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ANOXIC DEPRESSION OF THE MEDULLA IN THE NEW-BORN INFANT

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Previous work (Cross & Oppé, 1952) has shown that when the oxygen in the inspired air is reduced to 15%, the infant, like the adult, responds by an increase in the minute volume of respiration; but, unlike the adult, the infant does not maintain this response. If in such an experiment the infant is given pure oxygen after the 15% has ceased to produce an apparent response, there is an immediate and marked diminution in the minute volume. On this evidence it was suggested that the infant has an active chemoceptor reflex but that this becomes ineffective in maintaining hyperventilation when anoxia is continued beyond 2 min, because the medulla has become unresponsive to the stimuli it is receiving.

It was decided to test the hypothesis that mild anoxia produces medullary depression in the new-born infant by attempting to stimulate the medulla under normal conditions and when the infant was hypoxic. To do this carbon dioxide was given first in air and then in a 15% oxygen/85% nitrogen mixture. This work has been briefly reported (Cross, Hooper & Lord, 1953).

METHODS

Normal full-term infants and healthy premature infants (less than 2·5 kg birth weight) from the Maternity Department, Paddington Hospital, were examined in the body plethysmograph (Cross, 1949). After 20 min or more of rest in the plethysmograph and if the infant had settled to quiet sleep, the required gas mixture was passed over the infant's face in a chamber as previously described (Cross & Warner, 1951). During the first 5 min of the experiment (control period) air from a compressed air cylinder was led through a humidifying bottle to a chamber covering the baby's face. Other gas mixtures were given as required through the same bottle. Many of the babies remained quiet for the whole of the experimental period of 15 or 20 min, but, if a baby became restless or cried, results were only accepted for the earlier part of the experiment recorded during quiet sleep.

From each baby a record of minute volume, respiratory rate and tidal volume was obtained. The effects on respiratory rate and tidal air were not strikingly different from what would be expected with the minute volumes recorded, and for the sake of brevity these have been omitted from this report. The changes in minute volume in each individual baby have been expressed as percentages of the average minute volume during the control period. With the exception of Figs. 6 and 7, in which individual changes are shown, the tables and figures refer to average changes for groups of babies and the percentage effects can thus be compared. The statistical methods used are similar to those described previously by Cross & Warner. Although the results from premature and full-term infants have been separately analysed they are here presented together because there were no significant trends of difference between the two groups of babies from the point of view of the subject of this communication.

RESULTS

Table 1 shows the different experiments performed and the number of subjects and tests in each type of experiment. The same baby was used as frequently as possible for different experiments but only inadvertently for a reduplication of the same experiment.

TABLE 1. Experiments performed and number and type of subject used for each experiment. The totals for 'No. of subjects' refers to the total number of *different* babies used in the series. Experiments under 1 A have been previously reported (Cross, Hooper & Oppé, 1953). Each gas mixture was given for 5 min unless otherwise stated.

	Premature		Full term		
Expt.	No. of subjects	No. of expts.	No. of subjects	No. of expts.	Total expts.
1 A. Air → 2 % CO_2 in air → air	18	21	23	23	44
1 B. Air → 15 % O_2 + 2 % CO_2 → air	22	22	23	23	45
1 C. Air → 15 % O_2 → 15 % O_2 + 2 % CO_2 → air	22	22	20	20	42
2 A. Air → 10 min 0·5 % CO_2 in air → air	11	11	11	11	22
2 B. Air → 10 min 15 % O_2 in N_2 → air	13	13	31	31	44
2 C. Air → 15 % O_2 → 15 % O_2 + 0·5 % CO_2 → air	9	10	32	34	44
Total	70	99	107	142	241

Experiment 1. 2 % CO_2

1 A. *Air* → 2 % CO_2 *in air* → *air* (44 *tests*)

See Fig. 1 A. These results were reported previously (Cross, Hooper & Oppé, 1953), and only differ here in that the results for premature and full-term infants are shown combined together. From Fig. 1 A one can see that there is an immediate response to 2 % CO_2 when administered in air, but the response does not appear to become maximal until the 4th minute.

1 B. *air* → 2 % CO_2 + 15 % O_2 *in* 83 % N_2 → *air* (45 *tests*)

See Fig. 1 B. It will be observed that the apparently maximal response is rapidly reached and that from the 2nd to the 5th minute of CO_2 administration there is no notable increase in the minute volume of ventilation.

