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RESPIRATORY SINUS ARRHYTHMIA IN NEW-BORN INFANTS

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 measured in eleven healthy term infants during both quiet and active sleep, using the trunk plethysmograph, and instantaneous heart rate was derived from the electrocardiogram. Variations in individual respiratory and cardiac cycles were compared in each sleep state, and cross-correlations between ventilation and heart rate were used in the analysis of the data.

2. It was found that heart rate and respiratory rate were higher and more variable during active than during quiet sleep, with a small reduction in tidal volume.

3. Cross-correlations showed that respiratory sinus arrhythmia was present in both sleep states, but was more marked during quiet sleep.

4. Running cross-correlations using a 5 s window showed that phase relationships between ventilation and heart rate, were, on the whole, stable during quiet sleep, but markedly unstable during active sleep.

5. It is concluded that in the investigation of respiratory sinus arrhythmia in the new-born, it is important to take account of sleep state, the methods of measuring ventilation and heart rate, and to use analytical techniques suited to the specific purpose of the study.

6. Respiratory sinus arrhythmia is considered to be due to an interaction between systems controlling breathing and those controlling the cardiovascular system, and that this interaction is affected by sleep state.

INTRODUCTION

Respiratory sinus arrhythmia is usually described as an increase in heart rate during inspiration and a fall during expiration, and has been the subject of many studies over the past century. As a result, a number of different hypotheses have been advanced to explain this phenomenon, and these may be broadly classified as follows: (a) direct stretching of the atrium in the region of the sino-atrial node during inspiration increases heart rate; (b) stretch receptors in the lungs or chest wall are stimulated during inspiration, inducing a reflex increase in heart rate; (c) increased activity of the 'respiratory centre' in the lower brain stem has a direct effect on medullary centres controlling heart rate; (d) there is an interaction between the mechanisms controlling respiration and those controlling heart rate.

One of the problems in deciding between these alternatives is the determination of the precise temporal relationship between the phase of the respiratory cycle and

changes in heart rate. Some of the methods used to derive heart rate from the electrocardiogram are open to criticism. In addition, many studies have employed methods including decerebration, general anaesthesia, neuromuscular paralysis and artificial ventilation in studying this phenomenon; although useful in dissecting out some of the mechanisms involved, it is possible that these methods may have fundamentally altered the physiological state of the animal or subject.

Studies on conscious subjects have often involved the subjects' breathing at fixed frequencies or tidal volumes, and the number of studies on spontaneously breathing adults is small. In the new-born infant a number of studies have shown respiratory sinus arrhythmia to be present, but have taken little account of sleep state and have not provided evidence of the precise phase relationships between ventilation and heart rate. Therefore they cannot be used to test the above hypotheses.

For these reasons I decided to investigate the time relationships between ventilation and heart rate in spontaneously breathing new-born infants during different sleep states, as sleep state has profound effects on the pattern of breathing (Prechtl, 1968; Hathorn, 1974, 1978).

METHODS

Measurements were made on eleven healthy term new-born infants during the first week after delivery. All the infants had an Apgar score of 9 or 10, 10 min after delivery, and all except one who was 'small for dates' weighed over 2·6 kg at birth (Table 1). The measurements were made after the morning feed, with the mother's informed consent, and in some cases with the mother present.

Ventilation was measured using the trunk plethysmograph (Cross, 1949) as previously described (Hathorn, 1974). In addition, the electrocardiogram (e.c.g.) and electroencephalogram (e.e.g.) (leads C3 and C4) were recorded.

The sleep state was determined using the criteria of Prechtl & Beintema (1964) in conjunction with the amplitude of the e.e.g. (Prechtl, 1974). In summary, quiet sleep (state 1) is characterized by a fairly regular breathing pattern, and there are no eye movements beneath the closed lids and no body movements apart from occasional startles. The e.e.g. shows slow waves interspersed with bursts at intervals of about 10 s. By contrast, during active sleep (state 2), the breathing pattern is more irregular, and rapid eye movements are often seen below the closed lids; there are frequent small movements of the extremities, and grimaces and mouthing movements are common. The e.e.g. flattens to a lower voltage, with many slow waves.

