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Skin temperature and heart rate rhythms in infants of extreme prematurity

S W D'Souza, S Tenreiro, D Minors, M L Chiswick, D G Sims, J Waterhouse

Abstract

Nine preterm infants of 26 to 29 weeks' gestational age and 792 to 1200 g birth weight spent six to 17 weeks in our neonatal medical unit. Hourly recordings of skin temperature and heart rate were carried out. The first five to 15 weeks were spent in the intensive care ward, in continuous light, due to various medical conditions. After recovery they were moved to a nursery for one to nine weeks, with 12 hourly periods of light and darkness. Four infants developed circadian rhythms in temperature and three in heart rate in light-dark periods, the remainder failing to do so. Some infants take longer than others to develop circadian rhythms but the reasons for this are not clear. It is suggested that earlier exposure to a light-dark environment may synchronise the 'body clock' to a 24 hour period in more preterm infants.

In human fetuses circadian rhythms have been reported in heart rate, breathing movements, and motility.[1 2] There is some uncertainty, however, about whether such rhythms are imposed by the maternal environment or are due to the development of the fetal nervous system including the 'body clock'. A weak effect only from the body clock is inferred from the observation that the suprachiasmatic nuclei (the presumed site of the body clock in adults) are poorly developed histologically,[3] and that neonates have poorly developed circadian rhythms.[4] The direct imposition of rhythmicity on the fetus from the maternal environment is suggested by the observation that maternal and fetal rhythms appear to be phase locked.[1 2]

Two recent studies suggest a role for external rhythmicity in preterm infants nursed in intensive care units.[4 5] First, preterm infants appear to benefit from exposure to alternating periods of light and darkness in an intensive care unit.[5] Subsequent to leaving hospital they slept for longer periods and spent less time feeding but showed better weight gain than a control group exposed to continuous lighting after they had received intensive care. Second, in preterm infants nursed in an enviroment with day or night time cues comparable with those in term infants, circadian sleep-wake rhythms were observed at an earlier postconceptional age in those born preterm.[4]

In our neonatal medical unit we have investigated the development of rhythmic changes in heart rate and skin temperature in infants of extreme prematurity who had been with us for prolonged periods. In particular, we have investigated if the imposition of a rhythm of light and darkness produces a direct effect upon the infants with higher heart rates and skin temperatures in the light phase and lower values in the dark as occurs in infants who are diurnally active and sleep at night.[5] In this observational study we deliberately chose not to manipulate the light-dark environment in which the infants were nursed. Instead, we wished to examine the extent to which circadian rhythms develop naturally among very preterm infants who had prolonged neonatal illnesses requiring intensive care, and who, after recovery, were transferred to a special care nursery where it was the policy to dim the lighting during the night.

Subjects and methods

INFANTS

Nine preterm infants of 26 to 29 weeks' gestational age born between January 1989 and December 1990 had spent six to 17 weeks in our neonatal medical unit (table 1). These were the infants who had continuous measurements (at one hourly intervals) of heart rate and skin temperature for a prolonged period covering the time they were nursed in continuous light-light and subsequently in a light-dark environment. Initially all were admitted to the intensive care ward and nursed in incubators. Continuous recordings of skin temperature and heart rate were carried out using skin electrodes which were attached to a monitor (Hewlett-Packard). For skin temperature measurement the electrode was applied to the anterior abdominal wall. The heart rate and electrocardiogram were obtained simultaneously from electrocardiogram skin electrodes applied to the right and left chest wall and the right lower limb. The nursing staff entered the heart rate and skin temperature at hourly intervals on charts and data from these charts were used in the analysis. Medical and nursing care were provided as required including ventilatory support, phototherapy, antibiotics, and infusions of solutions containing electrolytes, glucose, and lipids for nutrition. Arterial, venous, or capillary blood samples were taken when indicated for clinical investigations. Parents visited their infants and handled them whenever possible. Nasogastric tube feeds at one hourly intervals were started when the infant's condition had improved. Ward lighting (of the order of 1300 lux) was continuous during this period. The duration each infant spent on this ward is shown in table 1.