1 C. *Air* → 15 % O_2 + 85 % N_2 → 2 % CO_2 + 15 % O_2 *in* 83 % N_2 → *air* (42 *tests*)

See Fig. 1 C. When 15 % O_2 is given after air there is a characteristic temporary increase in the minute volume of respiration which in this series lasts for 3 min. When 2 % CO_2 is added to the low oxygen mixture the minute volume of respiration rises more slowly towards a maximum value than it did in either of the two previous groups of experiments.

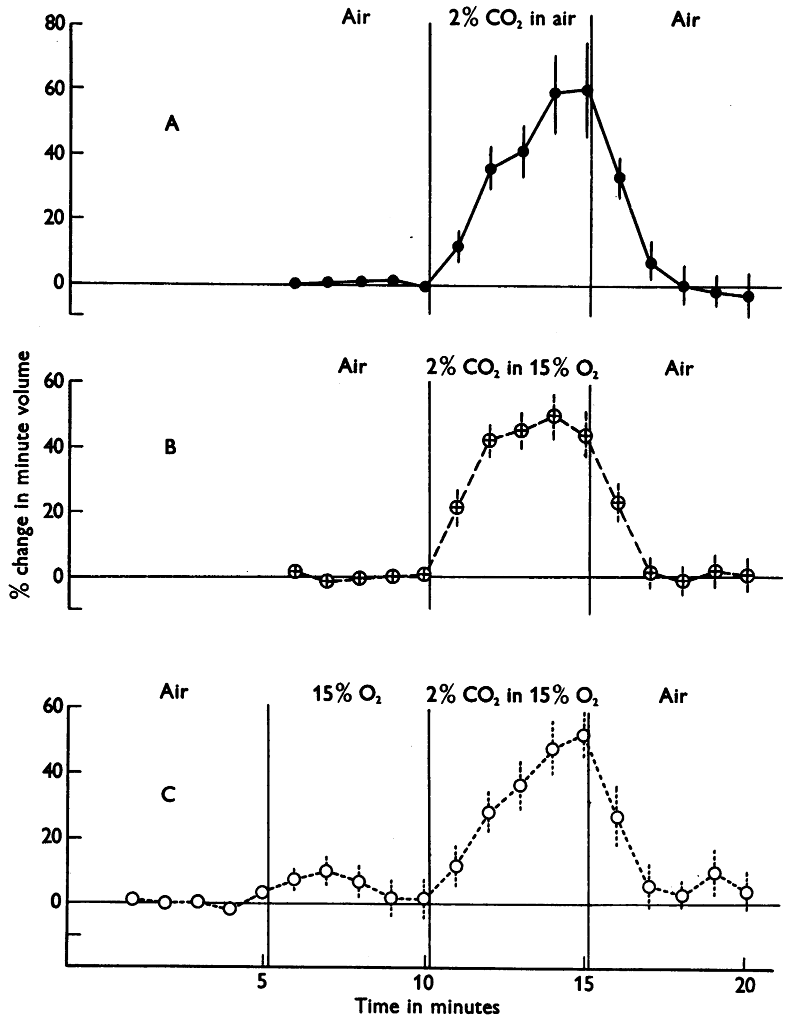

Fig. 1. A: —●— shows the percentage increase of minute volume in a group of forty-four experiments on full-term and premature babies who received air, 2 % CO_2 in air, and air, each gas for a period of 5 min. The points represent mean values and the vertical lines the 95 % confidence limits of the mean. B: - - - ⊕ - - - shows the results of forty-five experiments in which the test gas was 2 % CO_2 + 15 % oxygen in 83 % nitrogen. C: - - - ○ - - - shows the results of forty-two experiments in which the test gases were, first, 15 % oxygen in 85 % nitrogen and then 2 % carbon dioxide + 15 % oxygen in 83 % nitrogen.

From these results it was presumed that 2 % CO_2 was such a powerful medullary stimulant that it was able in a few minutes largely to overcome the anoxaemia produced by the 15 % O_2, and it was not possible to devise experiments like those of Nielsen & Smith (1951) where, by an ingenious technique, the alveolar partial pressure of O_2 (and hence presumably the arterial pO_2) was kept almost constant with a varying concentration of CO_2 in the inspired air. For this reason it was decided to proceed with experiments using only 0·5 % CO_2. This has already been shown to give an increase in minute volume in the new-born infant of about 10 %, which is comparable to the early stimulatory effect of 15 % O_2.

