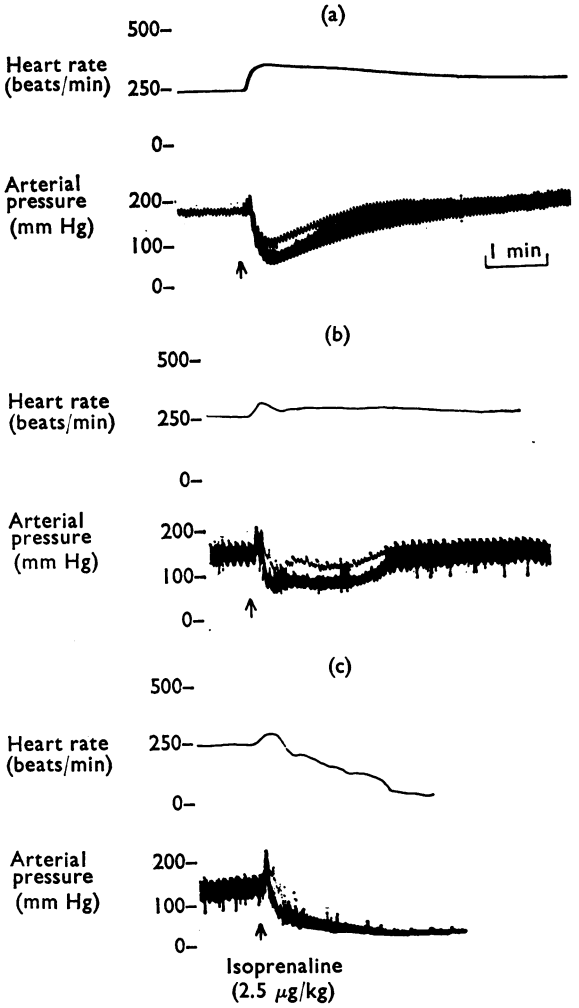

FIG. 2. Records of heart rate and arterial pressure in an anaesthetized dog. Responses to the intravenous injection of isoprenaline, 2·5 μg/kg, during respiration with room air (a, upper panel) and later with 12% oxygen—88% nitrogen (lower two panels). The middle (b) and lower (c) set of records are the responses to the fourth and fifth doses of isoprenaline respectively.

produced by isoprenaline 0·5 and 2·5 μg/kg were slightly greater in these hypoxic dogs than in the dogs respired with room air (compare Tables 2 and 3B). As in the previous experiments, doses larger than 2·5 μg/kg produced death. One of the dogs died after isoprenaline 10·0 μg/kg, two after 25·0 μg/kg, and the remaining one after 50·0 μg/kg (Table 5A). In each dog the final (fatal) dose of isoprenaline reduced heart rate and arterial pressure and produced asystole and death. The responses to non-fatal doses of isoprenaline included occasional ventricular ectopic beats but these never occurred in runs.

Responses to repetition of the same dose of isoprenaline

Respiration with room air

In four dogs the responses to the intravenous injection of six doses of isoprenaline, 2·5 μg/kg with 5 min between each dose, were recorded. Isoprenaline increased heart rate and reduced arterial pressure (Fig. 2a). The results are given in Table 4. The increase in heart rate and the decrease in arterial pressure were both significantly greater ($P<0·05$) with the first dose than with the second and subsequent doses. All four dogs survived the six doses of isoprenaline (Table 5B)

Respiration with 12% oxygen—88% nitrogen

In six dogs 5 min after starting artificial respiration with 12% oxygen—88% nitrogen, a number of doses of isoprenaline 2·5 μg/kg were given at 5 min intervals. All doses increased heart rate and reduced arterial pressure (Table 4, Fig. 2b). In one dog the third dose of isoprenaline produced death with cardiac asystole. The mortality rate increased as the number of doses was increased; no animal survived five doses (Table 5B). The pattern of response to the fatal dose of isoprenaline was similar to that described previously ; heart rate and arterial and pulse pressures decreased to reach low levels within 2 min as shown in Fig. 2c. Sinus rhythm was present until arterial pressure was less than 40 mm Hg when a slow nodal or ventricular rhythm developed which slowed progressively to asystole. Ventricular ectopic beats occurred in some dogs during the responses to all doses of isoprenaline.