The signals were recorded on a frequency-modulated tape recorder. The data were digitized at 100 Hz using an analog-to-digital converter and written to computer tape for subsequent analysis on a main-frame computer. The ventilation data were passed through a Dolph–Chebyshev low-pass filter (Laxminarayan, Spoelstra, Sipkema & Westerhof, 1978) in order to eliminate noise and to enable the accurate determination of the duration of the respiratory cycle. Fig. 1 shows the original and filtered digitized ventilation data, with neglible clipping or ringing and no measurable phase shift. The e.c.g. and e.e.g. signals were not filtered.

The sampling rate of 100 Hz was sufficient to capture the R waves in the e.c.g. (Fig. 1). Their positions were detected using the algorithm of Okada (1979), and individual R–R intervals were calculated by subtracting the accumulated times of adjacent R waves. In this way, cumulative errors induced by the relatively slow sampling rate were avoided. The instantaneous heart rate for each R–R interval was calculated as 60 times the reciprocal of the interval, and a continuous histogram of heart rate was constructed over the e.c.g. (Fig. 1). This histogram was also sampled at 100 Hz.

Data representing 100 s in duration were selected from steady-state periods of quiet sleep and active (rapid eye movement) sleep in which there were no deep sighs, startles or other gross body movements, or long-term changes in breathing pattern, as previously described (Hathorn, 1974). An example of the digitized ventilation and heart-rate data for one of the infants in both sleep states is shown in Fig. 2.

The duration of the respiratory cycle (T_{tot}), together with the inspired tidal volume (V_t), were calculated for each respiratory cycle. Many of the frequency distributions were found to be skewed and it was thus inappropriate to use means and standard deviations which assume a Gaussian distribution. Modified box-and-whisker plots (Fig. 3), as originally described by Tukey (1977), were used instead.

Cross-correlations of the digitized ventilation trace and the sampled instantaneous heart rate were performed according to Bendat & Piersol (1966). For comparisons between infants and between sleep states, the data were first normalized by subtracting the mean and dividing by the standard deviation.

The two-tailed Wilcoxon signed-ranks matched-pairs test (Siegel, 1956) was used to test the significance of paired comparisons.

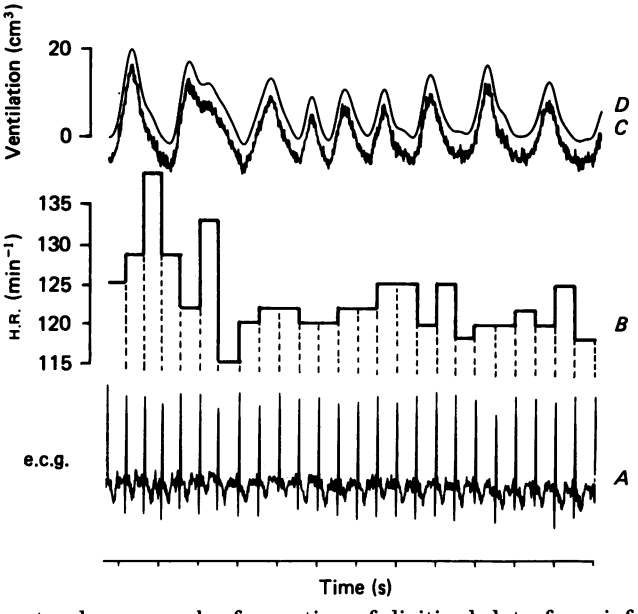

Fig. 1. Computer-drawn graph of a section of digitized data from infant no. 1 during active sleep. From below upwards: *A*, electrocardiogram; *B*, histogram, with positions of R waves on abscissa and instantaneous heart rate (H.R.) on ordinate; *C*, ventilation data before filtering; *D*, filtered ventilation data, displaced upwards for clarity of presentation.

RESULTS

The data for individual cardiac and respiratory cycles in both sleep states are depicted in Fig. 4 as box-and-whisker plots. Median heart rate was faster in eight of the eleven infants during active sleep, with shorter R–R intervals in these babies ($n = 11$, $P = 0{\cdot}04$). There was a larger interquartile range for heart rate and R–R interval in eight of the eleven infants during active sleep, showing greater variability in heart rate in this sleep state ($n = 11$, $P = 0{\cdot}04$). Median tidal volume was lower in most infants during active sleep ($n = 11$, $P = 0{\cdot}02$). The median value of T_{tot} was lower (and hence the instantaneous respiratory rate was higher) in all infants during active sleep ($P = 0{\cdot}003$). In addition, there was more variability in both the volume and duration of individual breaths during active sleep than in quiet sleep, as shown by larger interquartile ranges ($P = 0{\cdot}005$).

