

Independent Autonomic Modulation of the Sinoatrial and Atrioventricular Nodes Assessed Through RR and PR Interval Variation

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Abstract

The degree of coupling between autonomic nervous system influence on the sinoatrial (SA) and atrioventricular (AV) nodes is considered, using RR and PR intervals as indicators of ANS activity. Seventy minute recordings of electrocardiogram and respiratory measurements were made with data recorded in supine, standing, and sitting positions. Indices of respiratory sinus arrhythmia (RSA) for RR and PR intervals were calculated for 2-minute sections of deep breathing in both supine and standing positions. RSA indices for RR intervals were consistently higher in the supine position; no consistent pattern was seen for RSA in PR intervals. In addition, multiple regression analysis was carried out relating RR, PP, RP, and PR intervals in the three positions under the assumption of closely coupled ANS influence. The measured data was inconsistent with this assumption. We conclude that some independent ANS modulation occurs at the SA and AV nodes.

1. Introduction

A significant component of heart rate variability is contributed by variations in autonomic nervous system (ANS) activity at the sinoatrial (SA) and atrioventricular (AV) nodes. Accordingly, measures of heart rate variability (HRV) have been extensively used to yield information about ANS activity.

However ANS activity influences not only overall heart-rate (through its influence on the SA node, and hence RR variability), but also intra-beat timing through its effect on the AV node, which is manifested most clearly in changes in the PR interval. In fact, conduction through the AV node is affected by both ANS activity (the dromotropic effect) and an antagonistic effect by which AV conduction time is lengthened in response to higher heart rates (the chronotropic effect). However, the combination of how these factors interact *in vivo* is not well elucidated, primarily due to the difficulty in accurate measurement of PR intervals over long time records. In particular, it is not well established if overall ANS

activity at the SA and AV nodes is tightly coupled, or whether in fact independent modulation is taking place. At present, it is often implicitly assumed that the overall ANS activity affecting the SA and AV nodes is tightly coupled (e.g., see p. 107 of [1]).

The aim of this work is to determine the degree of coupling between the autonomic components affecting the SA and AV nodes. We considered two approaches to answering this question. Firstly, we determined the degree of respiratory induced arrhythmia (referred to colloquially as respiratory sinus arrhythmia - RSA) for both RR and PR intervals by quantifying the degree of RSA in different bodily positions. Secondly, we modeled the chronotropic and dromotropic effects on AV conduction time (and hence PR interval) assuming that ANS activity is tightly coupled, to see if the assumption was in agreement with measured data. , it is possible to assess if in fact the ANS component driving both nodes is closely coupled. Our results show (a) differences in the respiratory induced arrhythmia seen in RR and PR intervals, and (b) models assuming tight coupling of ANS activity at the SA and AV nodes are not consistent with observed changes in PR and RR intervals for different body positions.

1.1. Physiological background

The onset of the P-wave is a reasonable indicator of the time of firing of the SA node. The onset of the QRS complex marks the point when electrical activity leaves the AV node, so that the PR interval (time from the onset of the P-wave until the onset of the QRS complex) is taken as a common measure of conduction time through the intraventricular septum (fixed) and through the AV node (variable).

In normal sinus rhythm, the ANS regulates two processes; firstly, the overall cycle length and hence heart rate (typically assessed by PP or RR interval), and secondly the speed of conduction of the electrical activity through the heart including the AV node. Changes in cycle length or AV conduction delay usually involve a reciprocal action of the two divisions of the ANS. Shortened cycle lengths or AV conduction delays are produced by a diminution of parasympathetic and

simultaneous increase in sympathetic activity. Increased cycle lengths or AV conduction delays are usually achieved by the opposite mechanism [2]. In addition, AV conduction delay is also influenced by refractory effects. Encroachment upon the relative refractory period of the AV node has the paradoxical effect of lengthening AV conduction time as cycle length shortens.