Experiment 2. 0·5 % CO_2

In the second group of experiments the effect of adding 0·5 % CO_2 in air (Fig. 2A) was compared with the effect of adding 0·5 % CO_2 to 15 % O_2 (Fig. 2C). In the first experiment each baby breathed air for 5 min and then 0·5 % CO_2 was added for 10 min, and lastly a final control period of 5 min, on air alone was recorded. In the experiment combining the effects of low O_2 and 0·5 % CO_2 the experiment was divided into four experimental periods of 5 min each. In the first period the baby breathed air alone, in the second he breathed 15 % O_2, in the third 15 % O_2 with 0·5 % CO_2 and in the final period air once more. A further control experiment was necessary to show that 15 % O_2 alone did not alter the respiratory minute volume from normal values on air (apart from the initial period) even if it was continued for 10 min (Fig. 2B).

2A. *Air* → 10 *min* 0·5 % CO_2 *in air* → *air* (22 *tests*)

Fig. 2A shows that with this gas mixture from the 2nd to the 10th minute there is a significant rise of minute volume above the control values and this increase is maintained at around 10 %.

2B. *Air* → 10 *min* 15 % O_2 *in* 85 % N_2 → *air* (44 *tests*)

See Fig. 2B. Previous experiments had consistently shown that in the 4th and 5th minutes of 15 % oxygen administration the minute volume always returned to approximately normal values. It had been assumed (on other evidence) that the initial hyperventilation had not been maintained because of hypoxic depression of the medulla, but it is conceivable that the 2 min hyperventilation had so lowered the arterial partial pressure of CO_2 that the subsequent hypoventilation was due to hypocapnia. If this explanation were correct, there would presumably be a secondary episode of hyperventilation if the low oxygen administration were continued for a longer period and these experiments were undertaken to exclude this possibility. It will be seen that once again the minute volume is increased for the first 2 min of low oxygen administration and from the 2nd to the 10th minute the average values obtained do not differ significantly from the control levels on air. It is of considerable interest to note that in the final control period on air there is a marked diminution of minute volume for the first 2 min. This change would appear to be similar to that noted previously (Cross & Oppé, 1952) when 100% oxygen was administered after a period of hypoxia. The administration of normal air would appear to have diminished the chemoceptor drive of the medulla and the low level of purely 'medullary' respiration was revealed. Unlike the occasions when 100% oxygen was given after 15% oxygen, there is no subsequent hyperventilation.

