Pediat. Res. *13:* 1167–1171 (1979)

Arterial-alveolar differences
constant positive pressure breathing
Hyaline Membrane Disease
lung
low $\dot{V}A/\dot{Q}c$ units
100% oxygen
O_2-CO_2 diagram
venous admixture

Effects of Oxygen and Constant Positive Pressure Breathing on $aADCO_2$ in Hyaline Membrane Disease

T. N. HANSEN, A. J. S. CORBET, J. D. KENNY, J. D. COURTNEY, AND A. J. RUDOLPH

Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA

Summary

The effects of 100% oxygen breathing and constant positive pressure breathing (CPPB) on venous admixture (Qva/Qt) and arterial-alveolar difference for PCO_2 ($aADCO_2$) were examined in seven infants with hyaline membrane disease (HMD). Increasing FIO_2 from 0.63–0.99 with CPPB constant at 2 cm H_2O resulted in significant decrease in Qva/Qt from 0.67–0.47, but produced no change in $aADCO_2$ (13.0 torr vs. 15.0 torr). Increasing CPPB to 8 cm H_2O with FIO_2 returned to 0.63 also resulted in decreased Qva/Qt (0.50), but in addition $aADCO_2$ decreased significantly to 7.0 torr. The reduction in Qva/Qt with oxygen breathing and with CPPB is interpreted as a reduction in true right-to-left-shunt and a corresponding increase of effective blood flow through the lung. In 100% oxygen the increase in effective pulmonary perfusion occurred in a poorly ventilated compartment and as such was not reflected in the $aADCO_2$. On the other hand, with CPPB, the increase in perfusion was accompanied by an increase in ventilation and, hence, the $aADCO_2$ decreased. To illustrate these effects we constructed a three compartment model for the lung in HMD, calculated the $\dot{V}A/\dot{Q}c$ for the well-ventilated compartment in each circumstance, constructed O_2-CO_2 diagrams and arrived at predicted values for the $aADCO_2$ for each of the three clinical conditions. These predicted values agree well with those measured, considering the possible errors in our methods and assumptions and considering the absolute changes that may occur with CPPB, namely, increased cardiac output and decreased ventilation. This, in turn, provides strong support for the proposed three compartment model and for the existence of an open, but severely underventilated compartment in HMD.

Speculation

In HMD, the $aADCO_2$ seems to be responsive to the effects of CPPB on both ventilation and perfusion, and as such would be valuable clinically in determining optimal levels of CPPB.

The Qva/Qt in HMD is due to a true right-to-left shunt (Qs/Qt) through persistent fetal circulatory pathways (5, 14, 19, 20, 24, 30), pulmonary arteriovenous anastomoses (18), bronchial vein-pulmonary vein communications (20, 37), or capillary perfusion of atelectatic air spaces (23, 31) or areas of the immature lung where alveolar formation is not yet complete (18, 37).

Previous authors have shown that this shunt is reduced by 100% oxygen breathing (7, 28) and CPPB (2, 4, 8, 12). Recently, it has been suggested that most of this reduction is secondary to relief of hypoxic vascular constriction in an open severely underventilated compartment of the lung with indeterminately low $\dot{V}A/\dot{Q}c$, resulting in increased effective pulmonary blood flow (8, 9).

To obtain further evidence for this hypothesis we have examined the effects of oxygen and CPPB on the arterial-alveolar carbon dioxide difference ($aADCO_2$), a measurement that is sensitive to changes of blood flow in well-ventilated units of the lung (6, 27). It was predicted that with equivalent changes in Qva/Qt, the $aADCO_2$ would be reduced by CPPB, but not by oxygen breathing.

SUBJECTS

Seven infants with severe HMD were studied in the Neonatal Intensive Care Unit of Jefferson Davis Hospital in Houston. HMD was diagnosed clinically by retractions, expiratory grunting, and a typical reticulogranular pattern chest radiograph, and confirmed by blood gas studies.

