CLINICAL RESEARCH

Respiratory and heart rate patterns in infants destined to be victims of sudden infant death syndrome: average rates and their variability measured over 24 hours

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Abstract

From a prospective study in which 24 hour recordings of the electrocardiogram and respiratory activity (abdominal wall movement) were made on a population of full term infants, 22 recordings were obtained from 16 infants who later were victims of the sudden infant death syndrome. The average heart rate, average heart rate variability, average breath to breath interval, and average breath to breath interval variability over the whole of each recording for the 22 recordings were compared with those from a control group of 324 infants selected at random from the rest of the population. No significance was found in the number of recordings from those infants who suffered the sudden infant death syndrome which lay outside the 5th-95th percentile range of the control group for the four variables studied.

In a group comparison no difference was found between the sudden infant death syndrome group and the controls either in terms of the respiratory variables studied or in terms of the average heart rate variability. The results did, however, suggest that there may be a group difference in terms of the average instantaneous heart rate.

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Introduction

Studies of the sudden infant death syndrome, or "cot death," show that the respiratory and heart rate patterns in those babies at "high" risk of dying in this way are different from those of "low" risk babies and that these differences might form the basis for a screening test. In one study higher respiratory rates were found in babies at increased risk of unexpected death.[1] In that study the scoring system developed by Carpenter *et al*[2] was used to determine the risk of unexpected death. Subsequent siblings of victims of the syndrome are thought to be at a higher risk of dying suddenly and unexpectedly and a study based on this group found that respiratory rates were higher in the study group than in a control group.[3] Another group of infants believed to be at risk of the sudden infant death syndrome are those who suffer an episode of hypotonia, apnoea, cyanosis, or collapse—the so called "near miss" infants. On studying these infants, a higher heart rate and a lower beat to beat variability were found immediately after the episode when compared with a control group.[4]

A major problem with all previous work is that the babies studied were not victims of the syndrome, nor in most cases did they go on to die, but formed groups which are believed to be at increased risk of sudden and unexpected death. A second major problem is that the high risk state of the groups may have influenced their care, which in turn may have influenced the results. Many of the studies carried out on "near miss" infants have been performed immediately after the attack while undergoing observation in hospital. Differences found between these infants and controls may reflect the effects of the episode itself rather than any underlying difference present before the event.

In order to investigate the relevance of these findings to predicting the sudden infant death syndrome 24 hour tape recordings of the respiratory waveform and of the electrocardiogram taken from a prospective study of the syndrome have been analysed. The respiratory waveform was obtained by monitoring abdominal wall movement using a Pye Dynamics MR10 (pressure capsule) respiration monitor. The analysis was based on studying the breath to breath intervals and instantaneous heart rate values over the 24 hours. The analysis

was performed completely automatically and was therefore without operator bias.

Subjects and methods

The prospective study providing the data on the sudden infant death syndrome cases and controls has been described[5] and only the main points are summarised here. Twenty four hour tape recordings of the respiratory waveform and of the electrocardiogram were made on 6914 full term infants. In 97% of these infants recordings were obtained in the first and sixth weeks of life. In the remainder a single recording was made in the third week of life. Most of the recordings made after the first few days of life were performed in the infant's own home. Of this group of infants, 13 subsequently died with a necropsy diagnosis of sudden infant death syndrome.

tape speed variations. The techniques used for determining the time interval between breaths are based on detecting "peaks" and "troughs" in the respiratory waveform, the amplitudes of which must exceed a certain "threshold" before a breath is detected.[7] The threshold used was determined from the amplitude of breaths during the preceding 60 seconds of respiratory waveform. The time interval between breaths was taken as the period between the half amplitude points on the inspiratory phase of respiration on two consecutive breaths. The computer also performed additional pattern recognition primarily concerned with artefact rejection.

