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CONTRIBUTION OF THE VAGUS TO THE HAEMODYNAMIC RESPONSES FOLLOWING INTRAVENOUS BOLUSES OF ISOPRENALINE

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1 Eight healthy subjects (six male, two female, aged 18–21 years) received graded intravenous bolus injections of isoprenaline sulphate. Heart rate and intra-arterial blood pressure were continuously monitored PRE- and POST-atropine (0.04 mg/kg).

2 PRE-atropine, an increase in heart rate of 25 beats/min was produced by 2.15 ± 0.53 μg of isoprenaline and was associated with a fall in mean, systolic and diastolic pressures (18.9 ± 2.8, 17.7 ± 3.4 and 20.4 ± 2.3 mm Hg respectively).

3 POST-atropine, the heart rate dose response curve was shifted to the right so that the dose of isoprenaline which increased heart rate 25 beats/min PRE-atropine, produced a significantly smaller heart rate rise of 20.3 ± 1.7 beats/min ($P < 0.001$). This was associated with a shift of the blood pressure dose-response curves to the left, and larger falls in mean, systolic and diastolic pressures (30.9 ± 2.8, 31.8 ± 3.3, 30.1 ± 3.3 mm Hg respectively; $P < 0.01$).

4 It is concluded that there is a significant contribution from a reflex withdrawal of cardiac vagal tone, to the tachycardia produced by a bolus of isoprenaline.

Introduction

Isoprenaline is used frequently as an agonist in the investigation of β-adrenoceptors, mediating an increase in heart rate and a fall in blood pressure. On the basis of studies in conscious and anaesthetised animals, it was suggested that the tachycardia induced by isoprenaline resulted not only from direct stimulation of cardiac β-adrenoceptors but also from a reflex withdrawal of cardiac vagal tone secondary to the fall in mean blood pressure consequent on the β_2-adrenoceptor mediated dilatation of peripheral blood vessels (Dunlop & Shanks, 1968), and this idea has received general acceptance (McDevitt, 1977).

Cleaveland *et al.* (1972) described a standardised isoprenaline sensitivity test for use in man, based on measurement of heart rate response to increasing boluses of isoprenaline given intravenously. They investigated the possible contribution of reflex vagal withdrawal using standard sphygmomanometry before and after atropinisation of their subjects. They found that atropine did not affect either the chronotropic or hypotensive effects of the isoprenaline dose which increased the heart rate by 25 beats/min and concluded that the isoprenaline tachycardia induced by this technique was due predominantly to direct cardiac β_1-adrenoceptor stimulation.

However, using this technique and examining drug doses which had been shown to have an equipotent effect on exercise tachycardia, Perucca *et al.* (1981) have found that the cardioselective β_1-adrenoceptor antagonists, atenolol and metoprolol, are less effective than the non-selective drug, propranolol, at blocking isoprenaline tachycardia. Since the cardioselective β-adrenoceptor antagonists, unlike propranolol, do not block peripheral β_2-adrenoceptors, it could be construed that they allow isoprenaline to lower blood pressure resulting in reflex vagal withdrawal and a vagally mediated component to the increase in heart rate. Such an explanation would be at variance with the conclusions of Cleaveland *et al.* (1972).

Therefore, using continuous intra-arterial monitoring of blood pressure, the present study was undertaken to re-evaluate whether withdrawal of vagal tone in response to hypotension contributes to the tachycardia produced by an isoprenaline bolus.

Methods

Approval was obtained from the University Ethical Committee. Eight healthy non-smoking volunteers (six male, two female, aged 18–21 years, weight

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50.5–81.0 kg), who were familiar with the effects of intravenous isoprenaline, gave informed consent. The study was performed by the same investigator throughout in a quiet temperature controlled room. After a light lunch containing no caffeine, a teflon catheter (Abbocath T, 20G) was inserted under local anaesthesia into the radial artery and the blood pressure continuously measured (Bell and Howell transducer 4–422) and recorded (Devices MX4). An intravenous cannula (Butterfly 19G) was inserted into an antecubital vein on the contralateral arm. Subjects lay supine with head and shoulders supported. A respiration transducer (Lectromed 4320) applied around the chest wall continuously recorded the breathing pattern on the Devices recorder. Electrocardiogram leads were attached and the heart rate recorded continuously through an instantaneous ratemeter (Devices 2750) onto the Devices recorder, and intermittently through a Minigraph ECG machine (Cardiac Recorders Ltd) as a rhythm strip.