TABLE 4. *Average changes* (±SEM) *in heart rate, systolic and diastolic arterial pressure produced by the intravenous injection of a series of doses of isoprenaline, 2·5 μg/kg, given at 5 min intervals, in dogs respired with room air or with* 12% *oxygen–*88% *nitrogen*

	No. of doses		1	2	3	4	5	6
	No. of dogs		4	4	4	4	4	3
Room air	Heart rate (beats/min)	R	216±20·8	235±19·3	241±17·8	237±16·9	233±16·7	225±21·5
		I	+101± 4·3	+75± 7·2	+60± 3·2	+60± 3·3	+57± 2·9	+56± 4·4
	Systolic pressure (mm Hg)	R	172± 9·4	141±11·6	139±11·0	141± 9·2	143± 7·7	146±10·7
		I	−98±15·6	−45± 9·5	−44± 4·6	−48± 4·2	−48± 3·6	−39± 3·4
	Diastolic pressure (mm Hg)	R	133± 3·7	116± 8·7	112± 9·6	113± 9·7	114± 8·9	118± 8·7
		I	−93± 2·8	−68± 5·7	−57± 2·2	−62± 3·9	−58± 4·8	−48± 2·5

	Number of doses		1	2	3	4
	Number of dogs		6	6	6	5
12% oxygen–88% nitrogen	Heart rate (beats/min)	R	193±17·4	215±20·3	214±21·2	202±17·1
		I	+70±17·4	+51± 7·8	+48± 6·8	+42± 4·2
	Systolic pressure (mm Hg)	R	192±25·2	178±19·0	172±28·1	166±23·4
		I	−66±12·0	−49± 6·5	−46± 9·6	−47±17·5
	Diastolic pressure (mm Hg)	R	139±18·8	130±12·9	119±13·2	113±10·7
		I	−73±11·8	−63±10·7	−55± 7·8	−52± 8·8

R, Resting value; I, maximum change produced by isoprenaline.

As the fatal dose of isoprenaline in the above experiments was given 20–25 min after starting respiration with the hypoxic mixture, observations were made in two dogs which were respired with this mixture for 30 min before administering a series of doses of isoprenaline, 2·5 μg/kg given at 5 min intervals. One dog died after the fifth dose of isoprenaline and the other after the sixth (Table 5B).

A series of doses of isoprenaline, 0·5 μg/kg was given to two dogs respired with the hypoxic mixture. One received six doses and the other ten without death (Table 5B). Similar studies were made in two dogs given isoprenaline at doses of 25·0 μg/kg. Death occurred in both after the second dose of isoprenaline (Table 5B).

Studies of cardiac function during responses to isoprenaline

A probe for an electromagnetic flowmeter was placed around the ascending aorta in three dogs in order to measure stroke volume and the rate of ejection of blood from the left ventricle. The responses to the injection of isoprenaline, 2·5 μg/kg, were recorded in each dog when respired with room air and at 5 min intervals after starting respiration with 12% oxygen–88% nitrogen. Similar results were obtained

TABLE 5. *Effect of isoprenaline on survival of dogs respired with room air or with* 12% *oxygen*–88% *nitrogen*

(A) Increasing doses of isoprenaline

Gas	Isoprenaline (μg/kg)					
	0·5	2·5	10·0	25·0	50·0	100·0
Room air	6/6	6/6	6/6	6/6	6/6	6/6
12% O_2–88% N_2 (i)	5/5	5/5	2/5	1/2	0/1	—
12% O_2–88% N_2 (ii)	4/4	4/4	3/4	1/3	0/1	—

(i) Followed isoprenaline given during respiration with room air.
(ii) No preceding dose of isoprenaline.

