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RESPIRATORY SINUS ARRHYTHMIA IS A LIMITED MEASURE OF CARDIAC PARASYMPATHETIC CONTROL IN MAN

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SUMMARY

1. Respiratory modulation of cardiac parasympathetic activity and the relationship between respiratory sinus arrhythmia and parasympathetic control has been studied in twenty-nine conscious, healthy young adult subjects.

2. Changes in heart period in propranolol-treated subjects were taken as the measure of changes in cardiac parasympathetic activity; respiratory sinus arrhythmia was quantified as the difference between maximum and minimum heart periods in a given respiratory cycle; cardiac parasympathetic control was defined as the change in heart period after administration of a full dose of atropine.

3. During normal quiet breathing the inspiratory level of cardiac parasympathetic activity was not reduced to zero. The expiratory level was influenced by excitatory inputs whose activation was related to respiratory cycle length.

4. Slow breathing was associated with augmented sinus arrhythmia, but in different individuals the influence on minimum and maximum heart periods varied so that mean heart period was increased in some subjects but decreased in others. This occurred both in control conditions and after administration of a full dose of propranolol.

5. During normal breathing the correlation across subjects between respiratory sinus arrhythmia and parasympathetic control, although significant, was not close ($r = 0{\cdot}61$). The relationship was not affected by β-adrenergic blockade ($r = 0{\cdot}63$). The strength of the correlation improved when multiple regression of respiratory sinus arrhythmia was performed on three variables: parasympathetic control, respiratory cycle length and tidal volume ($R = 0{\cdot}93$).

6. It is concluded that in conscious human subjects the respiratory modulation of cardiac parasympathetic activity is different from that observed in the anaesthetized dog, and that variations in the amplitude of respiratory sinus arrhythmia do not necessarily reflect proportional changes in cardiac parasympathetic control.

INTRODUCTION

A non-invasive approach to measuring cardiac parasympathetic control in the anaesthetized dog was introduced by Katona & Jih (1975), who suggested that changes in the magnitude of sinus arrhythmia indicated proportional changes in cardiac vagal tone. The method was based on the linear relationship between

parasympathetic control, measured as the change in mean heart period after cooling of the vagi, and respiratory sinus arrhythmia, measured as the difference between maximum and minimum heart periods averaged over several respiratory cycles. The linear relationship between parasympathetic control and sinus arrhythmia was predicted on theoretical grounds (Katona & Jih, 1975), based on three assumptions: (a) the change in heart period is a linear function of vagal efferent activity (Warner & Russell, 1969), (b) during inspiration cardiac vagal efferent activity stops (Iriuchijima & Kumada, 1964; Jewett, 1964; Katona, Poitras, Barnett & Terry, 1970; Koizumi, Kollai & Terui, 1986), and (c) the respiratory pattern and rate are constant. The first two assumptions were verified experimentally in the anaesthetized dog, and the third is usually ensured by the anaesthetized state.

The method has been transferred to man and is widely used in physiological and clinical studies (Wheeler & Watkins, 1973; Hilsted & Jensen, 1979; Sundkvist, Almer & Lilja, 1979; Eckberg, Kifle & Roberts, 1980; Ewing, Borsey, Bellavere & Clarke, 1981; Smith, 1982; Fouad, Tarazi, Ferrario, Fighaly & Alicandri, 1984; Eckberg, Nerhed & Wallin, 1985; Kallenbach, Webster, Dowdeswell, Reinach, Scott Millar & Zwi, 1985). Direct recording of cardiac vagal nerve activity, however, has not been performed in man, and it is not clear to what extent the experimental data, obtained in the anaesthetized dog, can be applied to man. As for the aforementioned three assumptions: (a) it seems reasonable to assume that the basic cholinergic mechanisms operating in the sinus node are similar in man and in animal models, but (b) the vagal activity level during the inspiratory phase of normal respiration has not been established in man, and (c) respiratory rate and pattern are usually not constant, unless voluntarily controlled by conscious human subjects. In view of these uncertainties, we have examined the method's applicability in man. The aim of the present work was to establish in a group of volunteers: (1) the inspiratory level of cardiac vagal activity; (2) the influence of respiratory parameters on cardiac vagal activity pattern; and ultimately (3) the strength of the relationship across subjects between parasympathetic control and sinus arrhythmia at normal resting ventilation.

METHODS

Subjects. Twenty-nine healthy men and women, aged 18–26 years, were studied in recumbency, in a quiet darkened room. Most of the subjects were medical students, familiar with the methods and procedures. All volunteers gave their written consent to participate in this study. All were normotensive (average blood pressure: 117/72 mmHg), and none was taking medication.

Measurements. The electrocardiogram, beat-by-beat cardiac interval (heart period), integrated tidal volume (Fleisch pneumotachograph) and end-tidal carbon dioxide concentration (infra-red analyser) were recorded on a polygraph and by FM tape-recorder. All recordings were done in the early afternoon, at least 3 h postprandially.