Following a rest period of 30 min, graded bolus injections of isoprenaline sulphate (freshly prepared in normal saline with sodium metabisulphite preservative) were given rapidly into the sleeve of the fast running intravenous drip, by the method of Cleaveland *et al.* (1972), and flushed with a total of 15 ml saline (0.9%) from a Buretrol administration set. At least five doses were injected so that satisfactory dose-response curves could be constructed for the changes in heart rate and blood pressure. At least 10 min was allowed between injections for heart rate and blood pressure to return to baseline. A placebo injection (0.5 ml saline, 0.9%, with sodium metabisulphite 0.1%), was also given. The subjects were unaware of the concentration of individual injections, which were not necessarily in ascending order of concentration, though the first injections were always small. Heart rate was measured as the shortest time between four consecutive R waves on the ECG rhythm strip which was recorded for 45 s before injection as a control period, and for a further 60 s, starting 30 s after the injection had been given. Control blood pressure was measured as the minimum blood pressure during a stable control period of normal quiet breathing immediately prior to each injection. Following isoprenaline, the peak change in blood pressure was recorded when the diastolic pressure was minimum, with the simultaneous minimum systolic pressure. Mean blood pressure was calculated as diastolic plus one third of the pulse pressure. The timing of events was read from the Devices recording except for maximum heart rate, which was read from the ECG rhythm strip.

Having constructed the PRE-atropine dose-response curves for heart rate and blood pressure, atropine 0.04 mg/kg was given slowly intravenously. When heart rate and blood pressure had restabilised the POST-atropine dose-response curves for heart rate and blood pressure were constructed at the same doses of isoprenaline sulphate. Forty five min after the injection of atropine, a further 0.6 mg atropine was given intravenously to ensure continued vagal blockade.

The results were statistically compared by analysis of variance and Student's *t*-test for paired or unpaired data.

Results

The placebo injection tended to produce a small fall in heart rate (-3.0 ± 1.0 PRE; -2.5 ± 1.0 beats/min POST; mean ± s.e. mean) with very little change in either systolic (0.0 ± 0.6 PRE; 1.8 ± 1.2 mm Hg POST) or diastolic blood pressure (-0.6 ± 0.7 PRE; -1.0 ± 1.0 mm Hg POST). The rapid bolus injection of isoprenaline sulphate, however, produced a change in breathing pattern, followed by an increase in heart rate and a fall in blood pressure. A typical tracing of these changes is shown in Figure 1.

Effects of atropinisation

Atropine 0.04 mg/kg increased the heart rate from 67.8 ± 2.2 to 118.0 ± 2.2 beats/min, with a mean increase of 50.3 ± 2.2 beats/min. There was no significant change in mean blood pressure (77.9 ± 1.5 PRE, 78.8 ± 5.4 mm Hg POST) systolic pressure (120.5 ± 5.8 PRE; 120.0 ± 7.6 mm Hg POST), or diastolic pressure (56.6 ± 1.5 PRE; 58.3 ± 5.6 mm Hg POST). Analysis of the dose-response curves for heart rate, mean, systolic and diastolic pressure showed no significant change in the correlation coefficients r though the slope of the blood pressure curves was steeper after atropinisation (Table 1). The second injection of atropine, 0.6 mg, did not significantly change the new resting heart rate, 109.5 ± 2.2 to 111.3 ± 3.1 beats/min, or mean blood pressure, 80.7 ± 3.8 to 81.6 ± 3.8 mm Hg.

