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Adaptation of hypertensives to treatment with cardioselective and non-selective beta-blockers

Absence of correlation between bradycardia and blood pressure control, and reduction in slope of the QT/RR relation

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SUMMARY Thirty mild hypertensives were treated for more than two months with either cardioselective (atenolol or metoprolol) or non-selective (propranolol or pindolol) beta-blockers; the patients were assigned to the drugs in a double-blind manner. A procedure was designed to distinguish between the effects of the drugs themselves while treatment continued, and the development of adaptive changes which would persist when the drugs had been eliminated from the body. Though individual responses to treatment varied in both groups, the mean effect of the cardioselective and non-selective drugs in the control of hypertension was similar. There was no evidence of the development of supersensitivity or "rebound". On the contrary, an adaptive bradycardia (that is a fall of not less than 10% in heart rate persisting 52 hours after stopping treatment) was observed at rest in 17/30 patients, and peak heart rates and blood pressures during exercise were lower in both groups than before treatment. Cardioselective drugs induced a significantly greater bradycardia at rest than non-selective, but on exercise increases in heart rate were reduced more by the non-selective drugs, so that the same peak heart rates were reached on exercise in both groups. Adaptation also affected QT. The results suggest that two factors govern the shortening of QT by increases in heart rate, a "metabolic" effect, determined by sympathetic drive, and a "biophysical" effect determined by heart rate. The adrenergic effect is attenuated by acute beta-blockade, or by adaptation to prolonged blockade, leaving a shallow, rate-determined, slope to the QT/RR regression.

The efficacy of beta-receptor blocking drugs in the treatment of hypertension was discovered more than 15 years ago.[1 2] After an initial period of doubt,[3] beta-blockade became accepted as a major therapeutic procedure,[4 5] yet there is no universal agreement concerning its mechanism of action. There is abundant evidence, however, that the effect is a consequence (though often delayed) of the blockade of $beta_1$-receptors since cardioselective compounds[6 7] reduce blood pressure. Though cardiac output usually falls initially, and peripheral resistance increases, it has been found that after prolonged treatment the cardiac output may return to normal levels in spite of a persistent lowering of blood pressure, indicating a reduction of peripheral resistance.[8–11] Thus beta-adrenoceptor blockade must be responsible for some hypotensive action apart from a reduction of cardiac output, even though, in some other studies, it was found that cardiac output did remain moderately subnormal.[7 12]

It was suggested that the fact that beta-blockers reduce or prevent adrenergically-stimulated release of renin might be responsible for their hypotensive action,[13] yet later studies failed to show any consistent relation between levels of plasma renin

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activity and the efficacy of beta-blockers in hypertension.[14–18]

Another hypothesis advanced to explain the effect of beta-blockers in hypertension was that they may have a direct acute action on the central nervous system[19] causing a reduction in the outflow of sympathetic impulses by blocking beta-receptors in the brain. The effect was not observed with practolol, however, which does not substantially cross the blood-brain barrier, yet practolol is effective in hypertension.

The pharmacological analysis of the mode of action of drugs in animals is usually based upon the results of acute experiments. In man, beta-blockers are administered for weeks, months, or years. Moreover, the optimal beneficial effect of beta-blockers in hypertension is not usually immediately apparent. Prichard and Gillam[20] stated: "In the moderate and severe hypertensive treated with oral propranolol, though there is immediate full cardiac slowing, the full hypotensive effect is often delayed up to one or two months". Furthermore, in many patients bradycardia persists for some days after treatment has been stopped, and the hypotensive effect may persist even longer. Zacharias and Cowen,[4] in their study of propranolol in hypertension, expressed the opinion: "That a second factor is involved is suggested by the fact that even when patients have been off propranolol for 16 weeks their mean blood pressure did not rise to untreated levels".

It seemed logical, therefore, to study the effects of beta-blockers in animals which had been treated for prolonged periods. In order to distinguish a secondary adaptation to the drug from its acute effects, treated animals were killed at least 24 hours after the last dose, when the drug would have been eliminated from the body, and their hearts were then removed for electrophysiological and other investigations. The results of several such studies, initiated in 1972, indicated that prolonged beta-blockade produced several adaptive changes,[21] the most prominent of which were a large prolongation of action potential duration,[22] and an increase in the vascularity of the myocardium.[23] The experiments were carried out in rabbits, and it was naturally of interest to discover what, if any, adaptive responses occurred after prolonged beta-blockade in man. Though there have been numerous studies of the effects of long-term blockade, these have usually been carried out while the treatment continued.[8 9 12 24] In order to distinguish adaptive changes from the direct effects of the drugs, however, it is necessary to interrupt the treatment for a sufficient time to permit elimination of the compounds from the body before measurements are made.

This paper reports the effects of treatment with four beta-blockers (two cardioselective, two non-selective) in 30 mildly hypertensive patients. The main findings were that adaptive changes did occur, and that a clear distinction could be made between the effects of the cardioselective and non-selective agents. There was no correlation between the persistent bradycardia, when it occurred, and the hypotensive response. Furthermore, after acute intravenous blockade at any time, or after adaptation to blockade but in the absence of the drug, the slope of the regression relating the QT to the RR interval was reduced, especially during exercise.

Methods

SELECTION OF PATIENTS

Forty-seven untreated patients, referred for assessment of possible hypertension, agreed to participate in the study. Cuff blood pressure readings of 140/90 mmHg or more had been recorded on at least three occasions, either by their general practitioners or in the hospital outpatient clinic. Intra-arterial pressure was recorded for 24 hours,[25] and after computer analysis 17 of the patients were found to have pressures of less than 140/90 mmHg for 70 per cent or more of the working day, and were classified as normotensives. The remaining 30 patients (19 male, 11 female) were also included in a larger trial of the relative efficacy of various beta-blockers in hypertension, and were assigned in a double-blind manner to receive orally one of four beta-blockers, long-acting propranolol,[7] pindolol,[7] atenolol,[7] and metoprolol.[9] They were instructed to take their medication each morning, but to refrain from doing so on days 7 and 8, and on days 28 and 29 of the trial. The initial dosage was 160 mg of long-acting propranolol, 15 mg pindolol, 100 mg atenolol, or 200 mg metoprolol. On the 16th day blood pressure was measured in the clinic, and dosage was adjusted (decreased in two, increased in 14). Blood pressure was again measured in the clinic on the 42nd and 70th days.

The mean age of the patients was 44·8 years (range 16 to 69, SD 13·4). The nature of the trial was explained to them and written consent to their participation obtained. Their responses to exercise before and after administration of an intravenous injection of their assigned beta-blocker were measured on days 1, 8, and 29, in accordance with the following procedure.

PROCEDURE

Systolic and diastolic blood pressures were measured with a sphygmomanometer, and an electrocardiogram was recorded (lead II, Hewlett-Packard

1511A, 50 mm/s) while the patient rested in a seated position. The electrocardiogram was monitored continuously and records were obtained after three minutes of treadmill (Avionics E15) exercise at 2·9 kph and 10 per cent incline (exercise 1), and after three minutes at 4·0 kph at 12 per cent incline (exercise 2). Systolic and diastolic blood pressure were again measured after the peak of exercise 2 (at a standard time, 40 to 50 s after exercise).