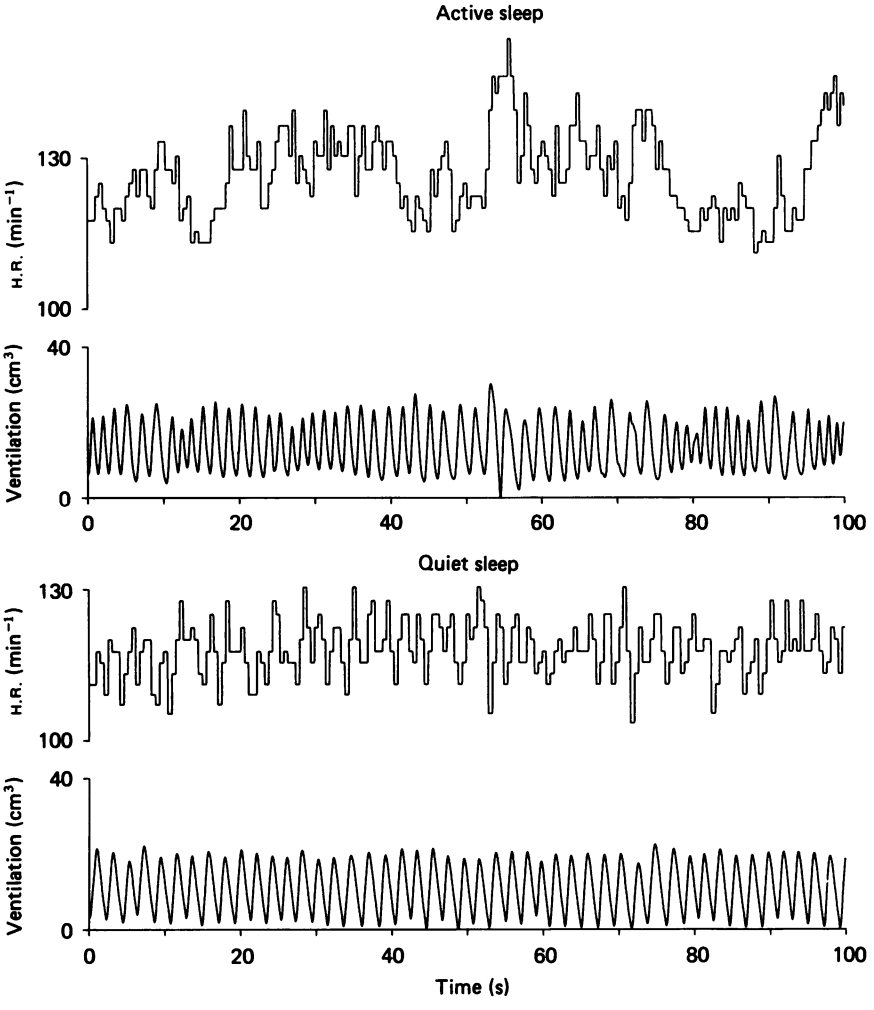

Fig. 2. Digitized data for heart rate (min^{-1}) and ventilation (cm^3) during active and quiet sleep for the whole period of 100 s in infant no. 7.

Cross-covariances between ventilation and heart rate, which are calculated as the sum of the cross-products as one signal is displaced in respect to the other, first in one direction and then the other, are useful in showing the temporal relationships between the main oscillations in the two signals. An example of these cross-covariances (cross-correlations, as the data were normalized) is shown in Fig. 5. The positions of the peaks in this infant are similar in both sleep states, with the maximum correlation occurring just before the zero-lag position, i.e. the oscillations in the two signals are nearly in phase with each other in this infant, with heart rate accelerating during inspiration but lagging slightly behind it. The amplitude, however, is smaller during active sleep than quiet sleep. The amplitude was smaller during active sleep in all eleven infants ($P = 0{\cdot}003$).

In most infants, however, there was considerable variation in the position of the peaks in the cross-correlations between different infants, and even in the same infant

in different sleep states (Table 1). This indicates that the timing of the rise in heart rate occurred at variable points during the respiratory cycle.