Isoprenaline-induced heart rate changes

Dose-response curves were drawn for the changes in heart rate produced by the increasing doses of isoprenaline sulphate before and after atropine was given. Figure 2a shows the results from a typical subject: it can be seen that the POST-atropine dose-response curve is shifted to the right of the PRE-atropine curve. From the individual PRE-atropine regression equations, the doses of isoprenaline required to increase the heart rate by 10, 15, 20 and 25 beats/min respectively (I_{10}, I_{15}, I_{20} and I_{25}) were calculated. For these doses, the corresponding rise in heart rate was determined from the POST-atropine regression equations. Isoprenaline produced a significantly smaller rise in heart rate POST-atropine

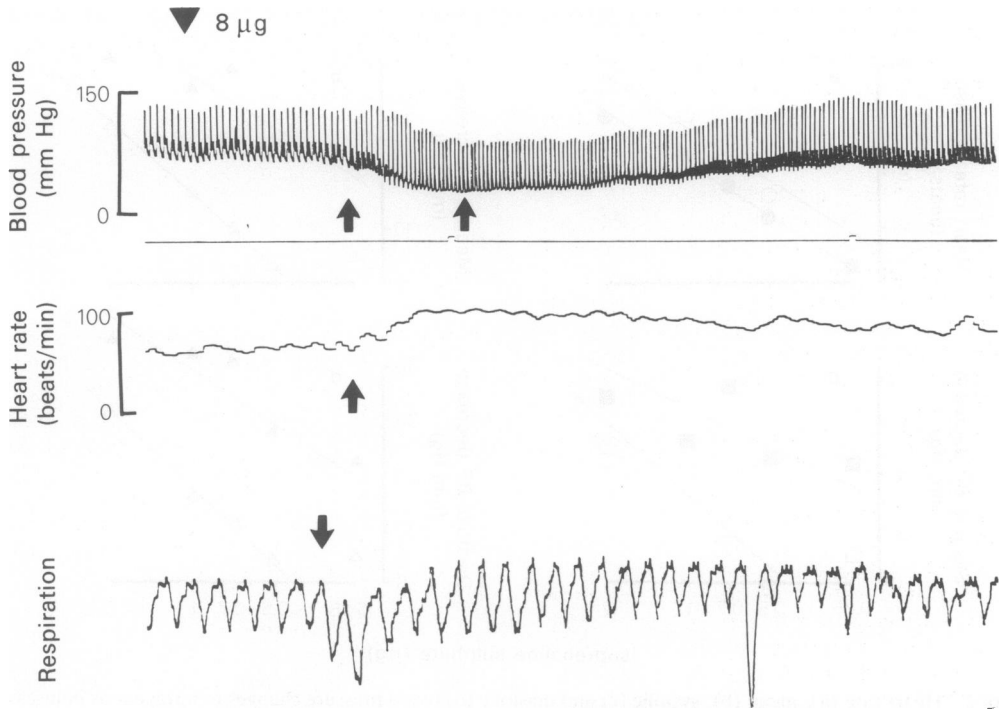

Figure 1 Tracing of changes in blood pressure, heart rate and respiration following an 8 μg intravenous bolus injection of isoprenaline sulphate in one representative subject. Time scale (1 min) is marked below the blood pressure tracing. Arrows indicate the start of breathing change, rise in heart rate and fall in blood pressure, and time of measurement of maximum blood pressure change.

than it did PRE-atropine (Table 2): the dose of isoprenaline which increased heart rate by 25 beats/min PRE-atropine, produced a rise of 20.3 ± 1.7 beats/min POST-atropine ($P < 0.001$). From the individual regression equations, the POST-atropine I_{10}, I_{15}, I_{20} and I_{25} were calculated and are compared with the PRE-atropine values in Table 3. Statistical comparison was made by analysis of variance of the log-transformed data. At each level of heart rate increase, significantly more isoprenaline was required to produce the same response after atropine was administered—thus the I_{25} was 2.15 ± 0.53 μg PRE-atropine and 3.42 ± 0.82 μg POST-atropine ($P < 0.01$).