The patients then rested for a few minutes seated, and were given, by intravenous injection, either propranolol 1 mg (in 1 ml over 2 min), pindolol 0·4 mg (in 2 ml over 2 min), atenolol 5 mg (in 10 ml over 5 min), metoprolol 10 mg (in 10 ml over 5 min), the drug selected being the same as that with which they were being treated.

After a further 10 to 15 minutes the electrocardiogram and blood pressure were recorded at rest, and after two periods of exercise as described above.

The patients were submitted to this procedure on day 1, before the start of treatment; on day 8, 52 hours after their most recent oral dose (taken on day 6); and on day 29, again 52 hours after their most recent dose, taken on day 27. All patients completed the procedure. One patient complained of breathlessness during the 6th minute on one occasion; another complained of leg pain on one occasion.

TREATMENT OF DATA

Before the code was broken, measurements of three QT and RR intervals at each of the six stages of the procedure (rest; exercise 1; exercise 2; and after the intravenous beta-blocker, rest; exercise 1 and exercise 2) were made by two observers independently, and averaged. The QT interval was defined as the distance between the beginning of the Q wave and the point at which a tangent to the descending limb of the T wave crossed the baseline. The RR interval was measured from the peaks of the R waves. There was no interobserver variation. All measurements of blood pressure were made, and all injections administered, by one of us (MOH).

Sixty-six observations were obtained from each patient. In view of the small number of patients on each drug, interest was concentrated upon detecting any differences in responses to the selective (atenolol, metoprolol) and non-selective (propranolol, pindolol) beta-blockers, and particular attention was paid to comparisons between the groups receiving these drugs. All the raw data were entered on tape, and analysed by various specially-made programs with an HP 9830 computer. Responses to individual drugs, and to all drugs, were calculated and compared. Linear and polynomial regressions were computed. The main points of interest have been extracted and are presented here. The significance of differences between groups was calculated by Student's t test, and of differences within patients by a paired t test.

Results

(1) CONTROL OF BLOOD PRESSURE AT REST

The systolic and diastolic pressures measured initially, and on the 16th, 42nd, and 70th days of the trial, are presented in Table 1. These measurements were made while the patients were still taking the drug, a few hours after their daily dose. By good fortune the groups selected at random for treatment with the non-selective and cardioselective drugs were extremely well matched, with identical initial mean systolic and diastolic blood pressures. Control of blood pressure was satisfactory in both groups, the onset of control appearing a little earlier in the patients in the cardioselective group. The hypo-

Table 1 *Control of blood pressure*

Day 1 *Mean ±SE*	*Day 16* *Percentage change ±SE*	*p value*	*Day 42* *Percentage change ±SE*	*p value*	*Day 70* *Percentage change ±SE*	*p value*
(A) Patients treated with propranolol or pindolol (non-selective) 9M, 5F						
Systolic blood pressure 173·0 ±8·65	−8·3 ±7·2	0·27	−7·9 ±3·3	0·036	−13·2 ±4·0	0·007
Diastolic blood pressure 109·7 ±3·63	−4·9 ±2·4	0·058	−10·6 ±2·6	0·0017	−16·2 ±2·7	0·00006
(B) Patients treated with atenolol or metoprolol (cardioselective) 10 M, 6 F						
Systolic blood pressure 172·0 ±6·5	−9·9 ±3·2	0·008	−14·4 ±2·4	0·00004	−18·4 ±3·0	0·00003
Diastolic blood pressure 109·8 ±3·6	−13·9 ±3·3	0·0009	−16·4 ±3·3	0·0002	−21·0 ±2·4	10^{-5}

NB—Statistical significances were calculated by a paired t test. Measurements in column 1 have been given in mmHg (1 mmHg = 0·133 kPa).

tensive effect appeared to be slightly larger with the cardioselective drugs, but the differences in reduction of mean systolic (−13·2 versus −18·4%) and of mean diastolic pressure (−16·2 versus −21·0%) were not, in fact, statistically significant ($p=0·31$ and 0·2, respectively). Thus, so far as the mean control of blood pressure was concerned there was little to choose between selective and non-selective drugs. There were, however, as might be expected from previous reports, some patients in each group whose response to treatment was minor. If an arbitrary criterion of a fall of less than 10 mmHg systolic and 5 mmHg diastolic is taken as constituting a minor response, then the incidence of minor responses was, for systolic pressures, for propranolol 2/7, and for pindolol 3/7; for atenolol 1/7, and for metoprolol 1/9. Only one patient (on metoprolol) had a fall of diastolic pressure of less than 5 mmHg.

(2) ADAPTATION OF BLOOD PRESSURE DURING TREATMENT, AT REST, AND ON EXERCISE

Measurements were made initially before the start of treatment (day 1) and, 52 hours after the most recent medication, on days 8 and 29. The results are presented in Table 2, and indicate a small difference in the effects of the non-selective and cardioselective drugs. The first two columns indicate that, with both groups of drugs, neither systolic nor diastolic pressures at rest returned to initial levels 52 hours after the last dose of drug, even after only one week's treatment, though the only statistically significant fall was of the systolic pressure in the cardioselective group. During exercise, however, there was a clear distinction between the groups. The *rise* in systolic pressure during exercise was significantly less pronounced on day 8 and day 29 in the non-selective group, but was not significantly altered in the cardioselective group. (As already mentioned the *absolute* levels reached during exercise were lower in both groups than before treatment.) There was hardly any change in diastolic pressure in either group during exercise on day 1 but on day 29 in the non-selective group diastolic pressure fell, but was still unchanged in the cardioselective group.

Table 2 *Adaptation of blood pressure at rest and during exercise (52 hours after last dose)*

	Percentage change in resting blood pressure		*Percentage change in blood pressure (from rest) during second exercise*		
	Day 8	*Day 29*	*Day 1*	*Day 8*	*Day 29*
(A) Non-selective beta-blockers					
Systolic					
Mean	−7·8	−8·9	+15·9	+6·2	+4·4
SE	6·2	6·2	3·2	2·6	2·1
			Difference from day 1	−9·7	−11·5
p value	0·2	0·17		0·012	0·0005
Diastolic					
Mean	−2·4	−5·0	+2·2	−0·7	−5·8
SE	3·6	3·03	1·3	1·4	2·1
			Difference from day 1	−2·9	−8·0
p value	0·47	0·86		0·19	0·009
(B) Cardioselective drugs					
Systolic					
Mean	−9·3	−10·1	+9·8	+5·6	+6·1
SE	5·6	7·5	2·5	2·2	2·6
			Difference from day 1	−4·2	−3·7
p value	0·019	0·016		0·18	0·22
Diastolic					
Mean	−5·4	−5·1	−0·9	−2·7	−1·3
SE	2·3	4·3	2·3	1·5	2·0
			Difference from day 1	−1·8	−0·4
p value	0·09	0·15		0·5	0·9

(3) ADAPTIVE CHANGES IN HEART RATE

There was a striking and highly significant difference in the adaptation of heart rate to treatment with non-selective and cardioselective drugs, presented in Table 3. With the non-selective drugs, 52 hours after the last dose, there was only a small number of patients with persistent bradycardia at rest, not statistically significant for the group as a whole. During exercise, however, in spite of the fact that no drug could have remained in the body (since both propranolol and pindolol have short metabolic half lives) there was a remarkable reduction of the heart rate increases in response to exercise, at both levels of effort.

