

CIRCADIAN DESYNCHRONIZATION IN PULSE RATE, SYSTOLIC AND DIASTOLIC BLOOD PRESSURE, RECTAL TEMPERATURE AND URINE OUTPUT IN TRAUMATIC TETRAPLEGICS

REKHA GOSWAMI, KEWAL KRISHAN, B. SURYAPRAKASH, S. VAIDYANATHAN,
K. RAO, M. S. RAO, A. K. GOSWAMI, A. K. GOEL AND P. L. SHARMA

*Departments of Urology, Gynaecology and Pharmacology,
Postgraduate Institute of Medical Education and Research,
Chandigarh - 160 012*

and

*Department of Statistics, Panjab University,
Chandigarh - 160 014*

(Received on February 19, 1985)

Summary : An investigation was undertaken to study the circadian rhythmicity in pulse rate, systolic and diastolic blood pressure, rectal temperature and urine output in eight traumatic tetraplegics in view of the fact that diurnal rhythmicity in prolactin response to thyrotropin-releasing hormone was absent in such patients. The data, analysed by single cosinor procedure, showed absence of rhythmicity in all five parameters. Analysis of variance also showed no significant difference in these parameters at various time points. Knowledge of the alterations in circadian biology subsequent to cervical spinal cord trauma would provide useful guidelines towards chronotherapy and vocational rehabilitation of tetraplegics besides possible restoration of euchronism by pharmacological means.

Key words : circadian rhythm

tetraplegia

INTRODUCTION

Approximately, 33,480 individuals sustain spinal cord injury every year in India. 84.7% of them belong to the poor socio-economic status with monthly income of less than one hundred rupees (10). It, therefore, becomes important and relevant to undertake studies towards improving their immediate survival and long term rehabilitation.

Whereas prolactin response to thyrotropin releasing hormone shows diurnal rhythmicity in healthy subjects, it was absent in traumatic tetraplegics (12). Knowledge of the alterations in biological rhythms would provide useful guidelines towards deciding the optimal time for therapeutic procedures and drug dosage schedules so that maximum therapeutic benefit is achieved with least side effects (5). Further, alteration in circadian biology has been shown to influence the adaptive capacity of a person as evidenced in physical training

ability, learning ability, as well as long term vigilance (6). Thus, rehabilitation of spinal cord injured may be improved by a proper understanding of the changes that occur in circadian biology subsequent to spinal cord trauma. Derangement in circadian rhythmicity, when experimentally induced by external stress, has been shown to cause duodenal ulcer and asthmatic attacks (14). When prolonged, it may even decrease the life span as shown in experimental studies (11). Therefore, a study was undertaken to investigate the circadian biology in traumatic tetraplegics soon after their admission to the emergency ward of Postgraduate Institute of Medical Education and Research, Chandigarh

MATERIAL AND METHODS

Eight male patients with acute cervical spinal cord injury participated in this study within 72 hours of trauma. It was ensured that they did not receive any drugs such as phenobarbitone which could interfere with circadian rhythmicity. None of the patients suffered from any infective episode before or during the period of the study. The following parameters were recorded every four hours beginning from 01-30 h for 24 hours. Pulse rate was recorded by counting radial pulse for one minute. Systolic and diastolic blood pressure were recorded with sphygmomanometer. Rectal temperature was recorded with a clinical thermometer sensitive to 0.1°C. Urine output was recorded every four hours through an indwelling urethral catheter. No fluid restriction was imposed on these subjects. The data were analysed by a single cosinor procedure (9) on DEC 2050 and by analysis of variance. Single cosinor procedure uses the cosine function $f(t) = M + A \cos(Wt + \phi)$ with $f(t)$ the value at the time of the function defined by parameters M (mesor=value about which oscillation occurs), A (amplitude=half the difference between the highest and lowest values), w (angular frequency=degree/unit time with 360° representing a complete cycle) and ϕ (acrophase=timing of highest point, in degrees). The parameters M , A and ϕ are estimated by the method of least squares under the null hypothesis $A=0$, the statistic $\frac{nA}{\sqrt{48^2}}$ is distributed as F with 2 and $(n-3)$ degrees of freedom where $\delta^2 = \frac{\text{Residual sum of squares}}{(n-3)}$. A is an estimate of the amplitude A , and n is the number of observations on a patient.