It is not fully established whether independent autonomic control of cycle length and AV conduction delay is apparent under normal physiological circumstances, and an aim of our study is to investigate this question. In other words, does the autonomic nervous system induce independent variation of RR and PR interval duration under normal physiological conditions? It is certainly physiologically plausible that independent autonomic modulation of cycle length and AV conduction time can occur. Parasympathetic innervation for both the SA and AV nodes originates in the cardiac inhibitory center in the medulla and is conveyed to the heart by way of the vagus nerve. However, the SA node is predominantly affected by the right vagus nerve, whereas the AV node is predominantly driven from the left vagus.

2. Methods

2.1. Data acquisition

In order to determine the relation between cycle length and AV conduction time in normal sinus rhythm, and to consider the effect of respiration on both, data was collected from normal healthy subjects. The data consisted of single lead ECG signals of 70-minute duration recorded using the Lewis lead electrode configuration with disposable silver-silver chloride electrodes (Table 1). The Lewis lead configuration was favored as it generally provides a good view of the P-wave, simplifying the task of automated PR interval measurement. Signals were amplified, bandpass filtered (0.1-100Hz) and digitised at a sampling rate of 1000 Hz using the Biopac (Biopac Systems Inc. California). Respiration was monitored simultaneously by measuring chest wall volume using a calibrated respiratory inductance plethysmograph (Respirace, Ambulatory Monitoring, Ardsley, NY). To consider the effect of different body postures, signals were recorded in three different positions: supine, standing and sitting. Subjects also performed two standard tests of cardiac autonomic responsiveness: two minutes of deep breathing, and the Valsalva manoeuvre. The Valsalva manoeuvre raises blood pressure and hence stimulates vagal input to the heart. Table 1 gives a summary of the data acquisition protocol.

The data presented here is drawn from nine subjects in sinus rhythm with a mean age of 24 (SD 3 years, range

22-31 years). Two of the subjects were female. All were believed to have normal autonomic function and no known history of heart disease. Informed consent was obtained from all subjects prior to data collection.

Table 1: Data collection protocol

Time (s)	Procedure
0	Start recording supine resting ECG
1200	2 mins deep breathing (5 seconds in, 5 seconds out)
1320	End deep breathing, remain supine
1800	Stand
2400	2 mins deep breathing (5 seconds in, 5 seconds out)
2520	End deep breathing, remain standing
3000	Sit
3600	Valsalva maneuver (15 s, 40 mmHg)
3900	Valsalva maneuver (15 s, 40 mmHg)
4200	End

2.2. Timing interval extraction

In this work, the parameters of interest are RR interval, PR interval, and respiration, so ECG processing is aimed at reliable extraction of the first two of these. This task can be considered as QRS and P-wave detection, followed by accurate measurement of the onset of these events. The RR interval is defined here as the time between R-wave peaks; the PR interval is defined as the time from the P-wave onset to the onset of the QRS complex. The method used in this paper is fully described by Sahambi *et al.* [3]. Slight modification was needed to account for the fact that our database contained Lewis lead recordings rather than the Lead II recordings used in their work.

3. Data analysis

3.1. Quantification of respiratory sinus arrhythmia

A large range of techniques have been proposed for the assessment of respiratory sinus arrhythmia (RSA) [4]. In general, the goal of all these techniques is to correlate increases and decreases in RR interval with corresponding cycles of inspiration and expiration. Figure 1 shows an RR and PR interval tachogram (with tidal volume superimposed) from a section of supine deep breathing in subject number TS190704, and illustrates subjectively the presence of RSA in both RR and PR interval variation. The method chosen here for assessing RSA is a peak-to-trough measure described in [4]. For RR intervals this involves determining the maximum RR interval (RR_{max}) during expiration and the minimum RR interval (RR_{min}) during inspiration, for each cycle of respiration. This was done manually for the deep breathing sections defined in the data acquisition protocol. A measure of RSA for the i^{th} cycle of respiration was defined as

$$RSA_{RR,i} = \frac{RR_{\max} - RR_{\min}}{RR} \quad (1)$$

If RR_{\min} exceeded RR_{\max} then a value of zero was assigned for that cycle. An overall measure of RSA for that section of deep breathing was calculated by averaging $RSA_{RR,i}$ over every cycle of respiration (12 cycles). We defined a similar measure of RSA for PR intervals by defining a per cycle PR RSA as

$$RSA_{PR,i} = \frac{PR_{\max} - PR_{\min}}{PR} \quad (2)$$

and then defining RSA_{PR} as the average over multiple cycles of deep breathing. We focused on the deep breathing sections since it is well known that deep slow breathing accentuates the presence of RSA.