All infants were managed on radiant warmers with abdominal skin temperature servo-controlled to 36.5°C. All were nasotracheally intubated, spontaneously breathing, and receiving CPPB (Baby Bird System, Bird Corporation, CA) with supplemental oxygen to maintain the PaO_2 50–70 torr. In our nurseries, CPPB is always administered via an endotracheal tube. Blood samples were drawn from an umbilical artery catheter with its tip in the descending aorta at the level of the fifth lumbar vertebra. Three infants subsequently required mechanical ventilation. One died with a suspected intraventricular hemorrhage.

METHODS

Measurements of the partial pressure of CO_2 in mixed alveolar gas ($PACO_2$), and $PaCO_2$, PaO_2 and pH were made first at low FIO_2 (0.49–0.80) with low CPPB (2 cm H_2O), then at high FIO_2 (0.96–1.00) with low CPPB (2 cm H_2O), and finally, at low FIO_2 (0.49–0.80) with high CPPB (8 cm H_2O). Infants were studied at 2 cm H_2O CPPB in an effort to approximate the conditions of the nonintubated infants with an expiratory grunt (3). Fifteen min were allowed at each setting for equilibration before measurements were made.

FIO_2 was measured using a Hudson Oxygen Monitor (#5552) calibrated with room air and 100% oxygen. Measurements of end-tidal PCO_2 have been performed in premature infants with and without HMD by several previous authors (5, 33). In these instances, end-tidal CO_2 was measured continuously using either nasal prongs or a single nasal cannula. $PACO_2$ was assumed to be the expired CO_2 concentration 4/5 of the way through expiration provided that the change in slope of the CO_2 plateau was less than 10%. More recently measurements of end-tidal CO_2 have been performed in intubated lambs (17) and infants (16) either breathing spontaneously or receiving IPPB with PEEP. Measurements of end-tidal CO_2 with CPPB were not performed because of problems with admixture of inspired and noninspired gas.

CO_2 was sampled continuously through a T-connector interposed in the endotracheal tube at the nose. This was connected to a Godart Statham Capnograph which sampled expired gas at a rate of 60 ml/min. With this system, the cyclical changes in expired CO_2 concentration were followed, CO_2 tracings much like those reported previously were achieved (Fig. 1). The effect of the endotracheal tube itself on the measurement should have been to decrease the dead space of the system and decrease the time

needed to attain a CO_2 plateau and possibly improve the correlation between end-tidal and alveolar PCO_2. Because of some concern about sampling noninspired gas, at the end of a spontaneous expiration, the endotracheal tube was occluded between the respirator and the T-piece and the Capnograph was allowed to sample directly from the distal segment of the tube and airways for 1–2 sec. This maneuver resulted in easily reproducible plateaus of CO_2 concentration (Fig. 1) that were within 1–2 torr of the plateaus obtained without occlusion. Had there been leaks around the endotracheal tube, incomplete expiration, or gross maldistribution of ventilation, stable plateaus could not have been obtained with this method.

The value for PCO_2 obtained at this plateau was assumed to represent $PACO_2$. All measurements were made in duplicate, only those agreeing within ± 1 torr were accepted, and the results averaged.

The sample for arterial blood gas analysis was anerobically collected at the same time as the second measurement of $PACO_2$. PaO_2 was measured with an oxygen electrode (Radiometer, model E 5046) maintained at 37°C and calibrated with saturated sodium sulfite solution and room air. The pH and $PaCO_2$ were determined by the method of Astrup *et al.* (1). As rectal temperature was always close to 37°C, no temperature correction was made. Arterial oxygen saturation was calculated from knowledge of PaO_2, corrected to 37°C, and pH, using an oxygen dissociation curve for neonatal blood (21). None of the infants had been transfused before the study. In an attempt to reduce total blood drawn hemoglobin in g% was assumed to be 1/3 of the spun hematocrit.