Isoprenaline-induced blood pressure changes

Dose-response curves were drawn for the change in mean, systolic and diastolic pressure produced by isoprenaline sulphate before and after atropine administration. The results from a typical subject show that the POST-atropine curves are shifted to the left of the PRE-atropine curves (Figures 2b, c and d). From the individual regression equations relating

Table 1 Slope of the dose response curves to isoprenaline of heart rate (beats min^{-1} ln μg^{-1}), mean, systolic and diastolic blood pressures (mm Hg ln μg^{-1}) PRE and POST atropinisation ($n = 8$, mean ± s.e. mean)

	PRE	*POST*	P
Heart rate	10.20 ± 1.03	11.99 ± 0.97	NS
Mean blood pressure	8.46 ± 1.15	11.21 ± 0.96	< 0.02
Systolic blood pressure	9.22 ± 1.52	16.03 ± 2.41	< 0.02
Diastolic blood pressure	8.45 ± 1.13	9.75 ± 1.13	< 0.05

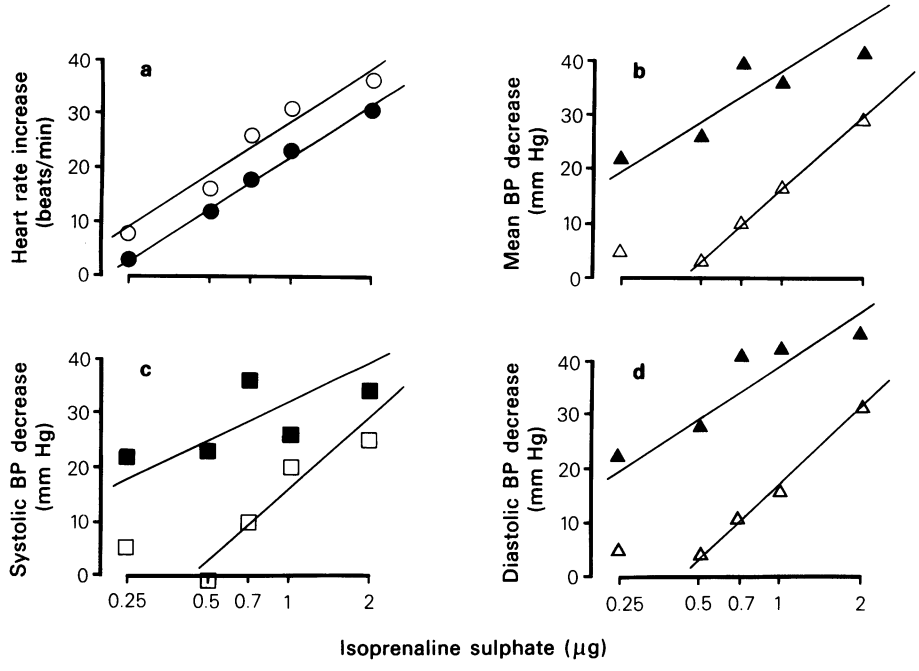

Figure 2 Heart rate (a), mean (b), systolic (c) and diastolic (d) blood pressure changes to intravenous boluses of isoprenaline in one representative subject, PRE- (open symbols) and POST- (solid symbols) atropine.

change in blood pressure with isoprenaline dose both PRE- and POST-atropine, the corresponding falls in mean, systolic and diastolic pressure (Table 4) were calculated at the PRE-atropine dose of isoprenaline required to increase heart rate by 10, 15, 20 and 25 beats/min. Thus, at the I_{25}, the fall in mean blood pressure was 18.9 ± 2.8 mm Hg PRE-atropine compared to 30.9 ± 2.8 mm Hg POST-atropine ($P < 0.001$): the corresponding values for fall in systolic blood pressure were 17.7 ± 3.4 mm Hg (PRE) and 31.8 ± 3.3 mm Hg (POST) ($P < 0.01$) and for diastolic pressure, 20.4 ± 2.3 mm Hg (PRE) and 30.1 ± 3.3 mm Hg (POST) ($P < 0.001$).

Table 2 Increase in heart rate (beats/min) POST-atropine, at the dose of isoprenaline which increased PRE-atropine heart rate by 10, 15, 20 and 25 beats/min. Mean of 8 subjects ± s.e. mean

PRE-atropine isoprenaline dose	*PRE*	*POST*	P
I_{10}	10	1.1 ± 2.2	< 0.001
I_{15}	15	7.5 ± 1.5	< 0.001
I_{20}	20	13.9 ± 1.3	< 0.001
I_{25}	25	20.3 ± 1.7	< 0.001

Following the maximum changes in blood pressure, when diastolic pressure had returned to control values, systolic pressure tended to be elevated above control. Analysis of the data for the response to isoprenaline which most nearly produced a heart rate increase of 25 beats/min in each subject, showed a significant residual increase in systolic pressure of 12.6 ± 2.0 mm Hg ($P < 0.001$) PRE-atropine, but a non-significant increase of 3.1 ± 2.4 mm Hg POST-atropine.