In contrast, in the cardioselective group, there was a pronounced and statistically significant bradycardia at rest. On exercise, however, the *increases* in heart rate when expressed as a percentage increase from the resting heart rate were just as large as they were initially, a fact that confirms, incidentally, that no drug could still be present after 52 hours, even though the half life of atenolol is longer than that of the other drugs.[26] (The mean increases in heart rate during the second exercise in the seven patients on atenolol were +44·6% on day 8 and +47·3% on day 29, as compared with +49% on day 1).

Thus the interesting result was obtained that the actual heart rates during exercise in the two groups were not significantly different from each other after treatment, though in both groups the peak rates reached were lower than those observed before

treatment was started. In the cardioselective group, the heart rates were lower at rest, but increased on exercise (to a mean during exercise 2, day 29, of 107·9 ±5·6 beats/min, in comparison with 129·3 before treatment) whereas in the non-selective group the resting heart rates were not significantly lowered, but rose less on exercise (to a mean during exercise 2, day 29, of 105·6 ±4·1, in comparison with 123·2 before treatment).

(4) ADAPTATION OF BLOOD PRESSURE AND HEART RATE TO ACUTE INTRAVENOUS BLOCKADE

Blood pressure

The immediate response to acute beta-blockade has often been reported to be a fall in cardiac output with increased peripheral resistance, resulting in no change in blood pressure. Column 1 of Table 4A and B, confirms the absence of significant blood pressure change, and indicates that there is no difference between the non-selective and cardioselective compounds in this respect. Table 4 also indicates that there is virtually no change in sensitivity to the effects of acute blockade on blood pressure, either at rest or during exercise. The only significant blood pressure statistic in the whole table is a slightly larger fall in systolic pressure at rest in response to intravenous beta-blockade in the non-selective group. The table indicates no developing supersensitivity (or decreased sensitivity) to acute blockade, in respect of systolic and diastolic blood pressure.

Heart rate

An acute injection of propranolol on day 1 did not reduce heart rate at rest, but lowered the increase in heart rate in response to exercise 2 from +45·3 to +33·3 per cent. There was no significance adaptive change during treatment in sensitivity to acute intravenous administration of propranolol at rest or during exercise, which is in contrast to the finding of Brundin *et al.*[27] A similar result was obtained for the non-selective group as a whole.

Acute injection of the cardioselective drugs, however, did cause an immediate bradycardia at rest, and this result was significantly different from that of the non-selective compounds. This bradycardic response was not significantly less on day 29. On exercise 2 acute blockade reduced the increase in heart rate from +46·1 to +34·8 per cent on day 1, and from +49·3 to +38·4 per cent on day 29, again showing an absence of adaptation.

Thus, even if prolonged beta-blockade increases the number of beta-receptors, such an increase does not appear to produce, at least at the doses employed in this study, any functional adaptation to the effects of an acute injection of beta-blocker, selective or non-selective, either on heart rate or blood pressure.

(5) EFFECTS ON QT INTERVAL

(A) *Initial QT/RR relation*

Prolonged treatment of rabbits with beta-blockers at clinical dose levels causes a lengthening of action potential duration, independently of heart rate, in both young[22] and adult animals.[28] It seemed possible, if a similar adaptive response were to occur in man, that it might be detected as a prolongation of QT interval. Raine and Pickering[24] reported that QT at rest was significantly longer in patients on long-term beta-blockade (with various drugs) than in matched controls, and that QT shortened less in these patients during exercise than in controls. There was, however, no record of the pretreatment QT intervals of the patients treated with beta-blockers, and since measurements were recorded while the subjects were still on medication there was no way of distinguishing the effects of the beta-

Table 3 *Adaptation of heart rate at rest and during exercise (measured 52 hours after last dose)*

	Percentage change in resting heart rate		*Percentage change in heart rate during first exercise*			*Percentage change in heart rate during second exercise*		
	Day 8	*Day 29*	*Day 1*	*Day 8*	*Day 29*	*Day 1*	*Day 8*	*Day 29*
(A) Non-selective drugs								
Mean	−4·1	−3·3	+33·8	+23·5	+21·1	+43·7	+35·4	+28·2
SE	3·4	4·1	4·3	3·9	2·8	4·9	5·3	4·2
			Difference from day 1	−10·2	−12·1	Difference from day 1	− 8·3	−15·4
p value	0·29	0·29		0·009	0·004		0·097	0·0005
(B) Cardioselective drugs								
Mean	−9·9	−16·3	+28·4	+28·6	+30·1	+46·1	+44·6	+49·3
SE	4·2	3·3	3·6	4·9	5·3	4·5	6·4	6·9
			Difference from day 1	+ 0·2	+ 1·7	Difference from day 1	− 1·6	+ 3·2
p value	0·007	0·00004		0·97	0·77		0·77	0·61

Table 4 *Adaptation of blood pressure and heart rate to acute beta-blockade (iv)*

	Percentage change in pressure at rest			*Percentage change in pressure during exercise*		
	Day 1	*Day 8*	*Day 29*	*Day 1*	*Day 8*	*Day 29*
(A) Non-selective group						
Systolic						
Mean	−3·1	−5·1	− ·7	+10·1	+9·4	+12·2
SE	1·5	1·5	1·3	2·2	2·4	2·3
Difference from day 1		−2·0	−5·5		−0·7	+ 2·1
p value		0·23	0·03		0·85	0·41
Diastolic						
Mean	+2·6	+0·8	−3·6	+ 1·0	−2·0	− 0·1
SE	2·5	1·4	2·4	1·9	1·4	2·0
Difference from day 1		−1·7	−6·2		−3·0	− 1·1
p value		0·53	0·15		0·12	0·6
(B) Cardioselective group						
Systolic						
Mean	−3·8	−5·0	−4·3	+ 8·2	+4·5	+ 4·8
SE	2·2	2·0	2·4	2·4	2·2	2·5
Difference from day 1		−1·2	−0·5		−3·7	− 3·3
p value		0·5	0·78		0·11	0·24
Diastolic						
Mean	+1·8	−0·3	0·00	− 1·3	−3·3	− 2·1
SE	2·7	1·9		2·0	2·0	2·8
Difference from day 1		−2·2			−1·9	− 0·8
p value		0·49			0·38	0·8

(C) Heart rate
Adaptation to acute intravenous beta-blockade (52 hours after last dose)

	Percentage change in heart rate at rest			*Percentage change in heart rate on exercise*		
	Day 1	*Day 29*	*p value*	*Day 1*	*Day 29*	*p value*
Propranolol alone	0·0 ±3·3	−7·8 ±4·2	0·18	+33·3 ±4·1	+35·8 ±6·0	0·63
Propranolol + pindolol	−4·0 ±2·5	−4·6 ±2·5	0·88	+32·4 ±2·5	+29·1 ±3·7	0·41
Atenolol + metoprolol	−13·0 ±1·3	−10·0 ±3·0	0·32	+34·8 ±4·3	+38·4 ±5·1	0·44
Difference between non-selective and cardioselective	9·0	5·4		2·4	9·3	
p value	0·002	0·19		0·64	0·16	

blockers themselves from an adaptation to the blockade.