The above methods of analysis assume that the data are stationary, i.e. that the variability of each signal remains constant over the whole 100 s period of measurement, and hence these methods only measure the average results over this interval. However, in the present study it was clear that there was considerable variability

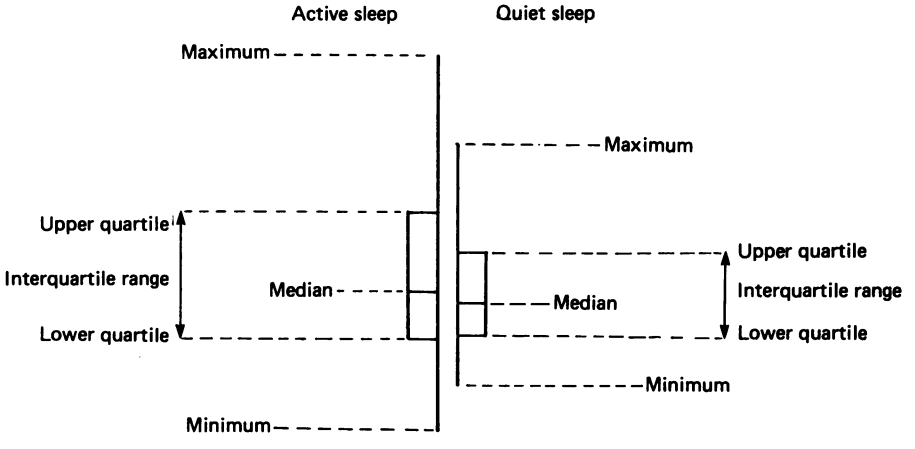

Fig. 3. Key to box-and-whisker plots shown in Fig. 4. (modified from those of Tukey, 1977) to compare distributions of samples during active sleep (left) and during quiet sleep (right).

in both the duration and amplitude of the respiratory and cardiac cycles, especially during active sleep (Fig. 4). I decided to investigate the stability of the cross-correlations over the whole 100 s period, using methods similar to those used to analyse breathing patterns in the new-born (Hathorn, 1979). This was done by calculating the cross-correlations over the first 5 s of data, using 500 data points with a lag of 200 in each direction, and then plotting these values on a graph at the mid-point, namely 2·5 s. The 5 s 'moving window' was then shifted along the trace by $95/129 = 0{\cdot}734$ s, as 129 is the maximum number of lines available for the graph plotting routine being used. The cross-correlations were then recalculated and plotted. This procedure was repeated until by the end of the 100 s trace 129 overlapping estimates of the cross-correlations had been plotted, the last being opposite the 97·5 s mark. The number of independent estimates was nevertheless $95/5 = 19$.

The results of this method of analysis in a typical infant are shown in Fig. 6. It will be seen that during quiet sleep there is considerable stability in the cross-correlations over the whole period of 100 s; by contrast, during active sleep the pattern shows a marked instability over this period. Ten of the eleven infants showed greater stability during quiet than active sleep. Fig. 7 shows the results in the only infant which did not show a clear difference between the two sleep states. No explanation for this could be found on re-examination of the data for this infant, except that they had the smallest median value of T_{tot}, and hence the highest respiratory rate, during quiet sleep (Fig. 4).

