Fremantle Hospital
Alma Street Centre

PSYCHIATRIC DISORDERS AND THEIR EFFECT ON CIRCADIAN HEART RATE PATTERNS

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Background

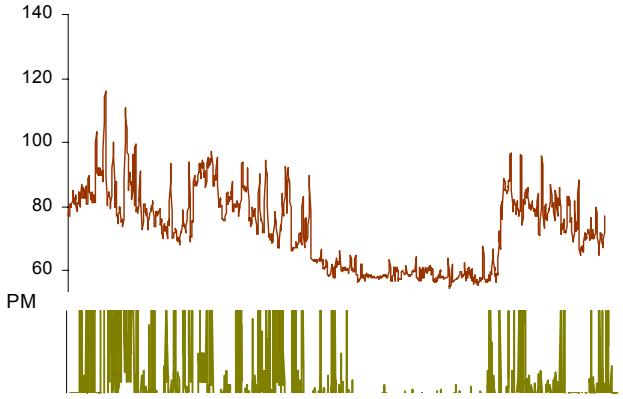
Research since 1991 led by Dr Hans Stampfer, University of Western Australia, has demonstrated a unique relationship between psychiatric illness and circadian, or 24 hour heart rate patterns. The data showed a clear correlation between circadian heart rate patterns and psychiatric disorders.(1)

Heart rate patterns corresponding to depression, anxiety, panic disorder, psychosis and schizophrenia have been identified. Each disorder shows distinctly different circadian features and this has been supported by clinical studies over the last 10 years.

Heart rate data is displayed graphically with beats per minute (bpm) on the x axis and time (24 hour period) displayed on the y axis.

The monitor also records body movement data as displacement in the x, y and z planes and is displayed graphically underneath the heart rate graph. Body movement provides adjunct data used to differentiate between physical activity and arousal due to anxiety. It is also useful in determining night time restlessness and insomnia.

Examples of Typical
Circadian Heart Rate Patterns



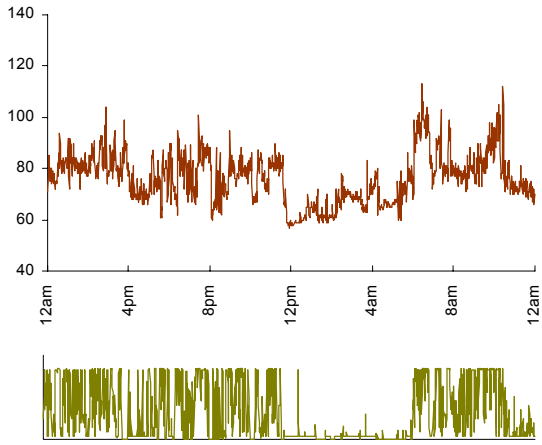
Normal

The sleep/wake 'architecture' is most clearly defined in normal circadian patterns. Both the onset of sleep and moment of waking show a clear change in the mean trend and sleep rates are visibly lower and less variable than awake rates. In normal subjects, waking is usually brief and return to sleep occurs quickly. Body movement data clearly correlate with heart rate, with a cessation of movement during the sleep period. Morning heart rate means continue at a similar rate to the previous day.

Sleep disturbances are most noticeable in clinical patterns, when night time wakings are often followed by a period of restlessness and insomnia before a return to sleep.

Mean heart rate in beats per minute (bpm)

24 hour	PM	Sleep	AM
73	81	60	78

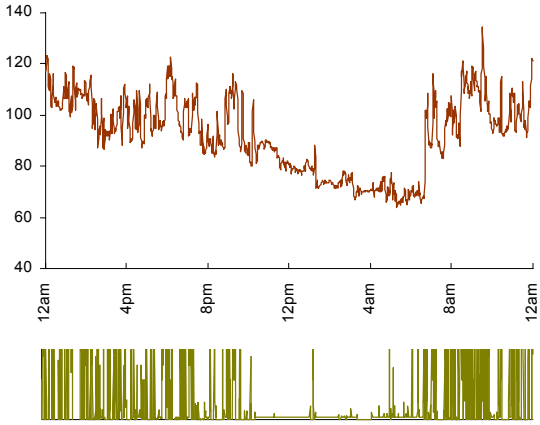


Depression

The 24 hour mean in this example is within the normal range, but the sleep mean is slightly elevated. Changes within the sleep period are the most relevant, diagnostically. Rates fall to their lowest level shortly after the onset of sleep, and rise progressively thereafter to awake values. It is often this rising trend which causes early waking, a common symptom of depression.

Mean heart rate in beats per minute (bpm)

24 hour	PM	Sleep	AM
76	78	66	82

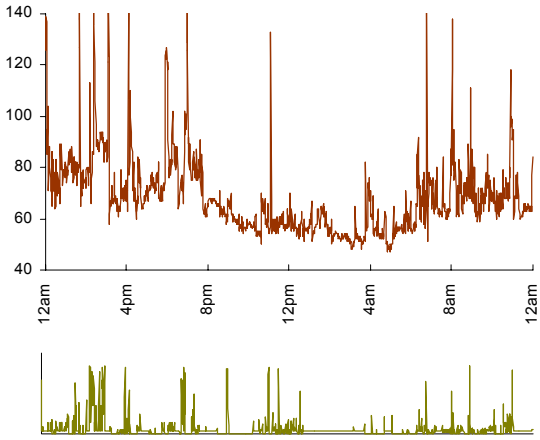


Anxiety

Both the 24 hour and sleep means are moderately elevated. Morning rates are also elevated, accounting for acute morning anxiety that is often experienced by sufferers. Rates are high at the onset of sleep due to sustained daytime physiological arousal and decline to their lowest values an hour or two before waking.

