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THE RATE AND DEPTH OF BREATHING IN NEW-BORN INFANTS IN DIFFERENT SLEEP STATES

BY M. K. S. HATHORN
From the Department of Physiology,
The London Hospital Medical College,
London E1 2AD

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SUMMARY

1. Ventilation was recorded on ten male and ten female healthy full-term infants during the first week after delivery, using a trunk plethysmograph. Tidal volume (V_T), respiration rate (f) and pulmonary ventilation ($\dot{V}$) for each respiratory cycle were measured during periods of rapid eye movement sleep (REM) and during quiet sleep when eye movements were absent (NREM).

2. It was found that mean instantaneous $\dot{V}$ and f were significantly higher in all infants during REM than during NREM sleep, while mean V_T was either unchanged or showed a decrease. In addition, there was significantly greater variation in instantaneous $\dot{V}$, V_T and f during REM as compared with NREM sleep.

3. Positive correlations were found in most infants in both sleep states between individual values of V_T and the duration of the respiratory cycle (T).

4. Periodic changes in T were found in all infants during both sleep states; these periodicities may reflect the behaviour of respiratory control mechanisms operating over a longer time span than the individual respiratory cycle.

INTRODUCTION

It has been shown by Prechtl, Akiyama, Zinkin & Grant (1968), amongst others, that respiration rate in healthy new-born infants is more rapid and more irregular during rapid eye movement sleep (REM) than in sleep when eye movements are absent (NREM). Prechtl & Lenard (1967) suggested that the eye movements and the irregular fluctuations in heart rate and respiration rate found in REM sleep may be the result of random noise in the C.N.S., caused by a lack of patterning due to inhibition of afferent input during this sleep state.

It was decided to measure ventilation in new-born infants during periods of NREM and REM sleep in order to elucidate differences in the rate and depth of breathing which might throw light on alterations in respiratory control in these two sleep states.

Some of these findings were presented at the Sir Joseph Barcroft Centenary Symposium on Foetal and Neonatal Physiology (Hathorn, 1973).

METHODS

Selection of infants. With their mothers' informed consent, new-born infants weighing over 2·5 kg were studied during the first week after birth; all had Apgar scores of 9 or 10 at 10 min after delivery. The ages, sexes and weights of the infants are shown in Table 1.

Measurement of ventilation. About 1 hr after the mid-morning feed, an oesophageal tube was introduced for monitoring intrathoracic pressure, and the infant was then placed in a trunk plethysmograph (Cross, 1949). There was no significant change in oesophageal pressure swings on inflation of the cuff of the plethysmograph (Cross & Lewis, 1971). Ventilation was measured by a pressure transducer connected to the plethysmograph, and was recorded directly by a pen-recorder, or on an FM tape-recorder for subsequent play-back. Routine checks were made for leaks and the plethysmograph was calibrated at the end of the recording session.

The sleep state was determined using the criteria of Prechtl & Beintema (1964) as follows: NREM sleep – eyes closed; no body movements apart from startles; short trains of spontaneous sucking. REM sleep – eyes closed, with rapid eye movements seen beneath the lids; frequent small movements of extremities; limb twitches and tremors common; frequent oral activity. In several trial infants, electro-oculograms were recorded using silver electrodes attached just above and below the eyes with collodion (Bolton & Herman, 1974). This procedure is potentially irritating to the baby's eyes, and in all the present infants, the occurrence of rapid eye movements was recorded with an event marker (Fig. 1) by the same observer closely watching the infant's eyes (Prechtl *et al.* 1968).

