

## ORIGINAL ARTICLES

## Twenty four hour heart rate variability: effects of posture, sleep, and time of day in healthy controls and comparison with bedside tests of autonomic function in diabetic patients

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### Abstract

**Heart rate variability was measured in 77 healthy controls and 343 diabetic patients by a count of the number of beat-to-beat differences greater than 50 ms in the RR interval during a 24 hour ambulatory electrocardiogram. In the healthy controls the lower 95% tolerance limits for total 24 hour RR interval counts were approximately 2000 at age 25, 1000 at 45, and 500 at 65 years. Six controls confined to bed after injury had normal 24 hour patterns of RR counts, while eight other controls showed loss of diurnal variation in both heart rate and RR counts during a period of sleep deprivation. RR counts in ten controls on and off night duty increased during sleep whenever it occurred. Nearly half (146) the 343 diabetic patients had abnormal 24 hour RR counts. The percentage of abnormal RR counts increased with increasing autonomic abnormality assessed by a standard battery of tests of cardiovascular autonomic function. A quarter of those with normal cardiovascular reflex tests had abnormal 24 hour RR counts. There were close correlations between 24 hour RR count results and the individual heart rate tests ( $r = 0.6$ ).**

**The assessment of cardiac parasympathetic activity by 24 hour RR counts was reliable. The diurnal variations in RR counts seen in the controls were probably related to sleep rather than either posture or time of day. The method was more sensitive than conventional tests of cardiovascular reflexes.**

Measurements of heart rate variability are increasingly being used as markers of cardiac autonomic activity. In diabetes and other clinical disorders affecting the autonomic nervous system their use is now well established.<sup>1</sup> The variability in heart rate may be an independent prognostic marker after myocardial infarction,<sup>2</sup> and an imbalance of normal cardiac autonomic control mechanisms, with reduced heart rate variation, has been proposed to explain sudden infant death syndrome.<sup>3</sup> Diurnal variation in the pulse rate was noted in a medical journal as long ago as 1815,<sup>4</sup> but the use of short term heart rate

variation as a clinical test of autonomic function both at rest<sup>5</sup> and during a short period of deep breathing<sup>6</sup> was only developed in the 1970s. More recently still, heart rate variation has been measured over longer periods by 24 hour electrocardiographic tape recordings.<sup>7</sup> As a diagnostic clinical test, the maximum – minimum heart rate during deep breathing has proved most popular<sup>8,9</sup> but for research purposes other methods of analysis, including the use of standard deviation<sup>2,5</sup> and spectral analysis,<sup>10-12</sup> have also been used.

Though these approaches are valid they also have drawbacks. For example, the “deep breathing” method has relatively poor reproducibility, is dependent on the subject’s cooperation, and only gives information about the brief period during which the heart rate is actually measured. Scrutiny of longer heart rate recordings often shows considerable discrepancies in the amount of heart rate variability present at different times of the day and night (fig 1). Spectral analysis is based on assumptions about the control of heart rate which depend on particular and consistent input stimuli and on the assumption that its rhythms can be broken down into discrete components, each representing specific and different autonomic activity. Spectral techniques are also unable to cope with recordings containing frequent ventricular arrhythmias. Standard deviation methods do not distinguish clearly between parasympathetic and sympathetic components.

Because of the limitations of these methods, we have developed an alternative approach. We noted that there were a large number of beat-to-beat changes in heart rate that occurred frequently but irregularly in healthy controls and that they were distinct from the smaller cyclical changes of respiratory sinus arrhythmia. We devised a method to measure these larger changes by counting the number of times successive RR intervals differed by more than 50 ms during a 24 hour tape recording (referred to subsequently as “RR counts”). This was first described in 1984 when we showed that RR counts reflected the integrity of cardiac parasympathetic pathways.<sup>7</sup>

The aim of our present study was to determine what factors affect heart rate variability—in particular the role of posture, sleep, and time of day. We evaluated the results from our