After recovery from their acute medical conditions the infants were transferred to an

Department of Child Health, St Mary's Hospital, Hathersage Road, Manchester M13 0JH
S W D'Souza

Department of Physiological Sciences, University of Manchester
S Tenreiro
D Minors
J Waterhouse

Neonatal Medical Unit, St Mary's Hospital, Manchester
M L Chiswick
D G Sims

Correspondence to:
Dr D'Souza.

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Table 1 Details of infants studied

	Case No								
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Delivery	Breech, vaginal	Cephalic, vaginal	Cephalic, vaginal	Cephalic, vaginal	Cephalic, vaginal	Cephalic, vaginal	Cephalic, vaginal	Caesarean section	Cephalic, vaginal
Apgar scores:									
1 min	3	7	6	6	2	2	6	6	3
5 min	3	9	3	8	2	2	8	8	9
Gestational age (weeks)	26	26	26	26	27	28	28	29	28
Birth weight (g)	1032	957	800	792	800	1200	1100	1001	957
Neonatal conditions:									
IRDS	+	+	+	+	+	+	+	+	
Pneumonia		+					+		
Pneumothorax	+				+	+		+	
Jaundice	+	+	+	+		+		+	+
Sepsis	+	+	+	+	+	+	+	+	+
IVH only								+	
IVH with dilated ventricles	+		+			+	+		
IVH with parenchymal extension			+						
IVH with periventricular cysts (leuco-malacia)		+							
Retinopathy	+	+	+		+				
Chronic lung disease	+	+	+	+		+	+	+	
Preterm bone disease			+	+					
Patent ductus arteriosus			+						+
Duration in intensive care ward (weeks)	9	13	6	9	15	13	9	5	5
Duration in nursery (weeks)	8	4	9	2	2	1	1	2	1

IRDS=idiopathic respiratory disease, IVH=intraventricular haemorrhage.
+=Condition present.

adjacent nursery where they spent a variable amount of time (table 1). They were fed at intervals of two, three, or four hours with milk by a nasogastric tube, as larger milk volumes were accepted (200–250 ml/kg/day); bottle feeds were offered subsequently. Visiting by parents was continued. While in the nursery the infants were nursed in a light-dark environment—that is, the light was dimed (20 lux) during the night (2000–0800 hours) and visitors and staff were urged to make less noise. For the rest of the time, the light was maintained at a higher level (180 to 300 lux) and there was also a higher level of general activity in the nursery.

ANALYSIS OF DATA

An effect of the light-dark cycle either direct or through synchronisation of the body clock would produce significantly higher mean heart rates and skin temperatures during the light as compared with the dark phase. We have, therefore, compared the skin temperature and heart rate values obtained in the last week in light-light with those obtained during the one or more weeks that each baby spent in light-dark. For statistical purposes, we have proceeded as follows.

For each day that a baby spent in light-dark we have calculated the mean value obtained in the light (hourly values from 0900–2000 hours) and the mean value in the dark (hourly values from midnight to 0800 and 2100–2300 hours). Dividing the results into weekly blocks then enabled us to compare the seven mean light and dark values (Student's paired t test, df=6). For comparison we have used the seven last days spent in light–light, calculating for each day the mean of the values obtained between 0900 and 2000 hours and the mean of the 12 values at the other times, and then comparing these seven means, again by paired t tests. For illustrative purposes we have divided the results into weekly blocks to calculate for each hour the mean value from the seven days.

Results

The statistical summary is given in table 2.

For skin temperature, the only significant difference between 'daytime' (0900–2000 hours) and 'night time') values in the last week in light–light was in case 2 where the night time values were *higher*. When placed in the light–dark environment three babies showed some response during the first week (cases 6, 8, 9), five babies showed no response (cases 1, 3, 4, 5, 7), and case 2 showed a delayed response. This last baby is particularly remarkable as the rhythm was initially inverted (daytime values lower than night time), as in light–light, and became phased as predicted (daytime values higher) only by week 3 in light–dark. Examples of this 'delayed responder' (fig 1), 'immediate responders' (figs 2, 3) and 'non-responder' (fig 4) are illustrated for cases 2, 9, 6, and 5 respectively.