Qva/Qt was obtained from the standard shunt equation:

$$Qva/Qt = C\dot{c}O_2 - CaO_2/C\dot{c}O_2 - C\bar{v}O_2$$

where $C\dot{c}O_2$ is the oxygen content of pulmonary end-capillary blood, CaO_2 is the oxygen content of mixed arterial blood, and $C\bar{v}O_2$ is the oxygen content of mixed venous blood. These were derived using a value of 1.34 ml oxygen for each of hemoglobin, a value of 0.003 ml/torr for oxygen dissolved in plasma and assuming that the difference between arterial and mixed venous oxygen saturation ($SaO_2 - S\bar{v}O_2$) was 0.15 (26). the $aADCO_2$ was calculated from the equation:

$$aADCO_2 = PaCO_2 - PACO_2$$

RESULTS

Clinical data in the seven infants are given in Table 1.

With FIO_2 0.60 ± 0.05 (mean ± SE) and 2 cm H_2O CPPB (Table 2, Condition 1), Qva/Qt was 0.67 ± 0.02 and $aADCO_2$ was 13.0 ± 1.2 torr. If FIO_2 was increased to 0.99 ± 0.01 and CPPB left the same (Table 2, Condition 2), Qva/Qt decreased to 0.47 ± 0.04 ($P < 0.005$). The $PACO_2$ decreased significantly from 30.0 ± 2.4 torr to 27. ± 1.3 torr ($P < 0.005$), but the $aADCO_2$ of 15.0 ± 1.3 torr was not significantly increased. Increasing CPPB to 8 cm H_2O while returning FIO_2 to 0.60 ± 0.05 (Table 2, Condition 3), resulted in decreased Qva/Qt of 0.50 ± 0.03 (Condition 1 *vs.* 3, $P < 0.001$) as well as decreased $aADCO_2$ of 7.0 ± 0.7 torr ($P < 0.001$).

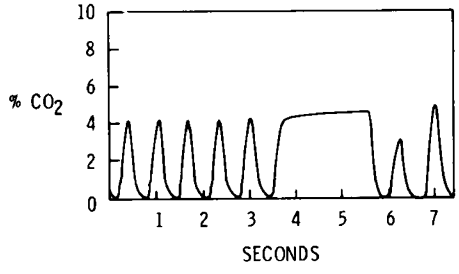

Fig. 1. Reproduction of typical mixed alveolar CO_2 tracing, included to demonstrate the plateau obtained with the method. Occlusion occurred at end of expiration.

Table 1. *Clinical data in premature infants*

N	GA[1] (wk)	BW[2] (kg)	AGE[3] (hr)	Hgb. (g%)
1	32	1.66	12	16
2	34	2.18	26	14
3	36	2.50	20	19
4	32	1.64	6	16
5	34	1.96	20	15
6	35	2.50	22	17
7	32	1.50	18	13
Mean	33.6	1.99	17	15.6
SD	±1.6	±0.41	±6.7	±1.9

[1] Gestational age.
[2] Birthweight.
[3] Study age.

There were no significant differences between pH and $PaCO_2$ under the three conditions.

DISCUSSION

The reduction in Qva/Qt with oxygen breathing and with CPPB demonstrated in this study is interpreted as a reduction in true right-to-left shunt and a corresponding increase of effective blood flow through the lung (8, 9). Reasons for this interpretation have been previously discussed, but basically a diffusion defect is considered unlikely to be significant, especially if FIO_2 exceeds 40% (32), and Qva/Qt due to low $\dot{V}A/\dot{Q}c$ units is known to be very small (9).