Time sequence of changes in breathing pattern, heart rate and blood pressure

The time from the rapid injection of isoprenaline

Table 3 Dose of isoprenaline sulphate (μg) required to increase the heart rate by 10, 15, 20 and 25 beats/min, PRE- and POST-atropine. Mean of 8 subjects ± s.e. mean

	PRE	*POST*	P
I_{10}	0.39 ± 0.06	0.86 ± 0.16	< 0.01
I_{15}	0.68 ± 0.12	1.35 ± 0.26	< 0.01
I_{20}	1.19 ± 0.25	2.15 ± 0.46	< 0.01
I_{25}	2.15 ± 0.53	3.42 ± 0.82	< 0.01

sulphate to the change in breathing pattern was significantly shorter after atropine: 24.9 ± 0.8 s ($n = 37$) PRE and 20.3 ± 0.7 s ($n = 36$) POST ($P < 0.001$). The sequence of changes in heart rate and blood pressure are shown in Table 5. The start of heart rate rise and start of blood pressure fall was significantly earlier after atropinisation ($P < 0.001$). Although the time to blood pressure minimum was also significantly shorter POST-atropine ($P < 0.001$), the time to heart rate maximum was not changed. It required significantly longer for blood pressure and heart rate to settle POST-atropine, this being more marked for heart rate, where the mean time was 4.4 ± 0.5 min PRE, but 7.5 ± 0.4 min POST-atropine ($P < 0.001$). If only the largest dose of isoprenaline for each individual is considered, the time to a settled heart rate was 7.8 ± 0.8 min PRE- and 10.9 ± 0.4 min POST-atropine.

Discussion

The results of this present study confirm that an intravenous bolus injection of isoprenaline produces a rise in heart rate and a fall in blood pressure. After atropinisation, the dose-response curve for heart rate is shifted to the right whereas that for blood pressure is shifted to the left: in these circumstances, isoprenaline causes a significantly greater fall in blood pressure but the associated rise in heart rate is less. These findings are in accord with the hypothesis that isoprenaline increases heart rate not only by direct stimulation of cardiac β-adrenoceptors but also by an indirect effect, produced by β_2-adrenoceptor mediated dilatation of peripheral blood vessels, a fall in arterial blood pressure and a reflex withdrawal of cardiac vagal tone (Dunlop & Shanks, 1968).

Previous apparent support for the hypothesis was obtained in man by Brick *et al.* (1968) who found that the cardioselective β-adrenoceptor antagonist, practolol, caused only a small, non-significant reduction in an isoprenaline tachycardia which was completely abolished by the non-selective drug, propranolol. Quadrupling the dose of practolol did not increase its effect but, following the administration of atropine 2.5 mg to abolish any vagal reflex contribution, practolol did significantly reduce the isoprenaline tachycardia. It was concluded that practolol and propranolol had different effects on isoprenaline-induced tachycardia because propranolol antagonised the β_2-adrenoceptor mediated dilatation of peripheral blood vessels and thus the fall in blood pressure, whereas practolol did not. This study may be criticised in that single concentration isoprenaline infusions were employed and dose-response relationships were not properly examined. However, the findings are supported by the recent study of Perucca *et al.* (1981), in which the cardioselective β-adrenoceptor antagonists, atenolol and metoprolol, were shown to be less effective than propranolol in reducing isoprenaline tachycardia when all three drugs were administered at doses demonstrated to be equipotent against exercise tachycardia.