Mean heart rate in beats per minute (bpm)

24 hour	PM	Sleep	AM
92	101	76	102

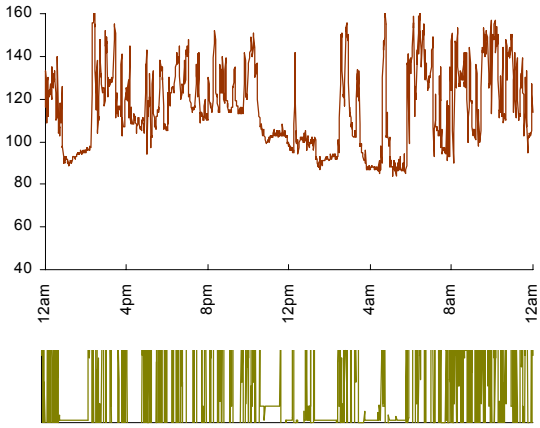


Panic

In this example the 24 hour and sleep means are within the normal range and this is not unusual in cases of panic disorder. Typically, the circadian pattern of panic disorder lacks a clearly defined sleep/wake variation and there are noticeable 'spikes' of sudden rate elevation throughout the 24 hour period. These spikes can be as high as 150 bpm and last up to 10 minutes and occur both during the day and at night. Body movement data indicate that this subject was resting or inactive for most of the day.

Mean heart rate in beats per minute (bpm)

24 hour	PM	Sleep	AM
68	78	57	70



Acute psychosis

The x axis has been scaled to 160 bpm to include the high rates. This example clearly shows a severe elevation of heart rate means in the 24 hour period, morning, afternoon and sleep epochs. Normal circadian functioning and regulation is severely disrupted. The sleep period is grossly disturbed with patchy sleep interspersed with abrupt wakings. These features are consistent and typical of acute psychosis.

Mean heart rate in beats per minute (bpm)

24 hour	PM	Sleep	AM
116	119	101	126

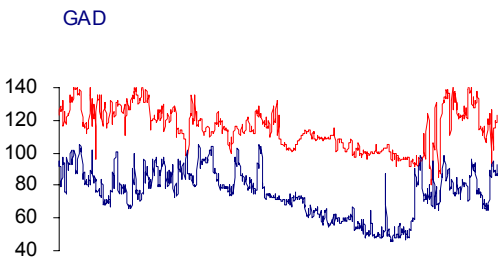
Analysis and Interpretation

Analysis is made by the application of manual and software routines to quantify various parameters of heart rate activity.

These include:

- Rate characteristics
- Rate-frequency distribution
- Spiking
- Difference mean
- Sleep cycle slowing

The 24 hour period is sub-divided into 3 epochs- morning, afternoon and sleep. Heart rate means for each of these epochs and the 24 hour mean are calculated. Onset of sleep and exact time of waking is calculated using software algorithms.

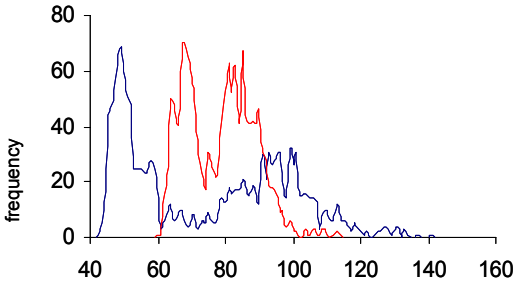


Means in bpm

	24 hour
Red	115
Blue	75

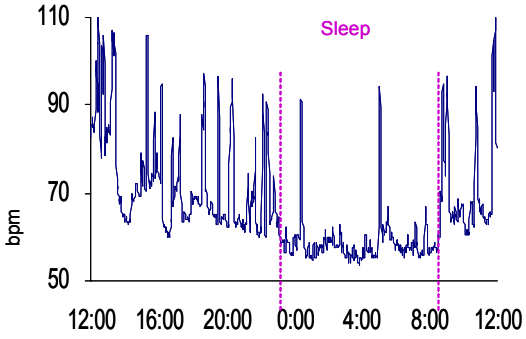
Rate characteristics

Mean heart rate is calculated for the 24 hour period and each epoch. Clinical deviation may be towards abnormally high or low rates. Generally, increased rate suggests increased clinical severity. The two patterns in the illustration have similar morphologies. However, it can be seen that the trend in mean heart rate in the red graph is significantly higher than the blue graph with an upward shift in rates across all epochs.