Experimental procedure. The subjects were studied on two occasions. On the first occasion, after a resting period of 15 min, control measurements were taken, then the following tests were performed: (1) isometric handgrip of 3 min duration at 35% of maximum voluntary contraction, with measurements obtained during the third minute prior to release of the effort. Subjects were trained to avoid performing Valsalva manoeuvres and their respiratory rate was maintained at the control rate with the aid of auditory signals. (2) Deep breath test: the subjects were simply asked to inhale as deeply as possible, but without gasping. (3) Orthostatic stress, by changing from supine to erect position. (4) Breathing at different rates, with the respiratory cycle length set at 3, 4, 6,

8 and 10 s by auditory signals. Following the tests, 0·2 mg/kg propranolol was injected intravenously over 5 min. After completion of the injection the tests were repeated.

On the second occasion, at least 3 days later, respiratory cycle length, tidal volume, mean heart period, and the amplitude of respiratory sinus arrhythmia were recorded in the control condition. Atropine sulphate was then injected intravenously in doses of 0·005 mg/kg at 3 min intervals, until two consecutive doses produced no further increase in heart rate or a total dose of 0·04 mg/kg was reached. The measurements were then repeated. After rest, the whole protocol was repeated during β-adrenergic blockade by I.V. propranolol administration.

TABLE 1. Minimum heart period values in control conditions and during various tests before and after propranolol. Data are expressed as means ± S.E.M. and are given in milliseconds

	Control	Handgrip	Deep breath	Orthostasis
Before propranolol	820 ± 13	762 ± 14	706 ± 18	768 ± 10
After propranolol	1010 ± 15	955 ± 15	895 ± 16	928 ± 11

Data analysis. Records of interest were replayed from tape and evaluated either manually from fast speed calibrated polygraph charts or with the aid of a computer. Respiratory sinus arrhythmia was quantified by the peak-to-trough method, i.e. the shortest R–R interval corresponding to late inspiration or early expiration was subtracted from the longest expiration-related interval. The breath-by-breath differences were then averaged across respiratory cycles for the measurement period, which lasted for at least 5 min to include several non-respiratory slow-wave fluctuations in R–R interval, if any existed. Statistical analysis was performed with the paired t-test, analysis of variance (ANOVA), and simple and multiple least-squares linear regression (Wonnacott & Wonnacott, 1981). Differences were considered significant when P was less than 0·05. Data are presented as means ± S.E.M.

RESULTS

Mean heart period (HP) for the twenty-nine subjects in the resting supine position was 870 ± 16 ms. They all exhibited respiratory sinus arrhythmia (RSA) of varying degree, the average peak-to-trough measure being 108 ± 12 ms at their normal respiratory cycle length and volume (4·64 ± 0·2 s and 0·52 ± 0·09 l, respectively). In response to propranolol administration HP and RSA increased to 1092 ± 19 ms and to 142 ± 15 ms, respectively. Both increases were significant compared to control values (paired t test, $P < 0·05$).

Inspiratory level of cardiac parasympathetic activity

Cardiac parasympathetic activity is inhibited during inspiration, causing a reduction in heart period to a minimum value in each respiratory cycle (Eckberg, 1983). We tested in control and in propranolol-treated subjects whether the minimum HP, observed at rest, could be reduced further by manoeuvres that result in cardioacceleration, i.e. whether inspiratory parasympathetic activity at rest was different from zero. The mean value of respiratory-related minimum HPs at rest was compared to the mean value of minimum HPs attained during the handgrip, deep-breath and orthostatic tests, while subjects maintained respiratory rate constant at their normal rate. The results are summarized in Table 1. Compared to control values, minimum HPs shortened significantly during all three tests, both before and after propranolol administration (ANOVA, $P < 0·05$).

Influence of respiratory rate on cardiac parasympathetic activity

It has been amply demonstrated that switching from fast to slow breathing results in the augmentation of RSA (for references see Hirsch & Bishop, 1981). If changes in the magnitude of RSA really reflect proportional changes in average parasympathetic activity, as it is generally held, then the increased RSA with slow breathing should be associated with a longer mean HP, provided sympathetic influence is constant or absent during alterations in respiratory pattern. That assumption was tested in our group of subjects, who were instructed to control respiratory cycle length between 3 and 10 s, both before and after propranolol administration. Subjects were able to keep the required respiratory cycle lengths with only small variations, the average standard deviation for all measurements being 0·05 s. No levels were set for tidal volume: the only requirement was to keep tidal volume fairly uniform through visual feedback. Tidal volumes varied from $0{\cdot}30 \pm 0{\cdot}02$ l (for the 3 s cycle length) to $1{\cdot}46 \pm 0{\cdot}12$ l (for the 10 s cycle length). The respective values for end-tidal CO_2 were $4{\cdot}3 \pm 0{\cdot}4$ and $5{\cdot}0 \pm 0{\cdot}3$ %.