The major finding in this study was that for a similar decrease in Qva/Qt there was no change in $aADCO_2$ with 100% oxygen breathing, but a significant change with CPPB. Our interpretation of this finding depends on the assumption that the measured $PACO_2$ reflects only well-ventilated lung units and not those that are poorly ventilated. When the infant with HMD is breathing 63% oxygen, oxygen tension in the proposed open severely underventilated low $\dot{V}A/\dot{Q}c$ compartment is reduced (34), and there is local hypoxic vasoconstriction (15, 25), limiting perfusion of this compartment and increasing true right-to-left shunt. In 100% oxygen, local, alveolar hypoxia in the open severely underventilated low $\dot{V}A/\dot{Q}c$ compartment (8, 9) is relieved (34) without change in ventilation, effective pulmonary perfusion is increased and true right-to-left shunt decreased. Because the compartment is still poorly ventilated, increased perfusion is not reflected in values obtained for $PACO_2$, and the $aADCO_2$ remains unchanged despite a significant change in Qva/Qt; however, a small decrease in cardiac output with 100% oxygen (36) might be expected to produce the observed decrease in $PACO_2$ as perfusion of the well-ventilated compartment decreased. On the other hand, when CPPB is applied and oxygen returned to previous levels, local alveolar hypoxia is relieved by an increase in ventilation of the former poorly ventilated but open compartment (8); although alveolar ventilation as reflected in $PaCO_2$ does not change. Under these circumstances, increased perfusion is accompanied by an increase in $PACO_2$, and hence a decrease in $aADCO_2$. At the same time, collapsed lung units may be recruited to form a new open severely underventilated compartment so that perfusion of low $\dot{V}A/\dot{Q}c$ units remains unchanged (8).

To illustrate these effects we have constructed a three compartment model for the lung in HMD (Fig. 2) using mean values obtained in this study for Qva/Qt (Table 2) and mean values previously obtained for perfusion of the open severely underventilated low $\dot{V}A/\dot{Q}c$ compartment ($\dot{Q}o/Qt$) (8, 9). If it is assumed that well-ventilated lung units receive most of the ventilation (99.9%) and that perfusion of these units ($\dot{Q}wv/Qt$) is equal to 1.00 − Qva/Qt, then $\dot{V}A/\dot{Q}c$ can be calculated. In patients breathing 49–80% oxygen $\dot{V}A/\dot{Q}c$ was calculated to be 3:1 (Condition 1, Fig. 2). In 100% oxygen, because the increase in perfusion occurred

Table 2. *Physiologic data in premature infants*

Infant N	FIO_2	pH	$PaCO_2$ torr	$PACO_2$ torr	$aADCO_2$ torr	PaO_2 torr	Qva/Qt
Condition 1: low O_2, low CPPB (2 cm H_2O)							
1	0.49	7.26	45	30	15	42	0.73
2	0.62	7.27	37	21	16	40	0.70
3	0.80	7.23	48	34	14	59	0.60
4	0.53	7.23	43	35	8	56	0.63
5	0.70	7.23	40	24	16	40	0.74
6	0.64	7.31	40	26	14	51	0.66
7	0.45	7.32	48	38	10	45	0.65
Mean	0.60	7.26	43	30	13	48	0.67
SE	±0.05	±0.01	±1.6	±2.4	±1.2	±3	±0.02
Condition 2: high O_2, low CPPB (2 cm H_2O)							
1	0.96	7.27	43	24	19	138	0.33
2	0.98	7.27	35	20	15	88	0.50
3	1.00	7.21	49	35	14	66	0.55
4	1.00	7.25	40	31	9	167	0.30
5	1.00	7.25	38	20	18	63	0.57
6	1.00	7.30	40	26	14	81	0.50
7	1.00	7.31	48	35	13	75	0.53
Mean	0.99	7.27	42	27	15	97	0.47
SE	±0.01	±0.01	±1.9	±2.4	±1.3	±15	±0.04
P value 2 *vs.* 1	<0.001	>0.8	>0.05	<0.05	>0.10	<0.02	<0.005
Condition 3: low O_2, high CPPB (8 cm H_2O)							
1	0.49	7.20	50	43	8	84	0.50
2	0.62	7.23	34	26	7	50	0.62
3	0.80	7.19	50	43	7	78	0.50
4	0.53	7.25	41	37	5	102	0.40
5	0.70	7.24	42	31	10	76	0.50
6	0.64	7.28	40	33	7	94	0.42
7	0.45	7.27	51	46	5	56	0.53
Mean	0.60	7.24	44	37	7	77	0.50
SE	±0.05	±0.01	±2.4	±2.8	±0.65	±7	±0.03
P value 3 *vs.* 1	0	>0.05	>0.3	<0.005	<0.001	<0.005	<0.001