Figure 2 shows the measured RSA indices for all nine subjects in both the supine and standing positions. Reasonably significant degrees of RSA can be seen in several of the PR interval series for the different subjects. The differing patterns of RSA in the supine and standing positions are of interest. For RR intervals, it is well known that RSA is more significant when supine, and for 7 of our 9 records, this pattern is observed. However, for PR intervals the degree of RSA is not predominantly associated with the supine position, since in 5 of 9 subjects the degree of PR-based RSA is higher when standing. One explanation is that variation in parasympathetic activity at the SA node due to deep breathing is not the same as at the AV node; some degree of independent modulation is taking place. Other measures of RSA show qualitatively similar results.

3.2. Model of the relationship between RR and PR intervals

A simple model can be used to assess the presence or absence of independent modulation of the SA and AV nodes. Firstly, the primary influence on the length of an RR interval in a resting state is the overall level of parasympathetic and sympathetic activity reaching the SA node. Therefore to a first approximation, the length of an RR interval can be modelled as

$$RR = RR_0 + f(PS, S) \quad (3)$$

where PS and S represent a measure of parasympathetic and sympathetic activity, respectively, and $f(PS, S)$ is some non-linear function, which in general increases as PS increases, and decreases as S increases.

Assume for the moment that the AV node experiences an identical pattern of ANS stimulation (*i.e.*, modulation at the SA and AV node is highly dependent). Therefore a reasonable model for the PR interval is the following:

$$PR = PR_0 + \alpha f(PS, S) + \frac{\beta}{RP} \quad (4)$$

where PR_0 is some inherent baseline interval, α is a scaling factor to account for different levels of influence of ANS activity at the AV node, β is an arbitrary

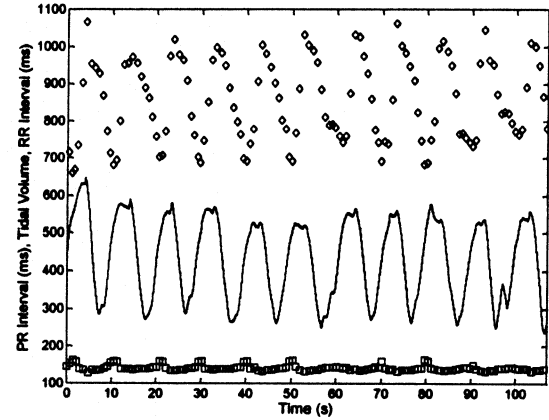


Figure 1: RR and PR interval tachograms, and respiration (tidal volume) shown for a section of supine deep breathing in subject TS190704. The tidal volume trace has been scaled and shifted to fit on the same axes as the tachograms.

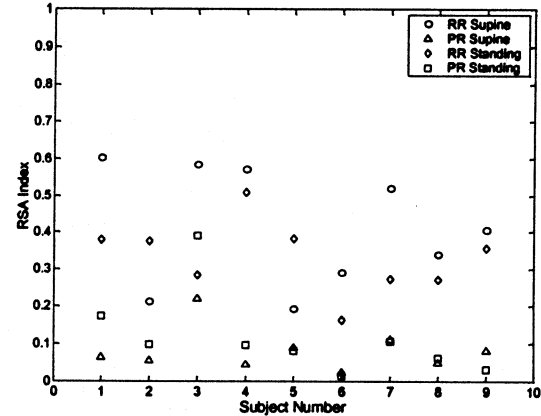


Figure 2: Indices for RSA in RR and PR intervals seen in nine different subjects, in both supine and standing positions.