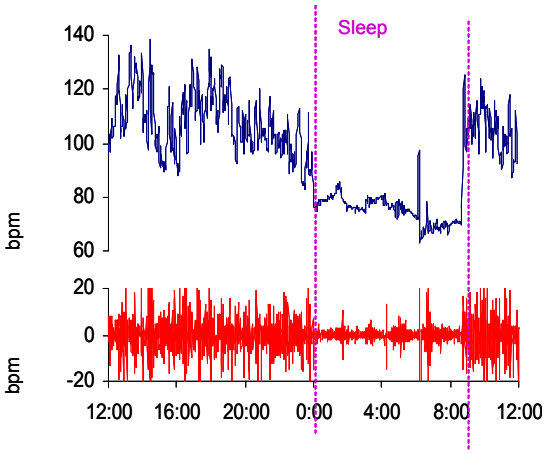
Rate frequency distribution

This is the frequency distribution of minute averaged heart rates occurring over a 24 hour period. Clinical patterns may show abnormally expanded or constricted distributions. The red graph on the illustration shows the rate-frequency distribution of a clinical subject compared to a normal subject (blue graph). The rate-frequency for the normal subject is clustered at around 50bpm, whereas the distribution in the clinical subject shows 2 peaks, one at around 70bpm, the other at 90bpm.



Spiking

Spiking is the occurrence of brief, large amplitude 'spikes' of rate elevation. Spikes can occur during the awake and sleep periods and last between 1 and 10 minutes. Magnitude of spiking can increase the heart rate by up to 40bpm for the duration of the 'attack'. This can temporarily raise rates to 160-180bpm and are symptomatic of panic-like anxiety. The example shows spiking of up to 120bpm during both the awake and sleep period.

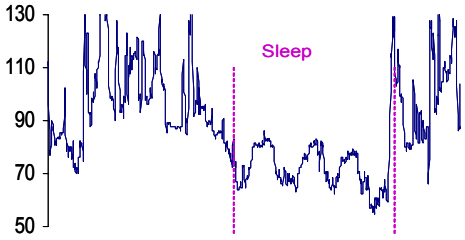


Difference mean

This is the mean of absolute differences between successive pulse rates over a specified time period, measured in beats per minute and referred to as pulse rate variability. This measure varies between clinical and non-clinical subjects. The normal range is 3-5bpm for the 24 hour mean and 2.0-3.2bpm for the sleep mean. Reduction in variability during the sleep period in clinical subjects may be a medication effect. The illustration shows difference mean and heart rate data plotted together. A noticeable reduction of pulse rate variability during the sleep period can be seen.

Mean heart rate in beats per minute (bpm)

	24 hour	PM	Sleep	AM
Raw	96	108	75	105
Difference	4.8	6.0	2.2	7.8



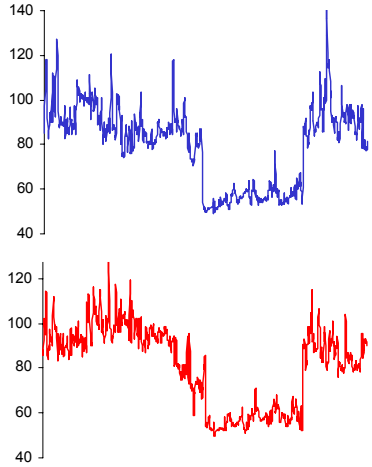
Sleep cycle slowing

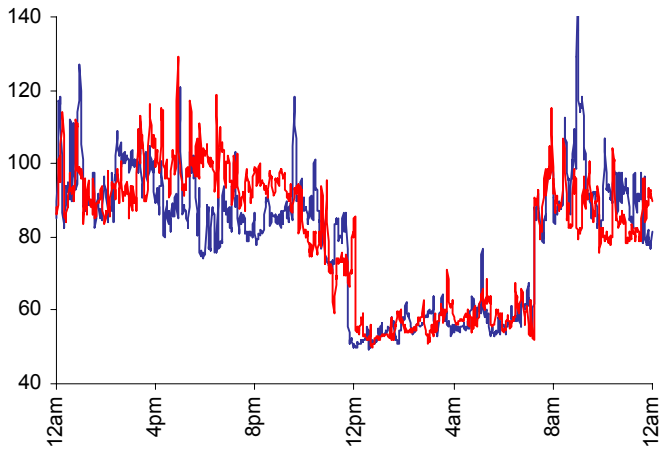
Variations in the mean trend in sleep cycles can be quantified and a slowing of the sleep cycle from 90 minutes to in excess of 120 minutes is invariably an indication of pathological changes. The illustration shows an example of sleep cycle slowing to 3 cycles during the night of approximately 150 minutes each.

Serial Monitoring

Serial recordings at intervals of days to years apart have shown circadian patterns to be clinically responsive. Clinical change, either an improvement or deterioration of symptoms is reflected in the circadian pattern. If there is no symptom change the pattern remains unaltered. Serial monitoring can be used as a measure of treatment response. Effective treatment will see a deviation towards normal means and a more clearly defined sleep/wake architecture.

Normal subjects also show stability over time assuming that circumstances are unchanged. However, mild stress caused by transient factors such as exams, job interviews or 'on call' duties is reflected in serial patterns of normal subjects. Serial monitoring has shown that temporary circadian disruption caused by these factors will revert to normal when the stressful events have passed.

