Relationships between heart rate and PR interval during physiological and pharmacological interventions

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1 The relationships between heart rates (HR) and corresponding PR intervals (PR) were studied in 12 healthy young subjects during rest, standing and graduated treadmill exercise to heart rates of 160 to 170 beats min⁻¹ and during the infusion of isoprenaline to heart rates of 100 to 110 beats min⁻¹.

2 During exercise, PR diminished with increasing HR. Over the range of HR from 60 to 160 beats min⁻¹ all 12 individual subjects exhibited negative linear correlations between HR and PR described by the equation: PR (ms) = $-0.351 \text{ HR (beats min}^{-1}) + 176.7$ for composite data.

3 During isoprenaline infusion the PR interval also diminished with increasing heart rate. Over the range of HR from 60 to 110 beats min⁻¹, 11 of the 12 subjects exhibited negative linear correlations between HR and PR described by the equation: PR (ms) = $-0.582 \text{ HR (beats min}^{-1}) + 186.5$ for composite data.

4 The exercise model was used to study the indirect (or rate-dependent) effects and the direct actions on atrioventricular conduction of β -adrenoceptor blocking drugs and calcium channel antagonists, alone and in combination, in three groups of healthy subjects.

5 Control and placebo observations on HR and PR at rest, standing and during exercise in these additional subjects also exhibited individual inverse linear relationships between HR and PR.

6 Following the administration of β -adrenoceptor blockers, PR were prolonged more than expected at the HR observed. Rate-adjusted PR prolongation during exercise exceeded standing which exceeded resting, indicating greater β -adrenoceptor blockade in atrioventricular nodal tissue than in sinoatrial nodal tissue at each level of activity.

7 β -adrenoceptor blocker/calcium antagonist combinations showed variable effects on individual HR-PR relationships, consistent with the known electrophysiological actions of verapamil, nifedipine and diltiazem. Significant prolongation of rate-corrected PR was observed at rest following combinations of verapamil with propranolol, metoprolol and timolol, but not with pindolol. Nifedipine tended to reverse the electrophysiological effects of β -adrenoceptor blockers, while the effects of diltiazem were intermediate to those of verapamil and nifedipine.

Keywords heart rate PR interval linear regression equations exercise isoprenaline β -adrenoceptor blockers calcium antagonists

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Introduction

In the normal human heart, heart rate (HR) reflects sinoatrial (SA) nodal activity and the PR interval (PR) is a measure of atrioventricular (AV) nodal function. The factors which influence the relationships between HR and PR include age, sex, body surface area, posture, autonomic activity, atrial pacing and rheumatic fever (Ashman & Hull, 1937; Lister *et al.*, 1965; Herbert & Sobol, 1970).

Ashman & Hull (1937) reported an inverse HR-PR relationship from resting heart rate observations and established upper limits for PR intervals at given resting HR, but they did not define the association between PR interval and HR within the same individual, nor did their observations include the effects of exercise. More recently, Atterhog & Loogna (1977) studied HR-PR relationships during supine exercise over a broad range of heart rates and described an inverse linear relationship in the HR range of 90 to 140 beats min⁻¹.

The investigation of the direct effects on atrioventricular conduction of drugs such as β -adrenoceptor antagonists and calcium channel antagonists is complicated by the fact that these drugs may also exhibit negative chronotropic, negative inotropic and direct peripheral vascular effects, in addition to autonomic reflex responses, which may lead to indirect actions on AV conduction because of neurohumoral changes and altered heart rate.

If the primary dromotropic actions of drugs or drug combinations are to be resolved from secondary dromotropic responses which result from altered heart rate, it is necessary to have a model which is appropriate for the individual subject and the range of autonomic activity within which changes in heart rate and atrioventricular function are to be assessed.

In the absence of a published correlation between heart rate and PR interval over a wide range of sympathetic activity which included physiological stimulation by upright treadmill exercise and pharmacological stimulation by isoprenaline, we conducted the following studies to establish and evaluate a model for the investigation of drug-drug interactions between β -adrenoceptor blockers and calcium channel antagonists with differing ancillary properties.