Each 24 hour recording was processed in consecutive non-overlapping time epochs of roughly 100 seconds. Thus the 24 hours of data were characterised by an equispaced series of data values which could be plotted in the form of a "trend plot" (fig 1). This process is fully described elsewhere.[6] Further data reduction was necessary in order to make comparisons between infants.

The following variables were measured: average time interval

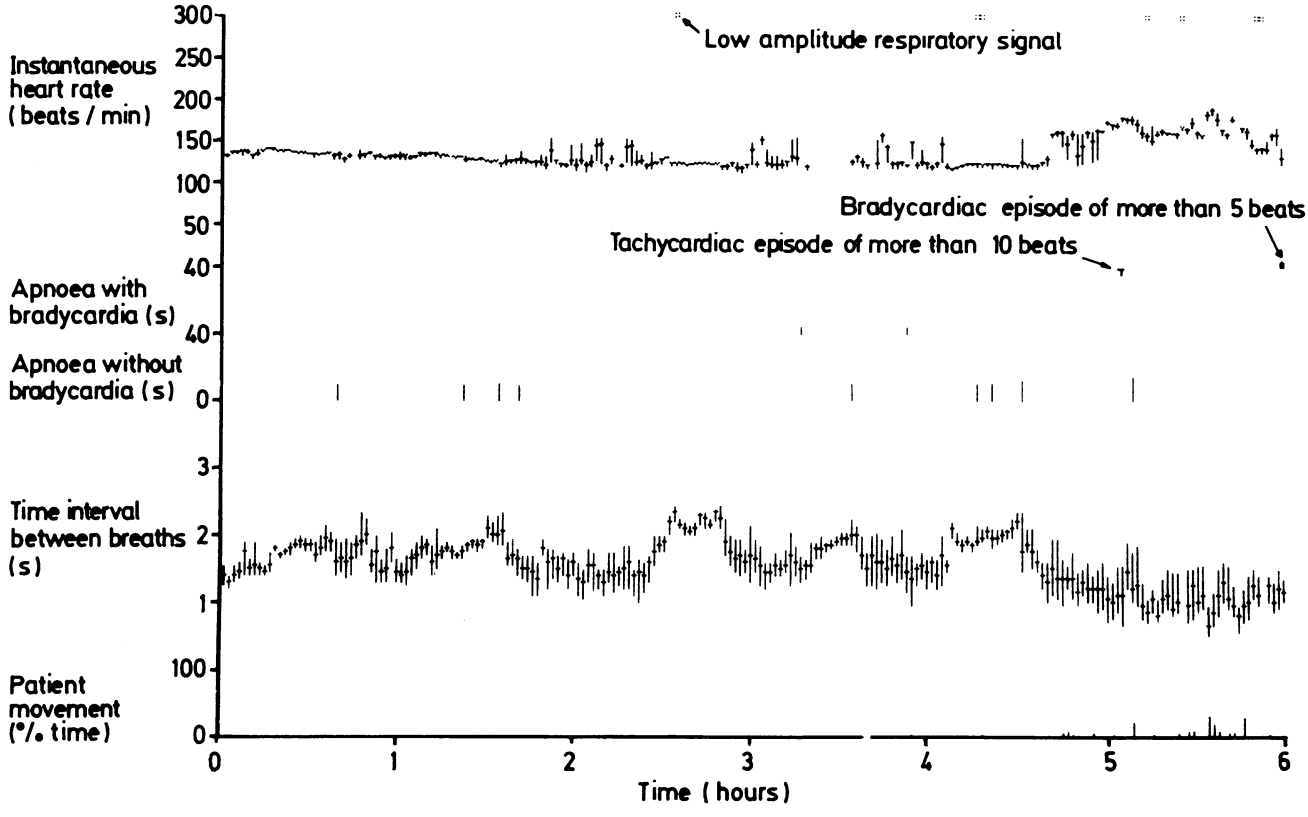

FIG 1—Annotated "trend plot" showing six hours of data. Each entry on trend plot shows set of results for 100 seconds of raw data. For time interval between breaths and instantaneous heart rate, horizontal bar gives median value and vertical bar interquartile range.