All these patients were hospitalised in the emergency ward. The lights were not switched off during night. The noise level was high. Seriously ill patients were being admitted during night. Less serious patients were being transferred to other wards. Medical, surgical and nursing interventions (e.g. venous cut down, abdominal tapping, etc.) were being carried out on adjacent patients. Death of an adjacent patient was a common occurrence. Some neighbouring patients were often on ventilatory support. Various teams of doctors used to examine and discuss the management of many trauma victims admitted to this ward during night.

'Control' subjects could not be included because the 'Control' patients in emergency ward were either awaiting an operation or had already undergone a surgical procedure. Some others suffered from acute blood loss, an infective episode or acute renal failure.

RESULTS

Single cosinor procedure showed absence of rhythmicity in pulse rate, systolic and diastolic blood pressure, rectal temperature and urine output (Tables I, II, III, IV and V).

TABLE I : Clinical data and analysis of pulse rate (beats/min.) by single cosinor procedure.

Case No.	Age	Level of lesion	Time						F
			01.30h	05.30h	09.30h	13.30h	17.30h	21.30h	
1	40	C/5-6	105	110	108	100	115	105	0.1483*
2	50	C/5-6	62	62	60	62	60	60	0.1999*
3	65	C/6	90	92	90	92	88	90	0.2571*
4	21	C/4-5	78	76	76	80	78	80	0.3182*
5	28	C/5-6	45	45	45	48	46	48	0.2981*
6	20	C/6	93	93	93	96	92	96	0.1062*
7	17	C/5-6	51	50	50	52	50	50	0.1111*
8	35	C/4-5	110	110	110	110	108	106	0.3333*
Mean		79.25	79.25	79.0	80.0	79.62	79.62	79.37	0.3223*

*P > 0.05

TABLE II : Analysis of systolic pressure (mm Hg) by single cosinor procedure.

S/ No.	Time						F
	01.30h	05.30h	09.30h	13.30h	17.30h	21.30h	
1	140	140	130	140	130	140	0.2143*
2	122	120	128	120	120	118	0.2890*
3	136	130	140	136	130	130	0.2613*
4	120	120	120	120	118	118	0.3461*
5	100.05**	100	100	100	100	100	0.0000*
6	100	104	100	100	104	100	0.0000*
7	110	110	110	110	110	100	0.2727*
8	110	120	116	120	120	110	0.3101*
Mean	117.25	118.0	118.0	118.25	116.50	114.50	0.3464*

*P > 0.05

**For validity of application of single cosinor procedure, this value was taken as 100.05 instead of 100.

TABLE III : Analysis of diastolic pressure (mm Hg) by single cosinor procedure.

Sl. No.	Time						F
	01.30h	05.30h	09.30h	13.30h	17.30h	21.30h	
1	80	86	76	80	70	88	0.2453*
2	80	80	82	80	80	78	0.3333*
3	74	70	70	70	70	70	0.2727*
4	50	48	46	50	50	50	0.3333*
5	80	84	80	80	80	76	0.3000*
6	78	80	76	80	80	80	0.2308*
7	74	70	70	70	72	70	0.2307*
8	76	80	80	80	80	76	0.3461*
Mean	74.00	74.75	72.50	73.75	72.75	73.50	0.2656*

*P > 0.05

TABLE IV : Analysis of rectal temperature (in celsius) by single cosinor procedure.

Sl. No.	Time						F
	0130	05.30	09.30	13.30	17.30	21.30	
1	37.90	38.00	37.80	37.80	37.80	38.40	0.2868*
2	36.80	36.80	36.80	36.90	36.80	36.60	0.2957*
3	38.20	38.20	38.20	38.20	38.20	38.30	0.272*
4	38.10	38.10	38.20	38.00	38.30	38.20	0.1764*
5	37.80	37.70	37.80	37.80	38.00	37.80	0.3253*
6	37.30	37.30	37.30	37.60	37.60	37.40	0.3605*
7	36.50	36.40	36.40	36.50	36.50	36.40	0.1999*
8	37.50	37.80	37.60	37.80	37.60	37.50	0.2901*
Mean	37.51	37.53	37.52	37.57	37.60	37.57	0.2725*

* P > 0.05

TABLE V : Analysis of urine output (ml/hr) by single cosinor procedure.

