J. Physiol. (1984), **356**, *pp.* 459–464
With 2 text-figures
Printed in Great Britain

DOES THE SYMPATHETIC NERVOUS SYSTEM INFLUENCE SINUS ARRHYTHMIA IN MAN? EVIDENCE FROM COMBINED AUTONOMIC BLOCKADE

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(*Received 22 May 1984*)

SUMMARY

1. The influences of vagal and sympathetic efferent activity on sinus arrhythmia in man have been studied in healthy subjects by administration of hyoscine butylbromide and atenolol alone and combined using a microcomputer-linked electrocardiogram (e.c.g.) system. Sinus arrhythmia was quantitated as the S.D. of the R–R interval.

2. Sinus arrhythmia was reduced by hyoscine butylbromide, in some subjects to near abolition, but this end-point was unchanged by pre-treatment with atenolol.

3. Atenolol alone prolonged the mean R–R interval and increased sinus arrhythmia.

4. It is suggested that sinus arrhythmia in man is mediated through vagal efferents alone but that atenolol increases the arrhythmia through a central vagotonic effect.

INTRODUCTION

It is widely accepted that sinus arrhythmia is neurological in origin and mediated by cyclical fluctuation in vagal activity, much of which is synchronous with respiration (Kunze, 1972). The evidence in favour of an exclusively vagal efferent pathway is that sinus arrhythmia is abolished in animals by vagotomy (Samaan, 1935; Anrep, Pascual & Rössler, 1936; Hamlin, Smith & Smetzer, 1966) and in both animals and man by cholinoceptor blockade with atropine (Hamlin *et al.* 1966; Wheeler & Watkins, 1973). Furthermore, the close relation in dogs between the R–R interval and its variation under conditions of variable cooling of the cervical vagus (Katona & Jih, 1975) supports the idea that sinus arrhythmia is largely, if not exclusively, of vagal origin. Yet rhythmic fluctuation of efferent activity in certain sympathetic nerves has been reported, some of which is synchronized with respiration in a way which could, if present in cardiac nerves, contribute to and enhance the arrhythmia (Adrian, Bronk & Phillips, 1932; Joels & Samueloff, 1956). Despite this, however, β-adrenoceptor blockade with propranolol is reported not to alter sinus arrhythmia in animals or man (Hamlin *et al.* 1966; Wheeler & Watkins, 1973; Katona & Jih, 1975). At present, therefore, the extent of a sympathetic component is uncertain.

It is to be expected that sympathetic effects on sinus arrhythmia would be most apparent at low levels of vagal activity because at high levels sympathetic influences on the cardiac pace-maker are suppressed (Levy & Zieske, 1969).

The present experiments were designed to elucidate the relative contributions of efferent parasympathetic and sympathetic influences on sinus arrhythmia in man by examination of the effects of appropriate neuro-effector blocking drugs alone and combined. The drugs chosen were selected for their exclusively peripheral site of action, namely hyoscine butylbromide (Pomeroy & Rand, 1969) and atenolol (Cruickshank, Neil-Dwyer, Cameron & McAinsh, 1980; Woods & Robinson, 1981), so as to avoid possible complicating influences exerted directly on the central nervous system.

METHODS

Experiments were carried out on twelve healthy student volunteers (five male, seven female), aged 20–24 years. Two of the female subjects were taking oral contraceptive agents, one of these also the antihistamine drug Terfenadine, but no other medication was reported. The subjects were permitted a light meal but refrained from tea, coffee, alcohol and cigarettes for 12 h before each experiment. The study received ethical approval from the Research (Endowments) Committee of the West Lambeth Health Authority, and the volunteers gave written consent to participate.

Each subject attended on two occasions, one of these being 2 h after pre-treatment with atenolol 100 mg orally. After a 10 min rest period, supine measurements were made of heart rate, mean R–R interval and S.D. of the R–R interval (as measure of sinus arrhythmia) over successive 100 heartbeat periods using an on-line microcomputer-linked electrocardiogram (e.c.g.) (Smith & Smith, 1981). Blood pressure was measured by sphygmomanometry. After control measurements, hyoscine butylbromide 20 mg was administered in a single intravenous bolus and the e.c.g. measurements continued until the heart rate returned to the control value. Values for mean R–R interval and S.D. of the R–R interval obtained during periods of rapid heart rate change (i.e. initially and during the injection) were discarded from the analysis because of the distortion of the S.D. of the R–R interval produced by the rapidly changing R–R interval. The investigation is based on all remaining values (fifteen to thirty-seven in each experiment per subject). Repeatability of the measurements was assessed by determination of the within-subject coefficient of variation. This was found to be: resting mean R–R interval, 3·3%; S.D. of the R–R interval, 23·8%: in agreement with a previous report (Smith & Smith, 1981).

Comparisons between individual subjects and between treatments were effected by analysis of variance and covariance and comparisons between means by Student's t tests, using conventional methods.