From other research studies being conducted simultaneously tape recordings on three further full term infants who subsequently died in this way were also available. Thus 22 tape recordings on 16 infants who subsequently died of the syndrome were available for analysis.

In order to make comparisons between babies who survived and those who died 24 hour tape recordings were taken from the remainder of the population studied. Infants who had died of other causes or who had congenital abnormalities or major postnatal illness were not included as controls. About 100 control infants were selected from each of the three postnatal age groups in which data were obtained. The control group consisted of 324 recordings on 230 infants.

The data were analysed using a microprocessor based version of the Sheffield respiration analysis system.[6] The R waves in the electrocardiogram were detected using an electrocardiographic trigger and the R-R interval determined using a clock and counter. The R-R interval was represented by a 10 bit binary word, and for data replayed at 60 times real time the frequency of the clock is 30 kHz. This 10 bit word together with the respiratory waveform were input to the computer, sampling at 1·2 kHz for data replayed at 60 times real time. Both the clock used to determine the R-R interval and the one used to control the sampling of the data were derived from a 60 Hz clock recorded on the original analogue tape to compensate for any

between breaths, variability of the time interval between breaths, average instantaneous heart rate, and variability of the instantaneous heart rate.

Average time interval between breaths and average instantaneous heart rate—The median value for each variable was determined for all 100 second non-overlapping time epochs throughout the recording. An average value for the entire recording was then obtained by calculating the arithmetic mean of the median values.

Variability of time interval between breaths and instantaneous heart rate—The interquartile range of the variable for each epoch was calculated. (The interquartile range is that range of values that lies between the 25th and 75th centile points of the distribution.) An average value of the variable for the entire recording was obtained by calculating the arithmetic mean value of the interquartile ranges over all the epochs analysed.

The three major postnatal age groups of the controls were divided into five subgroups so that maturational changes could be reflected more accurately (table). The five age groups were: 1-5 days, 6-15 days, 16-30 days, 31-47 days, and 48 days and over. The median ages in the groups were 3 days, 8 days, 22 days, 41 days, and 53 days respectively. For each of these age groups the percentile points of the distribution for each of the variables studied were calculated and linear interpolation used to evaluate the percentile points of the

variable between the median ages of the groups considered. Thus a set of maturational graphs were constructed against which infants of any age within the age range of the control group could be compared.

There were 22 recordings on 16 infants who subsequently were victims of the sudden infant death syndrome. In six of the infants two recordings were made. Since the number of infants for whom two recordings were available was small, statistical analysis was based on the first recording in each case. In one of the 22 recordings—the only one on the infant concerned—the amplitude of the respiratory waveform was below the minimum threshold used by the breath detection routine for much of the recording and thus an adequate estimate of the average breath to breath interval and breath to breath interval variability could not be obtained. Statistical results are therefore presented on 16 cases for instantaneous heart rate measurements and 15 cases for breath to breath interval measurements.

The numbers of cases of sudden infant death syndrome lying above the 95th centile or below the 5th centile were studied. This analysis provides a method of investigating the number of cases that might be considered to be outside the normal range. If these are found to be different from that expected by chance alone then this might form the basis for developing a discriminant function. Statistical significance for this part of the analysis was assessed using Fisher's exact probability tests.

In order to make a group comparison between the sudden infant death syndrome group and the controls the Wilcoxon rank sum test was used, suitably adjusted for age stratification. Since this is a non-parametric test using data from several different age groups it was impossible to study the magnitude of any group differences. For the time interval between breath measurements and for the instantaneous heart rate variability the age groups used were 2, 3, 4-6, 7-9, 10-15, 16-18, 19-39, 40-47, and 48 days and over. For the average instantaneous heart rate the age groupings used were 2, 3, 5, 6, 8, 10-15, 16-18, 19-39, 40-47, and 48 days and over. This second grouping was necessary to accommodate the very rapid rise in heart rate during the first few days of life.

