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THE EFFECT OF INHALATION OF CARBON DIOXIDE IN AIR ON THE RESPIRATION OF THE FULL-TERM AND PREMATURE INFANT

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Very varied results have been obtained by different workers when carbon dioxide has been administered to the new-born infant. Using 95 % oxygen and 5 % carbon dioxide, Gibberd (1949) states: '...indeed, if carefully controlled experiments are carried out, it is difficult to find evidence that the administration of 5 % carbon dioxide to an infant has any chemical effect in stimulating respiration.' Howard & Bauer (1950) however, state: 'The administration of 5 % carbon dioxide and 95 % oxygen was always a stimulant, and the longest the mixture could be given without causing crying was five minutes and thirty seconds.' These latter authors found an average increase in minute volume of 64·5 % in nine infants with a range varying between 22 and 137 %, when the gas had been administered on an average for 3·75 min. Even this latter result shows a marked discrepancy from the adult subject, for Haldane & Priestley (1905) showed that 5·14 % carbon dioxide (in the presence of mild anoxia) caused a threefold increase of minute volume.

It is clearly of considerable importance, in studying the respiration of the new-born infant, to determine whether in fact this subject does respond to carbon dioxide, and further, whether this response is quantitatively different from that of the adult. Oxygen cannot be regarded as an inert vehicle for the carbon dioxide, as the infant shows a marked and biphasic response to the administration of high concentrations of the former gas (Cross & Warner, 1951; Cross & Oppé, 1952*b*), and for this reason it is important that the carbon dioxide should be administered in air. Further, in order to test the effects of carbon dioxide on the sleeping baby, only low concentrations of the gas may be used, for as noted by Howard & Bauer and confirmed by ourselves, concentrations as low as 5 % cause restlessness and crying.

METHODS AND MATERIALS

The infants were examined at rest in the body plethysmograph described by Cross (1949), and modified with a mercury seal for the lid (Cross & Warner, 1951). The gas mixtures were kindly made up by the British Oxygen Company, and were administered to the baby after being bubbled through water and with an appropriate 'mask' as described by Cross & Warner (1951). To test this method, air was administered from a cylinder, and it was found that a group of resting babies did not vary in their respiratory behaviour significantly from a control period when they breathed room air.

The gas mixtures used were 0·5, 1 and 2% carbon dioxide made up in air. These mixtures thus had a slightly diminished percentage of oxygen when compared with room air (as low as 20·5% in the case of the 2% carbon dioxide mixture), but we have no evidence that such a minute variation in oxygen content would exert any physiological effect. Tests were carried out to determine whether a significant percentage of carbon dioxide was lost by bubbling the gas through water, but no difference was found by Haldane analysis between the percentage of carbon dioxide emerging into the mask at the beginning and end of a five minute rest run.

The subjects used in the experiments were full-term and premature infants in the nurseries of the Maternity Department at Paddington Hospital. Prematurity was taken to mean a baby of 2·5 kg or less at birth.

The plan of an individual experiment was that a baby was taken at any convenient time after a meal and placed in the plethysmograph. If the baby slept satisfactorily, the supply of room air was replaced by air given through the mask from a compressed air cylinder, and at a convenient moment the required carbon dioxide mixture was bubbled through the same humidifying bottle as had been used for the air. The carbon dioxide administration was continued for 5 min, and then air was again given from a cylinder or the mask was removed, and a final control period of respiration on room air was recorded. If the baby moved or cried at any time during or subsequent to the application of the test gas, the preceding minute of the record and all the following minutes were excluded from the final grouped results. These results have been reported briefly (Cross, Hooper & Oppé, 1953).

RESULTS

The results obtained from the three experiments on the two groups of babies were scaled and treated statistically in the same way as those of Cross & Warner (1951). Table 1 shows the mean values obtained from the two groups of babies during the initial control period. These results show that the full-term babies studied were significantly lighter than those reported previously (Cross, 1949), and the minute volume was correspondingly less.