Slower breathing was invariably associated with larger RSA, but mean HP changed in a non-uniform fashion: in response to slow breathing mean HP increased, decreased, or stayed at approximately the same level in the individual subjects. Figure 1 illustrates two examples of RSA patterns, obtained without propranolol administration. The patterns were designated as type 'A' and type 'Z', and represented the two extremes of a more or less continuous spectrum. In the case of the type 'A' pattern, a shift from 4 to 8 s in respiratory cycle length resulted in the augmentation of RSA mostly because of further shortening of minimum HPs; lengthening of maximum HPs was considerably less. Consequently, mean HP shortened. During apnoea, HP settled closer to maximum HP levels attained during prior expirations. In the case of the type 'Z' pattern, slow breathing was associated with larger RSA mostly because of lengthening of maximum HPs. Changes in minimum HPs were negligible. Consequently, mean HP lengthened. During apnoea HP tended to approach the minimum HP level. An intermediate type of pattern, designated as type 'A/Z', is illustrated in the left panel of Fig. 2. In this case, slow respiration produced symmetrical changes in minimum and maximum HPs, leading to almost no alteration in mean HP. During apnoea HP stayed in the mid-line, i.e. close to the prior mean value.

Mean HP and the mean amplitude of RSA were determined at each respiratory cycle length, and the relationship between them was approximated by linear regression. The regressions of HP on RSA for the representative RSA patterns are shown in the lower parts of Figs 1 and 2. The slope of regression (ΔHP/ΔRSA ratio) was negative for type 'A', positive for type 'Z' and closer to zero for type 'A/Z' patterns. The frequency distribution of ΔHP/ΔRSA ratios for all twenty-nine subjects is depicted in Fig. 3. The mean ΔHP/ΔRSA slope was $0{\cdot}08 \pm 0{\cdot}04$, significantly different from zero. Propranolol administration increased both mean HP and the magnitude of RSA (see before), but the character of the relationship between them remained largely unaffected. This effect of propranolol is illustrated in Fig. 2, in the case of an intermediate RSA pattern. The ΔHP/ΔRSA ratio was 0·13 before and 0·12 after propranolol. For the whole group of subjects, propranolol