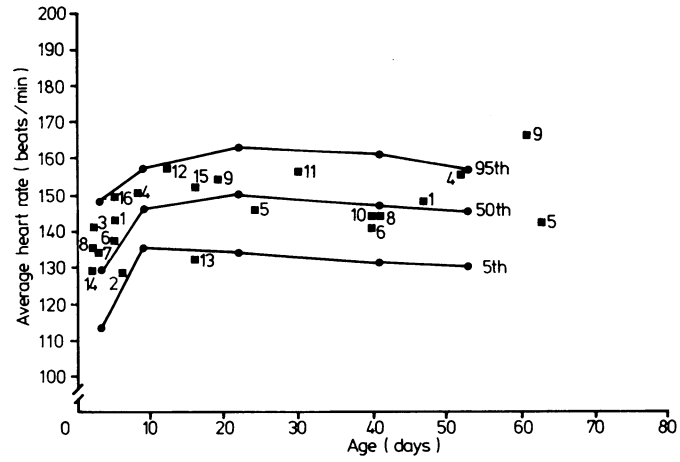

FIG 2—Average heart rate results. Fifth, 50th, and 95th centile points of distribution (●) plotted at median ages of control groups. ■=Case of sudden infant death syndrome.

group (fig 5) showed a positively skewed distribution with little change in the median values with age. There was a trough in the 95th centile at around 10 days of age and then a small peak at around 21 days of age. Two of the first recordings on infants in the sudden infant death syndrome group showed values above the 95th centile. One of these two infants exceeding the 95th centile at 3 days of age was completely outside the range of the control population. Manual analysis of this recording showed that most of the respiratory activity was periodic breathing[8] and that the high average breath to breath interval variability reflected this.

Summary of results in control groups

	Postnatal age group (days)				
	1-5	6-15	16-30	31-47	≥48
No of recordings	80	39	92	56	57
Average heart rate (beats/min):					
Mean (SD)	130 (9)	146 (6)	150 (9)	147 (9)	145 (8)
5th-95th centiles	115-148	136-158	135-164	132-162	130-158
Heart rate variability (beats/min):					
Mean (SD)	13·6 (3·5)	15·0 (3·2)	13·1 (3·3)	12·2 (3·2)	12·7 (3·2)
5th-95th centiles	8·8-21·8	10·2-21·0	8·7-19·2	9·0-16·2	9·2-18·0
Average breath to breath interval (ms):					
Mean (SD)	1176 (176)	1162 (158)	1222 (193)	1354 (189)	1386 (190)
5th-95th centiles	894-1517	915-1388	918-1567	1078-1656	1109-1700
Breath to breath interval variability (ms):					
Mean (SD)	487 (143)	438 (126)	427 (151)	429 (125)	396 (73)
5th-95th centiles	342-755	273-602	273-694	274-624	291-521

Results

Figures 2 to 5 plot the results for the four factors studied, giving the 5th, 50th, and 95th centiles of the distribution for the control groups together with the results for the sudden infant death syndrome cases plotted as single measurements identified by a code number.

The average instantaneous heart rate in the control group (fig 2) showed a rapid rise during the first eight days of life followed by a slow fall. Figure 2 shows that in the sudden infant death syndrome cases only one recording (a second recording) fell above the 95th centile and only one (a first recording) below the 5th centile.

The instantaneous heart rate variability in the control group (fig 3) had a positively skewed distribution and increased in value during the first eight days of life and then slowly fell up to 41 days of life. After 41 days there was again a slow increase. In the sudden infant death syndrome group there were two recordings (one first and one second recording on different infants) with values above the 95th centile and one first and only recording with a value below the 5th centile.

The average time interval between breaths in the control group (fig 4) showed a gradual increase with age—that is, a fall in respiratory rate. Only one recording in the sudden infant death syndrome group—a first and only recording on this infant—showed a value greater than the 95th centile. None of the recordings in the sudden infant death syndrome cases had values below the 5th centile.