The QT interval is traditionally corrected according to the equation derived from the work of Bazett,[29] $QT_c = QT/\sqrt{RR}$, QT and RR being expressed in seconds. The initial QT_c intervals in our patients, calculated according to this equation, varied from 0·373 to 0·482 which suggests that this correction procedure may not be appropriate for hypertensive patients. Correlations were, therefore, calculated between QT and RR, QT and $\sqrt{RR}$, for both linear and polynomial regressions. Similar calculations were made on all measurements of QT and RR obtained during the trial, and, since the linear relation was simplest and fitted the points equally well, the other calculated regressions have not been presented here.

The initial values of QT and RR (in ms) at rest have been plotted for all patients in Fig. 1, appropriate symbols indicating the drug to which each patient was subsequently assigned (P, propranolol; V, pindolol; A, atenolol and M, metoprolol). The plus signs depict the least-squares fit for a linear regression, and the asterisks plot a second order polynomial. Both lines were calculated from all the results, and had correlation coefficients of 0·769 and 0·77, respectively. (A plot of QT against $\sqrt{RR}$ also had a correlation coefficient of 0·77.) The regression equations for QT/RR before treatment (day 1) for all patients at rest, and for patients assigned to non-selective and cardioselective drugs at rest and at the peak of the second exercise, are set out in Table 5.

It is apparent that the QT/RR regressions were similar for both groups, and that on exercise the

Table 5 *Initial QT/RR regressions*

Rest		
All patients	(QT) = (RR) × 0·192 + 227	(r = 0·769)
Non-selective	(QT) = (RR) × 0·202 + 214	(r = 0·821)
Cardioselective	0·195 + 230	0·753
Exercise		
Non-selective	(QT) = (RR) × 0·242 + 175	(r = 0·866)
Cardioselective	0·354 + 130	0·881

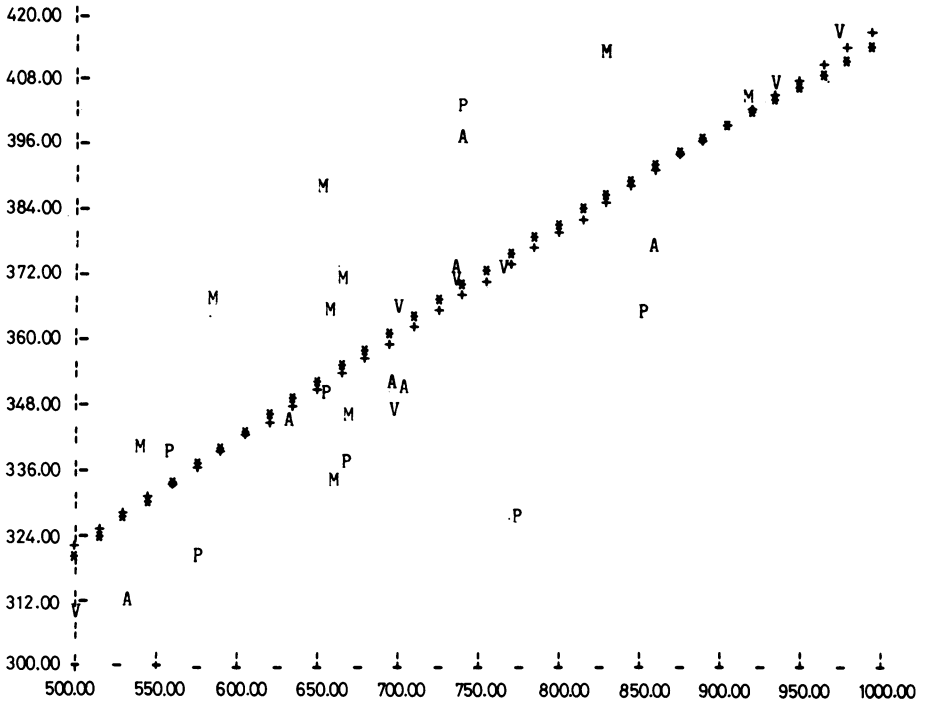

Fig. 1 *QT interval plotted against RR, all patients, at rest, before treatment, Ordinate: QT, ms. Abscissa: RR, ms. Symbols indicate drugs to which patients were subsequently assigned. P, propranolol; V, pindolol; A, atenolol; M, metoprolol. Plus signs: plot of calculated linear regression. Asterisks: plot of second order polynomial.*

regressions were steeper and the correlation coefficients higher. Also of interest, in view of what is reported below, is the fact that on exercise on day 1 the QT/RR slope appeared steeper in the group subsequently assigned to cardioselective drugs.

(B) *Adaptation to treatment*

These was a difference between the responses of the non-selective and cardioselective groups in the QT/RR relation.

In Fig. 2 the calculated linear regressions for QT/RR at rest have been plotted for the non-selective group (asterisks) and the selective group (plus signs) before the start of treatment. As already noted the slopes are similar. The P symbols plot the regression for QT/RR in the non-selective group on day 29 (52 hours after the last dose of drug). The slope has not changed, but at all heart rates QT is about 15 ms longer than before treatment. In contrast, on day 29 in the cardioselective group (A symbols) the slope is quite different ($p=0{\cdot}02$) from that observed on day 1. In patients with higher rates QT was prolonged, but in the patients with slower rates, QT was actually shorter than at the start of treatment.

There was a similar difference between the groups on exercise. The regressions for QT/RR at the peak of the second exercise have been plotted in Fig. 3; asterisks and P symbols depict the plots for the non-selective group on day 1 and day 29, respectively, and the plus signs and A symbols represent the cardioselective group on days 1 and 29. For comparison with the regressions already given for day 1, the equations for day 29 are given in Table 6.

The conclusion to be drawn from these results was that though both groups were responding in a similar manner to the non-selective and cardioselective drugs in relation to the control of blood pressure, their adaptive responses were different in relation to heart rate and the QT/RR relation.

Table 6 *QT/RR regressions on day 29*

Rest		
Non-selective	$(QT)=(RR)\times 0{\cdot}195+230$	$(r=0{\cdot}864)$
Cardioselective	$0{\cdot}075+329$	$0{\cdot}444$
Exercise		
Non-selective	$(QT)=(RR)\times 0{\cdot}238+183$	$(r=0{\cdot}773)$
Cardioselective	$0{\cdot}125+263$	$0{\cdot}470$

Nevertheless there was a resting bradycardia in *some* patients in the non-selective group, though there was no statistically significant slowing of heart rate at rest on day 8 or 29 for the group as a whole. The patients were, therefore, divided, irrespective of drug taken, into those whose resting heart rate on day 29 had fallen by 10 per cent or more (heart rate responders) and those whose heart rate had not fallen or had, in some cases, actually risen a little (non-responders). The score for the heart rate responders according to the individual drugs was atenolol, 7/7; metoprolol, 6/9; propranolol 3/7; pindolol, 1/7; total 17/30.