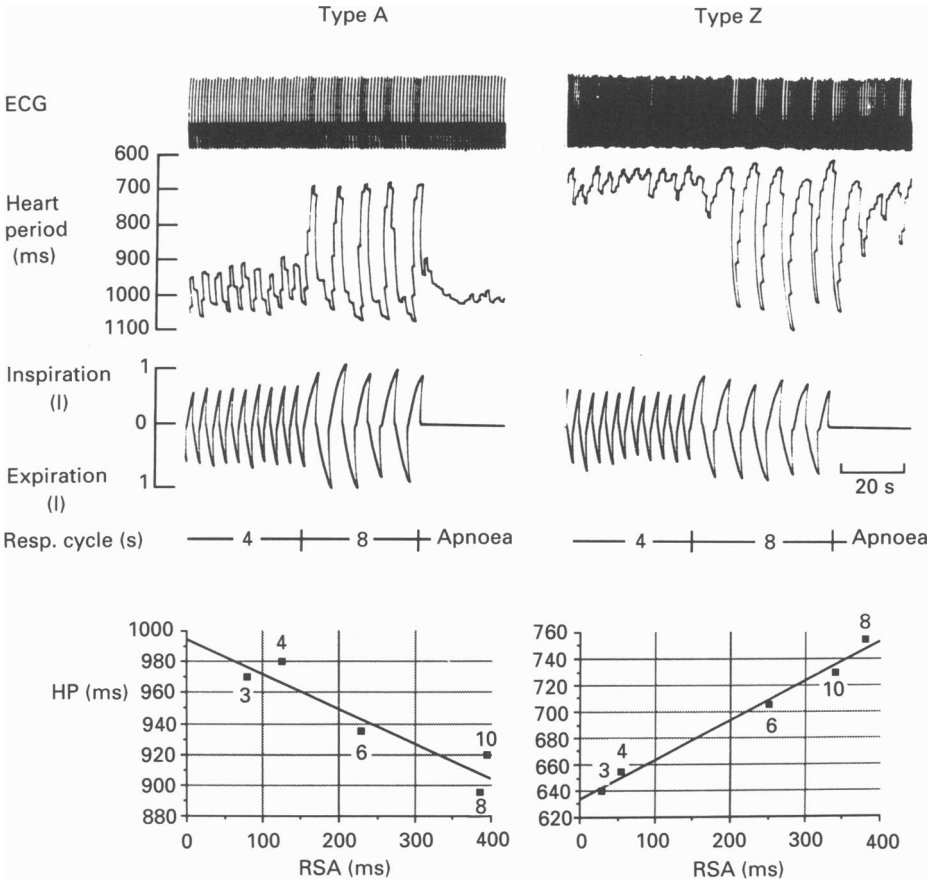

Fig. 1. Two extreme examples of sinus arrhythmia patterns, designated as type 'A' and type 'Z'. The data were obtained without propranolol administration. Upper panel, changes in sinus arrhythmia in response to changing the respiratory cycle length from 4 to 8 s. From top downwards: ECG, heart period and respiration. Lower panel, linear regression of mean heart period (HP) on the mean amplitude of respiratory sinus arrhythmia (RSA) as respiratory cycle length was varied and controlled at 3, 4, 6, 8 and 10 s. Numbers assigned to data points indicate respiratory cycle length. The regression coefficients for the type 'A' and type 'Z' patterns were $-0{\cdot}23$ and $0{\cdot}31$ ($P < 0{\cdot}001$), respectively.

treatment resulted in only minor reduction of the mean $\Delta HP/\Delta RSA$ value (from $0{\cdot}08 \pm 0{\cdot}04$ to $0{\cdot}03 \pm 0{\cdot}06$, $P > 0{\cdot}05$), and no appreciable change in the contour of the frequency histogram.

Relationship between parasympathetic control and respiratory parameters

A major objective of this work was to establish the strength of the relation between parasympathetic control (PC) and RSA across subjects who were breathing at their normal respiratory rate and volume. After a resting period of 15 min, RSA was averaged for 5 min in the supine position, then PC was determined by measuring the change in mean HP as a result of complete parasympathetic blockade by atropine

sulphate administration. The corresponding values were plotted and the relationship between PC and RSA was approximated by linear regression (Fig. 4). The relation appeared directly proportional; the correlation proved to be significant ($P < 0{\cdot}001$), but it could not be described as close ($r = 0{\cdot}61$). The scatter of RSA values increased

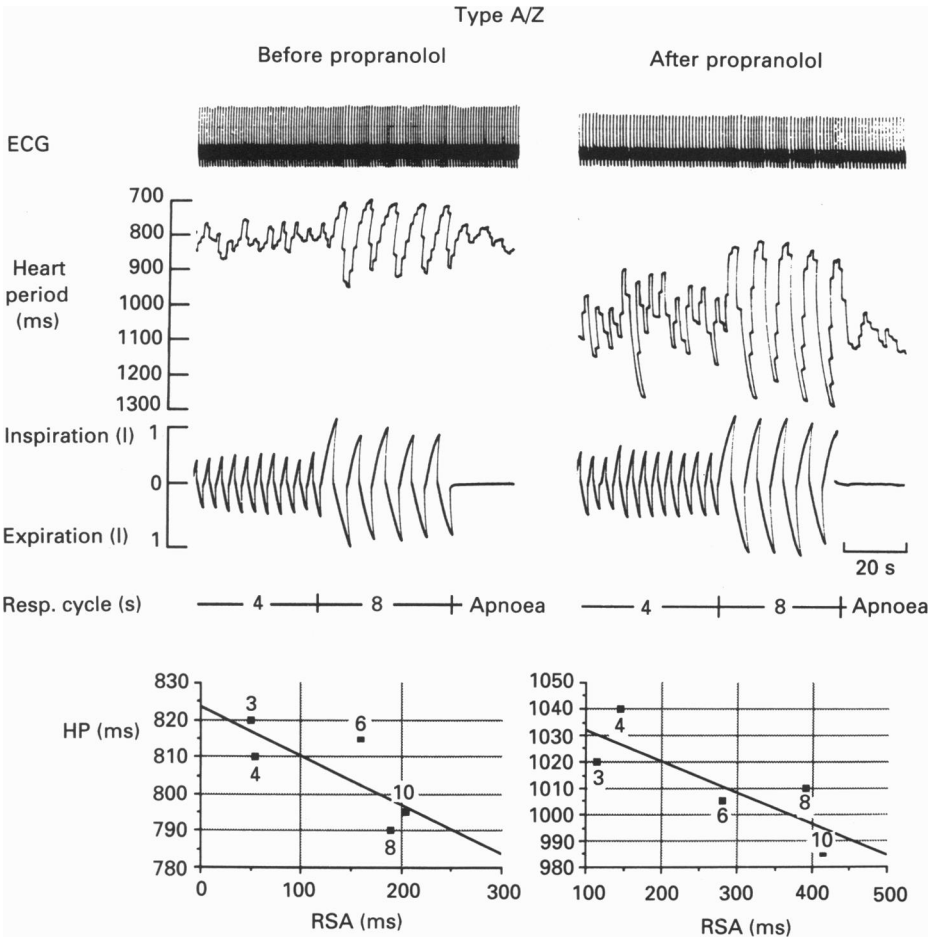

Fig. 2. Intermediate sinus arrhythmia pattern, designated as type 'A/Z'. Changes in sinus arrhythmia in response to switching the respiratory cycle length from 4 to 8 s were recorded in the same individual before (left panel) and after (right panel) administration of 0·2 mg/kg I.V. propranolol. The arrangement of the figure is identical to that of Fig. 1. The regression coefficients were 0·13 and 0·12 ($P < 0{\cdot}001$) before and after propranolol, respectively.

with increasing levels of PC; RSA values were scattered by as much as 150 ms when PC was larger than 300 ms. To assess the contribution of a presumably varying sympathetic input among subjects, the correlation between PC and RSA was determined after propranolol administration. β-Adrenergic blockade did not reduce the scatter, and essentially the same correlation was obtained between PC and RSA ($r = 0{\cdot}63$, $P < 0{\cdot}001$).