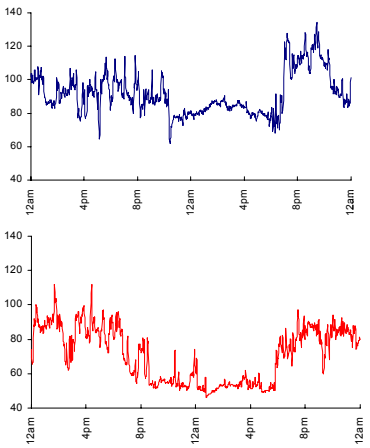


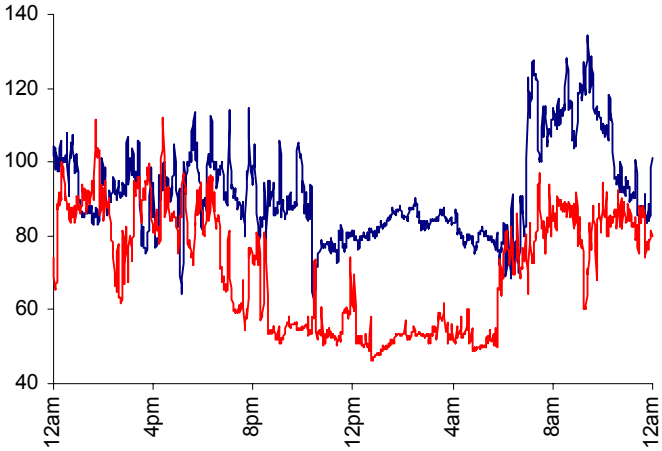


Normal subject

Serial recordings in normal subjects show remarkable consistency over time. If there is no change in circumstances, normal patterns are very stable over weeks, months and years.

	Means	
Date	**24 hour**	**Sleep**
9/8/01	81	59
20/8/01	80	56

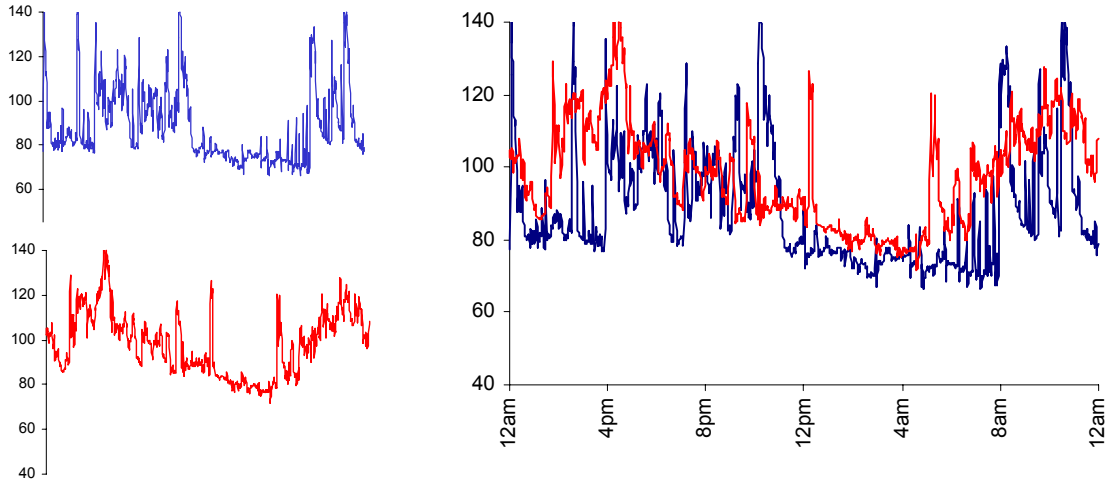




Improvement of depression

These two recordings show a significant treatment related improvement over a 6 week period of a severe depression pattern. The 24 hour mean has reduced by 20 bpm from 91 to 71. The most striking changes have occurred during the sleep period. Deviation towards normalisation in the sleep epoch is typical in cases of clinical recovery.

	Means	
Date	**24 hour**	**Sleep**
2/9/02	91	81
14/10/02	71	54



Deteriorating psychosis

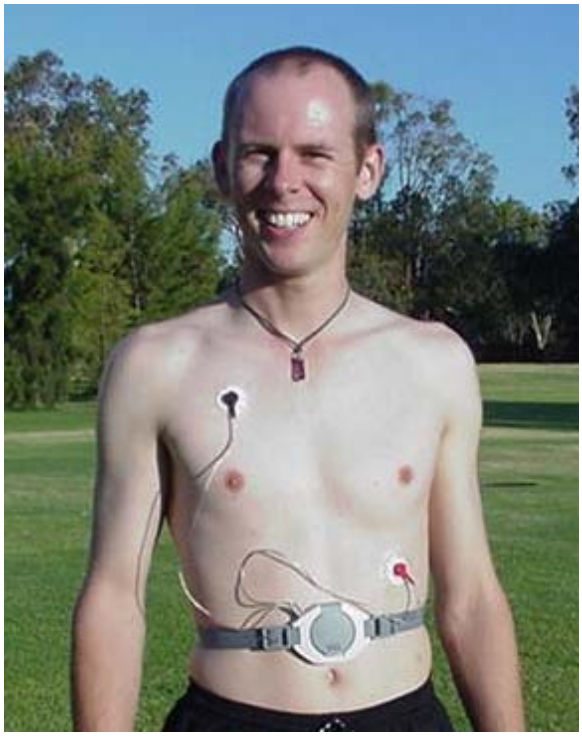
The second recording, coloured in red shows a worsening of a psychotic pattern with an increase in 24 hour and sleep means of 10bpm over a 3 week period. Means are moderately-severely elevated. The sleep period has shortened and there is evidence of initial insomnia and early morning waking.