TABLE 1. Average resting values of babies studied

	Full-term	Premature
No. of observations	70	57
No. of infants, Male	33 } 63	17 } 37
Female	30	20
Age (days)	2–12	1–34
Mean weight and S.D. about mean (kg)	$3·07 \pm 0·355$	$2·12 \pm 0·253$
Mean minute volume (ml.) and S.D.	$523·4 \pm 79·45$	$388·6 \pm 96·34$
Mean respiration rate/min and S.D.	$32·46 \pm 7·81$	$31·73 \pm 6·66$
Mean tidal air (ml.) and S.D.	$17·01 \pm 4·48$	$12·82 \pm 3·43$

Note. In order to obtain the final average results, the repeated results on any individual baby have been averaged before adding them to the total. This treatment is probably quite justifiable in the case of the full-term infants, who show little change during their short stay in hospital, but it is more dubious in the premature infants, who may undergo significant changes in weight and respiratory behaviour during their more prolonged period in hospital (Cross & Oppé, 1952*a*).

Table 2 shows the number of observations made and the number of subjects used in each of the six groups of experiments. The same experiment was repeated on the same baby rarely, but the same baby was used for different experiments as frequently as possible. In view of the greater respiratory irregularity of the premature infant, it would have been preferable to have had larger numbers of these than of full-term infants, but the supply of premature infants was limited.

Figs. 1–3 show the results obtained in each of the experiments on the two groups of subjects. In order to afford a direct comparison between the two

TABLE 2. Composition of groups of infants receiving carbon dioxide mixtures

	Full term infants		Premature infants	
% CO_2	Subjects	Observations	Subjects	Observations
0·5	21	21	18	18
1·0	26	26	18	18
2·0	23	23	18	21

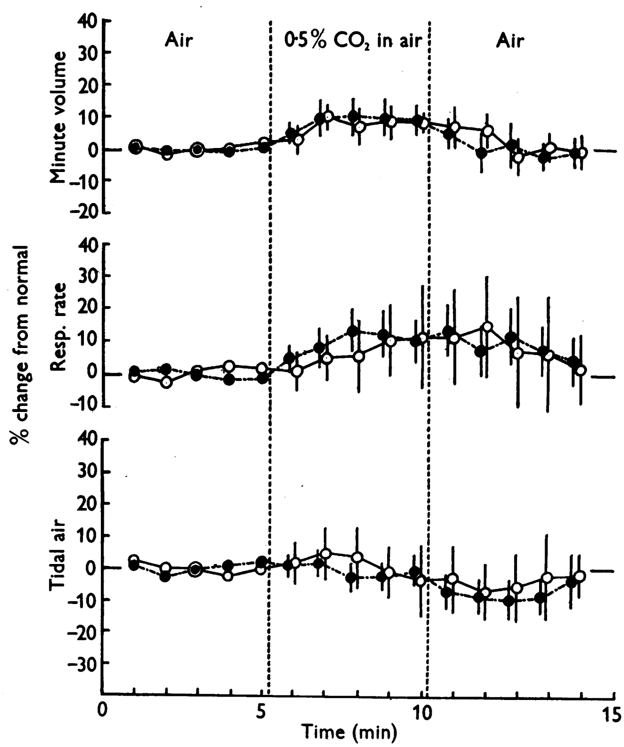

Fig. 1. Graphs showing the percentage change from normal of the minute volume, respiration rate and tidal air of a group of full-term (closed circles) and premature (open circles) infants, when 0·5% CO_2 is administered for 5 min after a period of 5 min on air. The vertical lines through the mean points represent the 95% confidence limits of the means. For clarity the points have been staggered where the confidence limit lines overlap.

groups, the mean of the control period of both the premature and the full-term infants has been scaled to 100 %, and the percentage changes from this resting value are shown. It will be seen that even with 0·5 % carbon dioxide there is a significant increase in the minute volume of respiration for the last 4 of the 5 min of the test period, and also the pattern and the degree of the