In an attempt to search for factors that might have influenced the PC–RSA

relationship, we studied the role of respiratory cycle length and tidal volume. We found that a significant direct relationship existed between RSA and respiratory cycle length across subjects ($r = 0{\cdot}69$, $P < 0{\cdot}001$). The slope of linear regression appeared steeper and the strength of correlation greater in the subgroup of subjects

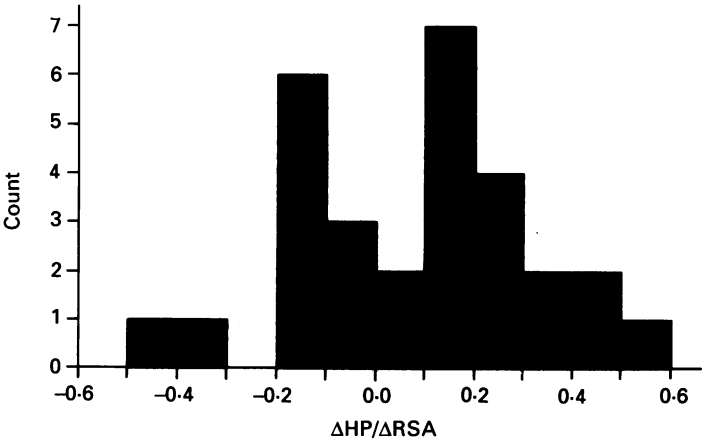

Fig. 3. Frequency distribution of ΔHP/ΔRSA ratios ($n = 29$).

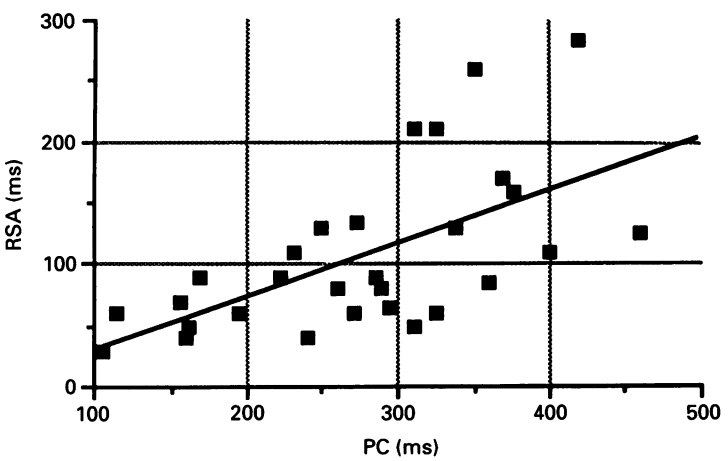

Fig. 4. Linear regression of respiratory sinus arrhythmia (RSA) on parasympathetic control (PC) across subjects without β-adrenergic blockade ($y = -13{\cdot}29 + 0{\cdot}44x$, $r = 0{\cdot}61$, $P < 0{\cdot}001$).

who had PC values higher than 300 ms, compared to those with PC values less than 300 ms (Fig. 5). Also, direct proportionality existed between RSA and tidal volume across subjects ($r = 0{\cdot}89$, $P < 0{\cdot}001$), with data scatter similar to that of the RSA–respiratory cycle length relationship. The similarity was probably the result of the close linear relationship that existed between respiratory cycle length and tidal volume across subjects ($r = 0{\cdot}89$, $P < 0{\cdot}001$). On the other hand, PC and respiratory

cycle length were not related ($r = 0{\cdot}24$, $P > 0{\cdot}1$) and PC and tidal volume were only loosely related ($r = 0{\cdot}46$, $0{\cdot}05 > P > 0{\cdot}01$) in our sample. Since RSA was found to be dependent on both PC and the respiratory parameters, multiple regression analysis was performed (Table 2). As expected, the regression of RSA on PC, respiratory cycle