	Means	
Date	**24 hour**	**Sleep**
16/8/02	88	75
4/9/02	98	85

The Monitor

The monitor used to record circadian heart rate is a small device attaching around the waist. It is a non-invasive procedure and the subject is fully ambulant for the duration of the test. Normal activities can continue while wearing the monitor.

The monitor records minute average heart rate and body movement for 24 hours. Movement data are used to locate rest and sleep periods and to control for high rates associated with increased physical activity.



CIRCADIAN HEART RATE PATTERNS AND SCHIZOPHRENIA

Objectives

To investigate abnormalities of the circadian heart rate pattern in schizophrenia and to compare these with normal.

To follow those cases who showed clinical improvement and demonstrate the corresponding change in heart rate pattern.

Method

Heart rate was recorded for 24-hours on two groups of subjects; a clinical group and a normal group.

Clinical subjects met ICD10 classification of schizophrenia (n=26) and were inpatients at one of two teaching hospitals in Perth, Western Australia.

The normal group (n=32) was recruited from the local community and work places of the 2 hospitals involved in the study.

Heart rate data was analysed blind to group referral. The data was de-identified and contained no clinical information.

Procedure for Normals

Initial screening process to confirm eligibility

Each subject monitored twice

Beck Depression Inventory completed

Second monitoring 14 days later

Procedure for Cases

Clinical diagnosis made by referring psychiatrist.

24 hour heart recording was performed as close to admission as possible and the Brief Psychiatric Rating Scale administered.

Second assessment 14 days later or at discharge (mean follow up 8.3 days).

Clinical assessment and 24-hour heart rate recordings were further repeated on those subjects who showed substantial change between recordings one and two.

Results

The 24-hour period was sub-divided into three epochs; morning, afternoon and sleep periods. Heart rate and pulse rate variability means were calculated for each epoch.

The two groups differed significantly in mean heart rates and this was a reflection of the differing circadian patterns in the two groups. Schizophrenia was associated with a highly elevated mean 24 hour heart rate compared to the normal group: 90 bpm compared to 72.5 bpm ($p=0.0001$). Difference in means was found to be more pronounced during the sleep epoch.

Internal consistency was measured by paired wise t-tests. At the two week follow up, mean scores across all epochs were unchanged in the case group- morning, p=0.748, afternoon, p=0.897, and sleep, p=0.138. These results were replicated in the control group- morning, p=0.544, afternoon, p=0.296 and sleep p=0.663.

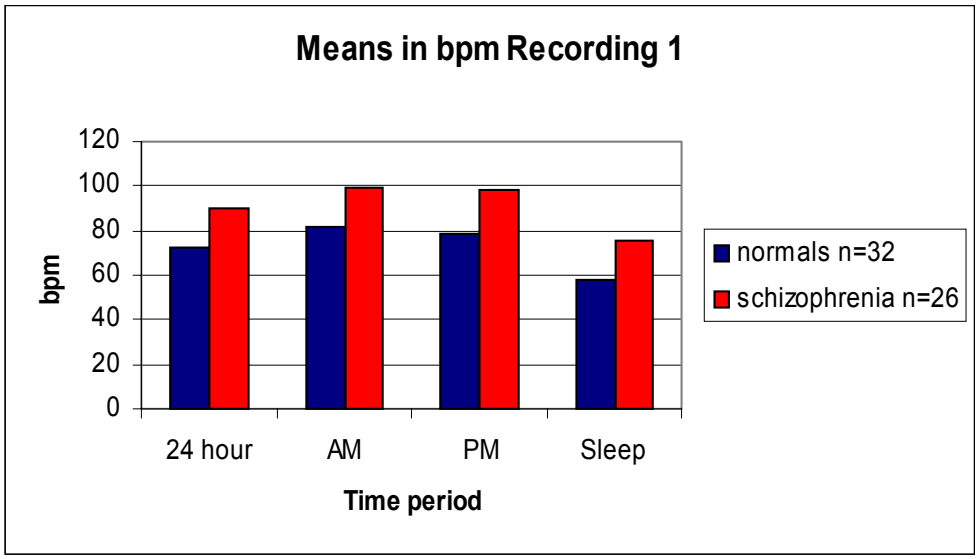
All normal subjects scored within the 0-11 range of the BDI, which indicates there were no symptoms of depression. All the cases scored within the clinically significant range for the BPRS. Eight subjects scored within the range for mild psychopathology and 16 in the range for moderate psychopathology. Five subjects were not assessed on this measurement due to the level of stress they were experiencing at the time of administration.