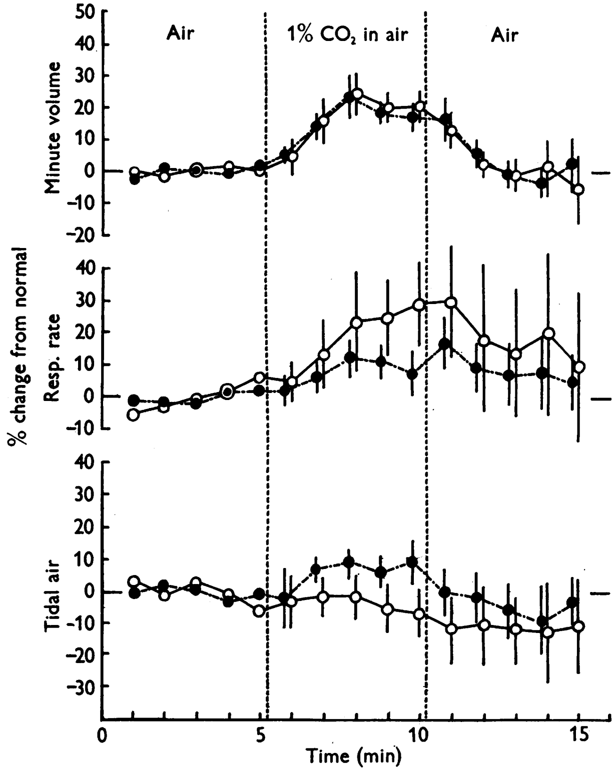

Fig. 2. Graphs showing the percentage change from normal of the minute volume, respiration rate and tidal air of a group of full-term (closed circles) and premature (open circles) infants, when 1 % CO_2 is administered for 5 min after a period of 5 min on air. Other conventions as in Fig. 1.

response is very similar in both groups of infants. It also seems likely that with 0·5 and 1 % carbon dioxide a 'steady state' has been reached in the last 2 min with the test gas, but this is less certain with 2 % carbon dioxide, where there is a greater variation in the response of individual babies.

The mechanism of the rise in minute volume

The pattern of the stimulation in the respiration rate and tidal air is less consistent between the two groups of infants than is the effect on total ventilation. Thus the full-term infants show a significant increase in respiration rate with all three carbon dioxide mixtures, and an increase in depth of respiration with the two higher concentrations of the gas. The premature infants show a significant increase in respiration rate with both 1 and 2% carbon dioxide, and depth is increased with only the highest concentration of the gas used.

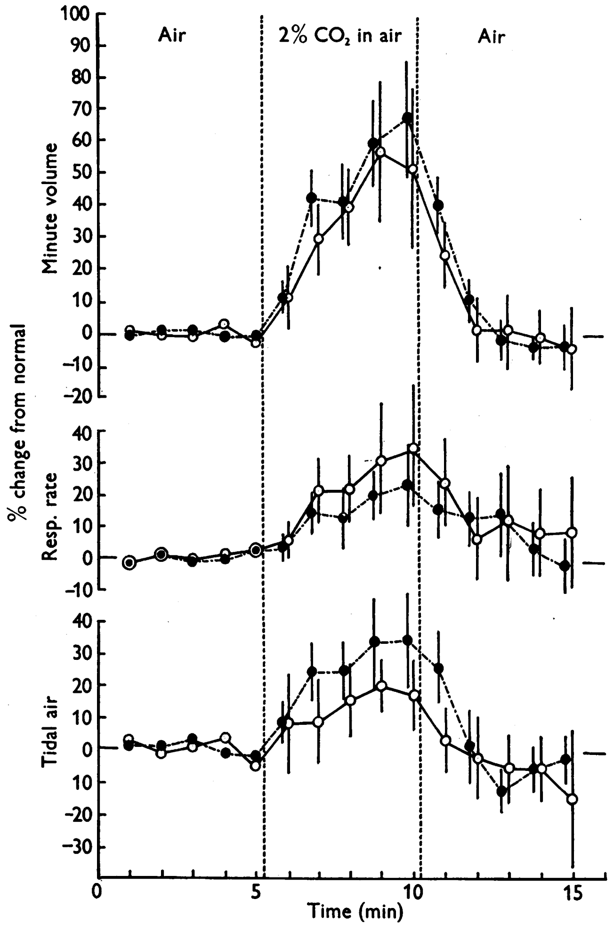

Fig. 3. Graphs showing the percentage change from normal of the minute volume, respiration rate and tidal air of a group of full-term (closed circles) and premature (open circles) infants, when 2% CO_2 is administered for 5 min after a period of 5 min on air. Other conventions as in Fig. 1.

It is noticeable that in the final periods on air the rate has returned to the original resting level only in the fifth minute with the full-term infants who had received 2% carbon dioxide. This increase in rate is reflected by a consistent decrease in depth of respiration during the latter part of this control period, and so the total ventilation returns very close to normal values. Some of the premature infants appeared to be particularly sensitive to carbon dioxide, and responded by a great increase in rate of respiration which did not return towards normal during the last five minutes on air. Such behaviour did not constitute 'restlessness' as defined above, and so the results obtained from them are included, with the consequent rather wide limits of variation shown in the rate and depth graphs for the premature infants.