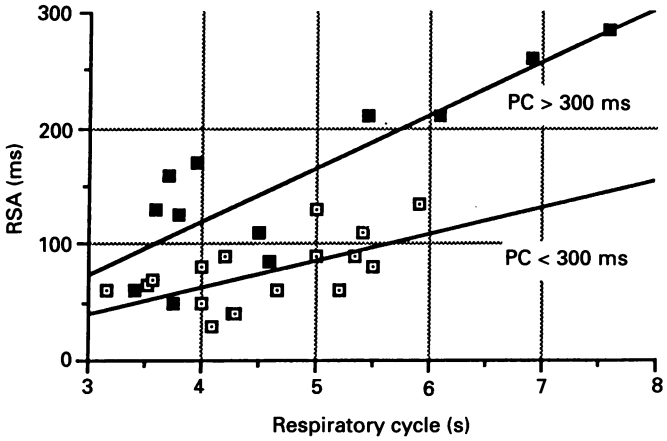

Fig. 5. Linear regression of respiratory sinus arrhythmia (RSA) on respiratory cycle length in subjects with parasympathetic control (PC) values higher than 300 ms (■: $y = -64{\cdot}33 + 45{\cdot}81x$, $r = 0{\cdot}86$, $P < 0{\cdot}001$) and in subjects with PC values less than 300 ms, without β-adrenergic blockade (⊡: $y = -28{\cdot}09 + 79x$, $r = 0{\cdot}60$, $P < 0{\cdot}01$).

TABLE 2. Statistics of multiple regression analysis of respiratory sinus arrhythmia (ms) on parasympathetic control (PC, ms), respiratory cycle length (Resp. cycle, s) and tidal volume (V_t, ml)

Variable	Coefficient	S.E.M. estimate	t statistic	$P > t$
Constant	−63·814	28·910	−2·207	0·036
PC	0·127	0·068	1·872	0·072
Resp. cycle	−21·050	11·338	−1·857	0·074
V_t	0·478	0·087	5·486	0·000

Source	Sum of squares	Degrees of freedom	Mean squares	F ratio	$P > F$
Model	104228·462	3	34742·821	50·521	0·000
Error	17192·227	25	687·689		
Total	121420·690	28			

Coefficient of determination (R^2), 0·858; adjusted coefficient (R^2), 0·841; coefficient of correlation (R), 0·927; standard error of estimate, 26·224; Durbin–Watson statistic, 2·034.

length and tidal volume yielded a higher correlation coefficient ($R = 0{\cdot}93$, $P < 0{\cdot}001$), compared to the simple correlation coefficient between RSA and PC alone ($r = 0{\cdot}61$).

Finally, we were interested in whether the character of individual responsiveness of RSA to slow breathing, expressed as $\Delta HP/\Delta RSA$ ratio, was related to resting parasympathetic control (Fig. 6). The linear regression indicated inverse propor-

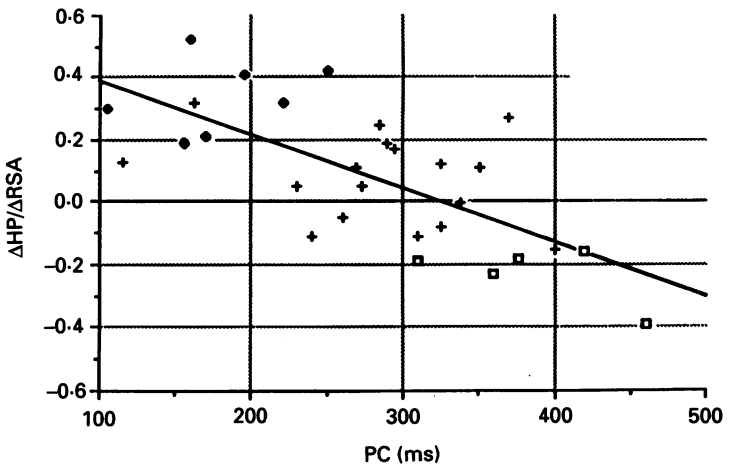

Fig. 6. Linear regression of ΔHP/ΔRSA ratio on parasympathetic control (PC) ($y = 0{\cdot}561 - 0{\cdot}002x$, $r = 0{\cdot}68$, $P < 0{\cdot}001$). Data points for type 'A', 'A/Z' and 'Z' subjects are marked by □, + and ◆, respectively.

tionality, and the correlation was significant ($r = 0{\cdot}68$, $P < 0{\cdot}001$). The inverse proportionality was interpreted as type 'A' subjects having high and type 'Z' subjects having low resting vagal tone.

DISCUSSION

Respiratory modulation of cardiac parasympathetic activity in the anaesthetized dog and in man

Activity from cardiac parasympathetic fibres has been recorded mostly in the anaesthetized dog (Iriuchijima & Kumada, 1964; Jewett, 1964; Katona, Poitras, Barnett & Terry, 1970; Koizumi *et al.* 1986). All studies reported inhibition of vagal motoneurone output during inspiration and release from inhibition during expiration. In most cases inspiratory inhibition of vagal activity resulted in complete cessation of background discharges. The expiratory level of parasympathetic activity was primarily set by afferent activity from arterial baroreceptors, and breathing phasically reduced the ability of this sensory input to stimulate cardiac vagal motoneurones (for references see Spyer, 1982). Our present data suggest that respiratory modulation of cardiac parasympathetic activity in man differs in two respects: the inspiratory level of parasympathetic activity is not reduced to zero and the expiratory level of parasympathetic activity is powerfully modulated by excitatory inputs that are related to the parameters of respiration. First, the inspiratory level of parasympathetic activity at rest is probably not reduced to zero, since the minimum heart period (HP) attained during inspiration was further reduced by simple interventions (handgrip, deep breathing and orthostatic tests) in propranolol-treated subjects. In the dog, the complete cessation of vagal activity during the inspiratory phase could partly be caused by anaesthesia. Many anaesthetic agents are known to inhibit parasympathetic activity (Price, 1960; McAllen & Spyer,