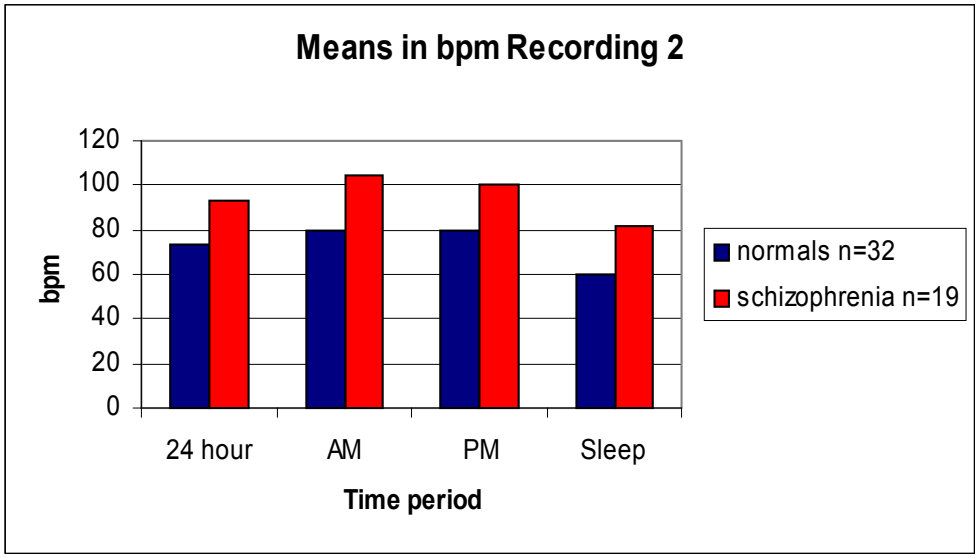
Blind classification was 100% for the case group and 96.5% for the normal group.

Pulse Rate Variability

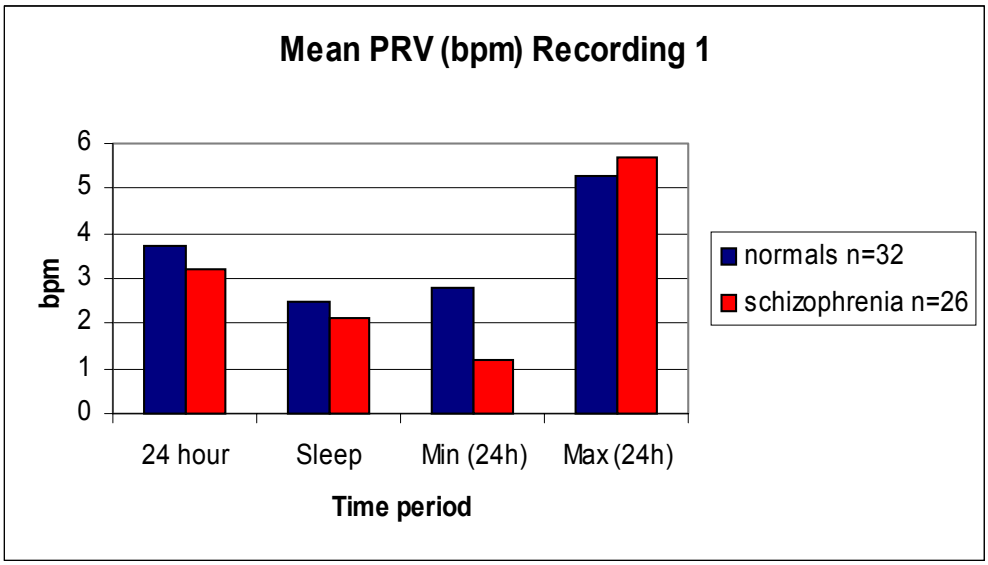
Pulse rate variability differed between the two groups, but not significantly.

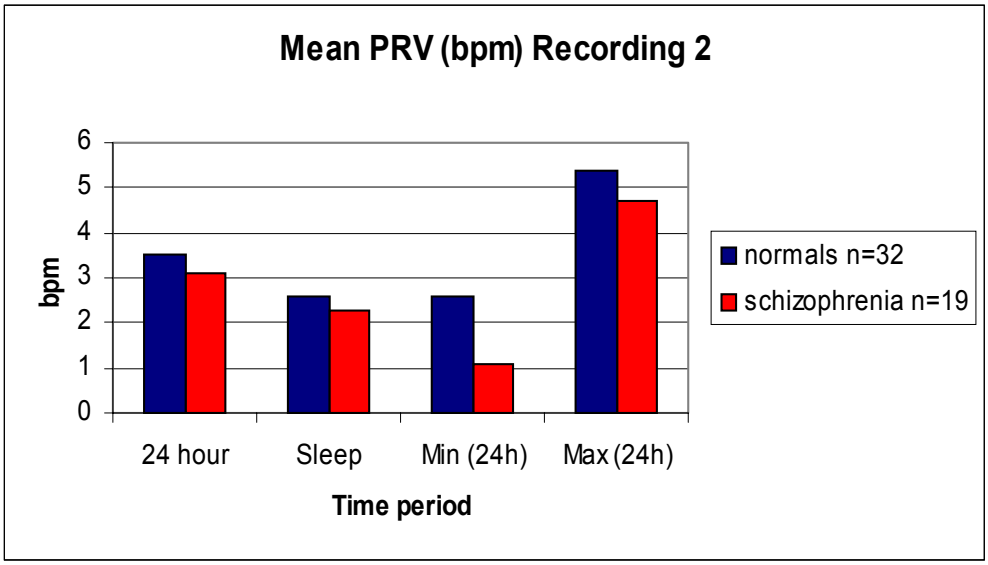
The usual range for pulse rate variability is between 3-5 bpm for the 24 hour period, 2.0–3.2 bpm for the sleep period. Reduction of PRV in the case group is probably caused by medication. Clozapine in particular is known to substantially reduce heart rate variability, other atypical anti-psychotics have less effect on PRV. (2)(3)