RESULTS

Hyoscine butylbromide and atenolol, alone and combined, had significant effects on mean R–R interval length and on S.D. of the R–R interval. Drug effects on one young female subject are illustrated in Fig. 1 and those on all subjects, using blocked data groups for clarity only, in Fig. 2.

Hyoscine butylbromide alone reduced the resting mean R–R interval of 973 ± 13 to a minimum of 620 ± 14 ms ($P < 0{\cdot}001$) and S.D. of the R–R interval 70 ± 4 to $11{\cdot}2 \pm 1{\cdot}7$ ms ($P < 0{\cdot}001$) (Table 1). Minimum values of S.D. of the R–R interval ranged from 5 to 22 ms. Within each subject a straight-line relation between mean interval length and S.D. of the R–R interval before, during and after drug administration was found (r values ranged from 0·658 to 0·971) and the mean slope of S.D. of the R–R interval on interval length was 0·16 ms/ms (Table 2).

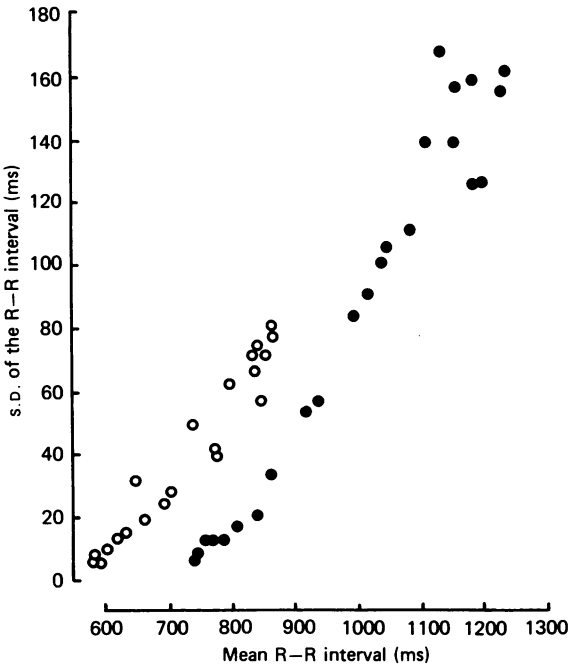

Fig. 1. Mean R–R interval length and S.D. of the R–R interval in one female subject before, during and after hyoscine butylbromide administration: alone (○) and with atenolol pre-treatment (●).

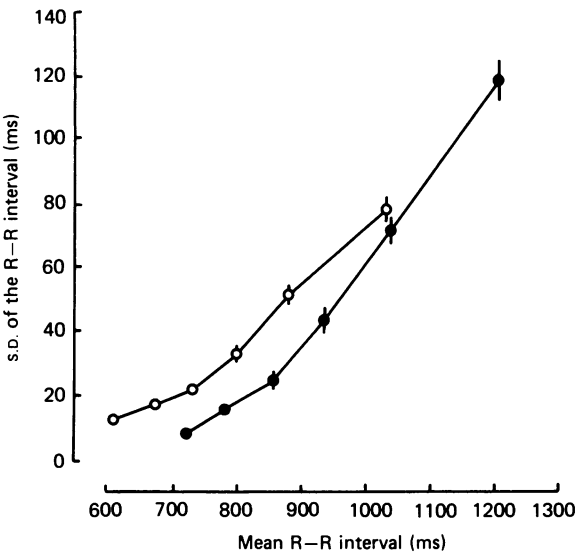

Fig. 2. Mean R–R interval length and S.D. of the R–R interval in twelve subjects before, during and after hyoscine butylbromide administration: alone (○) and with atenolol pre-treatment (●). For illustration only the data points have been grouped ($n = 55$) and shown as mean ± S.E. of mean.

TABLE 1. Mean R–R intervals and S.D. of the R–R interval ± S.E. of mean at rest and at peak effect of hyoscine butylbromide, and resting B.P. Effect of atenolol pre-treatment

			Between treatments		
	Control	Atenolol	*F*	d.f.	*P*
Mean R–R interval (ms)					
Resting	973 ± 13	1141 ± 19	86·29	(12, 88)	< 0·001
Minimum after hyoscine butylbromide	620 ± 14	740 ± 15	35·07	(1, 22)	< 0·001
S.D. of the R–R interval (ms)					
Resting	70 ± 4	103 ± 6	12·60	(12, 88)	< 0·001
Minimum after hyoscine butylbromide	11·2 ± 1·7	8·1 ± 1	2·47	(1, 22)	N.s
Resting systolic B.P. (mmHg)	113·3 ± 1·5	101·7 ± 2·4	$t = 5·191$		< 0·001
Resting diastolic B.P. (mmHg)	69·2 ± 2·3	66·2 ± 1·9	$t = 1·465$		N.s

TABLE 2. Analysis of the relation of S.D. of the R–R interval on mean R–R interval. Effect of atenolol pre-treatment

			Between treatments			Between subjects		
	Control	Atenolol	*F*	d.f.	*P*	*F*	d.f.	*P*
Slope	0·16	0·23	44·73	(1, 655)	< 0·001	11·33	(11, 635)	< 0·001
Elevation	−91	−167	78·23	(1, 656)	< 0·001	12·21)	(11, 646)	< 0·001

Atenolol alone prolonged the mean R–R interval to 1141 ± 19 ms ($P < 0·001$) and increased S.D. of the R–R interval to 103 ± 6 ms ($P < 0·001$) (Table 1). S.D. of the R–R interval was increased proportionally more than mean interval length, and the ratio S.D. of the R–R interval/mean interval was increased to a significant extent (0·071 to 0·090, $P < 0·001$).