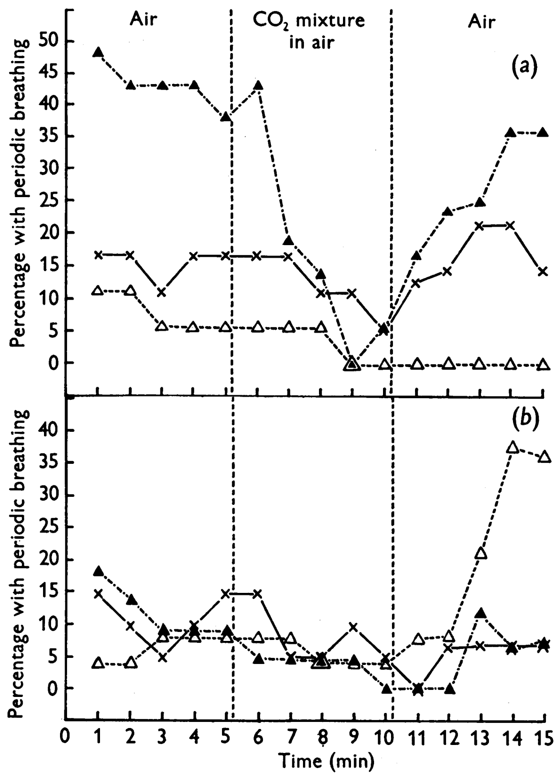

Fig. 4 (*a*). Graphs showing the percentage of occurrence of periodic breathing in the three groups of premature infants who received air, CO_2 in air and air, each for a period of 5 min. (*b*) Similar graphs for the full-term infants. ▲, infants receiving 2 % CO_2; △, infants receiving 1 % CO_2; ×, infants receiving 0·5 % CO_2.

Effect of carbon dioxide on the rhythm of respiration

Figs. 4*a* and *b* show the percentage occurrence of periodic breathing with each group of infants, and at each gas concentration. As in Cross & Oppé (1952*b*), we have used a simple definition of periodic breathing, namely: 'Breathing is included as periodic if groups of respiratory movements are interrupted by periods of apnoea of not less than 3 sec duration, the cycle lasting for 30 sec or less, and being repeated at least twice.'

It is very unfortunate that there is such a great disparity in the occurrence of periodic breathing during the control period, varying as it does in the premature infants between 5·5 and 40 %, but it seems likely that the stimulation of carbon dioxide tends to diminish the occurrence of this type of irregularity at all concentrations tested, but the differences noted are only significant in the groups receiving 2 % carbon dioxide.

DISCUSSION

Apart from the authors already quoted, there seems to have been little investigation into the effect of carbon dioxide on the respiration of the new-born infant. Wilson, Long & Howard (1942) gave 7 % carbon dioxide in high oxygen to a series of twenty premature infants, and noted a 'definite and marked hyperpnoea', but no quantitative measurements were made. In all the work quoted, high oxygen/carbon dioxide mixtures have been used, so that it would in any case be difficult to determine the precise effect of the carbon dioxide. Shock & Soley (1940) have shown that the adult human subject has a notably different response to carbon dioxide in 21 % oxygen with nitrogen than with the same concentration of carbon dioxide in pure oxygen.

Although, for the reasons stated above, it is not possible to make any quantitative comparison between the results reported here and the findings of other authors in babies, it is possible to compare our results with those reported on adults. The figures of Shock & Soley (1940) have been chosen for this comparison because those workers have taken great care to obtain complete rest in their subjects before administering the gas (in air), and have studied the effect of similar gas concentrations to those used in the present investigation. Their work differs from ours in that they used a Siebe-Gorman half-mask with valves and recording spirometers.

To make this comparison we have assumed that in the 4th and 5th min of carbon dioxide administration the babies have reached a steady state. We have confidence in this assumption from subsequent work, which shows that when 0·5 % carbon dioxide was given for 10 min to resting premature and full-term infants, the average rise in the 4th and 5th min was a fair sample of the mean increase in minute volume over the last 6 min of carbon dioxide administration. We have further assumed that there is no significant difference between premature and full-term infants in their response to carbon dioxide. It will be noted from Figs. 1–3 that at the 4th and 5th min of carbon dioxide administration the differences in minute volume between the premature and full-term infants are quite insignificant in all cases. In fact, the full-term infants reported here show a slightly greater rise in minute volume than the premature infants when both groups are receiving 0·5 and 2 % carbon dioxide, but this trend is reversed with 1 % carbon dioxide.

