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CIRCULATORY, RESPIRATORY AND METABOLIC RESPONSES TO ISOPROPYLNORADRENALINE IN MAN

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The effects of isopropylnoradrenaline on the heart and peripheral circulation in man were first studied by Barcroft & Konzett (1949). Since trace amounts of this amine have been reported in the adrenal glands of the cat, monkey and man (Lockett, 1954) and in the pulmonary venous blood of cats after stimulation of the cervical sympathetic chain (Lockett, 1957), a more detailed study has been made of its circulatory, respiratory and metabolic effects in man; a preliminary summary of the findings has already been reported (Cobbold, Galbraith, Ginsburg & Paton, 1958).

METHODS

The majority of experiments were performed on healthy adults; studies were also made in two patients after cervical sympathectomy and in one subject after lumbar sympathectomy. Subjects were tested at rest after a fast of 8–10 hr.

DL-Isopropylnoradrenaline (Isuprel, Winthrop) was infused intravenously in a dose of 0·1 μg/kg body weight/min for 30 min periods; the administration of the amine was preceded and followed by control infusions of sodium chloride solutions 0·9 % (w/v). Ascorbic acid 0·03 % was added to all solutions (Gaddum, Peart & Vogt, 1949).

Blood flow was recorded in hand, foot, forearm, or calf, at half-minute intervals by venous occlusion plethysmography (Barcroft & Swan, 1953). Blood pressure was measured at 2–5 min intervals by means of a sphygmomanometer; pulse rate was counted at the wrist. In some experiments arterial pressure and pulse rate were recorded continuously by a capacitance manometer system connected to a needle inserted into the brachial artery.

The rate of respiration was recorded by a chest pneumograph. Pulmonary ventilation was measured over successive 5 min periods by passing the expired air through low-resistance valves into a series of Douglas bags, or through a recording gas meter. In some subjects oxygen consumption was measured with the Benedict–Roth spirometer. In three subjects the pH of the arterial blood was estimated with the glass electrode, precautions being taken to prevent CO_2 loss from the blood.

Blood glucose was estimated by a modified Shaffer–Hartmann method (Haslewood & Strookman, 1939) in samples taken from the ear lobe or brachial artery. Lactic acid was measured by the method of Barker & Summerson (1941) in blood taken from a deep vein of the antecubital fossa.

In eighteen experiments isopropylnoradrenaline was infused into a brachial artery for 4–10 min, in doses ranging between 0·05 and 0·2 μg/min. Blood flow was measured in both hands in twelve of these infusions, and in both forearms in the remainder.

RESULTS

Intravenous isopropylnoradrenaline

Circulatory changes. Within 2 min of the start of the infusion heart rate and the blood pressure increased (Fig. 1). The mean rise in pulse rate was from 66 initially to 102 within 2 min; this rate was maintained throughout the infusion period, the mean rate at the end of the infusion being 108.

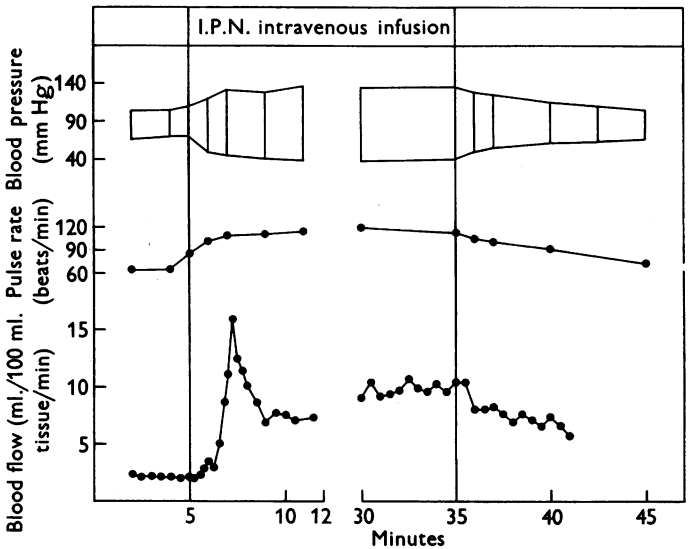

Fig. 1. The effect of intravenous infusion of isopropylnoradrenaline (I.P.N.) 0·1 μg/kg/min on the blood pressure, pulse rate and forearm blood flow; the period of infusion is indicated by the vertical lines. During the time between 12 and 30 min the blood pressure, pulse rate and blood flow were sustained at their increased values.