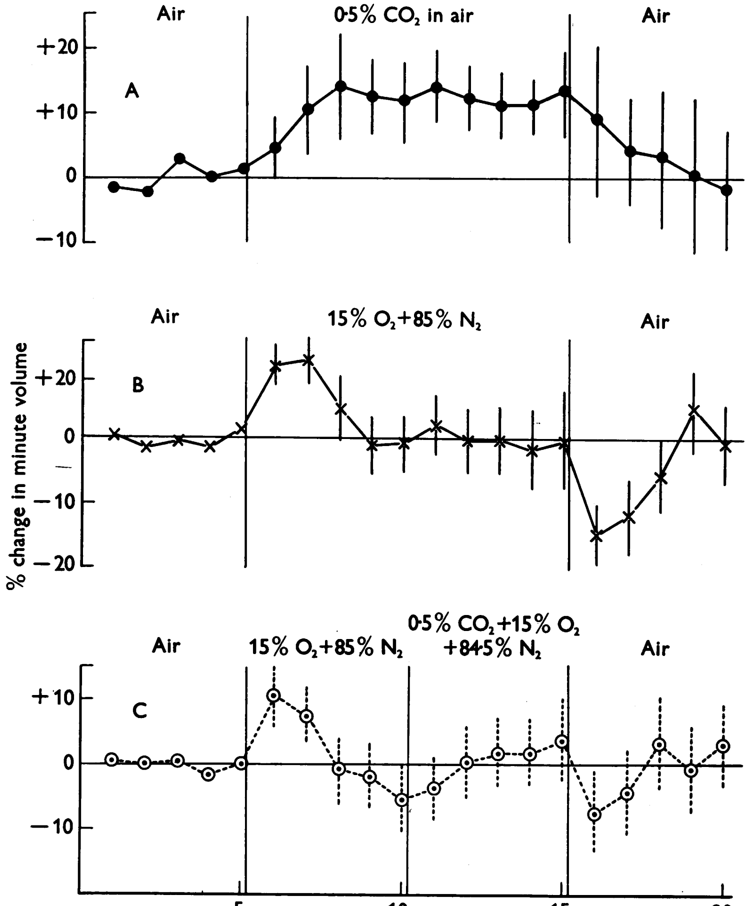

Fig. 2. A: —●— shows the percentage change of minute volume in twenty-two experiments when the infants were given 0·5% carbon dioxide in air for 10 min. Other conventions as in Fig. 1. B: ×—× shows the results of forty-four experiments in which 15% oxygen with 85% nitrogen was given for 10 min. C: - - - ⊙ - - - shows the results of forty-four experiments when 15% oxygen with 85% nitrogen was given for 5 min, followed by 0·5% carbon dioxide in 15% oxygen and 84·5% nitrogen.

2C. *Air* → 15% O_2 *in* 85% N_2 → 15% O_2+0·5% CO_2 *in* 84·5% N_2 → *air* (44 *tests*)

See Fig. 2C. In the 5 min of 15% oxygen administration the pattern of respiratory behaviour is very similar to that found in previous experiments, although the minute volume falls to 94·5% of control value ($P < 0·05$) in the 5th minute. When 0·5% CO_2 is added to the low oxygen mixture, there is an apparent tendency for the minute volume to rise but it is never significantly raised above the control levels recorded on air. When air is again given we see that the minute volume is lowered significantly below normal values for only 1 min. Presumably CO_2 retention in the previous 5 min nullifies effects due to diminishing chemoceptor stimulation of the medulla.

DISCUSSION

Table 2 gives the values obtained in the 1st and 2nd minutes and also the 4th and 5th minutes (combined) of the experiments when 2% CO_2 was administered. The 4th and 5th minutes of CO_2 administration have been chosen to give the nearest approximation to a 'steady state' on this gas mixture. Fig. 3 affords a comparison for the period when 2% CO_2 was given in these three different types of experiment.

TABLE 2. The results of 2% CO_2 administration obtained in the 1st and 2nd minute and also the 4th and 5th minute combined. The numbering of the minutes is in accordance with times shown in Figs. 1 and 3. 1A is 2% CO_2 in air. 1B is 2% CO_2 in 15% O_2 after air and 1C is 2% CO_2 in 15% O_2 after 15% O_2. The results of the '*t*' test within individual minutes are only shown where there is a significant difference.

	1A	1B	1C	1A	1B	1C	1A	1B	1C
Minute	11	11	11	12	12	12	14 and 15	14 and 15	14 and 15
No. of experiments	43	44	41	40	43	37	41	42	39
Average min volume	111·5	121·9	111·2	135·8	141·6	127·7	157·6	145·4	149·1
Standard deviation	16·43	15·89	20·23	21·10	16·81	19·35	39·44	24·01	21·35
Student's '*t*' test	3·000		2·716	—	3·448		—	—	—
P	<0·01		<0·01	—	<0·001		—	—	—
Conclusion	1B>1A		1B>1C	—	1B>1C		—	—	—

It will be seen that in the 1st minute of administration of 15% oxygen with 2% CO_2 the minute volume is significantly greater than when the same dose of CO_2 is given either in air or in 15% O_2 after preceding hypoxia. Again, in the 2nd minute this difference is maintained for the acute as compared with the longer lasting hypoxia, but here the carbon dioxide in air gives a ventilation which does not differ significantly from that of either of the two hypoxic experiments. In the latter part of the experiment, although the minute volume with CO_2 in air is greater than either of the minute volumes obtained with CO_2 in low oxygen there are no statistically significant differences, and it would be improper to draw any conclusions from this result. Shock & Soley (1942) found in adult male subjects that, on an average, 2% CO_2 in 12% O_2 produced a stimulation of ventilation which was the algebraic sum of the increases noted for 2% CO_2 in air together with that for 12% O_2 in N_2. The results obtained with the babies in the 1st minute of CO_2 administration agree with this finding.