1978; Donchin, Feld & Porges, 1985) and the effect of anaesthesia and inspiratory inhibition might summate to the extent that vagal motoneurone excitability does not reach threshold. Species difference could be another factor. The slope of the parasympathetic control (PC)–respiratory sinus arrhythmia (RSA) relationship appears many times steeper in the dog than in man. The reported regression coefficients were 1·81 for the dog (Katona & Jih, 1975) and 0·22 and 0·44 for man (Fouad *et al.* 1984 and this study, respectively). Second, the expiratory level of parasympathetic activity is influenced by respiratory-related excitatory inputs, since slow breathing lengthened maximum HP in propranolol-treated type 'A' and type 'A/Z' subjects. In the animal model, the study of respiratory-related modulations of parasympathetic activity or of RSA was necessarily limited: either artificial ventilation was employed, or anaesthesia rendered spontaneous respiration more or less uniform. Due to this limitation the concept emerged that when parasympathetic activity was released from inspiratory inhibition, it simply reached a level set by baroreceptor inputs (Spyer, 1982). Our present data indicate that both the expiratory and the inspiratory levels of parasympathetic activity are influenced by the respiratory pattern in co-operating human subjects: slower and deeper respiration was associated with higher levels of parasympathetic activity during the expiratory phase and with more effective inhibition during the inspiratory phase. The mechanism of these changes is not clear. Five factors have been implicated in mediating RSA: central inspiratory activity, stretch reflexes from the lung and thorax, Bainbridge reflex, arterial baroreflex and P_{CO_2} oscillations in arterial blood (Daly, 1986). The first three mechanisms are inhibitory in nature. Their increased activation associated with slow breathing could be responsible for the more complete inhibition of parasympathetic activity during inspiration, but not for the extra amount of activity generated during expiration. On the other hand, modulation of baro- and chemoreceptor activity, caused by augmented fluctuations in arterial pressure and P_{CO_2}, could lead both to reduced inspiratory and to increased expiratory parasympathetic activity, provided the phase relations are right.

Non-uniformity of respiratory sinus arrhythmia patterns

We found that in different individuals changes in respiratory cycle length affected minimum and maximum HPs in quantitatively different fashions, which in turn produced qualitatively different shifts in mean HP. In a group of subjects (type 'A'), slow breathing induced large reductions in minimum HPs, whereas changes in maximum HPs were slight or absent. In another group of subjects (type 'Z'), the changes were exactly the opposite, while in the majority of subjects (type 'A/Z'), both a reduction in minimum and a prolongation in maximum HPs contributed to the enhanced RSA. As a result, mean HP decreased, increased or remained unchanged in the different groups. This report is the first to recognize and to study this non-uniformity, although examples of these different types of RSA patterns can be identified in the figures of earlier studies (Davies & Nielson, 1967; Wheeler & Watkins, 1973; Hirsch & Bishop, 1981). As for the mechanism of this non-uniformity, we speculate that it is based on different levels of resting parasympathetic control. In the type 'A' subjects the average level of parasympathetic activity was likely to be high, and therefore available for inspiratory inhibition, but it represented

a saturation level for further expiratory excitation. On the other hand, type 'Z' subjects were likely to have such a low level of parasympathetic activity that it could not be reduced further by inspiratory inhibition, but this level was readily enhanced by the excitatory influences associated with expiration. This assumption is supported by the significant correlation that we found between PC and the ΔHP/ΔRSA ratio.