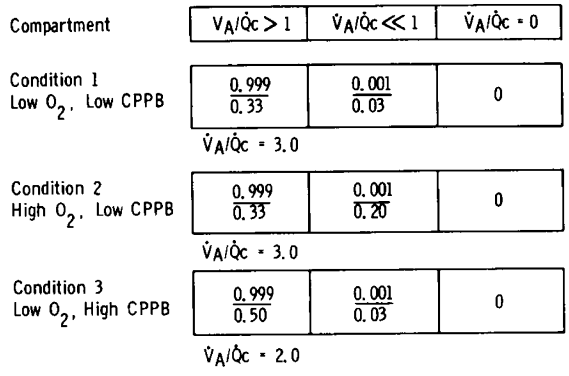

Fig. 2. Three-compartment model for the lung in HMD under the three different clinical conditions present in the study. Model assumes constant ventilation and perfusion.

only in the open severely underventilated compartment, $\dot{V}A/\dot{Q}c$ in the well-ventilated compartment remained unchanged (Condition 2, Fig. 2). However, with CPPB, an increase in perfusion occurred in the former severely underventilated units where ventilation also increased, and $\dot{V}A/\dot{Q}c$ in the well-ventilated compartment decreased to 2:1 (Condition 3, Fig. 2).

To test this model, O_2-CO_2 diagrams for infants under the three different sets of conditions in this study were constructed. An inspired gas point equivalent to mean inspired oxygen was assumed (Table 2) and mixed venous points of O_2 and CO_2 were based on previous assumptions (see *Methods*) and mean values for PaO_2 and $PaCO_2$ (Table 2). Values for $PACO_2$ at $\dot{V}A/\dot{Q}c$ 3:1 (Fig. 3) and 2:1 (Fig. 4) were found by trial and error (35). Knowing measured values for $PaCO_2$, values for $aADCO_2$ could be predicted and compared with those measured (Table 3). Under conditions of 49–80% oxygen and 100% oxygen breathing, measured and predicted values are in agreement (Table 3), providing considerable support for the model proposed in HMD.

With CPPB the measured decrease in $aADCO_2$ was greater than predicted (Table 3), the measured $PACO_2$ was higher than expected and the $\dot{V}A/\dot{Q}c$ calculated from Figure 4, was 1.5:1.0 instead of 2:1. Although this small discrepancy could simply be due to limitations in our measurements or within the limits of statistically probable variation, it could mean that the model is inappropriate or that one or more of the assumptions were incorrect. Because CPPB may alter both cardiac output (10, 11, 14, 22) and ventilation (2, 12), the latter possibility must be examined.

There are two major errors in predicting $\dot{V}A/\dot{Q}c$, and hence $PACO_2$. The first is in the assumption that SaO_2–$S\bar{v}O_2$ equals 0.15, in calculation of Qva/Qt. A decrease in SaO_2–$S\bar{v}O_2$ produces an error in Qva/Qt such that Qwv/Qt falls, $\dot{V}A/\dot{Q}c$ increases and the predicted $PACO_2$ falls (Fig. 4). Conversely an increase in Qva/Qt would increase the predicted $PACO_2$. Calculations have shown that varying the SaO_2–$S\bar{v}O_2$ between 0.10 and 0.20 produces relatively little error when compared to the overall changes in Qva/Qt noted (8, 9).