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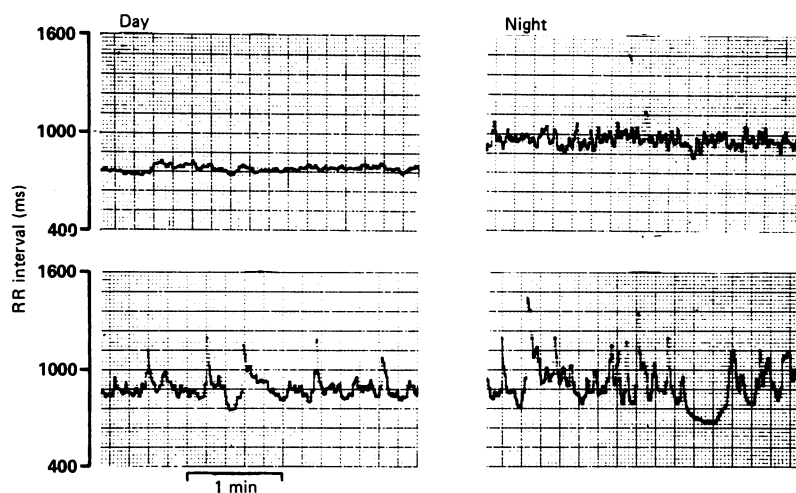


Figure 1 Four short RR interval recordings (3 minutes each) taken from the same diabetic patient at different times of the day and night, showing considerable differences in RR variation.

larger experience of 24 hour electrocardiographic tape analysis and defined the age related normal values for the RR counts. We also sought to establish how the results of 24 hour electrocardiographic tape recordings relate to conventional tests of cardiovascular autonomic function in a large group of diabetic patients.

### Patients and methods

#### CONTROLS

Twenty four hour electrocardiograms were recorded from 57 men (aged 18–65 years) and 20 women (aged 18–57 years). All were ambulant and going about their normal daily routines. None had any known disease or was taking regular medications (normal group). Tapes were also recorded from six young men (18–27 years) who were confined to bed with leg and pelvic fractures. The tapes were recorded several days after operation when the men were fully conscious (orthopaedic group). Eight other healthy young men (aged 19–29 years) took part in a sleep deprivation study, during which heart rate was monitored on to tape for 24 hours before, for two successive 24 hour periods during 48 hours continuous sleep deprivation, and then on two successive 24 hour recovery periods of normal sleep (sleep deprived group). The results from the two 24 hour tapes measured during sleep deprivation were averaged as were those from the 48 hours recovery period. Ten night nurses (three men and seven women, aged 26–47 years) had 24 hour tape recordings made during and after their night duty shifts (night shift group). Four recordings were made on each individual: at the beginning and end of seven days of night duty and at the beginning and end of their seven day recovery period off duty. The 24 hour RR counts in men in the normal group and the “posture” results in the orthopaedic group have been described briefly before<sup>13</sup> but are included here in greater detail.

#### DIABETIC PATIENTS

Three hundred and twelve diabetic patients (200 men and 112 women, aged 17–66 years) had 24 hour recordings as part of their assessment for autonomic involvement (diabetic group). Twenty four hour tape recordings and a standard battery of cardiovascular reflex tests were performed within 24 hours of each other in all these patients. A further 31 diabetic patients had an incomplete battery of cardiovascular tests. Their results are included in the correlations between the 24 hour tape results and individual tests.

The subjects in the various studies all agreed to 24 hour ambulatory electrocardiographic monitoring and the technique had the approval of the local hospital ethics advisory committee.

#### METHODS

##### Electrocardiographic recordings

Three chest electrodes were used to record electrocardiogram signals on to a cassette tape with an ambulatory electrocardiographic monitoring system (Medilog, Oxford Instruments or Tracker, Reynolds Medical). An adjacent tape track was used to record a simultaneous time frequency reference signal. The recordings were continued for 24 hours, while the subjects went about their routine daily activities, with the tape recorder carried on a belt worn around the waist. They noted meal times, unusual events, and the times of going to bed and getting up in a diary.