For the heart rate responders, QT/RR regressions, at rest (asterisks) and during the second exercise (minus signs) before treatment are compared in Fig. 4 with similar regressions calculated on day 29 (plus signs, rest; dots, exercise). It appears that the patients who adapted to beta-blockade by a lowering of heart rate, also adapted by changing the relation between QT and RR (Table 7).

In contrast, a similar plot of the data from the 13 non-responders (Fig. 5) indicates that the QT/RR relation at rest on day 29 was identical to that observed on day 1, and was only slightly flattened during exercise on day 29. Perhaps the most striking feature of these plots was that whatever the QT/RR relation before treatment, by day 29 the QT/RR regressions had become very similar, irrespective of whether they were "heart rate responders" or not. The regression equations are shown in Table 7. For the heart rate responders, the QT/RR regression at rest was not quite significantly different on day 29 from that on day 1 ($p=0{\cdot}076$), but during exercise the slope of the regression on day 29 was significantly different from that on day 1 ($p=0{\cdot}018$). In contrast, for the non-responders, the slopes of the regression were already low on day 1, and had not altered significantly by day 29.

Comparison of Fig. 4 and 5, and the equations in Table 7 suggests that the "heart rate responders" might have constituted a different population *initially*, because the slopes of QT/RR regressions, both at rest and on exercise, were steeper in the

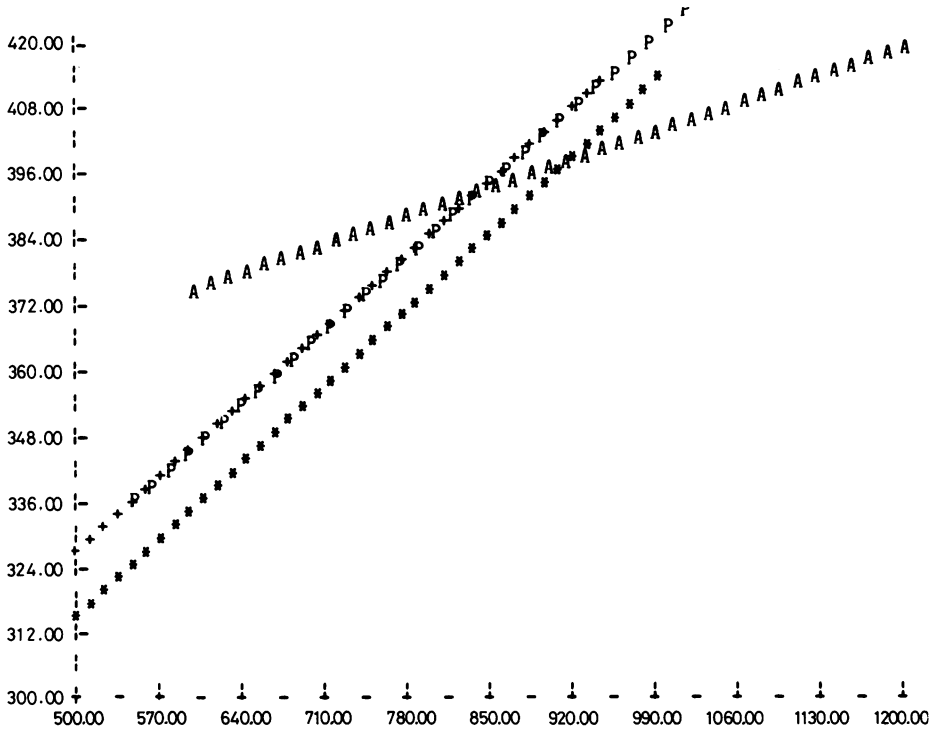

Fig. 2 *Adaptation of QT/RR relation at rest to treatment. Ordinate: QT, ms. Abscissa: RR, ms. Calculated linear regressions have been plotted of the QT/RR relation before treatment in the group on non-selective (asterisks) and cardioselective (plus signs) drugs. The regressions on day 29 are depicted by P symbols for the non-selective, and A symbols for the cardioselective group.*

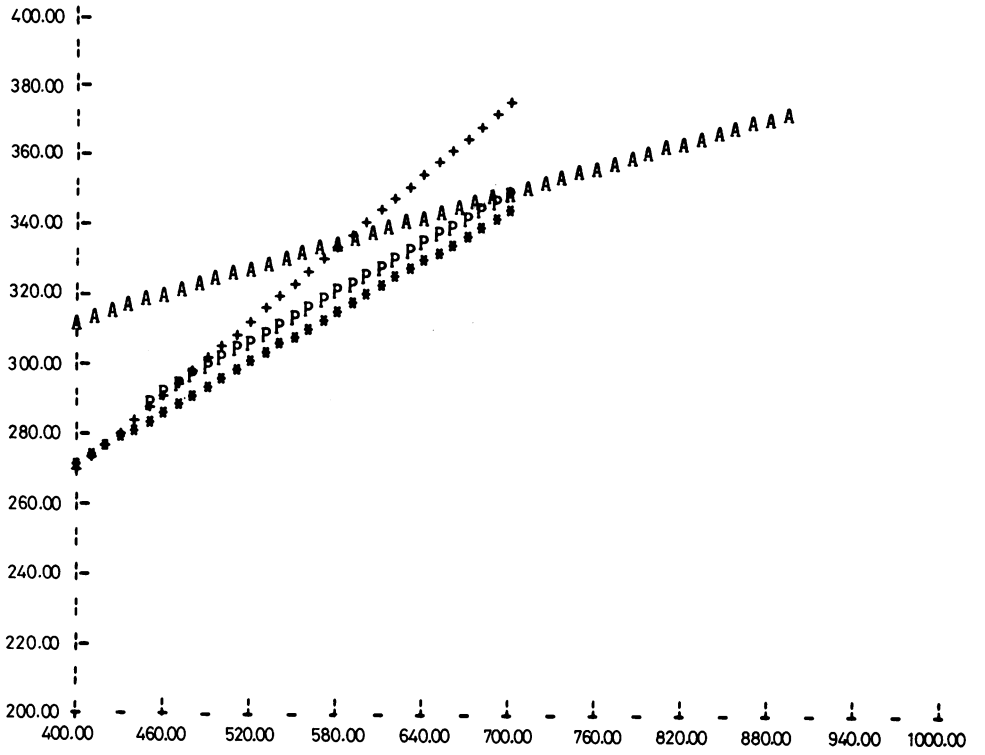

Fig. 3 *Adaptation of QT/RR relation on exercise. Ordinate: QT, ms. Abscissa: RR, ms. The calculated regressions of the QT/RR relation after the peak of the second exercise were steeper than at rest. Asterisks and P symbols, non-selective group on days 1 and 29, respectively. Plus signs and A symbols, cardioselective group on days 1 and 29.*

responders than in the non-responders. Though from Table 7 it is clear that the differences in these slopes were not statistically significant ($p=0{\cdot}13$ at rest, and 0·077 on exercise), the p values were close enough to significance to suggest that this phenomenon, the QT/RR relation, would be worthy of further study in a subsequent investigation.