The other source of error is in the assumption that $P\bar{v}CO_2$–

Table 3. *Comparison of predicted values for aADCO₂, based on 3-compartment model and O₂-CO₂ diagram, with measured values from Table 2*

Condition	Predicted VA/Qc[1]	Predicted $PACO_2$[2] torr	Predicted $aADCO_2$ torr	Measured $PACO_2$ (±SE) torr	Measured $aADCO_2$ (±SE) torr
1	3.0	29	14	30 ± 2.4	13 ± 1.2
2	3.0	28	16	27 ± 2.4	15 ± 1.3
3	2.0	34	10	37 ± 2.8	7 ± 0.65

[1] Calculated from 3 compartment model (Fig. 2).
[2] Derived from calculated VA/Qc and appropriate O_2-CO_2 diagram.

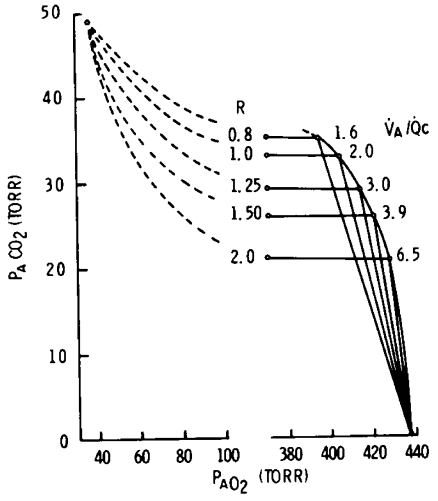

Fig. 3. O_2-CO_2 diagram drawn for conditions present with 60% oxygen breathing (Condition 1, Fig. 1). PIO_2 = 438 torr, $PICO_2$ = 0, $P\bar{v}O_2$ = 37 torr, $P\bar{v}CO_2$ = 49 torr (calculated from mean values in Table 2). Calculated $\dot{V}A/\dot{Q}c$ values are shown for points of intersection of equivalent blood and gas R lines. *Broken lines* are diagrammatic and do not reflect measured or calculated values. $PACO_2$ = 29 torr for $\dot{V}A/\dot{Q}c$ of 3:1.

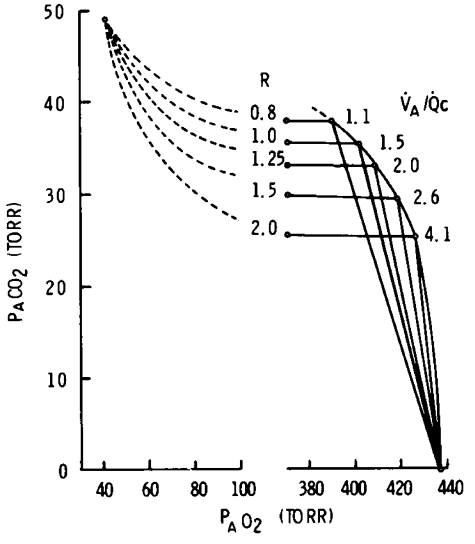

Fig. 4. O_2-CO_2 diagram for conditions present with CPPB (Condition 3, Fig. 2). PIO_2 = 438 torr, $PICO_2$ = 0, $P\bar{v}O_2$ = 42 torr, $P\bar{v}CO_2$ = 50 torr (calculated from mean values in Table 2). Calculated $\dot{V}A/\dot{Q}c$ values are shown for points of intersection of equivalent blood and gas R lines. *Broken lines* are diagrammatic and do not reflect measured or calculated values. $PACO_2$ = 34 torr for $\dot{V}A/\dot{Q}c$ of 2:1.

$PaCO_2$ equals 6 torr, in the construction of the O_2-CO_2 diagrams. Inspection of the O_2-CO_2 diagram (fig. 4) shows that when PIO_2 exceeds 250 torr the blood R lines have nearly zero slope and their position is dependent only on the $P\bar{v}CO_2$. Hence, a decrease or increase in $P\bar{v}CO_2$ would produce a corresponding decrease or increase in $PACO_2$. Again, however, errors resulting from small changes in $P\bar{v}CO_2$ are minimal when compared to the overall change in $aADCO_2$ noted.