For heart rate, three babies showed night time values higher than daytime in the last week in light–light (cases 2, 3, and 8). In light–dark again there were non-responders (cases 1, 3, 4, 7, 8, and 9), an immediate responder (case 6), and delayed responders (case 2 and 5). Figure 5 illustrates the immediate response of case 6.

Table 2 Mean difference (n=7 days) between average of 0900–2000 values and 2100–0800 values in heart rate and skin temperature

Case No		Skin temperature				Heart rate				First light–dark (weeks)	
		Last light-light	Light-dark			Last light-light	Light-dark			Postnatal age	Postconceptional age
			1	2	3		1	2	3		
1	Mean	−0·139	−0·183	+0·080	−0·139	+1·129	+0·114	+0·171	+0·529		
	SE	0·078	0·109	0·108	0·064	2·913	3·164	2·365	2·580	10	36
	p Value										
2	Mean	−0·261	−0·210	−0·081	+0·129	−6·528	−3·786	−1·614	+4·543		
	SE	0·132	0·089	0·075	0·057	3·357	1·661	1·064	1·328	14	40
	p Value	*	*		*	*	*		**		
3	Mean	−0·077	−0·099	−0·170	+0·103	−3·986	−4·271	−2·457	−4·857		
	SE	0·100	0·078	0·093	0·098	1·841	2·655	1·969	0·848	7	33
	p Value					*			**		
4	Mean	+0·033	−0·120	−0·144		−0·486	−5·743	+2·300			
	SE	0·072	0·070	0·098		2·324	2·591	2·244		10	36
	p Value						*				
5	Mean	+0·123	+0·047	+0·050		+4·929	+1·000	+5·514			
	SE	0·208	0·133	0·070		3·891	1·890	2·081		16	43
	p Value							**			
6	Mean	+0·041	+0·497			+0·357	+7·943				
	SE	0·106	0·100			1·524	2·276			14	42
	p Value		**				**				
7	Mean	−0·003	+0·100			−0·900	+1·400				
	SE	0·088	0·145			1·622	2·933			10	38
	p Value										
8	Mean	+0·080	+0·139	−0·131		−5·443	−0·943	−2·214			
	SE	0·082	0·060	0·093		1·977	3·240	1·398		6	35
	p Value		*			**					
9	Mean	−0·020	+0·266			+1·429	+2·743				
	SE	0·160	0·069			3·164	1·995			6	34
	p Value		**								

*p<0·05; **=p<0·02.

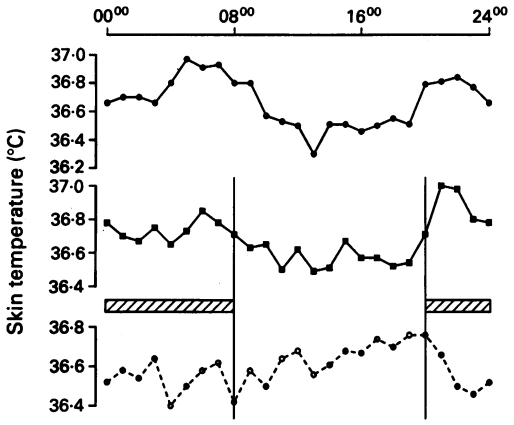

Figure 1 Mean hourly values of skin temperature in case 2 during the last week of light–light (●, upper), first week of light–dark (■, middle), or third week of light–dark (○, lower). Shaded area indicates when lights dimmed during weeks of light–dark, vertical lines separate light and dark phases.

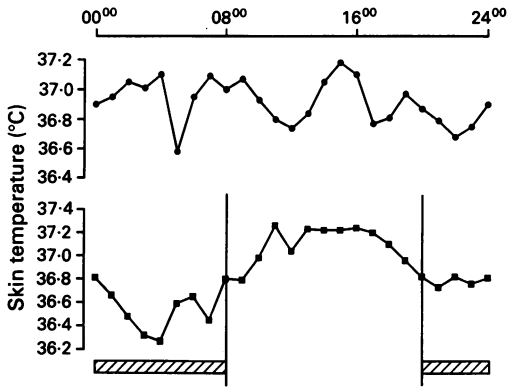

Figure 3 Mean hourly values of skin temperature in case 6 during the last week of light–light (●) or first week of light–dark (■). Shaded area indicates when lights dimmed during weeks of light–dark, vertical lines separate light and dark phases.