Initially there was a transient fall in both systolic and diastolic blood pressures coincident with the increase in heart rate (Fig. 2), lasting for some 10 sec; the pressure then rose from the resting average of 100/70 mm Hg to a mean of 120/45 mm Hg at 2 min, and 135/40 mm Hg 15 min after the beginning of the infusion. The pulse pressure was thus doubled.

There was a marked increase in forearm blood flow initially to a level about 700 % greater than the resting value; the flow then subsided rapidly to a level about 450 % above the control, and this was sustained throughout the period of infusion (Fig. 3, Table 1). Increases in calf blood flow were of a lesser degree, averaging 300 and 130 % above control values in the initial and sustained phases, respectively (Fig. 4, Table 1). There was a slight transient increase in hand or foot flow initially; thereafter the mean

flow was not greater than the resting flow (Figs. 3, 4, Table 2). During infusion the skin never became pale and in some subjects flushing of the face was observed. Similar changes in blood flow were recorded in sympathectomized limbs.

Forearm and calf blood flow remained high for at least 7 min after the infusion of isopropylnoradrenaline had ceased, the control level being gradually regained within 12–20 min. Heart rate and blood pressure

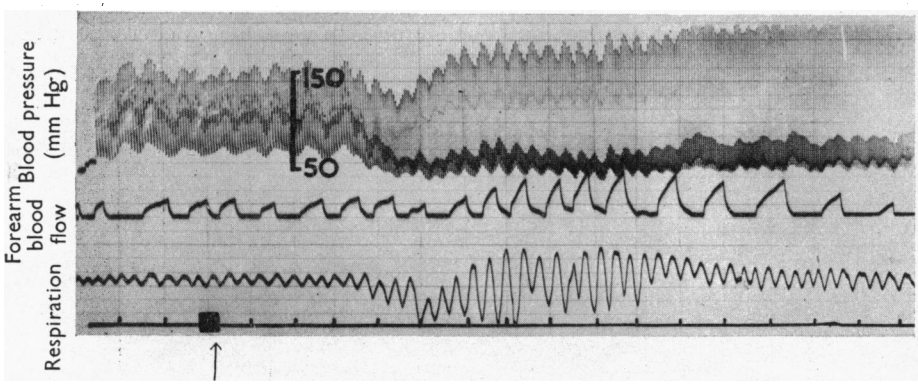

Fig. 2. The effect of isopropylnoradrenaline on blood pressure changes recorded from the brachial artery by capacitance manometer; forearm blood flow by plethysmograph and respiration from a chest stethograph. I.P.N. intravenous infusion 0·1 μg/kg/min commenced at arrow. Time marker, 0·25 min.

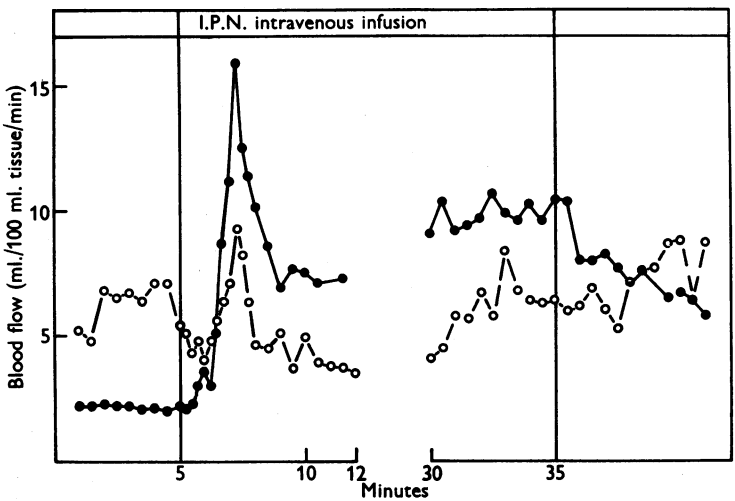

Fig. 3. Effect of intravenous infusion of isopropylnoradrenaline (I.P.N.) 0·1 μg/kg/min on forearm (●) and hand (○) blood flow. During the time between 12 and 30 min the flows were sustained at the levels shown before and after the break.

recovered more quickly, and were normal within 5 min of the end of the infusion.