Mean HR (bpm)	Normals	Schizophrenia
Recording 1	**n=32**	**n=26**
24 hours	72.5	90
AM	81.5	99
PM	79	98
Sleep	57.5	76
Recording 2	**n=32**	**n=19**
24 hours	73	93
AM	80	105
PM	80	100
Sleep	59.5	82





Mean PRV (bpm)	**Normals**	**Schizophrenia**
Recording 1	**n=32**	**n=26**
24 hours	3.7	3.2
Sleep	2.5	2.1
Minimum (24 hours)	2.8	1.2
Maximum (24 hours)	5.3	5.7
Recording 2	**n=32**	**n=19**
24 hours	3.5	3.1
Sleep	2.6	2.3
Minimum (24 hours)	2.6	1.1
Maximum (24 hours)	5.4	4.7

Discussion

Circadian heart rate data can reliably distinguish clinical subjects from normals independent of clinical information.

The characteristics of circadian heart rate patterns are stable over time and clinically responsive (eg, tend toward normal with clinical improvement)

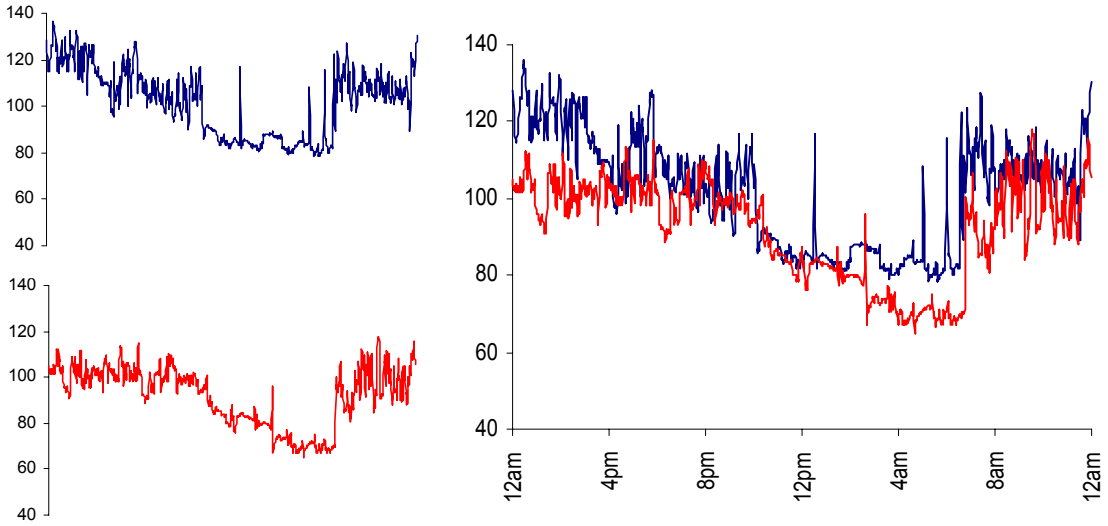
Mean heart rates across all time periods were significantly higher in the schizophrenia group than the normal group ($p=0.0001$).

Of particular importance is the sleep period, when external factors that could influence heart rate are absent.

Sleep rates are less variable in the normal group and the onset and transition to sleep has a higher rate change gradient.

Nocturnal disturbance, in particular waking and 'spiking' were greater in the case group. Transition periods into and out of sleep are less clearly defined in the case group compared to the normals.

Amongst the cases, rate frequency distribution was observed to be either abnormally constricted or expanded.