(B) Repetitive doses of isoprenaline

Gas	Dose of isoprenaline (μg/kg)	No. of dose of isoprenaline						
		1	2	3	4	5	6	7
Room air	2·5	4/4	4/4	4/4	4/4	4/4	4/4	2/2
12% oxygen–88% nitrogen	2·5	6/6	6 6	5/6	2/5	0/2	—	—
	2·5*	2/2	2/2	2/2	2/2	1/2	0/1	—
	0·5	2/2	2/2	2/2	2/2	2/2	2/2	1/1
	25·0	2/2	0/2	—	—	—	—	—

* First dose after 30 min respiration with 12% oxygen.
For each dose the numerator is the number of animals surviving the isoprenaline challenge out of the number tested (denominator).

in all three dogs and those from one are shown in Fig. 3. During respiration with room air the injection of isoprenaline increased heart rate, stroke volume and the rate of ejection of blood from the left ventricle, and decreased arterial pressure (Fig. 3a). With the hypoxic mixture similar responses were obtained with the first,

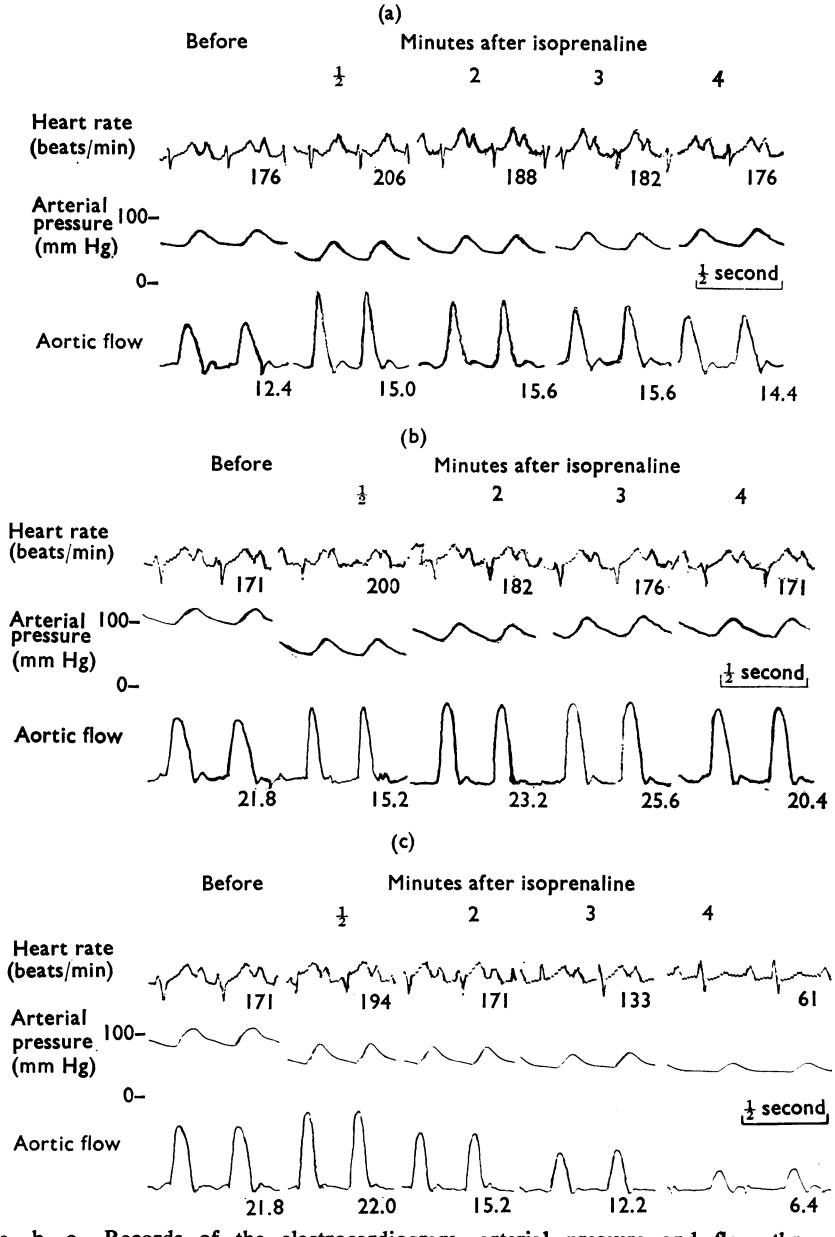

FIG. 3a, b, c. Records of the electrocardiogram, arterial pressure and flow through the ascending aorta in an anaesthetized dog. The heart rate (beats/min) and stroke volume (ml.) are shown. Responses to the intravenous injection of isoprenaline, 2·5 μg/kg, during respiration with room air (a) and later with 12% oxygen—88% nitrogen (b and c); b and c show the responses to the fourth and fifth doses of isoprenaline respectively.

second, third and fourth doses of isoprenaline; the responses to the fourth dose are shown in Fig. 3b. The fifth dose initially produced an increase in heart rate and the rate of ejection of blood, but 2 min after the injection of isoprenaline both had returned to the pre-injection levels and stroke volume was reduced (Fig. 3c). After a further 2 min, there was a marked reduction in all three parameters although sinus rhythm was still present. Stroke volume and arterial pressure continued to decrease and a slow irregular ventricular ectopic rhythm developed and lasted for about 1 min before cardiac asystole.

Effect of propranolol on the responses to isoprenaline