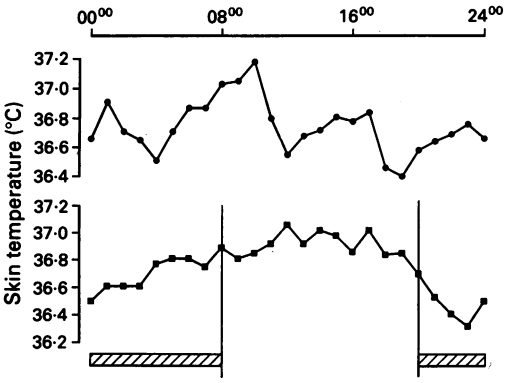

Figure 2 Mean hourly values of skin temperature in case 9 during the last week of light–light (●) or first week of light–dark (■). Shaded area indicates when lights dimmed during weeks of light–dark, vertical lines separate light and dark phases.

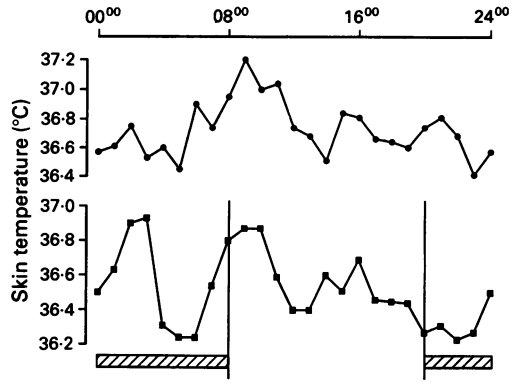

Figure 4 Mean hourly values of skin temperature in case 5 during the last week of light–light (●) or first week of light–dark (■). Shaded area indicates when lights dimmed during weeks of light–dark, vertical lines separate light and dark phases.

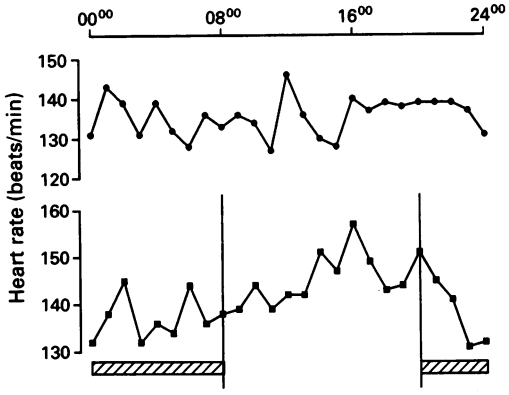

Figure 5 Mean hourly values of heart rate in case 6 during the last week of light–light (●) or first week of light–dark (■). Shaded area indicates when lights dimmed during weeks of light–dark, vertical lines separate light and dark phases.

The effect, or lack of it, upon heart rate of placing the babies in the light–dark environment was similar to that upon skin temperature in most cases, but different in babies 5, 8, and 9 as regards statistical significance.

The infants who had developed circadian rhythms did not seem to differ systematically from those who had not with respect to mode of delivery, Apgar scores, gestational age, birth weight, neonatal conditions, duration spent in the intensive care ward or postconceptional age (table 1). The extent to which a neurological insult will delay the development and entrainment of circadian rhythms is not clear. It is worthy of note that three of four infants who developed circadian rhythms in skin temperature and heart rate in a light–dark environment had a history of periventricular cysts (leucomalacia) or an intraventricular haemorrhage (cases 2, 6, 8; table 1). In the remaining five infants who did not develop circadian rhythms (non-responders) three had a history of intraventricular haemorrhage with dilated ventricles (cases 1, 3, 7). As these infants were not studied after leaving hospital it is not possible to say how long it took the non-responders to develop circadian rhythms.