In the presence of atenolol, hyoscine butylbromide reduced the mean R–R interval to a minimum of 740 ± 15 ms, a value which was greater than that obtained in the absence of atenolol ($P < 0·001$) (Table 1). The S.D. of the R–R interval was reduced to a minimum of 8·1 ± 1·0 ms (range 4–17 ms), a value which did not differ from that obtained in the absence of atenolol ($0·2 > P > 0·1$). Within each subject the relation between mean interval length and S.D. of the R–R interval was linear (*r* values ranged from 0·779 to 0·977) but the mean slope of S.D. of the R–R interval on interval length (0·23 ms/ms) was not parallel to, being significantly steeper ($P < 0·001$) than, that found in the absence of atenolol (Table 2).

Atenolol treatment lowered systolic B.P. (113·3 to 101·7 mmHg, $P < 0·001$) but had no significant effect on diastolic pressure (69·2 to 66·2 mmHg, $0·2 > P > 0·1$).

DISCUSSION

This study has shown that hyoscine butylbromide caused cardio-acceleration, which is in keeping with its known anticholinergic property. At the same time it reduced R–R interval variation in parallel with the reduction in interval length, a finding which is strongly indicative of a dominant vagal component to sinus

arrhythmia and in agreement with the observations on dogs by Katona & Jih (1975). The minimum values for S.D. of the R–R interval obtained (5–6 ms in some subjects) probably represent near total abolition of sinus arrhythmia because measurement of S.D. of the R–R interval from an e.c.g. pulse generator yielded a value of 2 ms (irrespective of the mean R–R interval) and under experimental conditions this value may be increased by differences in pulse triggering from a variable upstroke of the R wave from the e.c.g. The findings are therefore consistent with previous observations that sinus arrhythmia is abolished by atropine administration or vagotomy (Samaan, 1935; Anrep *et al.* 1936; Hamlin *et al.* 1966; Wheeler & Watkins, 1973).

Under conditions of maximal vagal blockade with hyoscine butylbromide, atenolol pre-treatment did not alter S.D. of the R–R interval, though the mean R–R interval was prolonged in keeping with the known influence of the drug on cardiac sympathetic drive. Again, this finding is consistent with the conclusion that the efferent sympathetic pathway is not involved in sinus arrhythmia.

In the absence of vagal block, i.e. before hyoscine butylbromide administration, atenolol increased the mean R–R interval and its variability. A similar observation was made with propranolol by Katona & Jih (1975) using anaesthetized dogs, though the authors did not comment upon it. Such an increase was unexpected and is difficult to explain largely because the timing of sympathetic nervous activity in relation to respiration is such as to promote, rather than reduce, sinus arrhythmia (Adrian *et al.* 1932; Joels & Samueloff, 1956), in which case blockade of the cardiac β-adrenoceptors with propranolol or atenolol should reduce and not enhance the arrhythmia. The findings are therefore inconsistent with a sympathetic contribution to sinus arrhythmia of respiratory origin. The question must then be asked as to why atenolol increases the arrhythmia. If sinus arrhythmia is exclusively of vagal origin, it can only do so by increasing vagal activity in synchrony with expiration or, less likely, by decreasing it with inspiration. In anaesthetized cats, atenolol reduces central sympathetic outflow, probably by the modification of afferent reflex inputs yet to be identified (Scott, 1983). In such a situation it may be that central sympathetic suppression is accompanied by reciprocal excitation of the vagal motor nuclei to the heart and possibly for similar reasons. If this is so, the other salient feature of β-adrenoceptor blockade, namely bradycardia, may arise in part from a similar origin. It remains to be seen whether other β-adrenoceptor antagonists which do not slow the heart rate at rest have the same apparent vagotonic influence.

There remains the possibility that the increase in arrhythmia produced by atenolol in these experiments was in some way a consequence of the associated reduction in B.P. Hypotension produced by vasodilators in the presence of β-adrenoceptor blockade in man increases rather than decreases the heart rate (Baxter & Lennox, 1977) indicating, as might be expected, that lowering B.P. decreases rather than increases vagal tone. It must therefore be assumed that if the arrhythmia increased in our experiments because of a vagotonic influence then it must have occurred despite, and not because of, the concurrent fall in B.P.

We thank Boehringer Ingelheim Ltd. for a gift of hyoscine butylbromide (Buscopan) injection and for generous financial support.

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