Respiratory changes. Intravenous isopropylnoradrenaline had an immediate, powerful stimulatory effect upon respiration, the most marked action being upon the depth of breathing (Fig. 2). Pulmonary ventilation increased initially to about 66 % above the resting level and subsequently fell to a level of 30 % above the resting ventilation, which was maintained throughout the period of infusion of the amine. There was only a small increase in the rate of respiration. The changes in ventilation corresponded

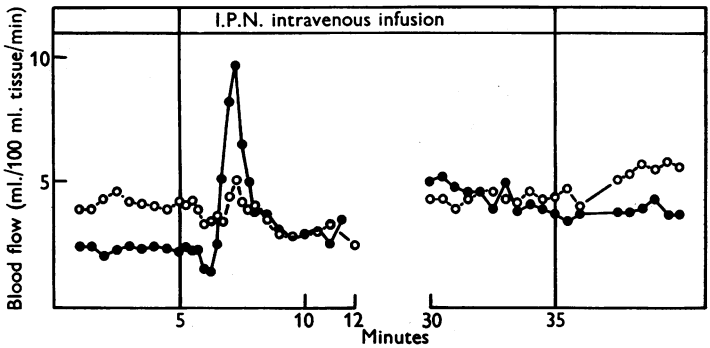

Fig. 4. Effect of intravenous infusion of isopropylnoradrenaline (I.P.N.) 0·1 μg/kg/min on calf (●) and foot (○) blood flow.

with an increase in oxygen consumption to an average of 30 % above the control level (Fig. 5). In the three subjects in whom arterial blood pH was measured this showed either no change or a small rise (Table 3).

Blood sugar and lactate. There was a slow rise in blood glucose concentration during the infusion, the average increase of 30 % above the fasting sugar level being reached after about 20 min (Fig. 6). The raised level of blood glucose was maintained for about 30 min after the end of the infusion, and then slowly fell to the control values. The lactate content of the venous blood remained unchanged during and after the infusion.

Intra-arterial isopropylnoradrenaline

There was no change in heart rate, blood pressure or venous lactate during intra-arterial infusions of isopropylnoradrenaline at different doses into the brachial artery. Blood flow in the forearm receiving the intra-arterial infusion showed changes similar to those recorded in the forearm during intravenous infusion (Fig. 7, Table 4). The mean increase in forearm flow was 350 % during the initial phase and 250 % during the sustained phase of activity. There was no change in flow in the contralateral uninfused forearm.

TABLE 1. Changes in forearm and calf blood flow during intravenous infusions of isopropylnoradrenaline (0·1 μg/kg/min) for 30-min periods

Subject	Blood flow (ml./min/100 ml. tissue) A	B	$B-A$	$\frac{B-A}{A}\times 100$
		Forearm		
C.P.	2·2	9·1	6·9	314
R.K.	2·0	4·6	2·6	130
A.C.	1·3	6·7	5·4	415
C.Q.	2·0	8·3	6·3	315
R.C.	3·0	15·3	12·3	410
H.G.	1·0	17·1	16·1	1610
I.D.	3·2	8·6	5·4	169
R.C.	2·4	6·3	3·9	163
J.D.	2·0	13·7	11·7	585
Mean	2·1	10·0	7·8	457
		Calf		
J.P.	3·3	4·8	1·5	45
J.G.	1·5	2·2	0·7	47
P.M.	5·5	7·9	2·4	44
E.G.	2·7	5·5	2·8	104
M.M.	1·3	5·4	4·1	315
H.B.	1·7	2·3	0·6	35
J.C.	1·7	3·6	1·9	112
M.M.	1·0	5·9	4·9	490
H.B.	2·0	3·2	1·2	60
M.D.	2·3	4·1	1·8	78
Mean	2·3	4·5	2·2	133

A, mean flow during the 4 min before infusion; *B*, mean flow during the last 4 min of the infusion.