##### Analysis of RR interval variation

The 24 hour tapes were later replayed through a Pathfinder (Reynolds Medical) high speed arrhythmia analyser at 120 times the original recording speed. The replay speed was controlled to within 0.5% by means of the time reference track recorded on each tape.

The trigger section of the analyser detected individual QRS waves in the electrocardiogram signal and distinguished them from P and T waves and from muscle noise and artefact by means of a continuously adaptive threshold derived from the noise components by independent filtering. The accuracy with which QRS waves can be detected depends on the quality of the recorded electrocardiogram; with tapes of routine quality there were only about 12 false positive and false negative errors of detection in 24 hours.<sup>14</sup> Excessive noise, such as would cause QRS waves to be missed, automatically inhibited analysis until the noise subsided, whereupon analysis was resumed. The Pathfinder detects any QRS waves with a shape that differs significantly from the subject's “normal” QRS complex; a continuously updated example of this normal complex is held in the analyser memory for comparison. Such abnormal complexes are indicated as ventricular extrasystoles.<sup>15</sup> The signal is closely monitored throughout the analysis by the operator to exclude tapes with atrial fibrillation and other non-sinus rhythms, and appreciable numbers of supraventricular extrasystoles.

For each electrocardiographic complex in the recording the Pathfinder generates an ex-

ternal pulse to signify a beat, and another if that QRS complex is of normal (sinus) configuration. These pulses are passed to a microcomputer which times the arrival of each beat and calculates the length of each RR interval and the difference between each successive beat. If this increases by more than 50 ms between successive beats a positive count is added to the total being accumulated. Likewise, if the change shows a decrease of more than 50 ms the total negative count is increased. Because we found no significant differences between positive and negative counts<sup>7</sup> the results reported here are positive counts.

The program also continuously maintained time thresholds corresponding to 63% and 175% of the prevailing normal RR interval. Beats with intervals outside these limits together with all those indicated by the Pathfinder as being "not normal" in shape were rejected and the interval calculations were restarted from the next normal QRS. The intervals thus excluded and all periods during which the analyser was inhibited were accumulated and used to calculate the percentage of the time actually analysed. Using this technique we can now analyse tapes with large numbers of ventricular extrasystoles.<sup>16</sup> For each tape the program gave an output of total 24 hour RR counts, mean hourly wake and mean hourly sleep RR counts, and mean wake and mean sleep heart rate. Where the tape recording is incomplete the results are normalised to the equivalent of 24 hours. Recordings shorter than 18 hours or with less than 40% of beats analysed were rejected.

#### Cardiovascular autonomic function tests

We used a standard battery of cardiovascular autonomic function tests to assess all diabetic patients: the heart rate responses to the Valsalva manoeuvre, standing up, and deep breathing; and the blood pressure responses to standing up and sustained handgrip. We have described these tests and the grading of severity in detail elsewhere.<sup>9</sup> In brief, autonomic involvement was categorised as normal (all tests normal), early (one heart rate test abnormal), definite (two or more heart rate tests abnormal), severe (abnormal heart rate tests plus one or both blood pressure tests abnormal), or atypical (any other combination of abnormalities). Autonomic scores were derived by giving each test a score of 0 for normal, 1 for

borderline, and 2 for an abnormal result. This gave a total score of between 0 (normal) and 10 (most severe).

#### STATISTICAL ANALYSIS

Conventional statistical methods were applied to the results as appropriate; we used regression calculations and paired *t* tests. Where the data were not normally distributed calculations were performed on the log transformed data. Results are accordingly presented as mean (SD) or geometric mean and range.