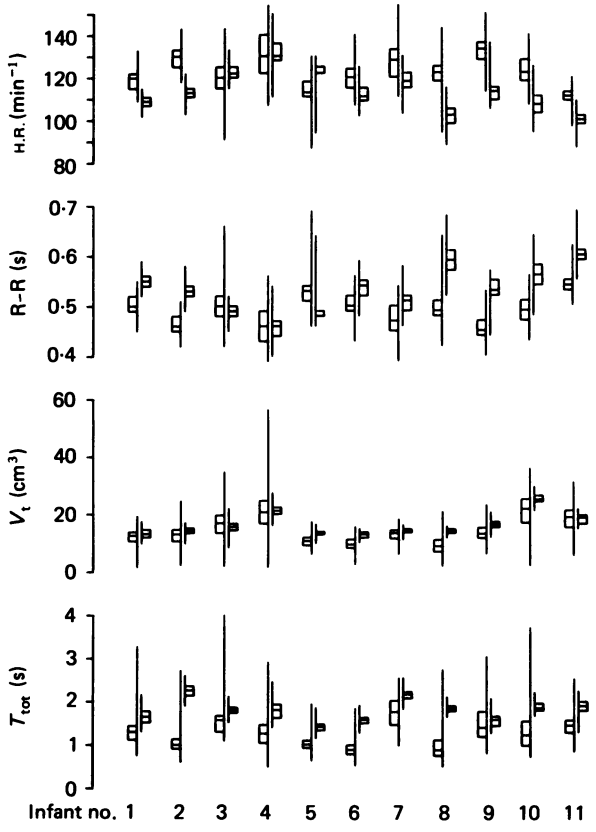

Fig. 4. Box-and-whisker plots (see legend to Fig. 3), from above downwards, of heart rate, R–R interval of the electrocardiogram, V_t and T_{tot}, for individual cardiac and respiratory cycles. Active sleep is on the left, and quiet sleep on the right of each pair.

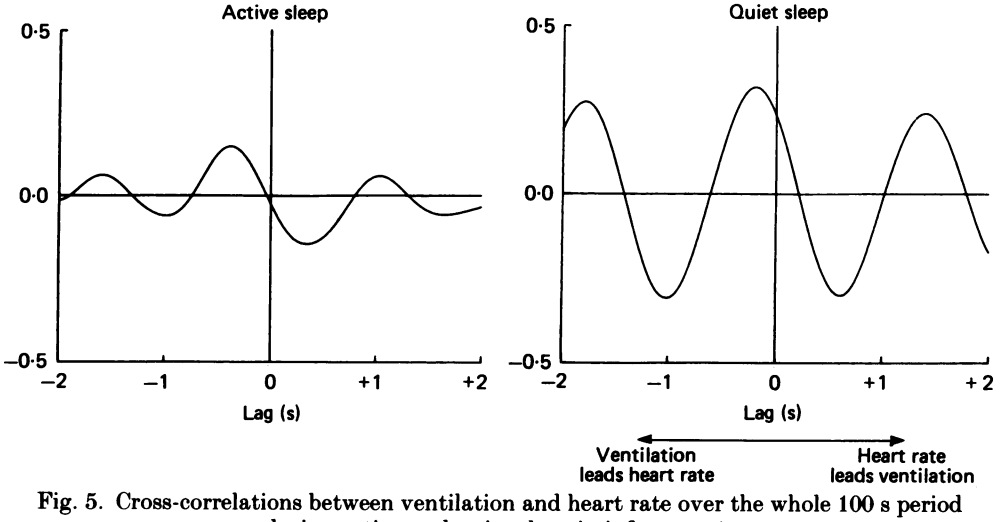

Fig. 5. Cross-correlations between ventilation and heart rate over the whole 100 s period during active and quiet sleep in infant no. 1.

TABLE 1. Subject details, and lags in cross-covariances between ventilation and heart rate

Infant no.	Sex	Age (hours)	Weight (kg)	Lag of peak in cross-covariances (s)* Active sleep	Quiet sleep
1	M	47	2·63	−0·36 (0·09)	−0·20 (0·06)
2	F	51	2·92	+0·43 (0·10)	−0·25 (0·04)
3	F	122	2·95	−1·24 (0·11)	−0·44 (0·03)
4	F	43	3·61	−0·44 (0·08)	−0·26 (0·03)
5	F	71	3·08	−0·22 (0·07)	+0·26 (0·08)
6	M	66	3·31	−0·31 (0·08)	−0·34 (0·02)
7	M	141	3·07	−0·45 (0·07)	−0·32 (0·02)
8	F	59	3·34	+0·13 (0·07)	−0·30 (0·02)
9	M	117	3·47	−0·51 (0·11)	−0·37 (0·06)
10	F	94	2·42	+0·33 (0·10)	+0·49 (0·12)
11	M	67	4·26	−0·50 (0·13)	−0·40 (0·06)

* A negative number indicates that ventilation leads heart rate, and a positive number that heart rate leads ventilation. The numbers in parentheses are the standard deviations of the displacements of the individual peaks from the zero-lag position in the running cross-covariances.