The variability of the time interval between breaths in the control

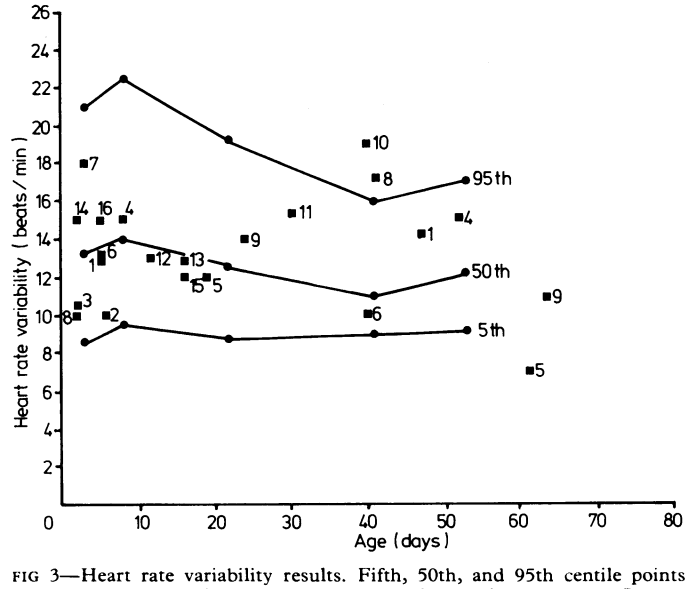

FIG 3—Heart rate variability results. Fifth, 50th, and 95th centile points of distribution (●) plotted at median ages of control groups. ■=Case of sudden infant death syndrome.

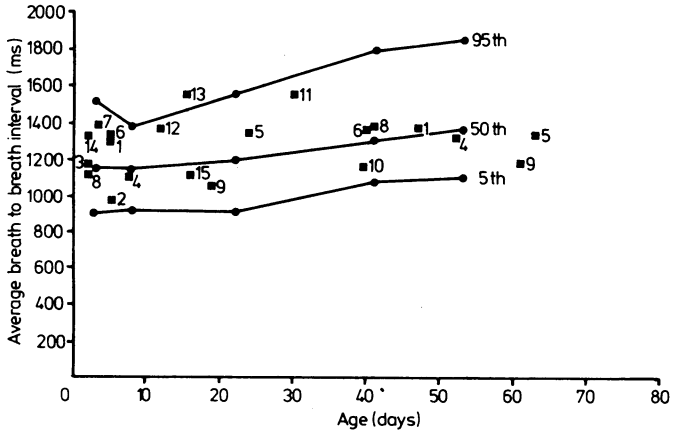

FIG 4—Average breath to breath interval results. Fifth, 50th, and 95th centile points of distribution (●) plotted at median ages for control groups. ■= Case of sudden infant death syndrome.

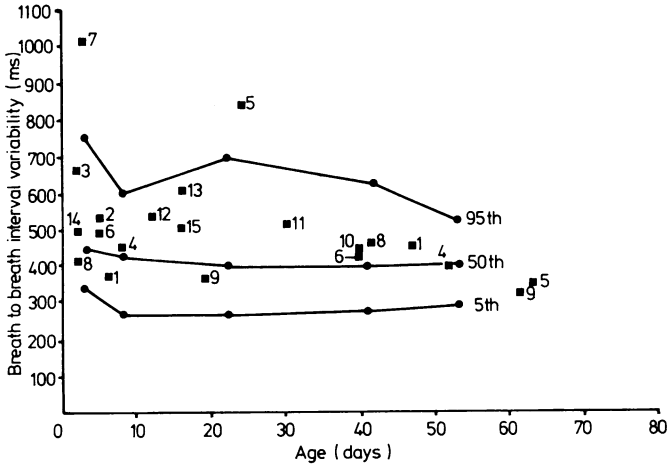

FIG 5—Breath to breath interval variability results. Fifth, 50th, and 95th centile points of distribution (●) plotted at median ages of control groups. ■= Case of sudden infant death syndrome.