Selection of traces. Over a period of time, the records of ventilation showed the presence of deep sighs (Fig. 1) which occur at random intervals (Prechtl *et al.* 1968). In order to study the steady-state characteristics of ventilation in NREM and REM sleep, therefore, sections of tracings (Fig. 1) were selected from infants in whom (*a*) adjacent periods of NREM and REM sleep were recorded during the same session, (*b*) there were no sighs, startles or other movements, (*c*) there were no long-term changes in respiratory rate which would invalidate the criterion of a steady state. These requirements imposed severe limitations on the lengths of trace available for study: the shortest trace measured was one of eighty-six breaths (over a period of 132·6 sec), and the longest consisted of 271 breaths (lasting 273·8 sec). Traces satisfying these criteria were obtained from ten male and ten female infants.

Measurement of traces. The co-ordinates of the points of onset of inspiration and the onset of expiration in each respiratory cycle were measured from fixed volume and time axes; this procedure avoided the possibility of cumulative errors. The volumes of air breathed in (V_T), the times for inspiration (T_I) and expiration (T_E) and hence the total duration (T) for each respiratory cycle, were calculated from these co-ordinates and the volume and time calibrations. Instantaneous respiration rate (f) was calculated as $60/T$, to express it as a rate per min. Instantaneous pulmonary ventilation ($\dot{V}$) was the product of V_T and f. The results for each respiratory cycle were stored on computer cards, which served as the data for all subsequent analyses. The maximum, non-systematic errors found on remeasuring several traces were 0·2 ml. for V_T and 20 msec for T. All volumes were measured at b.t.p.s

Statistical methods. Means, standard deviations and errors, regression and correlation, and significance tests using these parameters, were performed according to Snedecor & Cochran (1967), and the Mann–Whitney U-test was carried out according to Siegal (1956). In the statistical analysis of the intervals between successive respiratory cycles, use was made of the methods of Cox & Lewis (1966), many of which are implemented in a computer programme (SASE IV) written by Lewis, Katcher & Weis (1969).

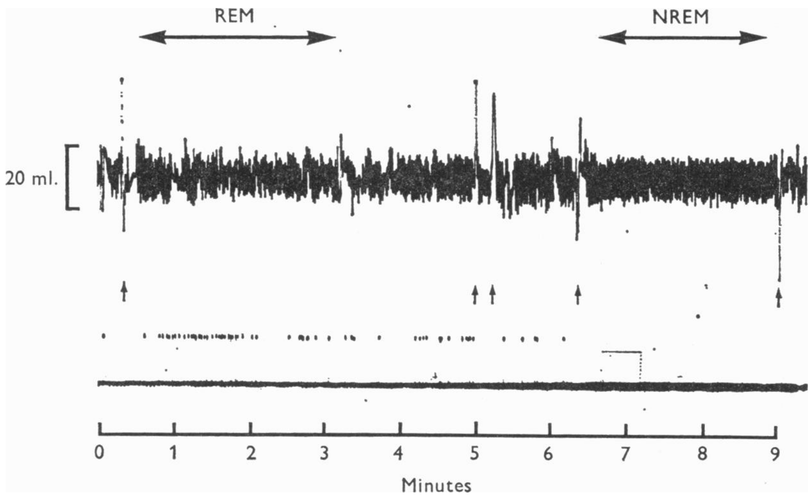

Fig. 1. Compressed section of trace showing record of ventilation (above) and rapid eye movements on the event marker (below). The vertical arrows (↑) indicate deep sighs, and the horizontal arrows show the portions of relatively regular ventilation measured for REM and NREM sleep in this infant.

Detection of long-term trends in ventilation. One of the objects of this study was to measure short-term variability in ventilation in the two sleep states. It was thus necessary to establish a criterion for 'steady state' in the traces of each sleep state selected for study, since any progressive or long-term change in the mean level of ventilation over a period of time would contribute disproportionately to the over-all variance.

The presence of a steady state was confirmed, firstly, by plotting the accumulated duration of respiratory cycles against the accumulated number of respiratory cycles, and secondly, by calculating the test statistic U (Cox & Lewis, 1966, p. 47) which compares the middle (centroid) respiratory interval with the mid point on the time axis (Fig. 2). If U was significant ($P < 0{\cdot}05$), the infant was not included in the series; the twenty infants included in this study showed no significant trend in mean values for cycle duration using this test.