### Results

#### CONTROLS

There were significant inverse correlations between age and total 24 hour ( $r = -0.55$ ), mean hourly wake ( $r = -0.54$ ), and mean hourly sleep ( $r = -0.51$ ) RR counts in the 57 male controls. Figure 2 shows the individual total 24 hour RR counts in these men and in 20 female controls. Because there were no significant differences between the results of the men and women and because the age distribution of the women was skewed (most were < 30 years old), the lower 95% tolerance limits for the RR counts were calculated from the results for the 57 men. The normal lower 95% tolerance limits for total 24 hour RR counts are 2000 at age 25, 1000 at age 45, and 500 at age 65 years. Table 1 shows the equivalent values for mean hourly wake and sleep RR counts.

#### ORTHOPAEDIC GROUP

All six young men confined to bed after injury had total 24 hour RR counts well within the normal range for their age (fig 3). The counts rose appropriately at night during sleep in five subjects (geometric mean of hourly wake counts 235 (84-792) and hourly sleep counts 484 (249-716)). All wake and sleep values were in the normal range. Mean heart rate fell from 77 (7) beats/min awake to 61 (6) beats/min asleep.

#### SLEEP DEPRIVED GROUP

Table 2 shows the group mean RR counts and heart rate during normal sleep and during sleep deprivation. There were no significant differences in results between the normal 24 hour period before and the 48 hour period after sleep deprivation. Mean RR counts rose as expected during normal sleep from 452 to 614 (+36%,  $p = 0.034$ ), but not at night during sleep deprivation (460 to 471) (+2%, NS). Heart rate fell substantially during normal sleep, but during sleep deprivation day and night values remained similar. There were, therefore, considerable differences between the night time

Figure 2 Individual total 24 hour RR counts in 57 healthy men and 20 healthy women. The broken lines are the age related 95% normal tolerance limits, derived from the counts in the 57 men.

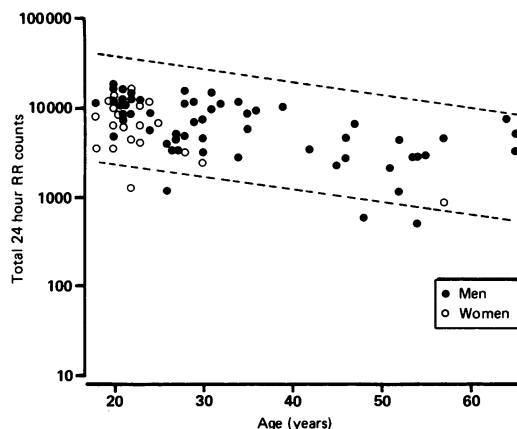


Table 1 Approximate normal lower 95% tolerance limits for total 24 hour, mean hourly wake, and mean hourly sleep RR counts related to age

Age (yr)	Total 24 hour counts	Mean hourly wake counts	Mean hourly sleep counts
25	2000	60	90
45	1000	30	45
65	500	15	20

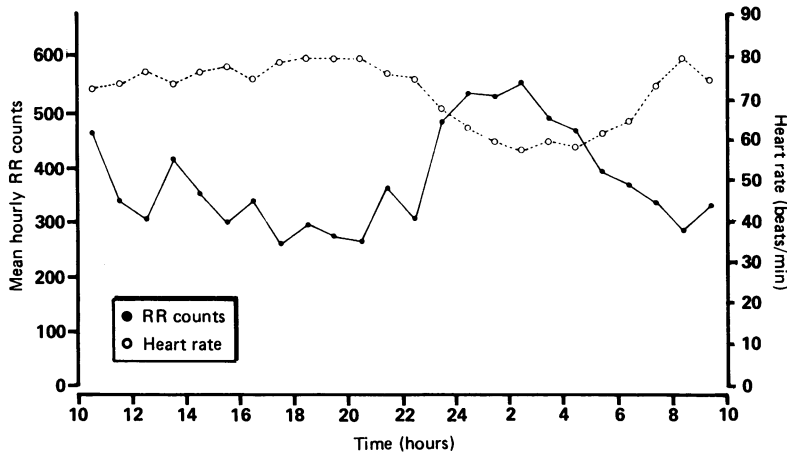


Figure 3 Group mean hourly RR counts and hourly heart rate in six young men confined to bed.

counts ( $p = 0.059$ ) and heart rates ( $p < 0.001$ ) during the normal and the sleep deprived periods.