The effects of the above assumptions on the $PACO_2$ require that they do not change from condition to condition. If cardiac output were to change between conditions 1 and 3, then this prerequisite would not be met and the error introduced might become significant. If cardiac output is increased by CPPB and ventilation is stable, then calculated $\dot{V}A/\dot{Q}c$ would decrease and predicted $PACO_2$ would rise to the measured value. But increased cardiac output would decrease both SaO_2–$S\bar{v}O_2$ and $P\bar{v}CO_2$ which as shown above would decrease $PACO_2$. Calculations show that an increase in cardiac output with CPPB approximating 75% must be postulated for the measured and predicted values to agree. If cardiac output is decreased by CPPB, then calculated $\dot{V}A/\dot{Q}c$ would rise and predicted $PACO_2$ would be lower. Calculations show that the expected increase in $PACO_2$ from higher SaO_2–$S\bar{v}O_2$ and $P\bar{v}CO_2$ does not counteract this effect. Thus, it would appear that only a large increase in cardiac output could explain the discrepancy between the measured and predicted values. Similarly, only a large decrease in cardiac output would produce enough error to significantly affect the validity of the $aADCO_2$.

A recent study has shown that CPPB produces a decrease in minute ventilation of 32% without significant change in $PaCO_2$ (2). $\dot{V}A/\dot{Q}c$ abnormalities are known to affect $PaCO_2$ nearly as much as PaO_2 and any improvement in $\dot{V}A/\dot{Q}c$ should be reflected in a significant reduction of $PaCO_2$ if minute ventilation and cardiac output remain unchanged (34). With CPPB (Condition 3, Fig. 2) the postulated improvement of $\dot{V}A/\dot{Q}c$ was not accompanied by a decrease in $PaCO_2$ (Table 2) suggesting that either minute ventilation decreased or cardiac output increased. Changes that have been seen in cardiac output must be large to explain the changes. However, if ventilation were to decrease by as much as 25% then predicted $\dot{V}A/\dot{Q}c$ would be 1.5:1 instead of 2:1 (Condition 3, Fig. 2), and measured (Table 2) and predicted (Table 3, Fig. 4) values for the $aADCO_2$ would be identical. This decrease in ventilation is well within the observed discrepancy and is probably related to an overall reduction in minute ventilation with CPPB, although changes in cardiac output cannot be excluded.

Thus, considering the possible errors in our method and assumptions, and considering absolute changes which may occur with CPPB, namely, increased cardiac output (10, 11, 14, 22) and decreased ventilation (2, 12), it is considered that measured values for $aADCO_2$ agree well with those predicted, especially for 63 and 100% oxygen breathing, but also under conditions of CPPB. This, in turn, provides strong support for the proposed three compartment model, and for the existence of an open, but severely underventilated compartment in HMD.

REFERENCES AND NOTES

1. Astrup, P., Jorgenson, K., Siggaard-Anderson, O., and Engel, K.: The acid-base metabolism: a new approach. Lancet, *1:* 1035 (1960).
2. Bancalari, E., Garcia, O. L., and Jesse, M. J.: Effects of continuous negative pressure on lungs mechanics in idiopathic respiratory distress syndrome. Pediatrics, *51:* 4850493 (1973).
3. Berman, L. S., Fox, W. W., Raphaely, R. C., And Downes, J. J.: Optimum levels of CPAP for tracheal extubation of newborn infants. J. Pediatr., *89:* 109 (1976).
4. Chernick, V., and Vidyasagar, D.: Continuous negative chest wall pressure in hyaline membrane disease: one year experience. Pediatrics, *49:* 753 (1972).
5. Chu, J., Clements, J. A., Cotton, E. K., Klaus, M. H., Sweet, A. Y., and Tooley, W. H.: Neonatal pulmonary ischemia. Pediatrics, *40:* 709 (1967).