The question arose, therefore, whether there could have been some accidental bias in the blind assignment of patients, so that the higher proportion of heart rate responses in the cardioselective group might have been the result, not of a difference in the effect of the drugs, but of the inclusion of a larger number of "heart rate responders" in the groups assigned to the cardioselective compounds. Correlations were calculated between heart rate response and observations made before treatment and some of these are listed in Table 8.

Regression analysis was undertaken on the relation between the ultimate heart rate response against (a) initial resting heart rate ($r=0{\cdot}29$), (b) initial increases in heart rate on exercise ($r=0{\cdot}2$), and (c) initial QT_c ($r=0{\cdot}17$), and several other

Table 7 *QT/RR relation in "heart rate responders" and non-responders on days 1 and 29*

	Slope	*Intercept*	*Correlation coefficient*
Day 1			
Rest: Responders	0·236	198	0·697
Non-responders	0·139	266	0·654
Significance of difference in slopes Responders/non-responders	p=0·13		
Exercise 2: Responders	0·346	130	0·891
Non-responders	0·217	194	0·769
Significance of difference in slopes Responders/non-responders	p=0·077		
Day 29			
Rest: Responders	0·127	285	0·654
Non-responders	0·126	282	0·537
Exercise 2: Responders	0·150	242	0·519
Non-responders	0·158	237	0·534

Significance of difference between slopes for QT/RR regressions.
Responders: day 1 compared with day 29. Rest: p=0·076
Second exercise: p=0·018
Non-responders: day 1 compared with day 29.
Rest: p=0·87
Second exercise: p=0·52.

Table 8 *Comparison of initial data*

	Responders	*Non-responders*	*Difference*	*p value*
Initial heart rate	90·5 ±3·8	82·9 ±3·5	7·6	0·16
Initial increase in heart rate on exercise	48·1 ±4·9	40·9 ±3·8	7·2	0·28
Initial QTc	0·436 ±0·008	0·431 ±0·008	0·005	0·6

initial measurements, but no significant correlations were found. It was concluded, therefore, that the bradycardia observed at rest on day 29 in the cardioselective group was indeed the result of an adaptation to the treatment, and that the order of potency in causing adaptive bradycardia at rest was atenolol > metoprolol > propranolol > pindolol. On day 29 in four of seven patients on pindolol, heart rate at rest was actually a little faster than on day 1.

(6) EFFECT OF ACUTE INTRAVENOUS BLOCKADE ON THE QT/RR RELATION

Increases in heart rate on exercise were reduced by acute intravenous beta-blockade. When QT was plotted against RR for observations obtained in the period after injection, both at rest and during exercise, the regression became flatter, that is QT interval became less closely related to heart rate. This was very similar to the adaptation after prolonged treatment observed in the absence of the drug. This less steep relation between QT and heart rate after intravenous beta-blockade did not alter significantly during treatment. For comparison with the figures given above, the equations after acute blockade are given in Table 9.

(7) LACK OF CORRELATION BETWEEN BRADYCARDIA AND CONTROL OF BLOOD PRESSURE

Both bradycardia and reduction of hypertension may persist after stopping treatment after prolonged

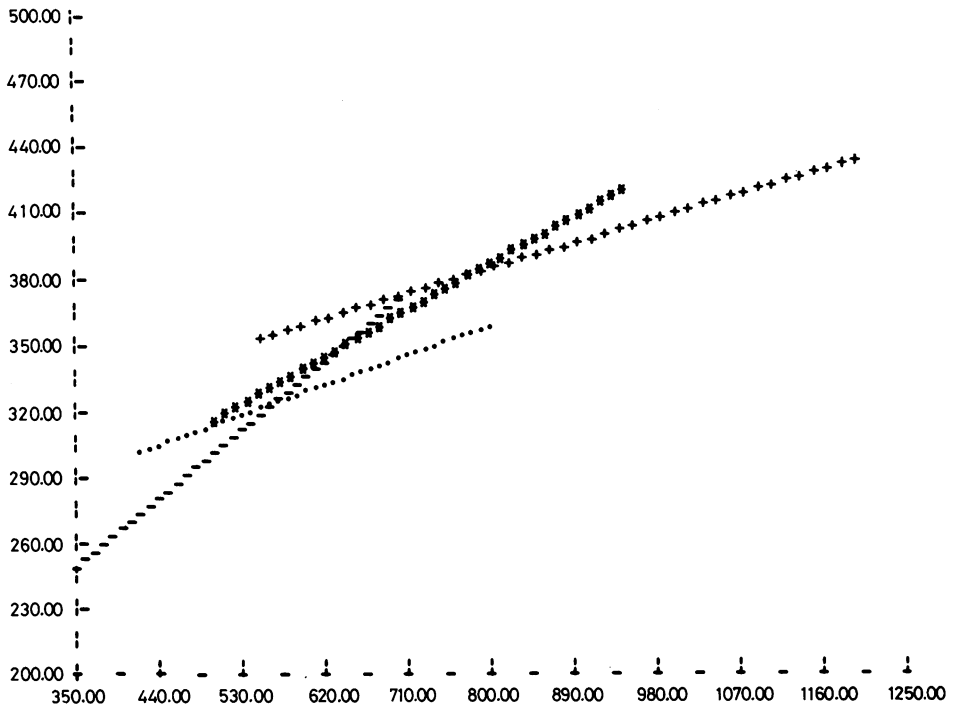

Fig. 4 *QT/RR relation before treatment in patients who ultimately had an adaptive bradycardia during treatment. Ordinate: QT, ms. Abscissa: RR, ms. The calculated regression of the "heart rate responders" is plotted at rest (asterisks) and at the peak of the second exercise (minus signs) on day 1, and at rest (plus signs) and on exercise (dots) on day 29. At rest, the difference in slopes on days 1 and 29 was not quite significant ($p=0·076$), but on exercise the slope on day 29 was significantly different from that on day 1 ($p=0·018$) (see Table 7).*