The effect of propranolol on the responses to isoprenaline during hypoxia was studied in four dogs. In two dogs respired with room air, the intravenous infusion of propranolol, 10 mg/kg for 15 min greatly reduced the cardiovascular responses to isoprenaline 25·0 μg/kg. Artificial respiration with 12% oxygen–88% nitrogen was then commenced and 5 min later a series of increasing doses of isoprenaline was given intravenously. A maximum dose of 100 μg/kg was given to one dog and 800 μg/kg given to the second dog; death did not occur in either. In two other dogs respired with room air the cardiovascular responses to isoprenaline 2·5 μg/kg were almost completely abolished by the intravenous infusion of propranolol 3 mg/kg. During respiration with 12% oxygen–88% nitrogen, six repetitive doses of isoprenaline 2·5 μg/kg were given at 5 min intervals without harmful effects. One dog was subsequently given repetitive doses of 100 μg/kg and died after the seventh; the other died after the sixth dose of 250·0 μg/kg. In these two dogs the increases in heart rate produced by isoprenaline 100·0 μg/kg and 250·0 μg/kg were similar to those produced by 2·5 μg/kg given before propranolol.

Discussion

The cardiovascular effects of isoprenaline in man and animals under normal conditions are similar. On intravenous administration there is an increase in heart rate, cardiac output and rate of left ventricular ejection; stroke volume may be increased or unchanged; in man diastolic arterial pressure is reduced although mean arterial pressure is unchanged, but in dogs both pressures are reduced (Krasnow, *et al.*, 1964; Harris, Schoenfeld, Brooks & Weissler, 1966; Shanks, 1966; Noble, Gabe, Trenchard & Guz, 1967). The inhalation of isoprenaline in man increases heart rate and forearm flow (Chamberlain, 1967; Cohen, Keates & Young, 1967) and presumably will produce the other changes in the circulation. The effects of isoprenaline on the circulation result from stimulation of adrenergic β-receptors and can be prevented or abolished by propranolol (Harris *et al.*, 1966; Shanks, 1966; Chamberlain, 1967). The present experiments in dogs breathing room air, show that these cardiovascular effects of isoprenaline are similar over a wide dose range (0·02–250 μg/kg). Cardiac arrhythmias, (for example ventricular ectopic beats) occurred occasionally at all doses; ventricular fibrillation only occurred in one dog out of three given isoprenaline 250 μg/kg.