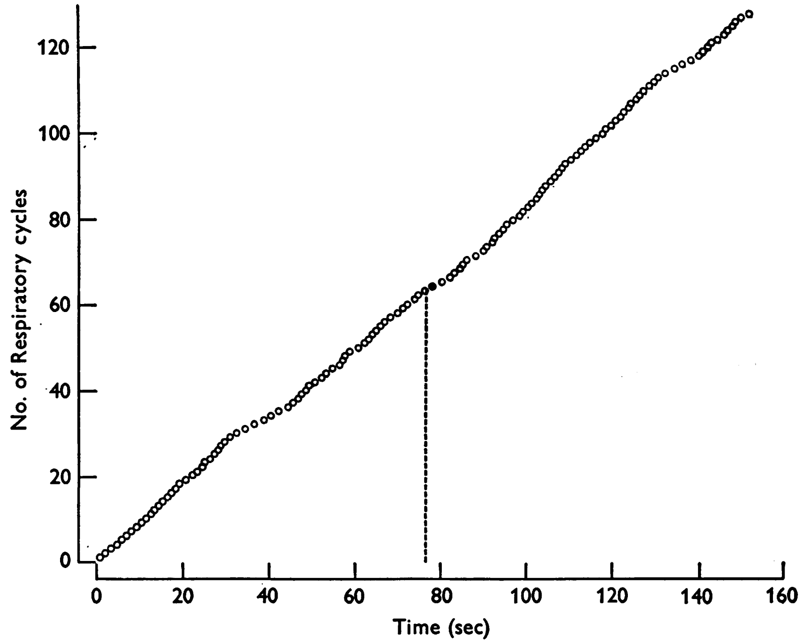

Fig. 2. Examination for a trend in the duration of the respiratory cycle (T) in Baby 44 during REM sleep by plotting the accumulated number of respiratory cycles against accumulated T (○). The test statistic $U = 0.068$ ($P > 0.05$) is based on the interval between the centroid interval (●) and the mid point of accumulated time (----).

RESULTS

Changes in V_T, f and $\dot{V}$ in the two sleep states

Means, variances and standard deviations for the above were calculated on a breath-by-breath basis. The variances of V_T, f and $\dot{V}$ were greater during REM than during NREM sleep in all twenty infants (Fisher's variance ratio test, $P < 0.01$) with the exception of V_T in Baby 59. This infant nevertheless showed a greater coefficient of variation for V_T in REM sleep (12·9 %) than in NREM sleep (8·9 %).

In addition to the increased overall variation in V_T, f and $\dot{V}$ found in REM as compared with NREM sleep, it was decided to look for short-term changes in variation of T during the time course of each trace. This was done by dividing each trace into consecutive sections, and calculating Bartlett's statistic for homogeneity of variance (Lewis *et al.* 1969). Significant changes in the variance of T ($P < 0.01$) in the course of each trace were found in ten of the infants during REM sleep and in only five during NREM sleep.

TABLE 1. Weights and ages of the infants studied, with mean values for V_T, f and $\dot{V}$ for n respiratory cycles in two sleep states