No significant group difference between the cases of sudden infant death syndrome and the controls was found for the respiratory variables studied ($p > 0.05$). Similarly, our results for average instantaneous heart rate variability suggested that there was no group difference ($p > 0.05$). The results for average instantaneous heart rate showed that there was a group difference between the sudden infant death syndrome cases and the control group at the 5% level using a one tailed test. For this factor the number of infants in the sudden infant death syndrome group above the median for the control group was higher than that expected by chance alone, which therefore suggested that the average instantaneous heart rate for the sudden infant death syndrome cases was higher than that for the control group.

In none of the variables studied was the number of sudden infant death syndrome cases above the 95th centile or below the 5th centile of the control population significant. To put this finding into perspective, three first recordings on infants in the sudden infant death syndrome group would need to lie outside the appropriate centile level for the result to be significant at 5%. Four first recordings on infants in the sudden infant death syndrome group would be necessary for significance at the 1% level.

Discussion

There were two major problems in making comparisons between recordings in a control group and those from infants destined to be victims of the sudden infant death syndrome. Firstly, there were only a small number of infants who subsequently died of the syndrome available for analysis; and, secondly, because of logistic problems not all infants were recorded at exactly the same age, and therefore maturational effects on the factors studied must be taken into consideration. In particular, the heart rate and its variability change very rapidly during the first few days of life, and our findings and those of Richards *et al* confirm this.[9] The maturational changes which do occur are non-monotonic—that is, they do not change uniformly in one direction with age and it is therefore impossible to use a linear trend correction technique that would permit a simple comparison to be made.

The increase in the heart rate during the early part of life was reported by Harper *et al*, and their data suggested that the peak was at about 1 month of age.[10] Measurements, however, were taken only at 1 week, 1 month, 2 months, and 3 months of age. In another study, where measurements were taken at two week intervals,[11] a similar peak in the heart rate was found at between 4 and 6 weeks of age. Neither study identified the very rapid rise in heart rate which we observed during the first few days of life. Richards *et al* also found a rapid rise in heart rate during the first few days of life when the heart rate was measured during periods of regular breathing.[9] The changes in instantaneous heart rate variability that we found in the control group have been reported by others.[4 10]

The average time interval between breaths in the control group showed a gradual rise with age, which agrees with the finding of Franks *et al*.[1] We found little change in the median value of variability of time interval between breaths in the control group. There was a slight peak in the 95th centile at around 21 days of age. The most probable reason for this is that there was a peak in the incidence of periodic breathing at around that time[9] which would in turn produce an increase in the variability of time interval between breaths. Both this and the trough at 10 days of age, however, may have resulted from the uncertainty in estimating the tails of the distribution.

It has been suggested that the respiratory rate should be incorporated into scoring systems designed to assess the "risk" of sudden infant death syndrome.[12] Our results showed that there was no group difference between the sudden infant death syndrome cases and the controls in terms of the respiratory rate variables studied when measured over 24 hours. In addition, our finding on the number of cases lying outside the 5th to 95th centiles of the control group does not provide a method for identifying infants who go on to die of the syndrome. A previous study showed that infants at "high" risk of unexpected death have significantly higher respiratory rates when compared with control infants beyond 3 months of age.[1] A similar finding[3] showed a significantly higher respiratory rate in siblings of infants who had died of the syndrome at 3 months of age, though no difference existed for these infants above or below that age. Our findings in infants who subsequently died of the syndrome agree with those in infants believed to be at high risk of sudden and unexpected death. We do not, however, have data on sudden infant death syndrome cases at 3 months of age or beyond, and therefore we cannot either confirm or refute the findings of others at these ages.