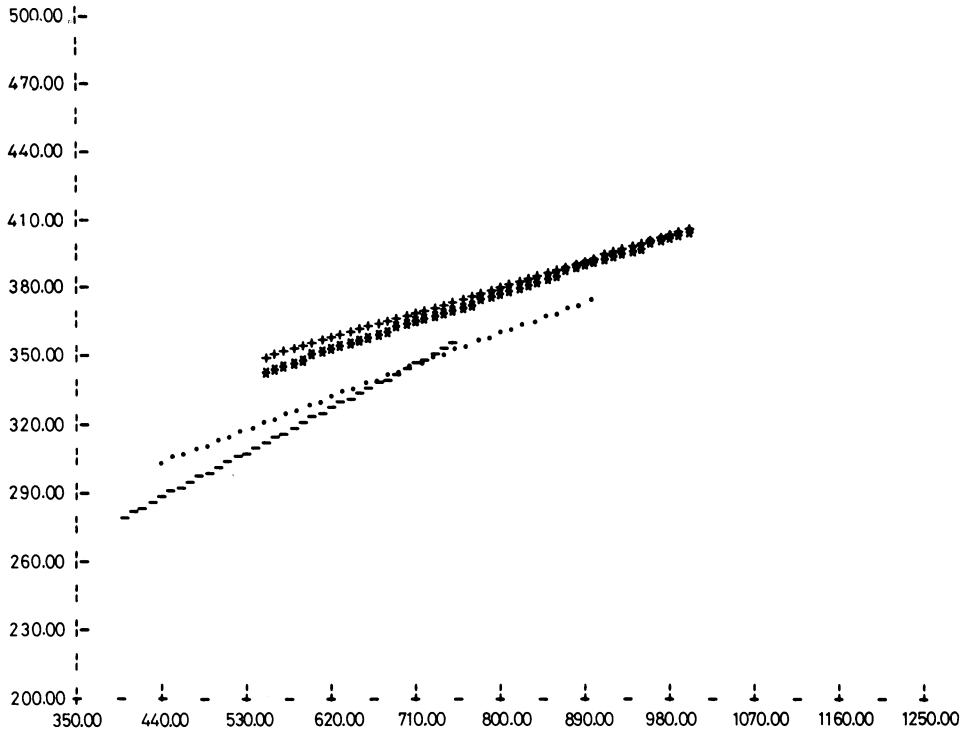

Fig. 5 *Non-responders. The QT/RR regression at rest on day 1 (asterisks) was the same as on day 29 (plus signs). On exercise, the slope of the regression on day 29 (dots) was less steep than on day 1 (minus signs) (that is a change in the same direction as that exhibited by heart rate responders), but the slopes were not, in fact, significantly different (see Table 7).*

beta-blockade, and it might be thought that patients who are adapters in the one respect, might also be adapters in the other. Fig. 6 indicates that this is not the case. Changes in heart rate have been plotted against changes in diastolic blood pressure at day 29, for all patients. Heart rate responders (HR change >10%) are denoted by R, and non-responders by N. The correlation coefficient for all patients was 0·108, for responders 0·092, and for non-responders 0·038.

(8) TIME COURSE OF DEVELOPMENT OF HYPOTENSIVE RESPONSE TO TREATMENT AND OF ADAPTIVE RESPONSE

(A) *Hypotensive response to treatment*

In estimating the response of hypertensives to treatment with beta-blockers, blood pressure is normally measured while patients are still taking the drugs. By this criterion all patients "responded", in that, by the 70th day of treatment, there was no patient on any drug whose diastolic pressure was not lower than on admission to the trial, and only one (on metoprolol) in whom this fall did not exceed 5 mmHg. There were, however, two patients on pindolol, and one each on propranolol and atenolol, in whom diastolic pressure had not fallen by the 42nd day of treatment, and in these four individuals systolic pressure had not fallen even by the 70th day. On the 16th day the "non-responder" scores were, for atenolol and pindolol, one each for both diastolic and systolic pressures; for propranolol, three for diastolic, two for systolic; and for metoprolol, three for diastolic, four for systolic.

Table 9 *Effect of acute beta-blockade on the QT/RR regression*

At rest after intravenous beta-blockade			
Non-selective	Day 1	(QT)=(RR)×0·131+270·2	r=0·581
	Day 29	0·150+260·4	0·736
Cardioselective	Day 1	0·102+296·9	0·485
	Day 29	0·092+327·5	0·465
During second exercise after intravenous beta-blockade			
Non-selective	Day 1	(QT)=(RR)×0·178+215·2	r=0·784
	Day 29	0·232+186·9	0·882
Cardioselective	Day 1	0·206+210·6	0·703
	Day 29	0·170+238·9	0·685

(B) *Adaptation*

An adaptive response to treatment may be defined as a lowered blood pressure persisting after withdrawal of treatment, at a time when no significant concentration of the drug remains in the body. Obviously this cannot be estimated at the same time as the response to treatment already described. By this criterion, on day 29, for diastolic pressure, there were two adapters on propranolol, four on pindolol, five on metoprolol, and six on atenolol, a total of 17/30, but these patients were not, of course, as already shown in Fig. 6, the same 17 who showed an adaptive bradycardia. For systolic pressure, adaptation was present on day 29 in six patients each on metoprolol and atenolol, in four on pindolol, and in five on propranolol. The scores were almost identical on day 8, indicating that in those patients who adapt, the adaptation occurs quite early, though it may progress further during treatment. There were insufficient patients for a full quantitative analysis to have been worth while, but the time-course of the development of adaptation seems to merit further study.

Discussion

Experimental work in animals has shown that prolonged treatment with doses of beta-blockers equivalent to those used clinically induces profound adaptive readjustments which include a decrease in peripheral sympathetic background activity,[30] and a lengthening of cardiac action potential duration. Such changes long outlast the end of treatment. In man, the hypotensive effect of beta-blockers does not develop optimally for days or weeks, and the implication is that some sort of adaptation to repeated interference with the sympathetic control of the heart is involved. The problem has been to identify the site at which such an adaptation occurs, and there have been no lack of candidates. The myocardium, the arterioles, the baroreceptors, the brain, the renin-angiotensin system, and the peripheral sympathetic have all had their advocates.

The present study was designed to distinguish adaptive changes, induced by prolonged beta-blockade and persisting when the drugs had been eliminated from the body, from the immediate