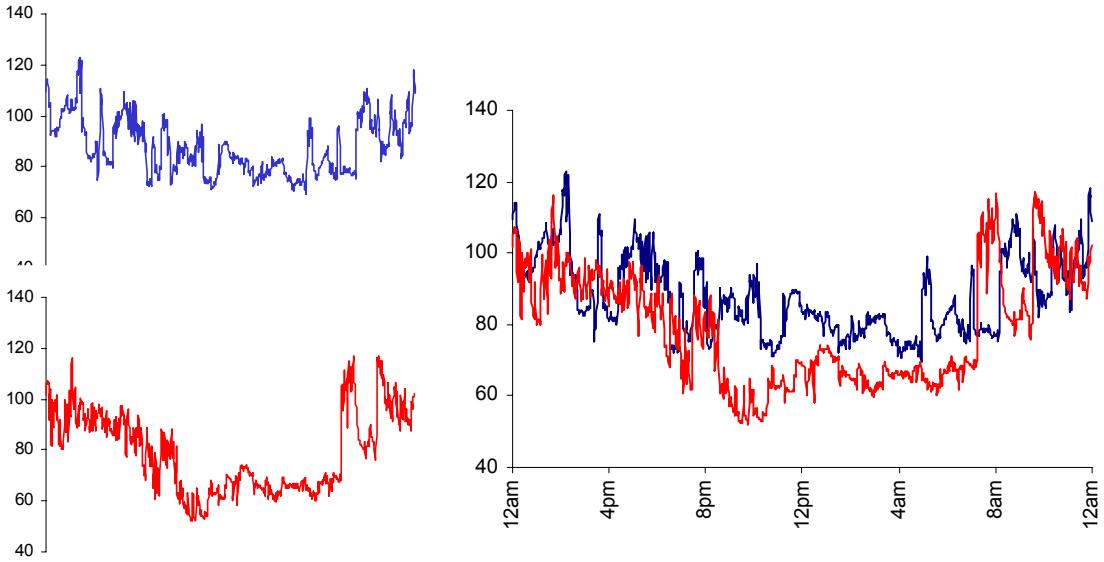


Study case 1

27 year old male diagnosed with schizophrenia in his early 20's. Since then he has had multiple admissions. His first recording shows a severe elevation of 24 hour and sleep means and a reduction in total sleep time. Pulse rate variability is reduced, most likely due to medication. Medication at monitoring one was risperidone 1mg mané, and 2mg nocte. The second CHRP shows a lowering of 24 hour and sleep means, an improvement although the pattern is not fully returned to normal. Medication: risperidone 2mg BD, valproate 500mg mané and 100mg nocté.

Means in bpm

Date	**24 hour**	**Sleep**
20/6/01	112	85
29/6/01	92	76

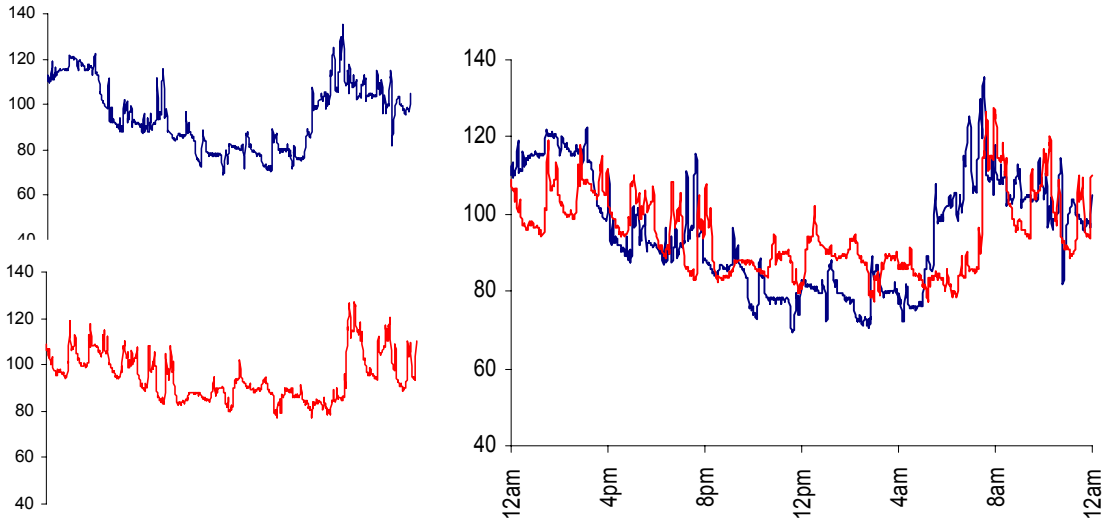


Study case 2

This patient is a 39 year old woman with a history of chronic paranoid schizophrenia. One week prior to the first recording her medication was changed from olanzapine 20mg daily and paroxetine 30mg daily to zuclopenthixol. She presented for admission at the psychiatric unit with a relapse of psychotic symptoms. She was restarted on olanzapine 20 mg daily. Her second recording shows a marked improvement after approximately 3 weeks of taking olanzapine with a lowering of 24 hour and sleep means and more clearly defined onset of sleep.

Means in bpm

Date	**24 hour**	**Sleep**
16/8/02	86	81
12/9/02	79	64



Study case 3

This patient was a 43 year old woman with a diagnosis of schizophrenia. She had a first episode of psychosis in 1997 and has had two hospital admissions between then and December 2001 when these recordings were made. She started on clozapine on 06/11/01. At the time of both monitorings she was taking clozapine 150mg daily and fluvoxamine 100mg nocte. The sleep mean in the second record is slightly more elevated than the first, and overall there is a slight deterioration between the two patterns.

Means in bpm

Date	**24 hour**	**Sleep**
6/12/01	95	80
20/12/01	95	87

Conclusion

Heart rate means, reflecting abnormal circadian heart rate patterns, were found to be significantly higher in case than control group.

Means in the schizophrenia group are consistently over 100 bpm. This elevation persists during sleep when between-group rate difference is greater.

Use of this data clinically can assist in the diagnosis of schizophrenia and be used as an objective indicator of clinical change.

References

Stampfer HG. 'The relationship between psychiatric illness and the circadian pattern of heart rate'. *Australian & New Zealand Journal of Psychiatry* 1998:33:187-198.

Rechlin T *et al.* 'Correlation between plasma clozapine concentration and heart rate variability in schizophrenic patients'*. Psychopharmacology* 135(4) :338-41, 1998 Feb.

Cohen H *et al*. 'Heart rate variability in schizophrenic patients treated with antipsychotic agents.' *Harefuah* 140(12):1142-7,1231,2001, Dec.

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