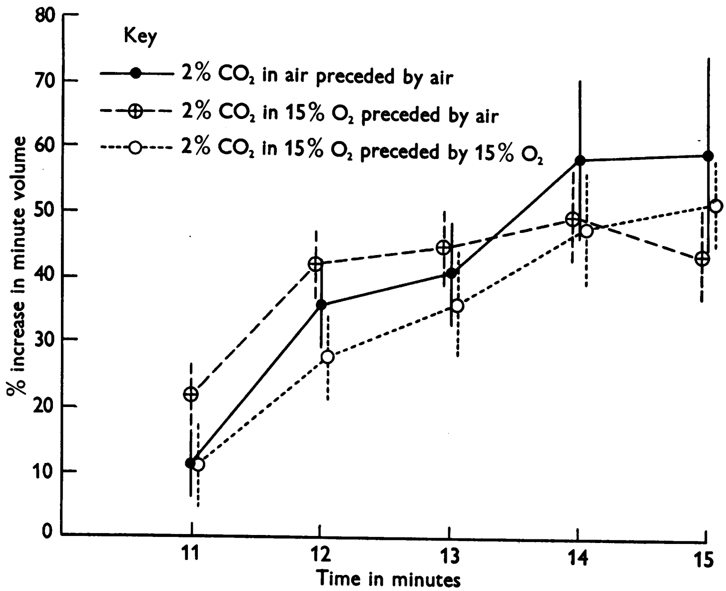

Fig. 3. Direct comparison between the results shown in Fig. 1 for the period when 2% carbon dioxide was administered in air or in 15% oxygen. Symbols and conventions are as in Fig. 1.

When we examine the results obtained with 0·5% CO_2 given during the administration of 15% O_2, there is certainly no longer evidence of summation of the two stimuli, and it is now necessary to examine the results obtained in order to see whether the hypoxia has substantially inhibited the normal effect of the carbon dioxide. It can be seen from Fig. 2 that 0·5% CO_2 in air has an apparently greater effect in increasing the minute volume than has the same dose of CO_2 given in 15% O_2, but it is necessary to make a direct comparison. Fortunately a direct comparison can be made as the minute volume on 15% O_2 falls, by the end of 5 min, to essentially normal (control) levels. In Fig. 4, where Figs. 2A and 2C are superimposed, one can observe the effect of giving CO_2, with and without hypoxia, and Fig. 5, where Figs. 2B and 2C are superimposed, affords a direct comparison of the effect of hypoxia with and without CO_2. A clear-cut difference in the 11th to 15th minutes of the first pair of experiments (Fig. 4) would, of itself, be sufficient to establish the presence of medullary depression by hypoxia: the degree of this depression (if present) would be recognized as complete if it were shown (Fig. 5) over the

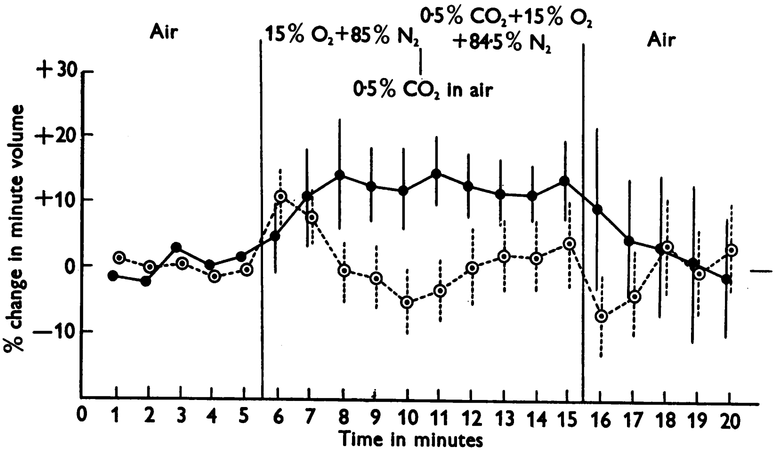

Fig. 4. Direct comparison between two of the groups of infants shown in Fig. 2. —●—, 0·5% carbon dioxide in air, and - - -⊙- - -, 0·5% carbon dioxide in 15% oxygen and 84·5% nitrogen after 5 min of 15% oxygen and 85% nitrogen.