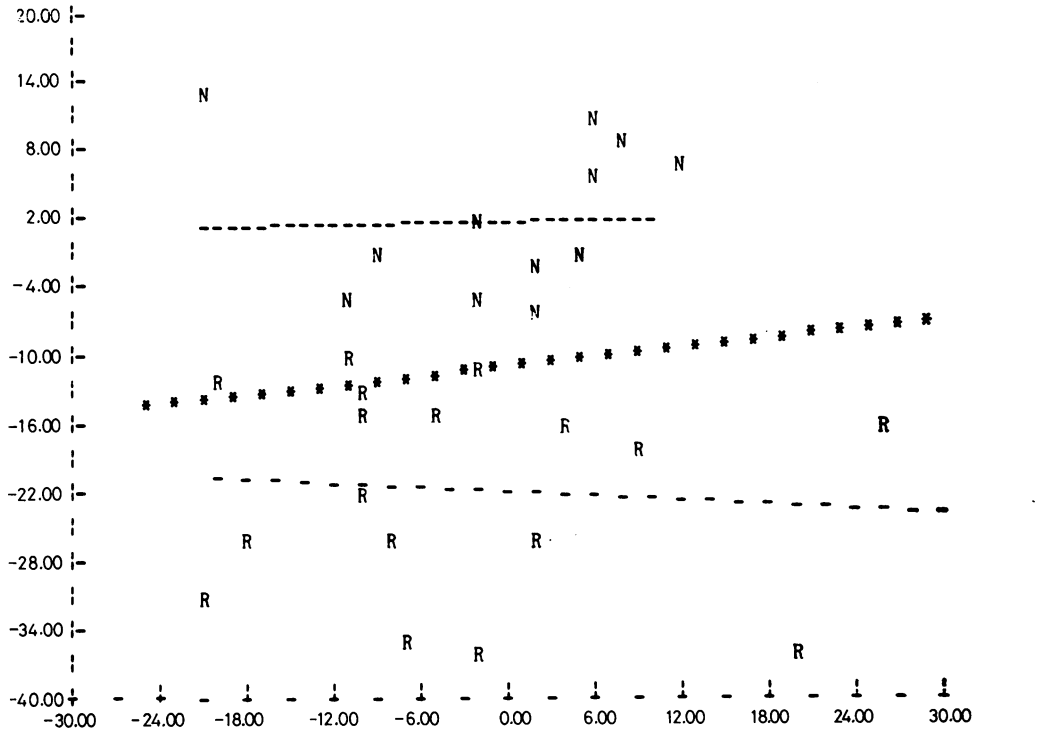

Fig. 6 *Absence of correlation between adaptive bradycardia and control of blood pressure. Ordinate: percentage change in heart rate at rest on day 29. Abscissa: percentage change in diastolic blood pressure on day 29. R=patients with a bradycardia greater than 10 per cent (heart rate responders). N=non-responders. The minus signs shown least squares fits to the R (r=0·092) and N (r=0·038) points, and the asterisks give the fit for all results (r=0·108).*

effects of the drugs themselves. There was no evidence, 52 hours after the last dose of drug, of the development of any "supersensitivity". In no patient in the cardioselective group was the resting heart faster than before treatment, but in four of seven patients on pindolol heart rate was up by 1·6, 6, 12, and 13 per cent, a change that may be related to the intrinsic sympathomimetic activity of this compound. In 17 of 30 patients heart rate at rest was slower by a margin of more than 10 per cent. Furthermore, the peak heart rates on exercise were also lower in both groups. There was no evidence of a "rebound" of blood pressure 52 hours after withdrawal of treatment.

Brundin *et al.*[27] reported that in eight hypertensives treated with propranolol for two months or more, and examined 72 hours after the last oral dose, effects remaining after withdrawal of the drug could be detected—"the persistent effects appeared as: (1) a considerable reduction of heart rate (2) an almost total lack of acute haemodynamic response to intravenous propranolol administration". In our study, though a persistent bradycardia (>10%) was observed in all seven patients on atenolol, and in six of nine on metoprolol, it was found in only three of seven patients on propranolol. No significant adaptive changes in the response to acute intravenous administration of any of the drugs used were observed, either in heart rate or blood pressure responses.

In the present investigation the doses used were adjusted in an attempt to produce what was regarded as a satisfactory response to treatment, that is to say a reduction of diastolic pressure to approximately 90 mmHg (11·97 kPa). As already noted, however, there were a few patients in each group in whom the control of hypertension was minor (fall of less than 10 mmHg systolic or 5 mmHg diastolic). It is possible, of course, that further treatment beyond the limit of this trial would have ultimately improved the response. Regression analysis indicated that there was no correlation at all between the adaptive response of the blood pressure to treatment and the adaptive changes in resting heart rate ($r=0·1$ for all patients).

The adaptation to treatment with beta-blockers involved a less steep relation between heart rate and QT interval. The traditional correction derived from the work of Bazett,[29] $QT_c=QT/\sqrt{RR}$ measured in seconds, resulted in a wide range of QT_c values in the patients before the start of treatment. Recently, Milne *et al.*[31] have questioned the appropriateness of the Bazett correction. Extensive statistical analyses indicated that a linear regression of QT/RR gave as good (or as bad) a fit as $QT/\sqrt{RR}$ or polynomial regressions. It was apparent that with all the drugs the correlation between QT and RR was diminished during treatment, and was also reduced by acute beta-blockade even before the treatment started.

The questions remain how these results may be explained, and whether they have any clinical significance. The QT interval measures the time between the beginning and the end of the flow of ventricular current in the axis of the recording electrodes; that is, from depolarisation of the first to repolarisation of the last cell. It does not, therefore, measure action potential duration, but contains within it a variety of disparate individual action potential durations and can also be altered by changes in conduction pathway. A lengthening of QT can only be taken to measure prolongation of action potential duration if the latter is uniform, and if conduction is unchanged. Action potential duration itself can be interpreted in terms of mathematical equations involving time and voltage-dependent ionic conductances, but the applicability of such models to cardiac muscle is dubious for two main reasons. First, the experimental data put into the equations are suspect, because membrane voltages assumed to be uniform are not, in fact, uniformly distributed even in Purkinje fibres, much less in ventricular muscle, and the injected currents themselves not only control the membrane voltages (the desirable effect), but also alter the extracellular ionic concentrations, an undesirable effect, because it is upon the constancy of these concentrations that the validity of the calculations is based.

Such technical matters have been discussed in detail elsewhere,[32] but there is a second more fundamental reason for doubting whether the cardiac action potential can be assumed to be determined solely by conductances through voltage and time-dependent channels analogous to those of nerve. Cardiac muscle fibres are of small diameter (atrial 6 to 8 μ, ventricular 10 to 15 μ),[33] and 35 to 40 per cent of the intracellular volume is occupied by mitochondria. The surface to volume ratio is high, and the energy turnover is rapid: "passively" determined membrane conductance changes can be overridden by metabolic control. Action potential duration is rapidly and dramatically shortened by hypoxia or ischaemia, and this effect is exacerbated by fatty acids[34] or ameliorated by glucose.[35] Action potential duration is also shortened in hyperthyroidism,[36] or by beta-adrenergic stimulation, and is lengthened by hypothyroidism, or certain drugs.[37 38] In contrast to these major effects on action potential duration, the changes produced in intracellularly recorded action potential duration *in vitro* by large alterations in pacing frequency are minor, two or three milliseconds only.[39]

If such considerations are applicable to man, QT interval in the short term would be controlled by two main influences. The first, a comparatively small "biophysical" effect, would be the heart rate; the second would be changes in the concentration of intracellular metabolities, subject to control by beta-receptor agonists, substrate availability, etc. The clinical validity of this hypothesis can be tested. For example, changes in heart rate produced by pacing should cause less shortening of QT than comparable changes induced by the natural agonist, noradrenaline, released from nerve endings during exercise. Conversely, in patients with fixed-frequency pacemakers, QT should shorten during exercise in spite of the absence of any change of heart rate. The flattening of the QT/RR relation, after acute intravenous blockade, and as an adaptation to prolonged treatment, could thus be explained as a reduction of the "metabolic" control of action potential duration, the more important of the two. We found in our hypertensive patients no evidence that prolonged beta-blockade induced any supersensitivity to adrenergic stimulation, such as has been described in human volunteers.[40]

An adaptive bradycardia (>10%) occurred in 17 of 30 of our patients. In this group of "heart rate responders" the QT/RR relation appeared to be somewhat steeper before treatment than in the non-responder group. Though not statistically significant in this study, the difference was so close to significance ($p=0{\cdot}13$ at rest, and 0·077 on exercise) as to suggest that this phenomenon would be worth looking at again in a prospective trial, in an attempt to identify probable responders before the start of treatment. Such identification would not, of course, be of help in the treatment of hypertensives, since there was no correlation between heart rate response and blood pressure control, but it could be useful in the selection for treatment with beta-blockers of anginal patients, for whom bradycardia may be of greater therapeutic significance.

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