Our conclusions differ from those of Cleaveland *et al.* (1972) who reported that atropine did not alter the hypotensive effect of isoprenaline in a dose which increased heart rate by 25 beats/min. However, these authors employed a sphygmomanometer to measure the blood pressure changes. Since the fall in blood pressure following an isoprenaline bolus is relatively short lived, the maximum change may be missed by indirect measurement techniques. Even so, Cleaveland *et al.* (1972) found a mean fall in diastolic pressure of 24 mm Hg with isoprenaline doses which produced heart rate increases of 25 beats/min in their subjects: however, they did not find the hypotensive effect of isoprenaline to be enhanced by atropine. In contrast, our results demonstrate a dose-related decrease in diastolic pressure, resulting in a fall of 20.4 ± 2.3 mm Hg at a heart rate increase of 25 beats/min with a further significant decrease to 30.1 ± 3.3 mm Hg following atropine administration (Table 4). Comparable and significant decreases in diastolic pressure were also recorded POST-atropine at the other doses of isoprenaline studied. Similarly there

Table 4 Decreases in mean, systolic and diastolic blood pressures (mm Hg) PRE- and POST-atropine, at the isoprenaline dose which increased PRE-atropine heart reates by 10, 15, 20 and 25 beats/min. Mean of 8 subjects ± s.e. mean

Pre-atropine isoprenaline dose	*Mean pressure*		*Systolic pressure*		*Diastolic pressure*	
	PRE	*POST*	*PRE*	*POST*	*PRE*	*POST*
I_{10}	5.8 ± 2.5	13.2 ± 3.4**	2.9 ± 1.7	5.7 ± 4.4	7.6 ± 2.7	15.3 ± 3.4**
I_{15}	10.2 ± 2.4	19.1 ± 3.1**	7.8 ± 1.9	14.4 ± 3.4*	11.8 ± 2.4	20.2 ± 3.2**
I_{20}	14.6 ± 2.5	25.0 ± 2.8**	12.8 ± 2.5	23.1 ± 2.9**	16.1 ± 2.2	25.1 ± 3.2**
I_{25}	18.9 ± 2.8	30.9 ± 2.8**	17.7 ± 3.4	31.8 ± 3.3**	20.4 ± 2.3	30.1 ± 3.3**

$P < 0.05$* when compared to corresponding PRE-atropine value
$P < 0.01$**

Table 5 Time from injection of isoprenaline sulphate to the change in breathing pattern, heart rate and blood pressure, PRE and POST-atropine. Time in seconds, except for settling of heart rate and blood pressure where it is indicated in min. n = number of observations.

	Heart rate						*Blood pressure*					
	Start		*Maximum*		*Settled*		*Start*		*Minimum*		*Settled*	
	PRE	*POST*	*PRE*	*POST*	*PRE*	*POST*	*PRE*	*POST*	*PRE*	*POST*	*PRE*	*POST*
Mean	30.8	21.0	50.6	51.6	4.4 min	7.5 min	34.1	23.7	47.5	40.4	1.6 min	2.0 min
(*n*)	(38)	(36)	(40)	(40)	(39)	(36)	(35)	(38)	(39)	(40)	(32)	(37)
s.e. mean	0.8	0.7	1.2	1.6	0.5	0.4	1.2	0.6	1.2	1.0	0.1	0.1
P	< 0.001		NS		< 0.001		< 0.001		< 0.001		< 0.001	

were further significant decreases POST-atropine with mean pressures at each level of measurement and with systolic pressure at the I_{15}, I_{20} and I_{25} (Table 4).

When the absolute heart rate is rapid (approximately 140 beats/min or greater), it has been suggested that the diastolic filling time is so reduced that further increases in cardiac output may not occur (Guyton *et al.*, 1973). Thus, after atropine, with the largest heart rate increases produced by isoprenaline, the blood pressure might be expected to fall proportionately more despite the inotropic effect of isoprenaline. This could explain why the slope of the dose-response curve for blood pressure tended to be steeper after atropinisation. However, even with the smaller heart rate increases, before diastolic filling time would be expected to be crucial, there was a significantly greater fall in blood pressure after atropine, suggesting that factors other than this mechanism were involved. One alternative explanation is that a reflex component to the heart rate increase was abolished.