#### NIGHT SHIFT GROUP

During the first and last night shift periods, which were separated by six days, the wake/sleep pattern was similar, with an average of seven hours sleep on each occasion, taken between about 9.00 am and 5.00 pm. On coming off night duty, the subjects usually slept during the day until about 5.00 pm, then got up, and went back to bed again around 12.00 midnight until 7.00 or 8.00 am the following morning. This meant that during the first day they had an average of 13 hours' sleep. Six days later, the last day shift, the sleep pattern had reverted to normal, but in preparation for their next night duty shift, the subjects slept longer—an average of 10 hours from midnight to 10.00 am.

The hourly RR counts during these four 24 hour periods reflect the wake and sleep patterns (fig 4) in that during the two night shift periods the average RR counts were highest during the day when the subjects were asleep (geometric mean of hourly counts: wake 123 (13–585) and 140 (35–462); sleep 188 (47–1167) and 234 (32–835)). The last day shift period, just before the subjects restarted night duty, shows a normal day/night pattern of RR counts (wake 174 (29–541); sleep 331 (96–1021)). The first day shift period, however, shows a somewhat different pattern, with two periods of higher and two

periods of lower counts, corresponding to the two periods of sleep and waking. This was coupled with higher and lower mean heart rates (geometric mean of hourly counts—wake first period 144 (34–673), wake second period 154 (46–640); sleep first period 255 (74–857), sleep second period 344 (82–940) and mean heart rates (beats/min)—wake 78 (10) and 78 (8); sleep 66 (8) and 62 (5) sleep). Because the counts were higher during sleep, the mean total 24 hour RR counts were greatest during the day shift periods when the subjects slept more (first night shift 3583 (582–18119), last night shift 4168 (811–13514), first day shift 6425 (2182–17644), last day shift 5905 (1922–16191)).

#### DIABETIC GROUP

Forty seven per cent (146 subjects) had total 24 hour RR count results that were less than the lower 95% tolerance limit for healthy controls related to age. Table 3 shows the proportion of normal and abnormal results related both to the autonomic category and to the autonomic score (based on results from a standardised battery of cardiovascular reflex tests done within 24 hours of the 24 hour tape recording). With increasing autonomic abnormality there was a higher percentage of abnormal 24 hour tape results; so that almost all with autonomic dysfunction in the "definite" and "severe" categories had abnormal total 24 hour counts. The fact that the 24 hour tape method is more sensitive than conventional autonomic function tests is shown by the 24% who had abnormal 24 hour counts despite normal cardiovascular reflexes. Table 3 also shows the group mean values for the 24 hour count results related to autonomic category and score. Counts were lower as the autonomic damage increased.

Table 4 shows the correlation coefficients between the 24 hour total counts, wake and sleep counts, and the individual cardiovascular autonomic function tests. In every case the relations were highly significant statistically, with the closest correlation between the counts and the heart rate tests. There were also extremely close correlations between the log total 24 hour counts and the log wake counts ( $r = 0.969$ ) and the log sleep counts ( $r = 0.957$ ) in this group of diabetic patients.

#### Discussion

Since we first reported our technique of assessing cardiac parasympathetic activity by

Table 2 Group mean RR counts and heart rates in eight healthy men aged 19–29 years who were deprived of sleep for 48 hours

	RR counts (geometric mean and range)			Heart rate (arithmetic mean (SD)) (beats/min)	
	Total 24 h counts	Mean hourly wake	Mean hourly sleep	Wake	Sleep
Normal sleep	12333 (7332–18050)	452 (300–737)	614 (263–877)	79 (8)	57 (8)
Significance	NS	NS	$p = 0.034$ NS Day (8 am–12 pm) 460 (217–761)	NS Day 77 (8)	$p < 0.001$ Night 76 (8)
Sleep deprived	11194 (5951–17723)	460 (217–761)	471 (310–754)		