Methods

Study 1: HR-PR relationships during exercise and isoprenaline infusion

Studies of HR-PR relationships were conducted

according to a protocol approved by the Health Sciences Standing Committee on Human Research of the University of Western Ontario. The subjects, 11 healthy men and one woman aged 19 to 26 years, were screened by medical history and physical examination. Each subject was observed during two separate study periods of physiological and pharmacological stimulation of heart rate, conducted in random order.

After a period of quiet supine rest, each subject stood and then undertook graduated upright treadmill exercise to HR of approximately 170 beats min⁻¹. ECG was recorded on lead II at 50 mm s⁻¹, at intervals of 1 min throughout the period of approximately 10 min required to achieve this goal. HR for each interval was calculated as the average of three consecutive complexes to the nearest complete beat min⁻¹. Corresponding PR were measured to the nearest 5 ms.

Each subject also received an intravenous infusion of isoprenaline, starting at 0.0025 μ g kg⁻¹ min⁻¹ and doubling the dosage every 5 min to increase HR by 30 to 40 beats min⁻¹. ECG was recorded at intervals of 2.5 min over the 25 to 30 min required on average to achieve the desired change in heart rate. At least 10 observations of concurrent HR and PR were conducted in each study. The possible associations between individual HR and PR measurements were examined visually and by subjecting the data to regression analyses and testing for linearity.

The interpolated PR measurements at HR of 80, 90 and 100 beats min⁻¹ for each subject following exercise and isoprenaline infusion were compared by Student's *t*-test for paired data.

Study 2: HR-PR relationships during administration of β -adrenoceptor blockers and calcium antagonists

The effects of four β -adrenoceptor blockers (propranolol, metoprolol, pindolol and timolol) and three calcium channel antagonists (verapamil, nifedipine and diltiazem), administered alone and in combination, were investigated in three groups of healthy male subjects.

The effects of verapamil/ β -adrenoceptor blocker combinations were investigated in Group A, *n* = 8, age 20 to 26 years, weighing 68.2 to 82.7 kg. Each subject received each of the ten oral drug or drug/drug combinations listed below in a placebo-controlled, double-blind, randomised manner, using the double-dummy technique.

1. placebo
2. verapamil 80 mg
3. propranolol 80 mg
4. propranolol 80 mg + verapamil 80 mg
5. metoprolol 100 mg
6. metoprolol 100 mg + verapamil 80 mg
7. pindolol 5 mg
8. pindolol 5 mg + verapamil 80 mg
9. timolol 10 mg
10. timolol 10 mg + verapamil 80 mg

The effects of nifedipine/ β -adrenoceptor blocker combinations were investigated in Group B, $n = 8$, age 20 to 26 years, weighing 68.2 to 81.8 kg. Apart from the substitution of verapamil with nifedipine 10 mg, each subject received each of the ten oral drug or drug/drug combinations listed earlier.

The effects of diltiazem/ β -adrenoceptor blocker combinations were investigated in Group C, $n = 8$, age 21 to 30 years, weighing 63.6 to 95.5 kg. In this part of the study, the calcium channel blocker was diltiazem 30 mg, with other medications remaining exactly the same.

Observations of HR and PR interval were recorded during quiet supine rest, standing and sub-maximal treadmill exercise. The control (0 h) observations for all 10 regimens at the three levels of activity ($n = 30$ points) were used to create a HR-PR regression line for each subject. The effects of each drug regimen on HR and PR at 2 h were examined in terms of absolute HR and PR, in terms of the changes in HR and PR from placebo and in terms of the digression or deviation of observed PR from that expected for the observed HR. Differences between

digressions were compared using analysis of variance.

Results

Study 1: HR-PR relationships during exercise and isoprenaline infusion

With standing and exercise, PR decreased with increasing HR. Although there was considerable inter-subject variability in PR at any given HR, the association between PR and HR was best described by a series of statistically significant inverse linear relationships for individual subjects (Table 1, Figure 1). During standing and upright exercise the composite HR-PR relationship was defined by the equation: $PR \text{ (ms)} = -0.351 \text{ HR (beats min}^{-1}\text{)} + 176.7$.

Likewise, during β -adrenoceptor stimulation with isoprenaline, PR decreased with increasing HR. Again, despite considerable inter-subject variability in PR at any given HR, the association between PR and HR was best described by a series of statistically significant inverse linear relationships for all but one of the subjects (Table 2). During isoprenaline infusion the composite HR-PR relationship was defined by the equation: $PR \text{ (ms)} = -0.582 \text{ HR (beats min}^{-1}\text{)} + 186.5$.

Composite HR-PR data for exercise and isoprenaline infusion are compared in Figure 2. The interpolated mean PR intervals at HR of 80, 90 and 100 beats min^{-1} were 149, 145 and 143 ms respectively for exercise and 140, 134 and 128 ms respectively for isoprenaline infusion and the differences between these paired data for individual subjects were statistically significant.

Table 1 The equation which best described the relationship between heart rate (HR, beats min^{-1}) and PR interval (PR, ms) over the heart rate range of 60 to 160 beats min^{-1} for the individual subjects during treadmill exercise.

Subject	HR-PR relationship	r	P
1	$PR = -0.192 \text{ HR} + 162.2$	-0.84	< 0.01
2	$PR = -0.229 \text{ HR} + 166.5$	-0.85	< 0.01
3	$PR = -0.209 \text{ HR} + 179.0$	-0.74	< 0.025
4	$PR = -0.242 \text{ HR} + 158.1$	-0.88	< 0.001
5	$PR = -0.382 \text{ HR} + 193.9$	-0.95	< 0.001
6	$PR = -0.453 \text{ HR} + 183.4$	-0.91	< 0.001
7	$PR = -0.248 \text{ HR} + 172.2$	-0.83	< 0.01
8	$PR = -0.503 \text{ HR} + 202.2$	-0.88	< 0.001
9	$PR = -0.559 \text{ HR} + 173.8$	-0.91	< 0.001
10	$PR = -0.287 \text{ HR} + 174.7$	-0.96	< 0.001
11	$PR = -0.566 \text{ HR} + 201.8$	-0.93	< 0.001
12	$PR = -0.333 \text{ HR} + 152.6$	-0.96	< 0.001

Figure 1 Individual regression lines relating heart rate and PR interval during treadmill exercise for each subject.

Study 2: HR-PR relationships during administration of β -adrenoceptor blockers and calcium antagonists

The relationship between HR and PR for each subject exhibited a highly significant inverse linear regression, in which the correlation co-

Figure 2 Composite regression lines comparing HR-PR relationships during treadmill exercise (○) and during isoprenaline infusion (●). Interpolated mean PR at HR of 80, 90 and 100 beats min⁻¹ are significantly different as indicated (**P* < 0.05, ***P* < 0.01).

efficient exceeded -0.9 . Placebo observations on HR and PR at rest, standing and during exercise in these additional subjects also ex-

Table 2 The equation which best described the relationship between heart rate (HR, beats min⁻¹) and PR interval (PR, ms) over the heart rate range of 60 to 110 beats min⁻¹ for the individual subjects during isoprenaline infusion.

Subject	HR-PR relationship	r	P
1	PR = $-0.889 \text{ HR} + 218.6$	-0.67	< 0.025
2	PR = $-0.852 \text{ HR} + 201.8$	-0.89	< 0.001
3	PR = $-0.485 \text{ HR} + 192.7$	-0.76	< 0.025
4	PR = $-0.656 \text{ HR} + 177.5$	-0.81	< 0.01
5	PR = $-0.953 \text{ HR} + 233.8$	-0.84	< 0.01
6	PR = $-0.114 \text{ HR} + 138.2$	-0.35	< 0.1
7	PR = $-0.563 \text{ HR} + 182.2$	-0.83	< 0.01
8	PR = $-0.655 \text{ HR} + 219.3$	-0.56	< 0.05
9	PR = $-0.826 \text{ HR} + 192.5$	-0.83	< 0.01
10	PR = $-0.224 \text{ HR} + 161.6$	-0.78	< 0.01
11	PR = $-0.446 \text{ HR} + 180.2$	-0.74	< 0.025
12	PR = $-0.312 \text{ HR} + 139.1$	-0.95	< 0.001

hibited inverse linear relationships between HR and PR.

Following the administration of β -adrenoceptor blockers, PR were prolonged more than expected at the HR observed at each of the three levels of activity. Rate-adjusted PR prolongation during exercise exceeded standing which exceeded resting, indicating greater β -adrenoceptor blockade in atrioventricular nodal tissue than in sinoatrial nodal tissue at each level of activity.

β -adrenoceptor blocker/calcium antagonist combinations showed variable effects on individual HR-PR relationships, consistent with the known electrophysiological actions of verapamil, nifedipine and diltiazem. Significant prolongation of rate-adjusted PR was observed at rest following combinations of verapamil with propranolol, metoprolol and timolol, but not with pindolol. Nifedipine tended to reverse the electrophysiological effects of β -adrenoceptor blockers, while the effects of diltiazem were intermediate to those of verapamil and nifedipine.

The mean effects of verapamil/ β -adrenoceptor blocker combinations (Group A) on each of these measurements are presented in Figure 3. Mean results for nifedipine (Group B) and diltiazem (Group C) are presented in Figures 4 and 5 respectively.

Discussion

There is considerable discrepancy in the literature relating HR and PR. Bazett (1920) used a series of supine cardiograms to develop the equation $P-R = 0.06 - 0.10 \sqrt{C}$, where C is cycle length in seconds, but many readings deviated from the predicted curve. Subsequently, Shipley & Hallaran (1936) found no constant relationship between PR interval and cycle length. Two German investigators, Scheer & Albers (1940), developed another curvilinear relationship described by the equation $P-Q = 1.73 \sqrt{C}$, but this was promptly disputed by the work of Benedetti (1940) in Italy.

The examination of large numbers of potential military recruits at the onset of World War II also provided Manning & Stewart (1945) of the Royal Canadian Air Force and Schlamowitz (1945) of the U.S. Army Medical Corps with access to large number of ECGs in apparently healthy young men. Manning and Stewart recognized the influence of posture on PR interval and related this to changes in vagal tone, a postulate that was confirmed by later investigators such as Lister *et al.* (1965), Das *et al.* (1975) and Atterhog & Loogna (1977).

Figure 3 Composite regression line relating heart rate and PR interval during control observations in Group A (verapamil). Mean HR and corresponding mean PR measurements at rest, standing and during exercise are shown for each of the 10 different treatments. The vertical lines represent the mean digressions of PR from those expected at the mean HR observed. x, placebo; *, verapamil; o, propranolol; •, propranolol + verapamil; Δ, metoprolol; ▲, metoprolol + verapamil; □, pindolol; ■, pindolol + verapamil; ●, timolol; ◐, timolol + verapamil.

Although Cohn & Swift (1924) had recognised the prolongation of PR in children with acute rheumatic fever, it remained for Clarke & Keith (1972) to attempt a systematic evaluation of the possible confounding factor of heart rate. Clarke & Keith (1972) established upper limits for PR interval from resting cardiograms in 672 healthy children and determined that it was appropriate to define upper limits according to age. Furthermore, they concluded that there should be adjustment of observed PR interval according to the formula of Mirowski *et al.* (1964) whose PR index is calculated by dividing measured PR by maximum normal PR. Clarke & Keith (1972) suggested that reversible PR prolongation (PR index greater than unity) should be used as a major criterion for the diagnosis of rheumatic fever, provided that there is evidence of preceding streptococcal infection, but their recommendation was not accepted, despite a substantial body of evidence to support it.

The only detailed assessment of HR-PR relationship over a wide range of HR was reported

Figure 4 Composite regression line relating heart rate and PR interval during control observations in Group B (nifedipine). Mean HR and corresponding mean PR measurements at rest, standing and during exercise are shown for each of the 10 different treatments. The vertical lines represent the mean digressions of PR from those expected at the mean HR observed. x, placebo; *, nifedipine; o, propranolol; ●, propranolol + nifedipine; △, metoprolol; ▲, metoprolol + nifedipine; □, pindolol; ■, pindolol + nifedipine; ○, timolol; ●, timolol + nifedipine.

by Atterhog & Loogna (1977). They conducted a series of studies in healthy subjects who exercised in the supine position before and after autonomic blockade with propranolol and atropine. Supine exercise heart rates between 90 and 140 beats min^{-1} were associated with progressive shortening of the PR interval according to the inverse linear regression equation: $\text{PR (ms)} = -0.287 \text{ HR (beats min}^{-1}) + 182.9$, but PR did not shorten further at HR greater than 140 beats min^{-1} . The contribution of sympathetic stimulation and vagal withdrawal to rate-related changes in PR during supine exercise was also defined by Atterhog & Loogna (1977), but individual variability was not discussed.