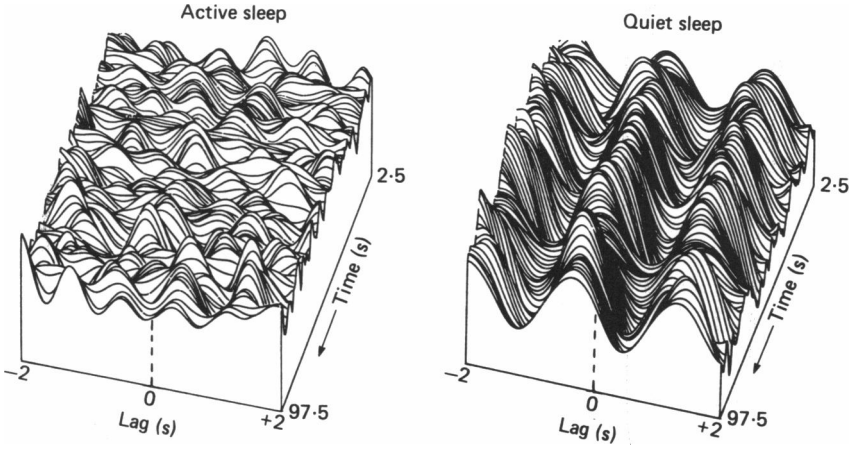

Fig. 6. Running cross-correlations (vertical axis) plotted against lag (first horizontal axis) and time from beginning of trace (second horizontal axis) during active and quiet sleep in infant no. 6 (see text for explanation).

In several infants during quiet sleep, the peaks in the running cross-correlations between ventilation and heart rate, although showing a 'strong' pattern, nevertheless tended to wander first towards and then away from the centre or zero-lag position (Fig. 8).

In order to characterize these differences between the two sleep states, the mean of the 129 differences between the central peak and the zero-lag position was calculated for each sleep state for each infant. Estimates of the mean are shown in Table 1, with the standard deviations of the displacement of these 129 central peaks in parentheses. It will be seen that the standard deviations were larger during active sleep than during quiet sleep in nine of the eleven infants ($n = 11$, $P = 0{\cdot}01$),

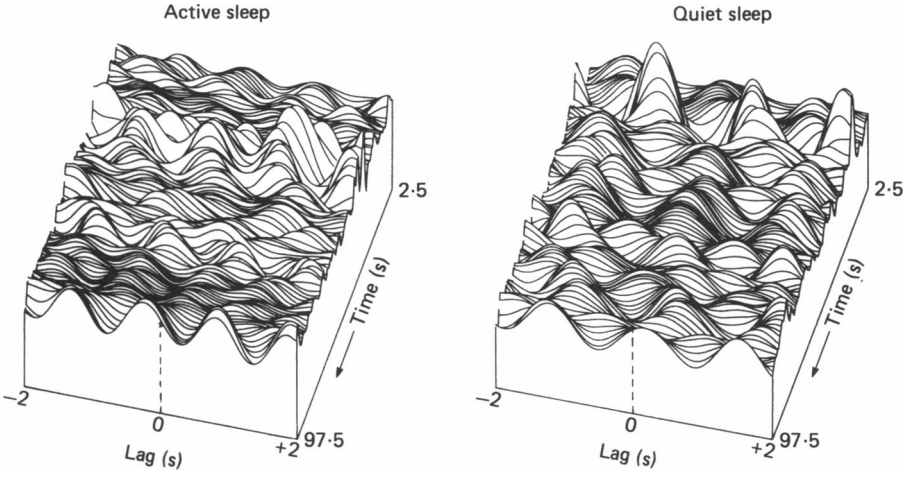

Fig. 7. Running cross-correlations for infant no. 5 (see legend to Fig. 6).