6. Comroe, J. H., Forster, R. E., Dubois, A. B., Briscoe, W. A., Carlson, E.: The Lung. p. 107–108 (Chicago, Year Book, 1974).
7. Corbet, A. J. S., and Burnard, E. D.: Changes of venous admixture with inspired oxygen in hyaline membrane disease and fetal aspiration pneumonia. Aust. Paediatr. J., *9:* 25 (1973).
8. Corbet, A. J. S., Ross, J. A., Beaudry, P. H., and Stern, L.: Effect of positive pressure breathing on $aADN_2$ in hyaline membrane disease. J. Appl. Physiol., *38:* 33 (1975).
9. Corbet, A. J. S., Ross, J. A., Beaudry, P. H., and Stern, L.: Ventilation-perfusion relationships as assessed by $aADN_2$ in hyaline membrane disease. J. Appl. Physiol., *36:* 74 (1974).
10. Cotton, R. B., Lindstrom, D. P., Kanarek, K. S., Sundell, B., and Stahlman, M. T.: Effect of positive-end-expiratory pressure (PEEP) on extrapulmonary shunts in experimental hyaline membrane disease (HMD) (Abstract) Pediatr. Res., *9:* 395 (1975).
11. Falke, K. J., Pontoppidan, H., Kumar, A., Leith, D. E., Geffin, B., and Laver, M. B.: Ventilation with end-expiratory pressure in acute lung disease. J. Clin. Invest., *51:* 2315 (1972).
12. Gregory, G. A., Kitterman, J. A., Phibbs, R. H., Tooley, W. H., and Hamilton, W. K.: Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. N. Engl. J. Med., *284:* 1333 (1971).
13. Gupta, J. M., Dahlenburg, G. W., and Davis, J. A.: Changes in the blood gas tensions following administration of amine buffer THAM to infants with respiratory distress syndrome. Arch. Dis. Childhood, *42:* 416 (1967).
14. Harken, A. H., Brennen, M. F., Smith, B., and Barsamian, E.: The hemodynamic response to positive end-expiratory ventilation in hypovolemic patients. Surgery *76:* 786 (1974).
15. Hughes, J. M. B.: Local control of blood flow and ventilation. In: J. B. West: Regional Difference in the Lung, p. 425–428 (New York, Academic Press, 1977).
16. Hunt, C. E., Matalon, S., Wagensteen, O. D., and Leonard, A. S.: Mass spectrometer evaluation of ventilation perfusion abnormalities in respiratory distress syndrome. Pediatr. Res., *8:* 621 (1974).
17. Matalon, S. V., Boros, S. J., Ewald, R., Leonard, A. S., and Hunt, C. E.: The respiratory effects of PEEP in premature lambs with severe RDS. Pediatr. Res., *10:* 465 (1976).
18. Murdock, A. I., Kidd, B. S. L., Llewellyn, M. A., McReid, M. C., and Swyer, P. R.: Intrapulmonary venous admixture in the respiratory distress syndrome. Biol. Neonate, *15:* 1 (1970).
19. Murdock, A. I., and Swyer, P. R.: The contribution to venous admixture by shunting through the ductus arteriosus in infants with the respiratory distress syndrome of the newborn. Biol. Neonat., *13:* 194 (1968).
20. Nelson, N. M., Prod'hom, L. S., Cherry, R. B., Lipsitz, P. J., and Smith, C. A.: Pulmonary function in the newborn infant: The alveolar-arterial oxygen gradient. J. Appl. Physiol., *18:* 534 (1963).
21. Oh, W., Arcilla, R. A., and Lind, J.: *In vivo* oxygen dissociation curve of newborn infants. Biol. Neonat., *8:* 241 (1965).
22. Powers, S. R., Mannal, R., Neclerio, M., English, M., Marr, C., Leather, R., Ueda, H., Williams, G., Custead, W., and Dutton, R.: Physiologic consequences of positive end-expiratory pressure (PEEP) ventilation. Ann. Surg., *178:* 265 (1973).
23. Prod'hom, L. S., Levinson, H., Cherry, R. B., and Smith, C. A.: Adjustment of ventilation, intrapulmonary gas exchange, and acid-base balance during the first day of life. Infants with early respiratory distress. