The heart rate–PR interval relationship: A model for evaluating drug actions on SA and AV nodal function

W. R. DANTER & S. G. CARRUTHERS

Divisions of Internal Medicine, Cardiology and Clinical Pharmacology, Departments of Medicine and Pharmacology & Toxicology, St. Joseph's Health Care Centre and University Hospital, University of Western Ontario, London, Canada

The relationship between heart rate (HR) and PR interval (PR) has been investigated to determine inter-subject variability, within-subject variability and potential reference standards. Eight healthy male volunteers underwent upright graded submaximal treadmill exercise during eight separate study sessions. All subjects exhibited statistically significant negative linear relationships between PR and HR. Although there was considerable inter-subject variability, there was little within-subject variability in the interpolated PR at HR between 80 and 120 beats min⁻¹. The HR–PR regression model has greatest validity within this HR range and for individual subjects rather than pooled or group data.

Keywords heart rate PR interval linear regression model

Introduction

The relationship between electrical impulse generation and conduction in the healthy human heart is incompletely understood. Heart rate (HR) is a reflection of sinoatrial (SA) node activity and the PR interval (PR) is an estimate of atrioventricular (AV) nodal function. Complex autonomic nervous system reflexes influence this electrical activity (Josephson & Seides, 1979).

Recent studies have suggested that a negative linear relationship exists between PR and HR over a wide range of both physiologically and pharmacologically stimulated heart rates (Atterhog & Loogna, 1977; Carruthers *et al.*, 1987; Carruthers & Bailey, 1987). The present study was conducted to investigate the following aspects of the linear regression model relating HR to PR: (i) inter-subject variability, (ii) within-subject variability and (iii) the possible value of specific interpolated PR measurements as reference standards.

Methods

The studies were conducted according to a protocol approved by the Health Sciences Standing Committee on Human Research of the University of Western Ontario. The subjects were eight healthy men between the ages of 19 and 27 years. Each subject was observed during eight separate study periods 3 to 7 days apart.

After a 10 min period of quiet supine rest each subject stood for 3 min and then underwent graduated submaximal treadmill exercise to HR of 160 to 170 beats min⁻¹. The ECG was recorded on lead II at 50 mm s⁻¹ at intervals of 5 min during supine rest and 1 min during standing and upright exercise. HR for each observation was calculated as an average of three consecutive R–R intervals and the corresponding PRs were measured to the nearest 5 ms by the same experienced technician. Results are expressed as means $\pm$ s.d.

Composite data from all eight sessions for

Figure 1 Plot of HR (beats min^{-1}) vs PR (ms) from a representative exercise session. The 95% confidence intervals for the slope of the line are included.

each of the eight subjects were used to assess inter-subject variability. The coefficient of variability (CV) was calculated for the slopes of linear regression equations and for interpolated PR at HR between 60 and 160 beats min^{-1} at intervals of 10 beats min^{-1} . The slopes and interpolated PR from composite data were also subjected to analysis of variance. Within-subject variability was assessed in a similar fashion.

Results

A mean of 16 observations of HR and associated PR were made during each of the eight study sessions in each subject. On standing and during submaximal treadmill exercise, PR decreased with increasing HR over the range of HR from 60 to 160 beats min^{-1} . The association between HR and PR was best described by a series of statistically significant negative linear equations for individual subjects.

Inter-subject variability in slopes

The composite HR and associated PR data from all eight subjects exhibited negative correlation coefficients in excess of -0.69 . All individual HR-PR relationships were statistically significant. The slopes of regression lines for each subject ranged from -0.169 to -0.553 and the CV was 48.3%.

Inter-subject variability in interpolated PR

The CV for interpolated PR at HR between 60 and 160 beats min^{-1} at intervals of 10 beats min^{-1} ranged from 6.6% to 12.7%. Analysis of variance (ANOVA) confirmed the presence of statistically significant inter-subject variability in both the slopes of the lines and interpolated PR.

Figure 2 Calculated CV for interpolated PR (ms) for each of the eight subjects plotted against the HR (beats min^{-1}) over the range of 60 to 160 beats min^{-1} .

Within-subject variability in slopes

The HR-PR relationship in a representative exercise session is presented in Figure 1. The slope of the regression line in Figure 1 is -0.384 and the 95% confidence interval around this slope ranges from -0.510 to -0.257 . The CV for the slopes ranged from 7.2% to 43.7% with a mean CV of $28.9\% \pm 11.3\%$.

Within-subject variability of interpolated PR

The calculated CV for interpolated PR over the HR range from 60 to 160 beats min^{-1} for each of the eight subjects is presented in Figure 2. Over this HR range the CV for individual subject's interpolated PR ranged from 1.4% to 7.4%. The lowest mean CV for interpolated PR was observed at HR = 100 beats min^{-1} ($2.8\% \pm 1.2\%$).

Discussion

The study of the direct effects of drugs (e.g. β -adrenoceptor blockers) and drug-drug interactions (e.g. β -adrenoceptor blockers and calcium channel blockers) on AV conduction is complicated by the fact that these drugs may also exhibit direct negative chronotropic and negative inotropic effects, in addition to reflex autonomic responses that may produce indirect actions on AV conduction. In order to resolve the primary dromotropic actions of drugs or drug combinations from secondary dromotropic responses with altered HR, it would be useful to have a model relating HR to PR. A satisfactory model should be appropriate for the individual subject and for the range of autonomic activity within which changes in SA and AV nodal function are to be assessed.

Our results have confirmed the findings of Atterhog & Loogna (1977) and the earlier observations in our laboratory of a statistically significant negative linear relationship between HR and PR.

The considerable inter-subject variability in regression slopes (CV = 48.3%) and interpolated PR (CV range = 8.8% to 11.4%) indicate that the inter-subject variability in the individual components of this model does not permit meaningful application of the model to pooled data. Indeed, it is not surprising that the correlation coefficient for the linear regression equation described by Atterhog & Loogna (1977) was relatively low ($r = -0.4$), since they used the composite data from a total of 15 subjects to develop their regression equation.

There is considerable within-subject variability in the slopes of the HR-PR regression lines during repeated observations. However, the mean CV for interpolated PR was less than 3.5% over the range of HR = 80 to 120 beats min^{-1} . The interpolated PR at HR = 100 beats min^{-1}

(i.e. PR₁₀₀) had the lowest mean CV. Since this HR is commonly observed during both physiological and pharmacological interventions, we propose that PR₁₀₀ may be useful as a reference standard for assessing the within-subject effects of interventions which may influence SA and/or AV nodal function independently. Interpolated PR at other HR in the range 60 to 160 beats min^{-1} may also be of interest, although the larger CV will limit their value as reference standards.

We conclude that the negative linear model relating HR and PR (Atterhog & Loogna, 1977) is a valid means for studying the relationship between SA and AV nodal function. Because of wide inter-subject variability, it is essential that baseline standards are described for individual subjects, rather than using pooled data or group standards. The reliability of the technique appears greatest at HR in the range of 80 to 120 beats min^{-1} . The technique has been shown to be useful in the evaluation of drug effects and drug-drug interactions on SA nodal and AV nodal function.

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