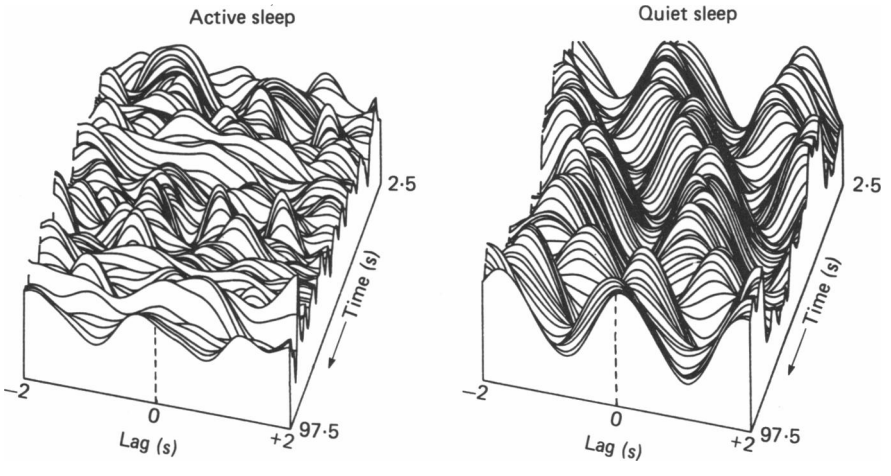

Fig. 8. Running cross-correlations for infant no. 10 (see legend to Fig. 6).

indicating that the positions of the peaks were more variable during active sleep. The exceptions were infant no. 5 (shown in Fig. 7) and infant no. 10 (shown in Fig. 8). The explanation in this last infant is clearly the 'wandering' nature of the central peak during quiet sleep; this is the infant who was 'small for dates' and who had the smallest weight (Table 1).

DISCUSSION

Although in the supine position, the new-born infant was sleeping comfortably in the trunk plethysmograph, breathing room air directly without the use of a mask or nasal prongs, valves or other procedures which may stimulate the upper airways, or increase dead space or airways resistance. This method also measures the volume of air breathed in or out, irrespective of the relative contributions of the intercostal

muscles and diaphragm to total ventilation. This is of importance because of the relative inactivity of intercostal muscles during active sleep (Finkel, 1972; Curzi-Dascalova, 1978).

The sampling rate of 100 Hz limited the resolution of the R–R interval to 10 ms, but any such errors were not cumulative. There are a number of different methods of calculating heart-rate variability; these have been reviewed by Kitney & Rompelman (1980), Scholten & Vos (1982) and more recently by de Boer, Karamaker & Strackee (1985). The latter emphasized that special data-processing techniques are required when heart rate is related to another physiological signal such as respiration. Almost all methods using analog or digital devices triggered by the e.c.g. introduce a delay of at least one R–R interval into the output signal, and as the R–R interval itself is variable the validity of such methods in studying the time delays in sinus arrhythmia is questionable. A number of studies on the phase relationships between ventilation and heart rate have been excluded from the discussion for this reason.

The alternatives are the instantaneous inter-beat interval (where the variable calculated is inversely related to rate) and the instantaneous heart rate, the latter being the method used in the present study. De Boer *et al.* (1985) concluded that the instantaneous heart-rate signal may be considered as the most appropriate method to approximate the neural influence on the cardiac pace-maker. The present method introduces step changes in heart rate between successive R–R intervals, but personal unpublished studies have shown no significant differences in the results if the heart-rate signal is first passed through a low-pass filter, or if a polygon instead of a histogram is sampled. Nevertheless, none of these methods can identify the exact point in the cardiac cycle at which changes in sympathetic or parasympathetic activity at the sino-atrial node effect a change in heart rate. Precise time relationships between ventilation and change in heart rate must therefore be treated with caution.

There have been a number of developments in techniques of signal analysis in recent years, for example the Fast Fourier Transform and auto-regressive techniques for estimating spectra (e.g. Heinze, Kunkel & Massing, 1984). These have been useful in exploring the wave form of the heart-rate signal, especially at frequencies smaller than the respiratory rate (Kitney, 1984; Giddens & Kitney, 1985). In the present study, however, the objective has been to study only the changes in heart rate at the frequency of respiration, and their time relationships; hence cross-correlations have been used. The results using running cross-correlations have provided convincing evidence of differences in respiratory sinus arrhythmia in the two sleep states.

Harper, Walter, Leake, Hoffman, Sieck, Sterman, Hoppenbrouwers & Hodgman (1978) found that respiratory sinus arrhythmia was present in normal infants. It was greater in both extent and coherence in quiet than in active sleep, and they concluded that sleep state appears to have a significant effect on cardiorespiratory coupling.

It is appropriate to discuss the findings in this study in relation to the various hypotheses that have been advanced to explain the mechanism of respiratory sinus arrhythmia. Brooks, Lu, Lange, Mangi, Shaw & Geoly (1966) showed that stretch in the region of the sino-atrial node in the anaesthetized dog, induced by a variety of methods, produced cardiac acceleration which persisted even after atropine administration or cardiac denervation. If stretching of the sino-atrial node due to increased negativity of intrathoracic pressure during inspiration is the explanation

for the acceleration in heart rate, one would expect a fairly constant time interval between the phase of inspiration and the acceleration in heart rate. While this tended to be true in most infants during quiet sleep this was not the case in active sleep.