Discussion

In preterm infants of less than 30 weeks' gestational age the postnatal onset of circadian rhythms in heart rate and skin temperature has shown considerable variability. In a third of our infants circadian rhythms were observed in the first week or so in light–dark while in the remaining two thirds none was detected during this time span. In a previous study Mirmiran *et al* investigated nine infants of 26 to 32 weeks' gestational age in whom circadian rhythms of rectal temperature were reported in five infants at postconceptional ages of 28 to 34 weeks, during a one to three day period of nursing in a light–dark environment.[6] Their group of infants were unusual in having remarkably few neonatal medical conditions which are known to occur in infants of extreme prematurity, including those mentioned in table 1. This raises the possibility that such medical conditions may have contributed to the delayed onset of circadian rhythms in our infants.

We defined appropriately phased circadian rhythms in skin temperatures and heart rates in our infants as those in which the mean values of the measurements carried out were significantly higher in light than in darkness. This is in keeping with observations which are well known in adults.[7] Mirmiran *et al* in their study reported circadian rhythms but with maximal rectal temperatures in periods of darkness rather than in light as was found for heart rate for case 3 in our study.[6] Another of our infants (case 2) showed a similar rhythm but for a transient period only while the infant was in light–light and the first two weeks in a light–dark environment. We suggest that this might represent a 'free running' rhythm that occurs in some infants until light–dark cycles or social cues from feeding or handling them act as external time cues (zeitgebers) to synchronise the endogenous pacemaker (body clock) to a 24 hour period.[7]

The earliest observation of an appropriately phased circadian rhythm in heart rate or skin temperature in our infants, suggesting that the body clock was synchronised, was at a postconceptional age of 34 weeks. By contrast diurnal variations in fetal heart rate have been reported as early as 20 to 22 weeks' gestation.[2] It may be that the fetus is affected by maternal influences (hormonal, temperature, or blood supply).[2] A direct effect of light–dark cycles in utero is unlikely and even full term infants do not always respond to a similar influence shortly after birth.[4] In our infants exposure to light–dark cycles took place after recovery from their medical conditions when they may have been more active in the daytime, the staff and parents would handle them more frequently and noise levels tended to be higher in the nursery. These associated events provide further environmental cues which may contribute to the development of circadian rhythms in light–dark periods.[7] The tendency for rhythms in skin temperature and heart rate to develop at a similar age, observed here and in other studies,[7] would be predicted as they both change with behavioural responses to the environment.

It has been suggested that a single caregiver (the mother) may convey circadian information to a newborn infant by either her pattern of behaviour or feeding routine.[4] In our nursery each infant would have been handled by various nurses and doctors when fed, given a bath or medically examined. In addition, they would have been handled by parents during a visit. By contrast while at home the mother would have had an overall role in handling the infant. However, it is not clear to what extent infants can perceive or recognise those who handle them. If it is thought that the development of circadian rhythmicity, and its entrainment, is to some extent related to increased sensory input then there would be an argument for increasing diurnal handling of infants in a nursery.

In neonatal intensive care units survival rates of very low birthweight infants have improved in recent years, including those of less than 30

weeks' gestational age who appear to approach the edge of viability. As such infants usually remain in hospital for prolonged periods an optimal environment for neonatal intensive care that includes exposure to periods of light and darkness may lead to subsequent benefits in sleeping pattern and weight gain.[5] If the fetus were not born prematurely it would continue in a rhythmic environment in utero. After preterm birth nursing infants in a rhythmic environment may therefore have important implications for subsequent development.[5] Our findings suggest that for such infants the duration spent in the nursery in light–dark periods appears to be important for the entrainment of circadian rhythms. Hence, some consideration should be given for the earlier introduction of light–dark periods as the preterm infant like the developing fetus may be influenced by a rhythmic environment.[2 5] The appropriate time for doing this after the infant's condition has stabilised in the intensive care ward and the importance of light intensity which varies between ours and previous studies require further investigation.[4–6]

Observational studies, such as this, provide a range of uncontrolled factors such as varying duration of exposure to continuous lighting before nursing in a light–dark environment, and different illnesses in a group of extremely preterm babies of different gestational ages. These are precisely the circumstances which commonly occur in busy neonatal units. Our results show that, given these usual circumstances, some but not all infants are capable of developing circadian rhythms relatively early (within three weeks) of exposure to a light–dark environment.

These results provide some ethical justification for further studies of the effect of manipulating the light environment of extremely preterm babies during intensive care to assess whether circadian rhythms can be induced earlier.

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