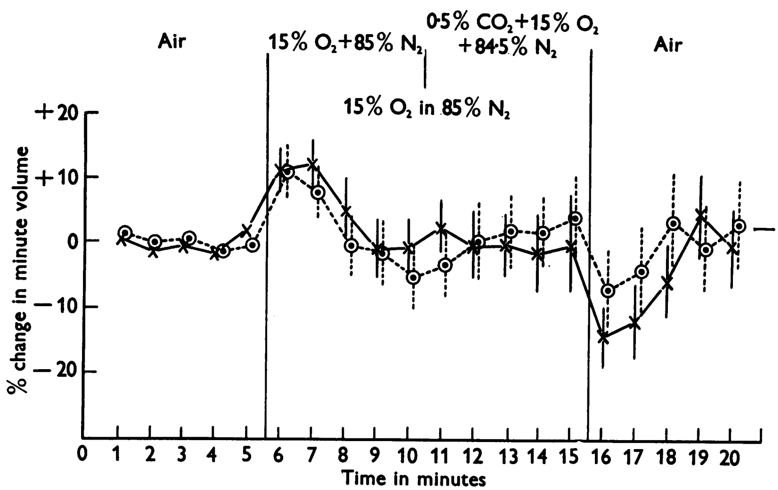

Fig. 5. A comparison between a group of infants receiving 15% oxygen in 85% nitrogen for 10 min (— × —) and the other group receiving the same gas for the first 5 min, followed by 0·5% carbon dioxide in 15% oxygen and 84·5% nitrogen (- - - ⊙ - - -).

same period that there was no difference in any individual minute, whether CO_2 were given to the hypoxic infant or not. Taking each individual minute of the period when 0·5% CO_2 was given in 15% O_2 it is seen from Fig. 4 that there is some considerable overlapping of the confidence limits, indicating that the differences observed are not all significant. So to complete the comparison and to obtain a more accurate picture of the responses of the babies the results of individual minutes have been averaged as in Table 2, where there has been something approaching to a 'steady state'. For this purpose minutes 9 and 10 and also 13 to 15 have been used as a basis of calculation. They were chosen after inspection of Fig. 2, and seem to be the nearest one can get to this ideal situation of the body state in a subject so irregular in its behaviour as the baby. In Table 3 the results of the experiments so calculated are shown and the comparisions made between the relevant periods. In making the comparison between CO_2 in air and CO_2 in 15% O_2, a difficulty arises because the carbon dioxide was given for 10 min in air and for only 5 min in low oxygen, and so both possible comparisons have been made, that is CO_2 + 15% O_2 compared with CO_2 in air for both the 9th and 10th minute and with the same gas from the 13th to 15th minute. It will be seen from the results of the 't' tests recorded in Table 3 that CO_2 in air gives rise to a significantly greater minute

TABLE 3. The average results in selected minutes of Expt. 2. 2A is 0·5% CO_2 in air, 2B is 15% O_2 for 10 min, 2C is 15% O_2 followed by 0·5% CO_2 in 15% O_2. The numbering of the minutes is as shown in Figs. 2, 4 and 5. The results of the relevant 't' test are shown both where the differences are significant and insignificant.

	2A	2B	2C	2A	2B	2C
Minute	9 and 10	9 and 10	9 and 10	13 to 15	13 to 15	13 to 15
No. of experiments	22	44	44	18	38	40
Average minute volume	112·5	100·1	96·3	112·3	99·00	102·4
Standard deviation	12·20	13·18	15·17	8·48	15·43	15·77
Comparing	2A and 2C	2B and 2C		2A and 2C		2B and 2C
Student's 't' test	4·347	1·264		2·506		0·961
P	<0·001	0·2–0·3		<0·02		0·4–0·3
Conclusion	2A>2C	—		2A>2C		—

Comparing 2A (9th and 10th minute) with 2C (13th to 15th minute) 't' = 2·603, $P < 0·02$
Comparing 2C (9th and 10th minute) with 2C (13th to 15th minute) 't' = 1·803, P 0·1–0·05

volume than the same dose of the gas in the presence of 15% O_2 ($P < 0·001$, $P < 0·02$). Further, there is no evidence from these figures analysed in this way that in fact the CO_2 exerts any stimulating effect when administered in low O_2, when the results are compared with other babies receiving 15% O_2 alone.

Although the average effect of 0·5% CO_2 in 15% oxygen has now been assessed it is still possible, by looking only at average results, that some trend of response has been missed which would have been observed if we examined the effect on individual babies. Thus it might be that a baby whose respiration became considerably depressed after the 4th minute of 15% oxygen might show no response to carbon dioxide, while another baby, whose respiration had not been notably altered, might show a vigorous response. In Fig. 6 we see the results in Expts. 2A, 2B and 2C on all those babies from whom a complete experiment was obtained, that is to say who had not become restless before the 8th to 10th minute on the test gas. It will be observed that there is no particular trend of response to 0·5% CO_2 after hypoxia compared with the effect of hypoxia alone. There is a very wide scatter of results which contrasts markedly with the results obtained when 0·5% CO_2 is given in air. (Also shown in Fig. 6.)