				NREM sleep				REM sleep			
Baby no.	Sex	Wt. (kg)	Hr after delivery	n	V_T (ml.)	f (min^{-1})	$\dot{V}$ (ml. min^{-1})	n	V_T (ml.)	f (min^{-1})	$\dot{V}$ (ml. min^{-1})
12	F	2·71	35	117	17·3	39·1	674	166	14·9	54·0	768
24	F	3·47	132	121	19·0	36·6	695	139	18·4	45·5	812
25	F	3·31	138	136	11·6	48·5	557	144	12·1	55·9	653
27	M	3·09	26	112	15·8	29·6	465	108	12·8	51·9	639
29	F	2·56	167	129	14·2	43·5	615	159	14·3	61·6	838
34	F	2·90	96	146	16·9	47·7	801	146	15·4	69·9	1052
42	M	3·36	115	99	13·9	41·2	573	146	12·7	53·9	685
44	M	3·17	101	95	15·4	35·8	551	128	15·4	54·6	814
45	F	3·16	62	139	16·0	43·3	691	104	14·6	71·5	1031
55	M	2·66	96	159	13·5	34·7	467	120	13·0	39·5	508
56	M	2·95	127	251	10·2	66·3	675	256	10·3	79·8	819
57	M	3·74	41	146	15·4	46·8	718	101	14·1	64·9	886
58	M	2·88	138	166	17·1	41·1	703	166	14·7	58·0	816
59	F	2·90	8	162	14·0	31·2	435	137	10·9	44·7	483
60	M	3·65	15	100	16·6	28·6	474	115	14·3	36·2	501
61	F	2·53	11	111	18·2	31·4	570	86	15·8	44·3	665
62	F	2·71	29	96	14·0	40·8	566	271	11·1	67·8	713
63	F	3·53	120	99	18·6	33·8	629	176	14·4	60·5	834
67	M	2·63	47	241	14·2	33·3	468	150	12·2	41·5	496
71	M	2·76	48	100	12·9	36·3	467	108	8·9	58·4	501
		Over-all means:			15·2	39·5	590		13·5	55·7	726

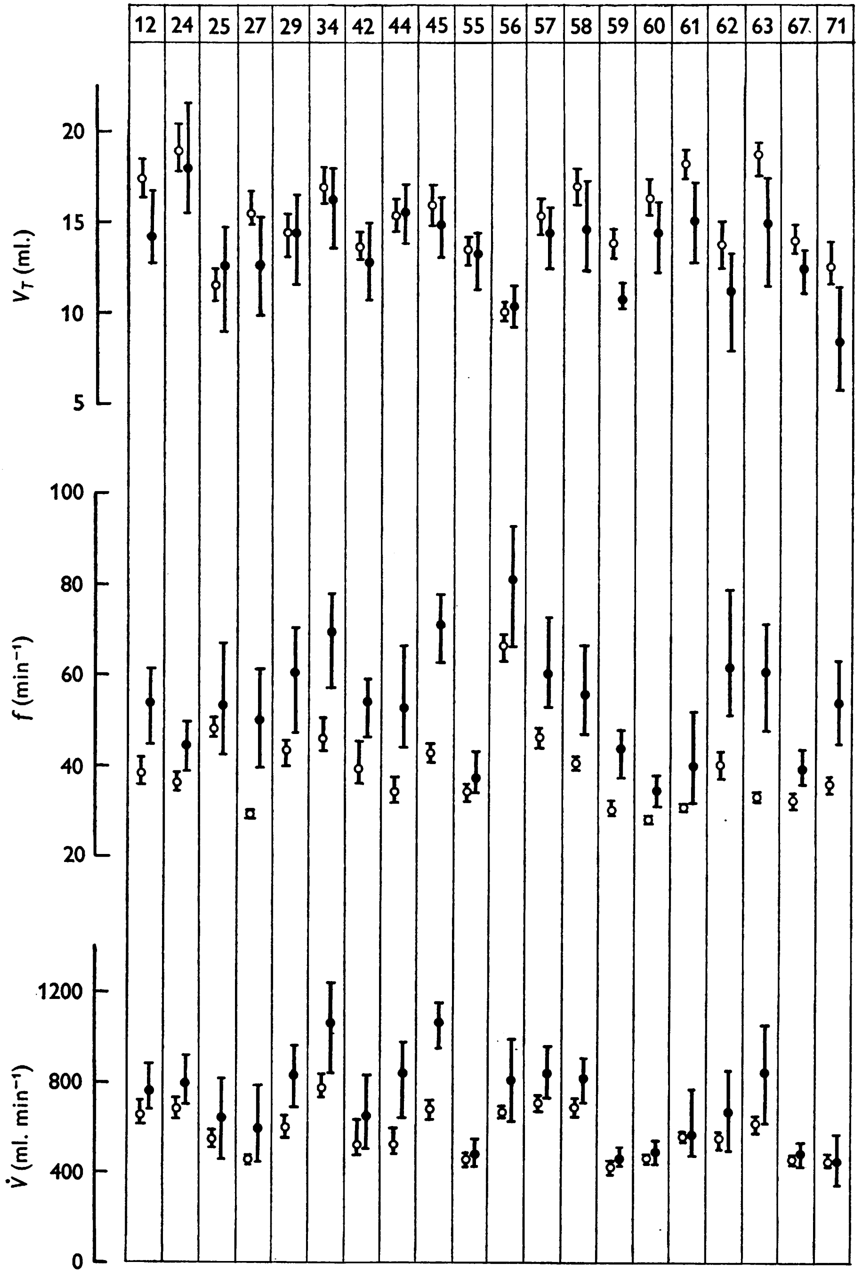

Fig. 3. Medians and interquartile ranges for V_T, f and $\dot{V}$ in all infants during NREM sleep (○) and REM sleep (●). Baby reference numbers shown at the top are in the same order as in Table 1.

During REM sleep, mean f and $\dot{V}$ were higher than in NREM sleep in all twenty infants (Table 1). Mean V_T was increased in three babies, showed no change in one and was decreased in the remaining sixteen infants.

The distributions around the mean showed significant skewness ($P < 0{\cdot}01$), usually positive, and significant positive kurtosis, in all the infants for one or more of the distributions of V_T, f and $\dot{V}$. Distribution-free measures of central tendency and dispersion, namely the median and interquartile range, were therefore calculated for the two sleep states and these are shown in Fig. 3.

TABLE 2. Mean coefficients of variation (S.D./mean, as %) in NREM and REM sleep in twenty infants, based on individual respiratory cycles

	NREM sleep (%)	REM sleep (%)
V_T	10·7	30·3
T	8·7	28·5
f	9·0	27·6
$\dot{V}$	11·3	32·3

The distribution-free Mann–Whitney U-test was used for comparing ventilation in REM and NREM sleep because of these departures from the normal distribution, and because of the significant inhomogeneity of variance in these two sleep states. This test showed that the increases in f found during REM sleep were significant ($P < 0{\cdot}001$) in all infants. V_T was significantly reduced ($P < 0{\cdot}01$) in fourteen infants during REM sleep, the remaining six babies showing no significant change in this sleep state. $\dot{V}$ was increased in all infants during REM sleep; this was significant ($P < 0{\cdot}01$) in eighteen babies. The remaining two babies both showed significant decreases in V_T during REM sleep.

Despite the frequent departures from the normal distribution found in the data, the coefficient of variation is nevertheless a useful measure of variability in data. The average values for these measures in the two sleep states are shown in Table 2; they indicate a two- to threefold difference in variation between the two sleep states.

Alveolar ventilation ($\dot{V}_A$). The reduction in V_T in most infants during REM sleep raised the possibility that some of the increase in $\dot{V}$ found in this sleep state may have been due to an increased contribution by dead-space gas to ventilation on these infants. Bolton (1974) measured dead-space in 104 new-born infants, and by the regression of dead-space (V_D) on weight, found the following relationship:

$$V_D \text{ (ml.)} = \text{wt. (kg)} \times 1{\cdot}03 + 3{\cdot}26.$$

This estimate resulted in a mean V_D for the present infants of 2·17 ml/kg. This is considerably higher than that of Koch (1968) (1·1–1·2 ml./kg), and closer to that of Strang (1961) who found a mean V_D of 9·2 ml. (2·78 ml./kg). Bolton's estimate of V_D was used to obtain an estimate of V_A in the twenty infants in both sleep states:

$$V_A = V_T - V_D,$$
$$\dot{V}_A = V_A \times f$$

for each respiratory cycle. As dead space gas is not separated from alveolar gas at an arbitrary front, it was assumed that the last one third of dead-space gas was proportionally mixed with alveolar air (Bolton, 1974).

Using these estimates, mean $\dot{V}_A$ was calculated for each sleep state. It was found that $\dot{V}_A$ was significantly higher during REM sleep than during NREM sleep in eight infants, decreased in two, with no significant difference in the remaining ten babies. The average increase in $\dot{V}_A$ in all the infants during REM sleep was 11·3 % over the NREM level, compared with an average increase in $\dot{V}$ of 22·7 %.

TABLE 3. Ranges of values for correlation coefficients (r) between various parameters of individual respiratory cycles in twenty infants in two sleep states

Correlations between	Sleep state	r (range)	No. of infants with significant values of r*
V_T and T	NREM	−0·153 to +0·685	18/20
	REM	−0·101 to +0·596	14/20
T_I and T_E	NREM	−0·238 to +0·658	12/20
	REM	−0·031 to +0·669	14/20
V_T and T_I	NREM	+0·029 to +0·679	15/20
	REM	−0·041 to +0·904	17/20

* Only positive values of r were significant ($P < 0·01$)

Correlations between V_T, T, T_I and T_E within each respiratory cycle. Correlation coefficients (r) between these values were calculated for each infant for the number of respiratory cycles shown in Table 1. The range of values of r found in all the infants in each of the two sleep states is shown in Table 3, together with the number of babies where the value of r was significant ($P < 0·01$).

It will be seen that V_T and T were positively correlated in most infants during both sleep states. Fig. 4 shows the distribution of individual points around the regression line of V_T against T in one of the infants.

From Table 3, it will be seen that significant positive correlations were also found between T_I and T_E, and V_T and T_I in the majority of infants in both sleep states.

Serial dependence in time between durations of successive respiratory cycles. Two different methods were used to determine whether there was significant serial dependence in successive values of T in the two sleep states. These were serial correlation coefficients, and the presence or absence of a significant spectrum of intervals. In both these tests, the

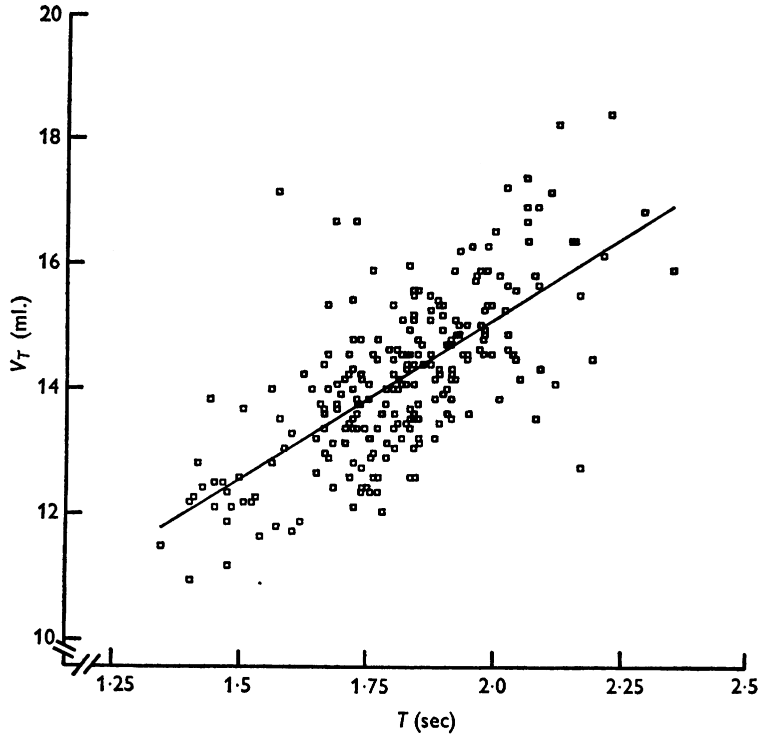

Fig. 4. Computer drawn graph of V_T against T for each respiratory cycle (□) in Baby 67 during NREM sleep, together with the regression line of V_T on T. $r = 0{\cdot}685$ ($P < 0{\cdot}01$).

successive values of T were considered to be intervals between events, i.e. the intervals between the onset of inspiration in successive respiratory cycles.