TABLE 2. Changes in hand and foot blood flow during intravenous infusion of isopropylnoradrenaline (0·1 μg/kg/min) for 30-min periods

Subject	Blood flow (ml./min/100 ml. tissue) A	B	$B-A$	$\frac{B-A}{A}\times 100$
		Hand		
C.P.	8·1	12·9	+4·8	+ 59
R.K.	7·8	2·4	−5·4	− 69
A.C.	3·7	1·7	−2·0	− 54
C.Q.	6·1	5·3	−0·8	− 13
R.C.	7·2	10·7	+3·5	+ 49
H.G.	2·9	4·4	+1·5	+ 52
J.C.	9·0	2·8	−6·2	− 69
M.M.	5·0	4·0	−1·0	− 20
H.B.	6·3	9·1	+2·8	+ 44
M.D.	8·1	8·9	+0·8	+ 10
Mean	6·4	6·2	−0·2	− 11
		Foot		
J.G.	7·3	5·9	−1·4	− 19
J.P.	4·6	4·4	−0·2	− 4
P.B.	3·7	9·7	+6·0	+162
E.G.	3·5	3·0	−0·5	− 14
M.M.	2·1	1·0	−1·0	− 48
H.B.	5·7	4·7	−1·0	− 18
M.B.	4·3	4·5	+0·2	+ 5
J.C.	2·3	1·6	−0·7	− 30
Mean	4·2	4·3	+0·2	+ 4

A, mean flow during the 4 min before infusion; *B*, mean flow during the last 4 min of the infusion.

Blood flow in the infused hand was unchanged initially and during short periods of infusion; there was, however, sometimes a slight increase in flow towards the end of intra-arterial infusions lasting 10 min.

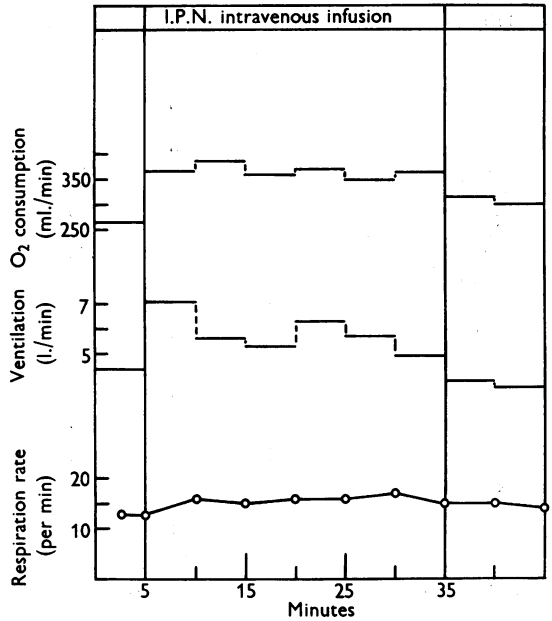

Fig. 5. Effect of intravenous infusion of isopropylnoradrenaline (I.P.N.) 0·1 μg/kg/min on the rate of respiration, pulmonary ventilation and oxygen consumption.

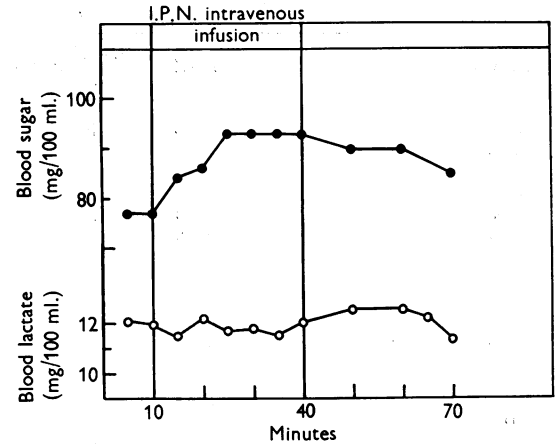

Fig. 6. Effect of intravenous infusion of isopropylnoradrenaline (I.P.N.) 0·1 μg/kg/min on the blood sugar (●) and blood lactate (○).