Leistner *et al* reported a significantly higher heart rate with a lower variability in those infants who were "near miss" for the sudden infant death syndrome.[4] No difference was found between the cases and the control group in terms of the average instantaneous heart rate variability. We did, however, find a group difference between the sudden infant death syndrome cases and the controls in terms of the average instantaneous heart rate which was significant at the 5% level using a one tailed test. In another analysis of these data[8] increased amounts of sinus tachycardia were found in some of the sudden infant death syndrome cases when compared with the control group. This finding suggests that an overall increase in the average heart rate is possible and therefore the use of a one tailed test in this study was justified. The number of sudden infant death syndrome cases that lay outside the 5th to 95th centile range of the control group for the heart rate variables was not significantly different from that which would have been expected by chance alone

and, therefore, this does not provide a specific method of predicting which infants will go on to die of the syndrome.

A major problem in comparing our results with those of other workers is that many have analysed the data in terms of the "sleep states." The differences seen in heart rate and its variability[4] and respiratory rate and its variability,[3] however, exist in all stages of sleep and therefore it might be expected that our approach would identify differences if these were present. It has been shown that the periodicity of sleep states is different in subsequent siblings of infants with sudden infant death syndrome[13] and it is possible that differences in rate and variability did exist in the cases studied here but were masked by differences in the organisation of the sleep states. It is not possible to "sleep stage" simple cardiorespiratory recordings directly. This has to be done indirectly using normative data collected in a similar manner but which include the electroencephalogram and electro-oculogram. Mason *et al* showed that the heart rate and heart rate variability probability density functions are different in different sleep states and that these could be used to classify sleep state.[14] The major problem with that approach, however, is that the variable being studied is also being used to classify the data, which in turn may mask differences.

Our findings suggest that the simplest of indices of respiratory rate, respiratory rate variability, heart rate, and heart rate variability measured over 24 hours are of little value in discriminating between infants who go on to be victims of the sudden infant death syndrome and control infants. There may, however, be a group difference, with the cases of sudden infant death syndrome showing a higher mean instantaneous heart rate than the controls.

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Brain shrinkage in chronic alcoholics: a pathological study

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Abstract

A quantitative neuropathological necropsy study of 22 control and 22 chronic alcoholic subjects showed a statistically significant loss of brain tissue in the chronic alcoholic group. The loss of tissue appeared to be from the white matter of the cerebral hemispheres rather than the cerebral cortex. This may reflect a primary alteration in the composition or structure of the white matter or it may be secondary to loss of nerve cells from the cortex with subsequent degeneration of the axons in the white matter. Further morphometric analyses including cortical neuronal counts will be necessary to clarify this issue.

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Introduction

A substantial proportion of chronic alcoholics and even heavy social drinkers have been shown to have brain shrinkage by neuroradiological techniques including pneumoencephalography[1] and computed tomography (CT).[2-4] Some of this shrinkage may be reversible after prolonged abstinence from alcohol.[5 6] There are associated cognitive defects,[7] and a more generalised global dementia may relate directly to chronic alcohol abuse.[8] Few objective neuropathological data are available to explain these changes, although studies of brain weight show that alcoholics have a lower mean brain weight than normal.[9 10] Brain weight is an unsatisfactory measurement, however, since it varies considerably from person to person.[11] As a result of the development of a relatively simple technique for measuring intracranial volume at necropsy using polyurethane foam casts[12] we have been able to derive accurate quantitative data on the volume of brain tissue lost in chronic alcoholic patients.

Brain volume (BV) bears a constant relation to intracranial volume (ICV) in normal adults.[13] The pericerebral space is an expression of this relation and is calculated (as a percentage) as: (ICV BV)/ICV ($\times$ 100). Any decrease in brain volume is reflected by an increase in pericerebral space and vice versa, since the intracranial volume remains constant throughout life. The mean pericerebral space was 8·3% in 44 controls and 11·3% in 25 alcoholic patients.[14] The loss of brain tissue appeared to be