A similar argument applies to those studies which conclude that receptors situated in the chest wall, or various structures in the lungs, are the afferent input to brain-stem centres reflexly altering sympathetic or parasympathetic outflow to the sino-atrial node (e.g. Clynes, 1960). There are also a number of studies (e.g. Joels & Samueloff, 1956) which suggest that medullary respiratory activity has a direct effect, by 'irradiation', on medullary centres controlling the heart rate.

Changes in central nervous activity with sleep state have an important bearing on these latter studies. It has been shown by a number of authors, particularly Prechtl (1972), that with change in sleep state there are profound changes in a number of central reflexes. Active sleep is also associated with inactivity of the intercostal muscles during inspiration, resulting in so-called paradoxical breathing (Finkel, 1972). It is thus possible that changes in heart rate in step with ventilation, induced either by means of reflexes or medullary irradiation, are present in quiet sleep, accounting for the fairly stable pattern found in ten of the eleven infants in the present study during quiet sleep; it is also possible that inhibition of some of these pathways occurs during active sleep, thus interrupting or abolishing this mechanism and leading to the disorganized time relationships found during active sleep. This is an attractive hypothesis.

However, despite the disorganized time relationships between ventilation and heart rate found during active sleep in the present study, respiratory sinus arrhythmia is nevertheless still present in this sleep state, as shown by the peaks in the cross-correlations. In addition, during quiet sleep some infants showed strong cross-correlations between ventilation and heart rate, but there were gradual but nevertheless marked changes in their phase relationships (Fig. 8). These findings make it difficult to accept a direct central nervous mechanism or reflex connecting heart-rate change with respiratory drive as the only mechanism involved in respiratory sinus arrhythmia.

Finally, there have been a number of studies over the past decade which suggest that the relationship between ventilation and heart rate is a more complex one. Many of these arise from an analysis of the different frequency components present in the heart rate. Hyndman, Kitney & Sayers (1971) identified three regions of activity in the heart-rate spectrum of adults: a low-frequency region around 0·05 Hz which they associated with thermoregulatory activity, a component around 0·1 Hz related to baroreceptor activity, and finally a component at the respiratory frequency.

The study of heart-rate variability has recently been extended to the new-born infant. It is first necessary to characterize the pattern of breathing in infants during quiet and active sleep. In both sleep states, there are low-frequency oscillations (0·08–0·15 Hz) in both the rate and depth of breathing (Hathorn, 1975, 1978, 1979). During quiet sleep the oscillations in tidal volume and respiratory rate are out of phase, resulting in a stable pattern of breathing. During active sleep, the amplitude of these oscillations is greater and their phase relationships are unstable, resulting in a more irregular pattern of breathing. Finally, during periodic breathing, the oscillations in the amplitude and rate of breathing are in phase with each other, resulting in marked oscillations in pulmonary ventilation.

The presence of these low-frequency oscillations in the depth of breathing during normal and periodic breathing during quiet sleep have been confirmed by Waggener, Frantz, Stark & Kronauer (1982) and by Finley & Nugent (1983). The latter authors also studied heart-rate variability in their infants. They found a modulation of heart rate, both at the respiratory frequency and at the frequency of these slow oscillations.

Kitney (1984) and Giddens & Kitney (1985) have also investigated heart-rate variability in the new-born. They found evidence of heart-rate variability modulated by ventilation at 0·1 Hz but little at the respiratory frequency itself.

Kitney, Linkens, Selman & McDonald (1982), in their study of heart-rate variability in conscious adults, suggested that respiratory sinus arrhythmia is due to the interaction of non-linear oscillatory control systems, where the dominant respiratory frequency causes lower frequency oscillations in heart rate related to the baroreceptor reflex, to entrain or synchronize at the dominant respiratory frequency.

It would be interesting to ascertain whether this occurs in the new-born infant, or whether the heart rate is driven both at the respiratory rate, and also in time with the low frequency respiratory oscillations found in both active and quiet sleep (Hathorn, 1978, 1979).

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