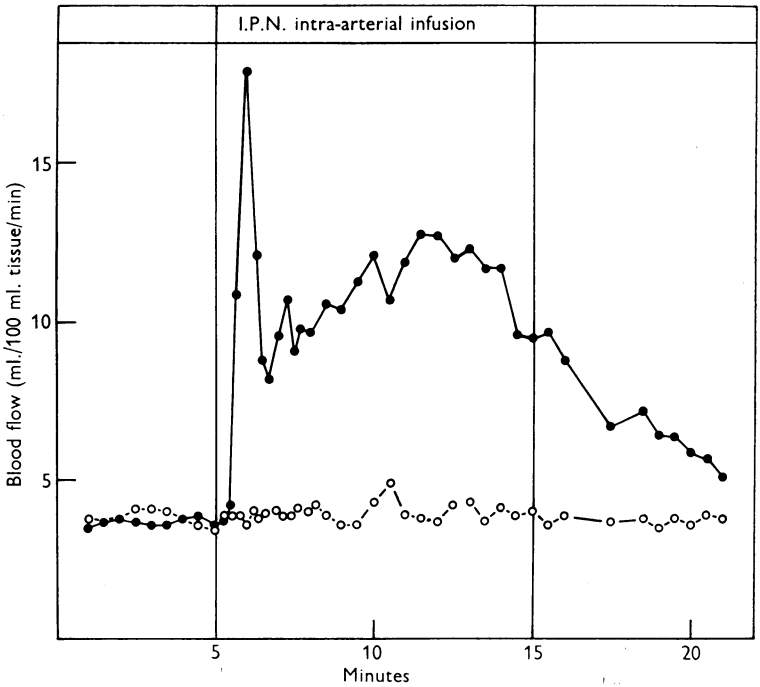

Fig. 7. Effect of intra-arterial infusion of isopropylnoradrenaline (I.P.N.) (0·05–0·2 μg/min) on forearm blood flow. ●, flow in the arm infused; ○, contralateral, uninfused, forearm. The points represent mean values for the three subjects of Table 4.

TABLE 3. Arterial blood pH during intravenous infusion of isopropylnoradrenaline (0·1 μg/kg/min)

Subject	Control	3 min after start of infusion	9 min after start	10 min after end of infusion
M.D.	7·28	—	7·33	7·32
J.P.	7·33	7·38	7·40	7·38
J.G.	7·44	7·43	7·42	7·37

TABLE 4. Changes in forearm blood flow during intra-arterial infusions of isopropylnoradrenaline for 10 min periods

Subject	Dose (μg/min)	Blood flow (ml./min/100 ml. tissue) A	B	a	b	$\frac{B-E}{E} \times 100$
J.P.	0·05	5·4	11·4	3·5	3·4	119
	0·1	4·0	9·8	3·6	3·3	165
	0·2	2·6	22·5	4·6	4·7	733
J.C.	0·05	2·4	5·7	4·3	4·7	119
	0·1	3·7	6·2	3·1	2·8	88
H.J.	0·1	4·0	15·8	4·0	5·9	164
	Mean	3·7	11·9	3·9	4·1	231

A, mean flow in test forearm during the 4 min before infusion; B, mean flow in test forearm during the last 4 min of infusion; a, mean flow in contralateral control forearm during the 4 min before infusion; b, mean flow in contralateral forearm during the last 4 min of the infusion; E, Ab/a.

DISCUSSION

The circulatory changes which have been observed during the administration of isopropylnoradrenaline are in agreement with those reported by Barcroft & Konzett (1949); the longer period of infusion used in the present study showed that the effects of the amine persist throughout the infusion and for a short time afterwards.

The increased flow in forearm and calf is probably due in the main to vasodilatation in the blood vessels of skeletal muscle. Direct measurement of blood flow in hind-limb muscles of the dog has shown marked dilatation after the administration of isopropylnoradrenaline (Green, Shearin, Jackson, Keach & Denison, 1954). The fact that dilatation occurred after intravenous and direct intra-arterial infusion, and in healthy and sympathectomized subjects, showed further that it was a direct effect of the drug.

The vasodilator action of intravenous isopropylnoradrenaline in forearm and calf resembles that of adrenaline—an initial large increase in flow and a subsequent secondary phase of dilatation which is sustained throughout the infusion (Whelan, 1952; Barcroft & Swan, 1953). Isopropylnoradrenaline is, however, much the more powerful dilator, causing sustained dilatation even after intra-arterial administration, whereas comparable doses of adrenaline produce only transient increases in flow (Barcroft & Swan, 1953). The action of isopropylnoradrenaline contrasts strikingly with that of noradrenaline, which has a marked constrictor effect on the blood vessels of muscle (Barcroft & Konzett, 1949; Cobbold & Vass, 1953).