There are many possible reasons for the disagreements regarding HR-PR relationships reported in the literature. They include the wide inter-subject variability observed at all heart rates. The majority of early studies were conducted using equipment which is less sophisticated than that available today, at paper speeds of 25 mm s^{-1} and during supine rest. The range of heart rates was narrow. The studies relied

Figure 5 Composite regression line relating heart rate and PR interval during control observations in Group C (diltiazem). Mean HR and corresponding mean PR measurements at rest, standing and during exercise are shown for each of the 10 different treatments. The vertical lines represent the mean digressions of PR from those expected at the mean HR observed. x, placebo; *, diltiazem; o, propranolol; ●, propranolol + diltiazem; △, metoprolol; ▲, metoprolol + diltiazem; □, pindolol; ■, pindolol + diltiazem; ○, timolol; ●, timolol + diltiazem.

heavily on single or at most a small number of recordings of HR and PR in individual subjects, rather than the wide range of heart rates investigated by Atterhog & Loogna (1977) and ourselves.

We were concerned with the dilemma of assessing the direct effects on AV conduction of β -adrenoceptor agonists which increase HR and β -adrenoceptor blockers which reduce HR. We were also concerned about the appropriate analysis of alterations in PR following combinations of the β -adrenoceptor blockers with verapamil which is known to prolong PR independently by direct effects on AV nodal conduction. We also wished to determine what direct effects, if any, the dihydropyridine class of calcium channel antagonists might have on AV nodal function, considering the reflex tachycardia associated with the vasodilation produced by drugs like nifedipine.

Unlike the regression line described by Atterhog & Loogna (1977) for supine exercise, the regression line during upright treadmill exercise exhibited a highly statistically significant linear relationship in all 36 subjects reported here and

in 10 subjects reported elsewhere (Carruthers & Bailey, 1986), over a wider range of heart rates, i.e. 60 to 160 beats min^{-1} rather than 90 to 140 beats min^{-1} .

The regression line has been used to investigate rate-related and direct effects of drugs on AV conduction by subtracting the observed PR interval at the actual HR measured. In general, regression lines following isoprenaline infusion were steeper than those following exercise and mean PR intervals were significantly shorter at HR of 80 to 100 beats min^{-1} , heart rates common to each part of the study. Three subjects (nos. 10, 11 and 12) showed similar regression equations during pharmacological and physiological stimulation of HR, but one subject (no. 6) exhibited little influence of changing HR on PR during isoprenaline infusion. The inter-subject variability observed during isoprenaline infusion was greater than that observed during exercise.

Our observations on the influence of isoprenaline are open to various interpretations. Possible reasons for the shorter PR intervals following pharmacological stimulation of the SA node in contrast to physiological increase in HR include

greater inhibition of vagal tone or predominant stimulation of β_2 -adrenoceptor in AV nodal tissue by isoprenaline. Differences between subjects may reflect variability in vagal tone or β -adrenoceptor populations in SA and AV nodal tissues. There is variability in the proportions of β -adrenoceptor populations in different cardiac tissues (Brodde *et al.*, 1983) and preliminary evidence that the human heart has a preponderance of β_2 -adrenoceptors in atrial compared with ventricular tissues (Stiles *et al.*, 1983). Extension of our studies with the appropriate use of selective β_1 - and β_2 -adrenoceptor agonists and antagonists in a setting of vagal blockade should help us to resolve these questions.

It is important to develop adequate control data for individual subjects or patients. There is too much inter-subject variability to apply global or generalised regression equations. Given these constraints, the model appears useful in comparing the effects of β -adrenoceptor blockers, calcium channel antagonists and their combinations and should be useful in assessing the effects of other drugs which, directly or indirectly, affect SA and AV conduction.

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