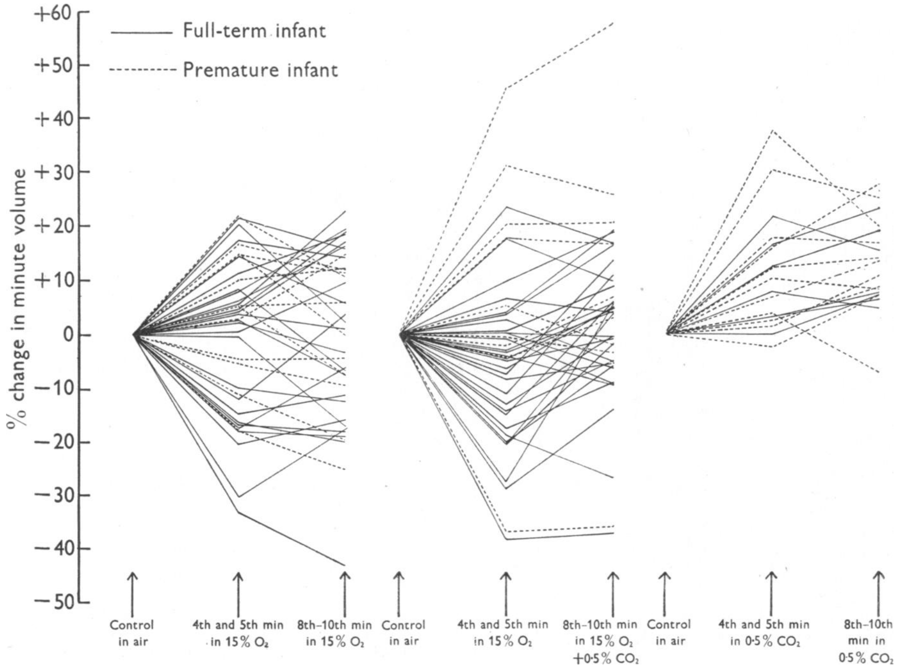

Fig. 6. The percentage change in minute volume of individual infants in the three series of experiments as indicated in the figure. The full-term infants are represented by continuous lines and premature infants by dotted lines. Thirty-eight infants received 15% oxygen for 10 min, forty infants received 15% oxygen for 5 min and 0·5% carbon dioxide + 15% oxygen in 84·5 nitrogen for the subsequent 5 min, and eighteen infants received 0·5% carbon dioxide in air for 10 min. These numbers are less than the babies who were initially in the experiments and represent those which had remained quiet until the end of the administration of the test gas.

As a final test to discover whether a baby who had received 0·5% CO_2 in 15% O_2 showed a definite tendency to increase its minute volume more than did a baby who continued to receive the unadulterated low oxygen mixture, the correlation coefficients of the paired observations of the 4th and 5th minute and 8th to 10th minute were calculated on individual babies. The correlation coefficients for 2B and 2C were $r = 0{\cdot}810$, $r = 0{\cdot}781$ ($P < 0{\cdot}001$ for both). The regression lines were calculated by the method of least squares, and it was found (Fig. 7) (as would be expected from the means), that the regression line for the babies who received 0·5 % CO_2 + 15 % O_2 was raised above that for the babies who continued on 15 % O_2 only. However, the two lines do not differ significantly from one another, nor are their slopes significantly different, thus