Whilst both adrenaline and noradrenaline have a powerful constrictor action on the vessels of the hand and foot, isopropylnoradrenaline caused weak but transient vasodilatation. During prolonged intra-arterial infusions dilatation was also observed, but whether this represents an action on skin blood vessels, similar to that recorded in dogs when blood flow was measured directly in the saphenous artery (Walters, Cooper, Denison & Green, 1955), or dilatation in muscle, is not clear.

As a cardiac stimulant isopropylnoradrenaline is more powerful than adrenaline, the tachycardia caused by adrenaline being marked only in the first few minutes of intravenous infusion, whereas that with isopropylnoradrenaline continued throughout. Our subjects, all of whom had previously received infusions of adrenaline, always remarked upon this difference and on the prolonged and powerful cardiac action which occasionally led to some degree of apprehension. This stimulating effect of isopropylnoradrenaline is in marked contrast to that of noradrenaline, which causes a transient bradycardia of reflex origin. Lands & Howard (1952) found that isopropylnoradrenaline was more effective than either adrenaline or nor-

adrenaline in increasing the rate and amplitude of contraction of the perfused heart.

The effect of isopropylnoradrenaline on blood pressure is also marked and prolonged. The increase in systolic pressure accompanies, and appears to be due to, the increase in rate and force of the heart beat. This phenomenon is also seen with intravenous infusions of adrenaline and noradrenaline, but whereas noradrenaline causes a rise in the diastolic pressure, both adrenaline and isopropylnoradrenaline produce a fall, the effect being much greater with the latter. The fall in diastolic pressure can, in part, be accounted for by the dilatation in muscle blood vessels. It is unlikely, however, that this can be wholly responsible for the marked fall in pressure and additional dilatation must occur elsewhere. A probable site is in the splanchnic bed, and it is interesting that Green, Deal, Bardhanabaedya & Denison (1955), who measured blood flow directly in the mesenteric artery of the dog, reported a large increase in flow after isopropylnoradrenaline. The renal blood flow may also increase (Aviado, Wnuck & de Beer, 1958).

The effect of isopropylnoradrenaline on respiratory activity resembles that described for adrenaline and noradrenaline by Whelan & Young (1953), an abrupt increase in pulmonary ventilation accompanied by a small change only in the rate of breathing. The stimulating action of isopropylnoradrenaline is, however, more powerful and persists throughout the infusion, whereas the effect of adrenaline or noradrenaline decreases during the period of infusion. Oxygen consumption increased along with the increase in pulmonary ventilation, and isopropylnoradrenaline is as potent as adrenaline in this respect. The calorigenic action is accompanied by a slow rise in blood glucose level but less than that observed with adrenaline (Bearn, Billing & Sherlock, 1951).

Since there was no change in lactate concentration it is not possible to attribute the vasodilator effects or the stimulation of respiration to a release of lactic acid. This contrasts with the rise in venous lactate observed during the administration of adrenaline (Bearn *et al.* 1951; Barcroft & Cobbold, 1956). The fact that there was no fall in arterial pH after infusing isopropylnoradrenaline suggests further that other acid metabolites can be excluded. The small rise in arterial pH could be attributed to over-ventilation, as was suggested for adrenaline (Bradley, Gaskell, Holland, Lee & Young, 1954).

Thus in general, the effects of isopropylnoradrenaline resemble those of adrenaline more than noradrenaline. The actions of the three related amines in comparable doses (0·1 μg/kg/min) in man are summarized in Table 5.

In the present study marked effects were obtained with the racemic

form, DL-isopropylnoradrenaline. The laevo isomer, however, which would be the compound expected to occur naturally, is even more powerful and is effective at very low concentrations (Lands, Luduena & Tullar, 1954).