Relationship between parasympathetic control and respiratory sinus arrhythmia

There are two approaches to this issue, a distinction that has not been addressed before: the relationship between PC and RSA can be defined either intra- or interindividually. Originally, Katona & Jih (1975) established the relationship *intraindividually* in the anaesthetized dog, varying PC and RSA values by setting the arterial pressure at different levels. In each animal the relationship between PC and RSA was directly proportional, with an average correlation coefficient of 0·97. The extremely close correlation was probably the result of a stable respiratory pattern and complete inspiratory silence of vagal activity even at elevated arterial pressures. When essentially the same study was repeated in unanaesthetized dogs, the average correlation coefficient was reduced to 0·83 (Lipson & Katona, 1979). In human studies the intraindividual approach was employed with a different method: gradual reductions in PC and RSA values were produced by increasing doses of parasympatholytic drugs. In the individual subjects the correlation analysis yielded coefficients in the range between 0·66 and 0·97 (Coker, Koziell, Oliver & Smith, 1984). The above method, however, is limited in the sense that the PC–RSA relationship was determined through gradual elimination of the effect of a given vagal activity pattern. In the present work the PC–RSA relationship was determined by changing the vagal activity pattern through varying respiratory cycle lengths. Changes in mean HP were taken as the measure of changes in PC. The character of the relationship varied in the different individuals: in one group of subjects there was no consistent effect on mean HP (type 'A/Z'), whereas in other subjects we found either a direct or inverse relationship (type 'Z' and type 'A', respectively). Propranolol administration did not alter the character of the relationship in the different subject groups. Determination of the average correlation coefficient for such a heterogeneous group of subjects would be meaningless, and these results question the general validity of the concept that the amplitude of RSA can be taken as the measure of PC.

The *interindividual* approach is based on the assumption that the direct proportionality between PC and RSA is valid across subjects. We tested this hypothesis in our group of subjects, and found that the correlation between PC and RSA, although significant, was not close ($r = 0·61$). β-Adrenergic blockade did not affect the correlation between PC and RSA ($r = 0·63$); this observation is in concert with earlier findings of Katona & Jih (1975) and Fouad *et al.* (1984). It seems reasonable to assume that some correlation should exist across individuals between PC and RSA. In the case of low cardiac vagal tone, the extent of its fluctuation, and therefore the magnitude of RSA, is necessarily limited. In the case of high vagal tone, its variations can be greater as well. However, this is only a possibility, and no mechanism is known that could serve as a close link between vagal tone and the extent of its respiratory fluctuations. In other words, no data are available that would predict close correlation across individuals between PC and RSA. Indeed, the

increasing scatter of the PC–RSA plot towards higher PC values indicated that high vagal tone could be associated with either small or large respiratory fluctuations. We found that resting RSA amplitude was significantly related to interindividual variations in respiratory cycle length and tidal volume, and the relations were more powerful among subjects with high PC values. We assume that variance in respiratory cycle length and tidal volume among subjects was one factor responsible for the scatter of the PC–RSA plot, since the strength of correlation increased (R = 0·93) when respiratory cycle length and tidal volume were introduced as co-regressors, and multiple regression of RSA was performed on both PC and the respiratory parameters.

Earlier studies reported closer correlation across subjects between PC and RSA than we found here. The reported correlation coefficients were: 0·96 (Katona & Jih, 1975), 0·83 (Lipson & Katona, 1979), 0·91 (Fouad *et al.* 1984) and 0·86 (McCabe, Young, Ackles & Porges, 1985). In the animal studies, in addition to the species difference already discussed, anaesthesia probably improved the correlation between PC and RSA by reducing inspiratory vagal activity to zero and by rendering the respiratory pattern uniform (Katona & Jih, 1975; Lipson & Katona, 1979; McCabe *et al.* 1985). As for human studies, the work of Fouad *et al.* (1984) is cited most frequently to justify the use of RSA as a measure of PC. That study, however, is open to criticism: the subjects comprised hypertensive patients and healthy volunteers and were treated as one group. Hypertensive patients were reported to have reduced PC and diminished RSA (Julius, Pascual & London, 1971; Eckholdt, Bodmann, Cammann, Pfeifer, Schubert & Kesper, 1976; Johnston, 1979): therefore their inclusion into the correlation analysis might have introduced bias. In the scatter diagram of Fouad *et al.* (1984, Fig. 4) a group of subjects – probably hypertensive ones – exhibited markedly reduced RSA values of 40 ms or less, while another group – probably healthy ones – exhibited normal values. Such data (and subject) polarization, as compared to the required bivariate normal distribution, could lead to overestimated correlation coefficients (Wonnacott & Wonnacott, 1981).

The question of excess tachycardia

Heart rate in the dog after atropine is higher than after bilateral vagotomy or cooling of the vagi (Rigel, Lipson & Katona, 1984). The additional increase in heart rate with atropine was termed as excess tachycardia and is produced by hitherto unknown pharmacological mechanisms. Although atropine is frequently used to estimate the degree of PC in man, the question of whether the drug produces excess tachycardia has not been raised before. If it does, excess tachycardia might introduce another variable that could adversely affect the strength of correlation between PC and RSA, provided the former was determined by administration of para-sympatholytic drugs. We found that mean HP after atropine was significantly shorter than the minimum HPs attained during any tests that produced cardio-acceleration. The difference could be explained by the inability of those tests to reduce vagal activity to zero or alternatively by excess tachycardia.

In conclusion, this study has shown that data describing respiratory modulation of cardiac parasympathetic activity in the anaesthetized dog cannot be applied unconditionally to man. The concept of taking the magnitude of respiratory

sinus arrhythmia as a measure of parasympathetic control, established in the anaesthetized dog, is of limited use in man.

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