Serial correlation coefficients (autocorrelation functions) were calculated for lags of 0, 1, 2 . . . 50 intervals. Many of the infants showed clear evidence of periodic changes in T (e.g. Fig. 5). Provided the marginal distribution of the intervals is not too highly skewed, the serial correlation coefficients may be considered as observed values of a standardized normal variate (Lewis *et al.* 1968). The serial correlation coefficient for a lag of 1 was tested in this way, and was significant ($P < 0{\cdot}01$) in seventeen infants in NREM sleep and nineteen of the twenty infants during REM sleep.

Secondly, the presence or absence of significant periodicities in respiratory intervals was determined using the homogeneity of variance statistic based on the periodogram (Lewis *et al.* 1968). This test confirmed the presence of periodicities in T ($P < 0{\cdot}001$) in all the infants in both sleep states.

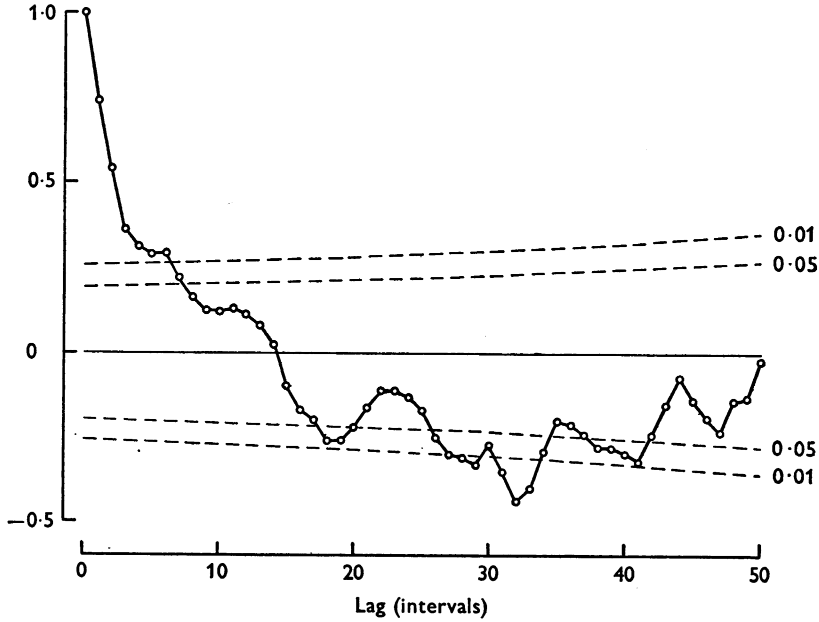

Fig. 5. Serial correlation coefficients (autocorrelation functions) of intervals (T) plotted for lags of 0, 1, 2...50 intervals in Baby 45 during REM sleep (○—○). Points lying outside the inner pair of dashed lines are significantly different from zero ($P < 0{\cdot}05$), and for those outside the outer pair of dashed lines, $P < 0{\cdot}01$.