The powerful action on the heart and respiration, and the accompanying marked vasodilatation, would make for a highly effective physiological agent, if isopropylnoradrenaline were normally released in the body. That this may occur was suggested by Lands & Tainter (1953), who speculated on the possibility that a substance like isopropylnoradrenaline might normally be formed to reinforce the effects of adrenaline in organs where

TABLE 5

	L-Noradrenaline	L-Adrenaline	DL-Isopropyl-noradrenaline
Muscle blood flow	Decrease	Increase	Large increase
Skin blood flow	Decrease	Decrease	Small increase
Heart rate	Decrease	Transient increase	Sustained increase
Systolic pressure	Rise	Rise	Marked rise
Diastolic pressure	Rise	Fall	Marked fall
O_2 consumption	Small increase	Increase	Increase
Pulmonary ventilation	Small increase	Increase	Large increase
Blood sugar	Small increase	Increase	Moderate increase
Blood lactate	No change	Increase	No change

sympathetic inhibitory action is dominant. The findings of Lockett (1954, 1957) in cats would support such an assumption. The effectiveness of even minute concentrations of isopropylnoradrenaline in stimulating the rate and amplitude of contraction of the isolated auricle led Garb, Penna & Ganz (1956) to suggest that small amounts of the amine could be of physiological importance. Walters *et al.* (1955) also suggested that the occurrence of both vasoconstrictor and vasodilator effects with adrenaline accords with it behaving as a mixture of noradrenaline and isopropylnoradrenaline, the action of the former being dominant before treatment with adrenergic blocking drugs, while isopropylnoradrenaline predominates after the administration of such drugs. Furthermore, the sustained vasodilatation seen in human muscle during intravenous infusions of adrenaline has been attributed to the release of some unidentified dilator compound (Whelan, 1952), and it has also been suggested that the stimulating effect of adrenaline and noradrenaline on respiration might be due to their conversion to a related substance (Young, 1957). It is tempting to assume that isopropylnoradrenaline plays a part in these responses, but no definite evidence yet exists.

The observation that infusions of isopropylnoradrenaline reproduced the normal left ventricular response to exercise in dogs more accurately than did adrenaline or noradrenaline (Rushmer & West, 1957; Rushmer & Smith, 1959) raises, also, the possibility that it is released during exercise.

The involvement of isopropylnoradrenaline in physiological responses must however remain speculative until unequivocal evidence has been provided of its release in man in such circumstances.

SUMMARY

1. Intravenous infusion of DL-isopropylnoradrenaline (0·1 μg/kg/min) in man increases the heart rate and systolic blood pressure and causes a fall in diastolic blood pressure. Blood flow in forearm and calf shows a marked initial transient increase followed by a lesser but sustained increase. Blood flow in hand and foot shows an initial, small and transient increase only. There is a small increase in respiratory rate and a sustained increase in the depth of breathing; oxygen consumption increases. Blood sugar rises slowly; there is no change in blood lactate. There is no difference between the response in normal and sympathectomized limbs.

2. Intra-arterial infusion of isopropylnoradrenaline (0·05–0·2 μg/min) causes the same change in blood flow in the infused limb as that recorded after intravenous administration, but with no systemic effect.

3. The response to isopropylnoradrenaline is discussed and compared with that to adrenaline and noradrenaline.

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REFERENCES

AVIADO, D. M. JR., WNUCK, A. L. & DE BEER, E. J. (1958). The effects of sympathomimetic drugs on renal vessels. *J. Pharmacol.* **124**, 238–244.

BARCROFT, H. & COBBOLD, A. F. (1956). The action of adrenaline on muscle blood flow and blood lactate in man. *J. Physiol.* **132**, 372–378.

BARCROFT, H. & KONZETT, H. (1949). On the actions of noradrenaline, adrenaline and isopropyl noradrenaline on the arterial blood pressure, heart rate and muscle blood flow in man. *J. Physiol.* **110**, 194–204.

BARCROFT, H. & SWAN, H. J. C. (1953). *Sympathetic Control of Human Blood Vessels.* London: Edward Arnold and Co.

BARKER, S. B. & SUMMERSON, W. H. (1941). The colorimetric determination of lactic acid in biological material. *J. biol. Chem.* **138**, 535–554.