Sl. No.	Time						F
	01.30h	05.30	09.30h	13.30h	17.30h	21.30h	
1	50	38	75	63	63	41	0.3213*
2	100	100	150	165	88	100	0.3304*
3	100	130	88	88	70	75	0.3552*
4	63	100	88	75	75	88	0.1773*
5	88	100	75	75	88	83	0.2738*
6	75	113	53	68	88	93	0.2198*
7	75	88	93	105	78	78	0.3485*
8	85	100	88	65	95	85	0.2017*
Mean	79.5	94.0	88.75	88.0	80.62	80.47	0.3310*

*P > 0.05

The least square fitting of cosine function to observations of rectal temperature is given in Fig.1. While recording the above physiological parameters, it was observed that these patients also exhibited disturbed sleep pattern. They slept for short spells of about 45 min. both during day and night. Analysis of variance showed no significant variation in each of these parameters at various time points (Table VI).

TABLE VI : Result of analysis of variance.

	F(d.f. = 5,35)	P
Pulse rate	0.1818	>0.05
Systolic pressure	0.8669	>0.05
Diastolic pressure	0.6287	>0.05
Rectal temperature	0.5355	>0.05
Urine output	1.039	>0.05

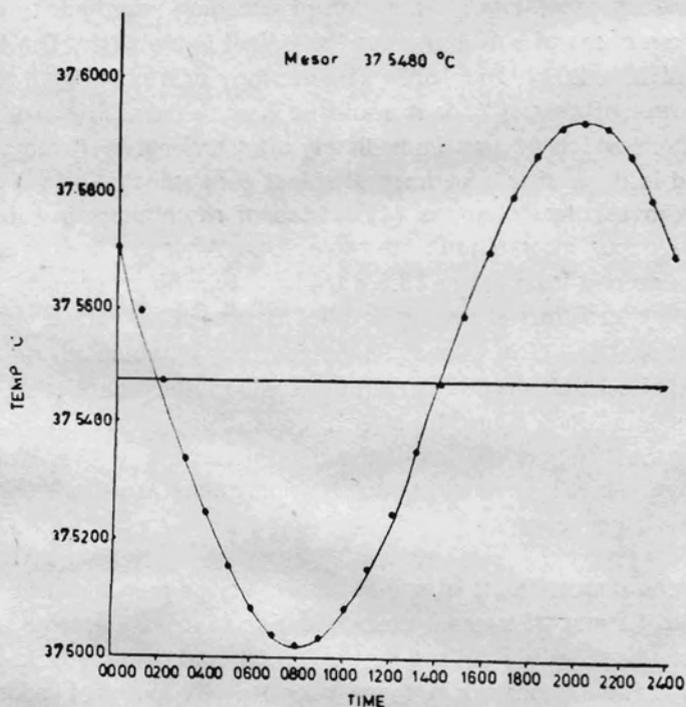


Fig. 1 : Best fitting cosine curve by least square method to 4 hourly data of observations (rectal temperature) M=37.548°C, Amplitude (A)=0.046, Acrophase (ϕ)=-299.91

DISCUSSION

Circadian rhythmicity in normal human beings has been described in pulse rate, blood pressure (13), rectal temperature, and urine output (2). This investigation shows absence of such circadian rhythmicity in these parameters in eight cases of cervical spinal cord injury. The constant phase relationship and identical periods of circadian rhythm of several diverse physiological variables monitored simultaneously is known as internal synchronization. However, when the different rhythms oscillate with independent frequency or free run due to either a change in internal environment, or external stress, a state of internal desynchronization is said to exist. This may be a steady state with mutual phase shift between the different rhythms of more than 360° . When it is a transient behaviour and not a steady state and the mutual phase shift between different rhythms is not more than 360° , the term 'internal dissociation' is used (16).