constant, and RP is the time since the last QRS complex. The last term in Eq. (4) captures the rate-recovery effect seen in the AV node. If a long time has expired since the last conducted impulse, then the AV node will conduct more quickly, and the PR interval will be shortened. This model of recovery has been verified in [5]. By combination of Eqs (3) and (4) it can be seen that

$$PR = K + \alpha PP + \frac{\beta}{RP}. \quad (5)$$

For a given set of PP , PR , and RP intervals, multiple regression analysis can be used to find parameters K , α , and β which model the intervals. This model also allows us to introduce the concept of an autonomic-adjusted PR interval defined as $PR_{AA} = PR - \alpha PP$. Plots of PR_{AA} versus RP are shown in Figure 3 for a single subject in the three different positions supine, standing, and seated. As predicted a hyperbolic rate-recovery function similar to those in [7] can be calculated which fits the measured

data quite accurately.

However, the usefulness of the autonomic-adjusted PR interval is that according to our model it should be independent of ANS influences, since the common ANS activity at the SA and AV nodes has been accounted for in its definition. The three measured rate recovery curves clearly differ. The simplest explanation for this behavior is to remove the requirement for the ANS terms in Eqs (3) and (4) to be totally dependent, or in other words to allow for the possibility of an independent ANS term at both SA and AV nodes. A better solution is to reformulate Eq. (4) as

$$PR = PR_0 + \alpha f(PS, S) + g(PS, S) + \frac{\beta}{RP} \quad (6)$$

where $g(PS, S)$ represents independent autonomic activity at the AV node.

The degree of independent autonomic modulation at the AV node is highly subject dependent. Of the nine subjects analysed so far, 5 had clearly distinct autonomic-adjusted PR interval curves for different body positions.

4. Discussion and Conclusions

Simultaneous measurement of PR intervals and respiration has shown that variability due to respiratory sinus arrhythmia can be seen in PR intervals during deep breathing, though not as significantly as for RR intervals. This confirms the manual recordings carried out by Rawles *et al.* [1], which have not been subsequently verified by an automated method. However, the influence of respiratory arrhythmia on PR and RR intervals is not consistent. RSA is more pronounced in the supine position for RR intervals; no consistent pattern is seen for RSA in PR intervals. This suggests that independent modulation of the SA and AV nodes is occurring.

Further evidence for independent modulation of the SA and AV nodes is given by showing that measured PR and RP intervals are not consistent with a model of the heart which assumes tightly coupled ANS activity at these two nodes.

Other authors have also considered some of these issues. In [6], the authors accounted for rate-recovery effects in the AV node in order to isolate the autonomic-induced variability in RR and PR intervals. They concluded that in general the autonomic influence on the SA and AV nodes is tightly coupled – however their results were from recordings in a single position only.

Kowallik and Meesmann [7] came to a different conclusion. By examining spontaneous changes in heart rate during sleep, they showed independent changes in RR and PR interval, even accounting for rate recovery effects. They concluded that independent modulation of the SA and AV nodes does occur under normal physiological conditions. Finally, Forester *et al.* [8] postulated that standing reduces the vagal outflow to the SA node, and possibly increases the overall sympathetic

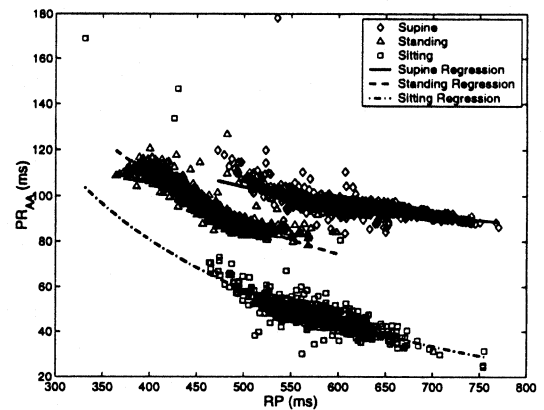


Figure 3: Autonomic-adjusted PR interval (PR_{AA}) versus RP interval for a single subject in three different positions.

tone, while the vagal input to the AV node remains relatively unchanged. Initial examination of the transient response to standing, also indicates a slow change in PR interval over the course of approximately 10-15 beats, which suggests that an increase in sympathetic activity at the AV node may be present.

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