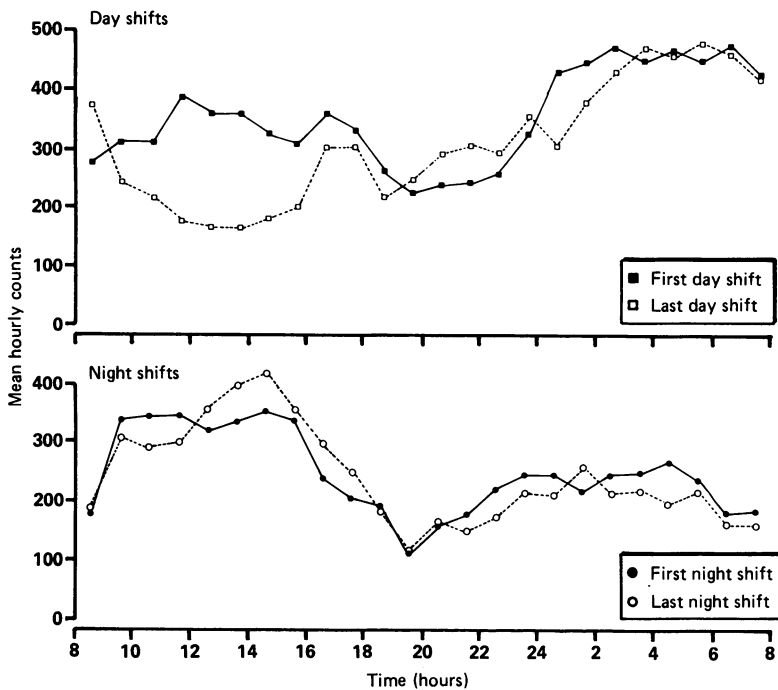


Figure 4 Group mean hourly RR counts in ten healthy individuals (three men and seven women) during and after night duty.

analysing 24 hour electrocardiograms,<sup>7</sup> we have gained considerably more experience in both healthy individuals and patients. The method has also been refined so that we can now exclude large numbers of ventricular extrasystoles without losing the essential data on heart rate variability.<sup>16</sup> This contrasts with the inability of spectral analysis methods to handle ventricular extrasystoles. Additionally, analysis can be done at 120 times real speed so that a full 24 hour tape recording can be read through in twelve minutes by the dedicated microcomputer system we have developed.

In a smaller study we showed that RR counts decrease with age in healthy individuals. We have expanded our normal results and in the present study we show the 95% tolerance limits not only for the total 24 hour RR counts but also for the mean hourly wake and mean hourly sleep counts. There was an extremely close correlation between these three measures in the results from the diabetic patients, which means that each index can be used to assess variability. We previously reported our data on

repeatability in healthy individuals, diabetic patients, and patients with cardiac disorders,<sup>7 16</sup> showing that this RR counts method can be used reliably for treatment and outcome trials.

There is normally a characteristic rise in RR counts at night and we wondered what factors might be responsible for this. We found a normal RR counts pattern in a group of fit but immobile young men. This suggests that being confined to bed is not a factor influencing the numbers of abnormal RR counts recorded.

To establish whether the variations in RR counts were part of a built-in diurnal clock we measured RR counts in another group of fit young men undergoing prolonged periods of sleep deprivation as part of a different study. Though total 24 hour RR counts were similar, the wake/sleep difference in counts during the period of "normal sleep" disappeared during the 48 hours of sleep deprivation. Similarly, in a group of nurses the daytime counts were higher while the nurses were on night shift and sleeping during the day. There is, therefore, no built-in diurnal clock to regulate the RR counts.

The third candidate for modifying RR counts is that of sleep itself, rather than either posture or time of day. The results from both the sleep deprivation and the night duty studies support this mechanism: both periods of sleep taken by the night duty staff on the same day increased the RR counts. Thus the increase in RR counts seen in most individuals occurs during sleep and seems to be due to sleep itself. This would fit in with current concepts of the relative activity of the autonomic nervous system whereby both sympathetic and parasympathetic components are active during the day, whereas at night during periods of non-rapid eye movement sleep there is predominantly parasympathetic activity. This is also reflected in the changes in heart rate which reciprocate the changes in RR counts in most individuals. We have not specifically related sleep stages to RR counts but during rapid eye movement sleep there are well documented changes in autonomic activity<sup>17</sup> which may be associated with increased RR counts.