Circadian desynchronization observed in traumatic tetraplegics may be caused by loss of circadian periodicities in the hormonal and nervous mediating systems, coupling the various spontaneous oscillators. Alteration in circadian rhythmicity in heart rate was demonstrated in three cases of sub-acute cervical spinal injury (3). The heart rate showed a variable rhythm of 20h, 20.5h and 15h. The etiology was postulated to be interruption of sympathetic control of heart (3) or it could be due to excessive and disorderly activity of sympathetic system which occurs immediately after trauma. Altered sympathetic activity was also noted in dogs after experimental spinal cord transection which in turn resulted in marked cardiovascular changes (4). Loss of rhythmicity in melatonin excretion has been found to occur in traumatic tetraplegics. After cervical spinal cord trauma, melatonin excretion ranged from 3.2 to 13.5 ng/4 hr in waking state and 1.8 to 10.5 ng/4 hr during sleep and darkness thus showing significant absence of normal nocturnal increase in melatonin excretion (8). The mammalian pineal body which is regulated at least in part, by the activity of central nervous system via sympathetic connection, is decentralised following cervical spinal cord injury by interruptions of the descending sympathetic fibers. Since pineal body probably acts as one of the biologic clocks with melatonin as its modulator (8), loss of rhythmicity in melatonin excretion may also lead to disturbance of rhythmicity in other physiologic variables.

Apart from the direct effects of spinal cord injury as mentioned above, other factors such as psychological stress of trauma, hospitalisation in a busy emergency ward, and alterations in rest-activity schedule subsequent to spinal cord injury could contribute to the internal desynchronization observed in these patients. A study of adrenal hormones in seven normal girls admitted to a hospital showed loss of rhythmicity in plasma 17-OHCS during the first week of hospitalisation (2). The light-dark cycle is a very important zeitgeber in normal physiology. The altered environment in the emergency ward together

with factors such as psychological stress of trauma probably contributed to the disturbed sleep pattern in these patients who slept for short spells of about 45 min, both during day and night. Such disturbances in zeitgeber and social cues may at least be partly responsible for the results observed in this study.

Although the circadian rhythm of heart rate was found to be restored in four cases of chronic spinal cord injury (3), the diurnal variation in urinary bladder response to terfenadine was found to be absent in patients with chronic neurogenic vesical dysfunction (15). Thus it is possible that such circadian desynchronization as observed in this study may persist for a long duration in at least some cases. Therefore, these patients should be studied continuously from the onset of trauma for a long period as in human isolation experiments.

If internal desynchronization was found to be present in a given case, drug dosage schedule will have to be suitably modified and so also institution of various therapeutic procedures. Should the elevated plasma beta-endorphin level in traumatic tetraplegics (7) be a triggering agent for circadian desynchronization, therapeutic measures with drugs such as naloxone, or thyrotropin-releasing hormone might help in restoring the normal circadian rhythmicity by decreasing the elevated levels of neuropeptides. In chronic tetraplegics, persistence of internal desynchronization would warrant appropriate modification in work schedule while planning their rehabilitation. Since human performance deteriorates in the state of internal desynchronization (18), the effect of circadian disorganization on vigilance parameters such as acoustical reaction time, and daily course of error frequency will have to be defined, as these dominate the circadian pattern of performance. Further, the host response to infection also may follow a circadian rhythmicity parallel to the rhythmicity in the number of peripheral blood cells (17). It is possible that the altered host response to infection induced by internal desynchronization may be one of the causes for the high incidence of pulmonary infection in these patients which perhaps takes a major toll of traumatic tetraplegics.

ACKNOWLEDGEMENTS

Our gratitude to the Department of Atomic Energy, Government of India for the valuable help rendered.