The most striking feature of the present experiments was the reversal that occurred in the cardiac actions of isoprenaline, leading to a reduction in heart rate and cardiac contractility in dogs with hypoxaemia. When this phenomenon occurred it was always fatal. This change in the responses to isoprenaline could be produced in two ways; either by giving increasing doses of isoprenaline when a dose was

reached which in normal animals gave a standard response, but during hypoxaemia produced cardiac depression; or by giving repeated doses of 2·5 μg/kg or greater to hypoxic animals. In all dogs the response to the dose preceding the fatal one was normal; moreover, the fatal dose initially increased heart rate and the rate of ejection of blood from the left ventricle before depressing these two functions. This cardiac depression did not follow the development of an arrhythmia or of peripheral circulatory failure. It may result from a direct action of isoprenaline on cardiac muscle or may be due to a reduction in coronary blood flow following an alteration in the haemodynamic actions of isoprenaline. It was probably related to stimulation of adrenergic β-receptors, as the lethal dose of isoprenaline was greatly increased in dogs pretreated with propranolol.

In these experiments this change in the cardiac response to isoprenaline was not due to changes in the tension of carbon dioxide in arterial blood. The mechanism responsible for these changes in the cardiac responses to isoprenaline is at present not known. Lockett (1965) has shown in the isolated heart lung preparation that in the presence of a high work load, small doses of isoprenaline produced heart failure and killed the preparation; this did not occur with much larger doses of isoprenaline when the work load was normal. The mechanism of this effect was not elucidated but it might be similar to that described in the present experiments.

These present results may be relevant to the increase in mortality from asthma in Great Britain (Speizer, Doll & Heaf, 1968) and Australia (Gandevia, 1968). The cause of this increased mortality is not known but it may be related to the excessive use of aerosols containing isoprenaline (Greenberg & Pines, 1967; Speizer, Doll, Heaf & Strang, 1968). Analysis of individual cases has shown that patients have died suddenly and unexpectedly. Descriptions of their clinical state before death are understandably scant but Greenberg & Pines (1967) found a marked tachycardia in their eight patients; in one an electrocardiogram showed multiple ectopic beats. It has been assumed that if isoprenaline is responsible for the increase in mortality in patients with asthma, it would produce death through arrhythmias—for example ventricular fibrillation (Speizer, Doll, Heaf & Strang, 1968). Read (1968) has criticized the findings of Speizer, Doll, Heaf & Strang (1968) and Speizer, Doll & Heaf (1968) and has suggested that sympathomimetic agents are not responsible for the increase in mortality, as no evidence of harmful effects has been ascribed to these drugs.

The present observations show that in anaesthetized dogs with normal blood gas tensions, it is possible to give large doses of isoprenaline intravenously without producing serious ventricular arrhythmias, but that during hypoxaemia much smaller doses of isoprenaline produce fatal cardiac depression. It is difficult to assess the relevance of the present results to the therapeutic use of isoprenaline in patients during a severe asthmatic attack. In the present experiments the tension of oxygen in the arterial blood was at the lower end of the range found in patients during an acute attack (Tai & Read, 1967). During an asthmatic attack hypercapnia may be present (Tai & Read, 1967), and this change may also influence the actions of isoprenaline in the presence of a normal or reduced tension of oxygen. Such studies have not been carried out in animals and might be of clinical importance. In patients isoprenaline is administered by inhalation, whereas it was given only by intravenous injection in the present experiments. Paterson, Conolly, Davies & Dollery (1968) have recently compared the effects on heart rate of isoprenaline given

by inhalation and by intravenous infusion. For similar increases in heart rate, the dose by inhalation had to be 100 times greater than that by intravenous infusion in healthy subjects, and in asthmatic patients 400 times greater. Thus, if the cardiac actions of isoprenaline are altered by hypoxaemia in man, this will probably occur after administration by inhalation and in patients with asthma. As accurate comparisons of the effects on the heart of isoprenaline in man and dog has not been made, and as there is still little information about the amount of isoprenaline absorbed into the blood-stream by patients during an acute asthmatic attack, it is not yet possible to predict the range of doses of isoprenaline which might be dangerous in patients.

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