Do RR counts merely reflect the overall heart rate? We argued in detail that this is not so<sup>7 13</sup> in view of the dissociation between heart rate and heart rate variability in our earlier studies.<sup>18</sup> There is a complex interrelation between beat-

Table 3 Number of diabetic patients with abnormal 24 hour RR counts according to autonomic category and score, and group mean values for RR counts

	Number with 24 hour RR counts		Group mean 24 hour RR counts (geometric mean)		
	Total	Number with abnormal counts (%)	Total 24 hour	Mean hourly wake	Mean hourly sleep
All	312	146 (47)			
By autonomic category:					
Normal	147	35 (24)	2845	84	170
Early	52	25 (48)	866	27	42
Definite	32	27 (84)	154	6	7
Severe	60	51 (85)	114	4	4
Atypical	21	8 (38)	1489	48	69
By autonomic score:					
0-2	175	42 (24)	2756	82	162
3-5	67	43 (64)	422	14	19
6-10	70	61 (87)	112	4	4

Table 4 Correlation coefficients between individual cardiovascular autonomic function tests and total 24 hour RR counts and mean hourly wake and sleep RR counts

RR counts	Valsalva ratio	30:15 ratio	Max - min heart rate	BP drop on standing	BP rise with grip	Autonomic score
Log total 24 hour	0.627 (n = 321)	0.557 (n = 342)	0.625 (n = 285)	-0.439 (n = 316)	0.314 (n = 312)	-0.683
Log mean hourly wake	0.636 (n = 318)	0.567 (n = 340)	0.637 (n = 286)	-0.433 (n = 313)	0.297 (n = 311)	-0.679 (n = 309)
Log mean hourly sleep	0.610 (n = 318)	0.539 (n = 340)	0.608 (n = 286)	-0.444 (n = 313)	0.323 (n = 311)	-0.692 (n = 309)

to-beat differences and prevailing average heart rate, but it is by no means a simple matter of the overall heart rate determining the amount of beat-to-beat heart rate variation, however measured.

Though we showed the clear relation between autonomic damage and RR counts in our original article<sup>7</sup> and briefly in a small group of diabetic patients<sup>19</sup> we have not hitherto reported in detail on the relation between conventional non-invasive tests of cardiovascular autonomic function and 24 hour RR counts in large numbers of diabetic patients. Our results clearly show not only the very close correlations achieved between individual cardiovascular tests (particularly the heart rate tests) and RR counts, but also the differing proportions of normal and abnormal results with increasing severity of autonomic damage. About 85% of those in whom definite or severe damage was detected by cardiovascular testing had abnormal RR counts. Because 24% of diabetic patients with apparently normal cardiovascular reflexes had abnormal RR counts we believe that the RR counts method is more sensitive than conventional tests of cardiovascular reflexes.

What are the clinical applications of this method? It is reliable and sensitive and gives an objective measure of cardiac parasympathetic activity.<sup>7</sup> Simple bedside tests of autonomic function in diabetes are widely available to diagnose autonomic neuropathy,<sup>19</sup> but our method of analysing 24 hour electrocardiographic tape recordings reveals earlier abnormalities of cardiac parasympathetic function. There has recently been increasing interest in the effect of autonomic influences on prognosis after myocardial infarction. With our method it should be possible to see whether low heart rate variability is indeed an adverse prognostic indicator. One such study has already been published,<sup>2</sup> and further studies are currently in progress by our own group and others. Conventional bedside tests are also inappropriate in the sudden infant death syndrome, where there has been evidence that reduced heart rate variation may be a factor.<sup>3,20</sup> Objective assessment of other conditions such as chronic renal failure, liver disease, and congestive cardiac failure may also be possible with this method of 24 hour electrocardiographic tape recording. Other work in progress suggests that measurement of RR counts may also be of relevance in assessing the effect of drugs on the cardiovascular system.<sup>16,21</sup>