REFERENCES

1. Aschoff, J., V. Gareche and R.A. Wever. Desynchronization of human circadian rhythms. *Jpn. J. Physiol.*, **17** : 450, 1967.
2. Barter, F.C. and C.S. Delea. A map of blood and urinary changes related to circadian variation in adrenal cortical function in normal subjects. *Ann. N.Y. Acad. Sci.*, **9** : 969, 1962.
3. Christ, J.E. An analysis of circadian rhythmicity of heart rate in tetraplegic human subjects. *Paraplegia*, **17** : 257, 1979.

4. Greenhart, J.H. and H.P. Mauck. The effect of cervical cord injury on cardiac rhythm and conduction. *Am. Heart. J.*, **83** : 659, 1972.
5. Halberg, F., E. Haus, S.S. Cardoso, L.E. Scheving, J.F.W. Kuhl, R. Shiosuka, G. Rosene, J.E. Pauly, W. Runge, J.F. Spalding, J.K. Lee and R.A. Good. Towards chronotherapy of neoplasia : Tolerance of treatment depends on host rhythm. *Experientia*, **29** : 909, 1973.
6. Hildebrandt, G. and H. Stempel. Chronobiological problems of performance and adaptational capacity. In : Proceedings of XII International Conference of International Society of Chronobiology (The Publishing House, Il Ponte) p. 103, 1977.
7. Khanduja, K.L., C.M. Pathak, B. Suryaprakash, A.K. Goel, S. Vaidyanathan, M.S. Rao and P.L. Sharma. Beta-endorphin response to thyrotropin releasing hormone in the spinal cord injured. *IRCS Med. Sci.*, **12** : 404, 1984.
8. Kneisley, L.W., M.A. Moskositz and H.G. Lynch. Cervical cord lesions disrupt the rhythm in human melatonin excretion. *J. Neural. Transm.*, **13** : 311, 1978.
9. Nelson, W., Y.L. Tong, J.K. Lee and F. Halberg. Methods for cosinor rhythmometry. *Chronobiologia*, **6** : 305, 1979.
10. Rama Rao, W.G. Needs of a paraplegic in developing countries. *Paraplegia*, **17** : 414, 1979.
11. Saint Paul, U. Von and J. Aschoff. Longevity among blowflies *Phormia terraenovae* R.D. kept in non-24-hour light dark cycle. *J. Comp. Physiol.*, **127A** : 191, 1978.
12. Sialy, R., K. Rao, B. Suryaprakash, S. Vaidyanathan, M.S. Rao, P.L. Sharma and P.T. Mahapatra. prolactin response to thyrotropin releasing hormone in traumatic tetraplegics, during the spinal shock phase. *IRCS Med. Sci.*, **11** : 944, 1983.
13. Smolensky, M.H., S.E. Tatar, S.A. Bergman, J.G. Losman, C.N. Barnard, C.C. Dasco and T.A. Kraft. Circadian rhythmic aspects of human cardiovascular function : A review by chronobiologic statistical method. *Chronobiologia*, **3** : 337, 1976.
14. Stroebel, C.F. Biologic rhythm correlates of disturbed behaviour in the rhesus monkey. *Bibl. Primatol.*, **9** : 91, 1969.
15. Vaidyanathan, S., M.S. Rao, P.L. Sharma, B. Suryaprakash and K. Rao. Does diurnal rhythmicity in detrusor responses to terfenadine persist in patients with chronic neurogenic vesical dysfunction? *IRCS Med. Sci.*, **11** : 783, 1983.
16. Wever, R.A. The circadian system of man : Results of experiments under a temporal isolation. 1st Ed, Schaefer, K.E. Ed. (Springer-Verlag, New York) p. 62, 1979.
17. Williams, R.M., C.J. Kraus, M. Inbar, D.P. Dubey, E.J. Tunis and F. Halberg. Circadian bioperiodicity of natural killer cell activity in human blood (individually assessed) In : Chronopharmacology and chronotherapeutics. 1st Ed. Walker, C.A., Winget, C.M. and Soliman, Eds. (Florida A & M University Foundation, Tallahassee) p. 269, 1981.
18. Winget, C.M. Circadian rhythms in human subjects. *Chronobiologia*, **2** : (Suppl. 1) : 78, 1975.