In Table 3 the averages of the fourth and fifth minutes of the babies regarded as a homogeneous group are shown, for comparison with the results recorded from Shock & Soley.

TABLE 3. Effect of carbon dioxide on babies and adults

% CO_2	No. of observations	Increase in minute volume (%)	S.D. about mean
		Babies	
0·5	38	8·91	7·93
1	44	18·95	8·39
2	41	57·61	39·44
		Adults (Shock & Soley, 1940)	
1	17	14·24	6·28
2	12	34·25	8·34
4	15	98·60	24·87

The percentage increase in minute volume is shown here for premature and full-term babies. The mean of the fourth and fifth minutes of carbon dioxide administration has been used. The results of the adults are taken from Table 2, p. 779, of Shock & Soley's paper. These subjects were in a steady state on the $CO_2/21\%\ O_2/N_2$ mixtures.

It will be seen that for a given percentage of carbon dioxide, the baby is more stimulated than is the adult. A 'Student's' *t* test comparing the means shows that the differences are significant at 1 and 2% carbon dioxide ($P < 0{\cdot}05$ at 1% carbon dioxide, $P < 0{\cdot}001$ at 2% carbon dioxide).

The relative degree of stimulation shown by the adults and the babies is somewhat reminiscent of the comparison made by Peabody (1915) on the effect of carbon dioxide on the respiration of normal and acidotic adults. The babies, like the acidotic adults of Peabody, show a greater increase in minute volume for the same dose of carbon dioxide. This finding is of particular interest in view of the acidaemia present in the 'normal' premature infant which was first described by Yllpö (1916). In papers from the same laboratory Reardon, Graham, Wilson, Baumann, Tsao & Murayama (1950) and Graham, Wilson, Tsao, Baumann & Brown (1951) find that while the adult has a plasma pH of 7·40, chloride 103 m.equiv/l. and CO_2 of 24 m.equiv/l., the full-term infant has pH of 7·39, chloride 106 m.equiv/l. and CO_2 20 m.equiv/l., while the premature infant has pH 7·31, chloride 111 m.equiv/l. and CO_2 20 m.equiv/l. The differences between the adult and the full-term infant tend to diminish during the first 24 hr of life (Graham *et al.* 1951), but the premature infant maintains its pH and electrolyte characteristics for some weeks.

If the greater stimulating effect of carbon dioxide in babies is to be attributed to an increased proportion of hydrogen ions in the blood of the babies, then one would expect that there would be a trend of response from the adult through the full-term to the premature infant, but in fact no such tendency is observed. As already noted, with two of the three test gases the full-term infants responded with a greater increase in minute volume than the premature, and from this evidence we feel that it must be concluded that the infantile respiratory centre is specifically more sensitive to carbon dioxide than that of the adult.

This investigation would be more complete, and the interpretations which could be applied would be more far-reaching if proof of a 'steady state' could be produced. If it were possible to measure the alveolar carbon dioxide and estimate the dead space of the infants at rest and while receiving the gases, then some of the present uncertainties would be resolved, but so far, although we are anxious to make those measurements, we have not devised methods which are successful.

SUMMARY

1. 100 infants have been examined on 127 occasions in the body plethysmograph for their response to 0·5, 1 and 2% carbon dioxide in air.

2. It is found that on an average both premature and full-term infants show a statistically significant response to all three concentrations of carbon dioxide.

3. The group of babies receiving 1 and 2% carbon dioxide show a significantly greater percentage increase in minute volume than the adults examined by Shock & Soley (1940).

4. It is concluded that the respiratory centre of the infant is more sensitive to carbon dioxide than that of the adult.

Once again we are indebted to many for helping us to undertake this work. Financial support for expenses, and the excellent technical assistance of Mr T. R. Nichols came from an M.R.C. research grant to Professor A. St G. Huggett until October 1951, and since then has been from a research grant from the St Mary's Hospital Research Fund. We have received most kind cooperation from the sisters and nurses of the Maternity Department, Paddington Hospital, Harrow Road, and we would like to thank the Management Committee for permission to do this work, and Miss Amy Fleming, Mr J. P. Erskine and Dr Reginald Lightwood, who were in clinical charge of the patients examined.

Note. Full tables giving the data from each experiment on each baby are available at St Mary's Hospital Medical School.

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