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- Ewing DJ. Recent advances in the non-invasive investigation of diabetic autonomic neuropathy. In: Bannister R, ed. *Autonomic failure. A textbook of clinical disorders of the autonomic nervous system*. 2nd ed. Oxford: Oxford University Press, 1988:667-89.
- Kleiger RE, Miller JP, Bigger JT, Moss AJ, and the Multicenter Post-Infarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;59:256-62.
- Schwartz PJ. The quest for mechanisms of the sudden infant death syndrome: doubts and progress. *Circulation* 1987;75:677-83.
- Knox R. On the relation subsisting between the time of the day, and various functions of the human body; and on the manner in which pulsations of the heart and arteries are affected by muscular exertion. *Edin Med Surg J* 1815;11:52-65 and 164-7.
- Murray A, Ewing DJ, Campbell IW, Neilson JMM, Clarke BF. RR interval variations in young male diabetics. *Br Heart J* 1975;37:882-5.
- Wheeler T, Watkins PJ. Cardiac denervation in diabetes. *Br Med J* 1973;iv:584-6.
- Ewing DJ, Neilson JMM, Travis P. New method for assessing cardiac parasympathetic activity using 24 hour electrocardiograms. *Br Heart J* 1984;52:396-402.
- Hilsted J, Jensen SB. A simple test for autonomic neuropathy in juvenile diabetes. *Acta Med Scand* 1979;205:385-7.
- Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care* 1985;8:491-8.
- Axelrod S, Gordon D, Madwed JB, Snyderman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. *Am J Physiol* 1985;249:H867-75.
- Pomeranz B, Macaulay RJB, Caudhill MA, et al. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985;248:H151-3.
- Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986;59:178-93.
- McAreevey D, Neilson JMM, Ewing DJ, Russell DC. Cardiac parasympathetic activity during the early hours of acute myocardial infarction. *Br Heart J* 1989;62:165-70.
- Neilson JMM. Detection of QRS waves in ambulatory monitoring signals. In: Hombach V, Hilger HH, eds. *Holter monitoring technique*. Stuttgart and New York: Schattner, 1985:15-25.
- Neilson JMM. Computer detection of ventricular ectopic beats: on line and off. Computers in Cardiology, Bethesda, USA, IEEE Cat No 75CH 1018-1C, 1975:33-5.
- Zuanetti G, Latini R, Neilson JMM, Schwartz PJ, Ewing DJ. Heart rate variability in patients with ventricular arrhythmias: effect of antiarrhythmic drugs. *J Am Coll Cardiol* 1991 (in press).
- Shapiro CM. Autonomic dysfunction during REM sleep. In: Peter JH, Podszus T, von Wichert P, eds. *Sleep and health risk*. Berlin: Springer-Verlag, 1991 (in press).
- Ewing DJ, Hume L, Campbell IW, Murray A, Neilson JMM, Clarke BF. Autonomic mechanisms in the initial heart rate response to standing. *J Appl Physiol* 1980;49:809-14.
- Matthews DM, Martyn CN, Riemersma RA, Clarke BF, Ewing DJ. Noradrenaline response to edrophonium (tensilon) and its relation to other autonomic tests in diabetic subjects. *Diabetes Res* 1987;6:175-80.
- Cauchemez B, Peirano P, Samson-Dolfus D, et al. The autonomic nervous system in sudden infant death syndrome. Analysis of heart rate and heart rate variability on Holter recordings. *Arch Mal Coeur* 1989;82:745-52.
- Flapan AD, Nolan J, Neilson JMM, Ewing DJ. Captopril therapy increases parasympathetic activity in patients with congestive cardiac failure [Abstract]. *Circulation* 1990;82(suppl 3):382.