Such a heart rate contribution might be expected to alter systolic pressure rather than diastolic, since it is generally accepted that the main determinants of systolic pressure are stroke volume and heart rate, whereas peripheral resistance is the main determinant of diastolic pressure (Rushmer, 1970). However, our results showed that after atropine the further fall in diastolic pressure was comparable to that for systolic pressure. If atropine altered the response of peripheral blood vessels to isoprenaline, then a greater change in peripheral resistance might occur. Against this, Brick *et al.* (1968) record that there was no significant difference in the forearm blood flow increment to isoprenaline before and after atropine though they did not measure peripheral resistance specifically. Another factor to be considered could be the effect of isoprenaline and atropine on the major veins. Also subtle relationships between acetylcholine and noradrenaline have recently been described at the synaptic level (Sharma & Banerjee, 1978; Bailey *et al.*, 1979): the extent to which these effects may interfere with the response to isoprenaline has not yet been elucidated in man. We have further assumed that atropine blocks the efferent limb of the baroreceptor reflex but if it interfered with the afferent limb then the possible contribution from corrective sympathetic reflexes might be important. In this respect, it is of interest that atropine abolished the small rise in systolic pressure observed after diastolic pressure had returned to baseline.

Cleaveland *et al.* (1972) also reported that, although, after atropine, the tachycardia appeared to be less with small doses of isoprenaline, there was no significant difference in tachycardia at isoprenaline doses sufficient to increase heart rate by 25 beats/min. Since they did not find the hypotensive effects of isoprenaline to be enhanced by atropine, they attributed these

effects of atropine to the abolition of sinus arrhythmia with doses of isoprenaline giving an increase in heart rate of more than 20 beats/min. However, in our experiments, using continuous recordings of respiration and heart rate, we found that sinus arrhythmia was still present at the maximum heart rate increases (Figure 1). We have also demonstrated that, following the administration of atropine, a significantly larger dose of isoprenaline is required to increase heart rate by 10, 15, 20 and 25 beats/min (Table 3) or conversely that the PRE-atropine I_{10}, I_{15}, I_{20} and I_{25} produce significantly lower increases in heart rate after atropine has been administered.

Atropine increased resting heart rate by 50.3 ± 2.2 beats/min. Although Cleaveland *et al.* (1972) found no relationship between resting heart rate and the response to isoprenaline, it has been suggested that the response to isoprenaline may be attenuated with higher resting levels. However, against this, we found no significant change in the slopes of the POST-atropine isoprenaline dose heart rate response curves compared to those obtained before atropine was given (Table 1). In addition, we have also demonstrated, using continuous infusions of isoprenaline instead of bolus injections, that the POST-atropine tachycardia is enhanced rather than reduced (Arnold & McDevitt, 1982). Therefore, we conclude that the changes in heart rate recorded after atropine and isoprenaline may be compared with the changes obtained before atropine.

We have described in detail the time sequence of changes in breathing pattern, heart rate and blood pressure following a bolus injection of isoprenaline sulphate. As the breathing pattern altered before the changes in either heart rate or blood pressure commenced, it would seem probable that the increased respiratory drive is a direct effect of isoprenaline, independent of the cardiovascular effects. After atropine the breathing change occurred earlier, presumably due to faster heart rate resulting in a shortened circulation time. Before atropine the maximum heart rate and blood pressure changes occurred at approximately the same time, but after atropine the changes became asynchronous. This would be compatible with the concept that PRE-atropine, part of the heart rate response is determined by the fall in blood pressure. The changes in heart rate and blood pressure were slower to settle POST-atropine suggesting that the vagus may also contribute to their return towards baseline. In view of this, boluses of isoprenaline should be separated by approximately 10 min, especially with the larger doses.

Our results demonstrate the complex interactions between heart rate, blood pressure and vagal tone following a bolus injection of the β-adrenoceptor agonist, isoprenaline. As the changes are dynamic in nature the contribution of the vagus may vary with the transient changes in mean pressure, pulse pressure and heart rate. For this reason we have interpreted our results when the changes in heart rate and blood pressure have been maximum. At this point dose-response curves were constructed for the rise in heart rate and the fall in blood pressure, and it would appear that the maximum changes in heart rate may not reflect pure cardiac β-adrenoceptor stimulation but are contributed to by reflex withdrawal of vagal tone secondary to a fall in blood pressure.

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