DISCUSSION

Ventilation during NREM sleep. Mean $\dot{V}$ during NREM sleep in the present study (590 ml. min^{-1}) was the same as that found by Cross (1949) in twenty-six full-term infants (589 ml. min^{-1}). His mean value for f, however, was 28·6 min^{-1} compared with the present rate of 39·5 min^{-1}. In the present study, periods of NREM sleep were selected because they were close in time to periods of REM sleep, whereas Cross measured ventilation only when an infant had been quiescent for at least 20 min, and when sleeping quietly without any limb activity, facial grimaces or sucking movements (a description compatible with that of NREM sleep). It is known that f declines with time during a particular sleep epoch

(Prechtl *et al.* 1968), and that f is lower in successive epochs of NREM sleep as the time since the last feed increases (Ashton & Connolly, 1971). These are the most likely explanations for the differences in mean f found in the present study and that of Cross (1949).

Changes in ventilation in the two sleep states. The increase in mean respiration rate in REM as compared with NREM sleep is consistent with findings in new-born infants described by Prechtl *et al.* (1968), Ashton & Connolly (1971) and other workers. Bolton & Herman (1974) measured $\dot{V}$, V_T and f, averaged over 20 sec intervals, in neonates and obtained results essentially similar to those in the present study, namely an increase in mean $\dot{V}$ and f, and a tendency towards reduction in V_T during REM sleep.

Prechtl *et al.* (1968) and others have reported that f is more irregular during REM than in NREM sleep. Since any averaging procedure tends to obscure variability in data, it was considered in the present study that variability could only be quantified if the correct unit of measure was chosen, namely the individual respiratory cycle. The present results indicate that not only f, but also $\dot{V}_T$ and $\dot{V}$ show increased variation during REM than in NREM sleep.

The increase in mean estimated $\dot{V}_A$ during REM sleep may reflect increased oxygen consumption by many infants in this sleep state, similar to that reported in adult subjects by Brebbia & Altshuler (1965), and may be related to increased muscular activity in REM sleep.

Correlations between V_T, T and f. The significant positive correlations between V_T and T (and hence negative correlations between V_T and f) found in most of the infants studied are similar to the findings of Priban (1963), Dejours, Puccinelli, Armand & Dicharry (1966), and Newsom Davis & Stagg (1972) in adults.

The preservation of this relationship between V_A and T in many of the infants during REM sleep suggests that the increased variation in V_T, T and f found in this sleep state may not be completely random in character, but may reflect a different pattern of breathing associated with REM sleep.

The significance of these relationships is not clear. The infants with the highest correlations between V_T and T tended to show the smallest variation in $\dot{V}$ for a particular sleep state, as expected. On the other hand, a number of infants were able to maintain relatively stable levels of ventilation without any significant correlation, within the same breath, between V_T and T. This suggests that the levels of V_T and T at any instant in time, during spontaneous breathing, are controlled not only by mechanisms operating during that particular respiratory cycle, but also by controls operating over a longer time interval.

Periodic changes in T. Tarlo, Välimäki & Rautaharju (1971) found evidence of periodicities in heart-rate in seven of twenty-one full-term neonates during the first 5 days after delivery, with serial dependence in time between successive R-R intervals in the e.c.g. No significant periodic variation or interdependence of intervals, however, was detected in respiration rate in their infants. This contrasts completely with the present study, where evidence of serial dependence in time was found in all the infants in both sleep states. A possible explanation is a Figure in the paper by Tarlo and his colleagues which shows what appears to be REM sleep immediately succeeded by periodic breathing. The serial correlation coefficient used by them is very sensitive to trends in variance as well as in the mean; correction was made only for the latter.

The detection of periodic changes in T in the present infants is in keeping with the findings of Priban (1963). He found evidence of small recurring changes in the rate of breathing of 11 healthy adult subjects during the resting state. The average length of these changes was 3–4 breaths, much shorter than those found in periodic breathing.

Such periodicities may reflect the behaviour of respiratory control mechanisms, such as those involving chemoreceptor activity, operating over a longer time span than the individual respiratory cycle. A detailed study of these periodicities in rate, as well as similar possible changes in V_T, is obviously needed; this might supply evidence of changes in respiratory control mechanisms during different sleep states in new-born infants.

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