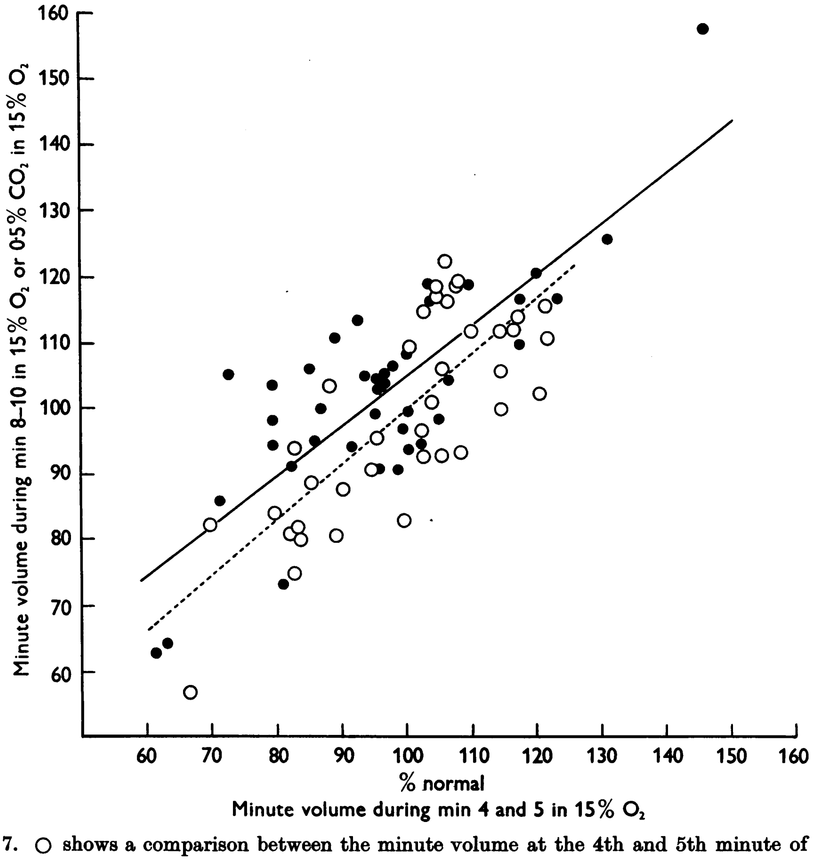

Fig. 7. ○ shows a comparison between the minute volume at the 4th and 5th minute of 15 % oxygen administration compared with that at the 8th to 10th minute of administration of the same gas. The dotted line is the calculated regression line of the 8th to 10th minute on the 4th and 5th minute. ● shows a similar comparison for the babies on the 4th and 5th minute on 15 % oxygen and the 8th to 10th minute on 0·5 % carbon dioxide in 15 % oxygen and 84·5 % nitrogen. The continuous line is the calculated regression line of this group.

there is no evidence that the CO_2 has an effect on the group as a whole, nor on those babies who were either markedly depressed or continued to be stimulated by the hypoxia.

This work seems to confirm the view that hypoxia acts only temporarily as a respiratory stimulant in the new-born baby because the medulla becomes very early depressed even with an oxygen mixture as high as 15 %. Similar respiratory depression has been demonstrated in animals with low O_2 when they were anaesthetized and the chemoceptor nerves were cut (Selladurai & Wright, 1933), but does not occur in the conscious adult human subject even when the oxygen percentage in the inspired air is approximately 6% (Nielsen & Smith, 1951). It should not be concluded from this work that such mild anoxia as 15% O_2 would prove lethal to the baby. These results are on the resting baby, and if O_2 in the inspired air is temporarily lowered further one observes not only cyanosis but also restlessness, which is accompanied by hyperventilation and may be a protective phenomenon. It is desirable that the evidence submitted here should direct more attention to the ability of young animals to undertake anaerobic metabolism, as was first hinted at by Paul Bert (1878) when he showed the long survival time of new-born mice in nitrogen. This has recently been reviewed by Himwich (1953).

SUMMARY

1. The effect on the respiratory minute volume has been compared in groups of full-term and premature infants who have received 0·5% CO_2 and 2% CO_2 in air and in 15% O_2/N_2 mixtures.

2. As in the adult, the stimuli of low O_2 and 2% CO_2 summate if the 2% CO_2 is given coincidently with the low oxygen mixture after the subjects have been breathing air.

3. If 0·5% CO_2 is given in low oxygen after the infant has already been receiving low oxygen, there is no significant response to the carbon dioxide.

4. It is concluded that after 5 min administration, 15% O_2 acts as a medullary depressant in the new-born baby.

Once again we are indebted to many for helping us to undertake this work. Financial support came from the M.R.C. research grant to Prof. A. St G. Huggett until October 1951 and since then has been from a research grant from St Mary's Hospital Research Fund. We have had excellent technical assistance first from Mr T. R. Nichols and later from Miss Jennifer A. Lowe. We have received most kind co-operation 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.

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