BEARN, A. G., BILLING, B. & SHERLOCK, S. (1951). The effect of adrenaline and noradrenaline on hepatic blood flow and splanchnic carbohydrate metabolism in man. *J. Physiol.* **115**, 430–441.

BRADLEY, R. D., GASKELL, P., HOLLAND, W. W., LEE, J. DE G. & YOUNG, I. M. (1954). The acid–base changes in arterial blood during adrenaline hyperpnoea in man. *J. Physiol.* **124**, 213–218.

COBBOLD, A. F., GALBRAITH, H. J. B., GINSBURG, J. & PATON, A. (1958). Circulatory, metabolic and respiratory effects of *iso*propylnoradrenaline in man. *J. Physiol.* **141**, 40*P*.

COBBOLD, A. F. & VASS, C. C. N. (1953). Responses of muscle blood vessels to intra-arterially and intravenously administered noradrenaline. *J. Physiol.* **120**, 105–114.

GADDUM, J. H., PEART, W. S. & VOGT, M. (1949). The estimation of adrenaline and allied substances in blood. *J. Physiol.* **108**, 467–481.

GARB, S., PENNA, M. & GANZ, A. (1956). Effects of epinephrine, norepinephrine and isopropylarterenol on the isolated auricles of four mammalian species. *Amer. J. Physiol.* **185**, 332–336.

GREEN, H. D., DEAL, C. P. JR., BARDHANABAEDYA, S. & DENISON, A. B. JR. (1955). The effects of adrenergic substances and ischemia on the blood flow and peripheral resistance of the canine mesenteric vascular bed before and during adrenergic blockade. *J. Pharmacol.* **113**, 115–123.

GREEN, H. D., SHEARIN, W. T. JR., JACKSON, T. W., KEACH, L. M. & DENISON, A. B. JR. (1954). Isopropylnorepinephrine blockade of epinephrine reversal. *Amer. J. Physiol.* **179**, 287–294.

HASLEWOOD, G. A. D. & STROOKMAN, T. A. (1939). A method for the estimation of 'true' sugar in 0·05 ml. of blood. *Biochem. J.* **33**, 920–923.

LANDS, A. M. & HOWARD, J. W. (1952). A comparative study of the effects of L-arterenol, epinephrine and isopropylarterenol on the heart. *J. Pharmacol.* **106**, 65–76.

LANDS, A. M., LUDUENA, F. P. & TULLAR, B. F. (1954). The pharmacologic activity of the optical isomers of isopropylarterenol (isuprel) compared with that of the optically inactive analog (1-3,4-dihydroxyphenyl)-2-isopropylamino ethane HCl. *J. Pharmacol.* **111**, 469–474.

LANDS, A. M. & TAINTER, M. L. (1953). The effect of changes in molecular configuration on inhibitory sympathomimetic action. *Arch. exp. Path. Pharmak.* **219**, 76–90.

LOCKETT, M. F. (1954). Identification of an isoprenaline-like substance in extracts of adrenal glands. *Brit. J. Pharmacol.* **9**, 498–505.

LOCKETT, M. F. (1957). The transmitter released by stimulation of the bronchial sympathetic nerves of cats. *Brit. J. Pharmacol.* **12**, 86–96.

RUSHMER, R. F. & SMITH, O. A. JR. (1959). Cardiac control. *Physiol. Rev.* **39**, 41–68.

RUSHMER, R. F. & WEST, T. C. (1957). Role of autonomic hormones on left ventricular performance continuously analysed by electronic computers. *Circulation Res.* **5**, 240–246.

WALTERS, P. A. JR., COOPER, T. W., DENISON, A. B. JR. & GREEN, H. D. (1955). Dilator responses to isoproterenol in cutaneous and skeletal muscle vascular beds; effects of adrenergic blocking drugs. *J. Pharmacol.* **115**, 323–328.

WHELAN, R. F. (1952). Vasodilatation in human skeletal muscle during adrenaline infusions. *J. Physiol.* **118**, 575–587.

WHELAN, R. F. & YOUNG, I. M. (1953). The effect of adrenaline and noradrenaline infusions on respiration in man. *Brit. J. Pharmacol.* **8**, 98–102.

YOUNG, I. M. (1957). Some observations on the mechanism of adrenaline hyperpnoea. *J. Physiol.* **137**, 374–395.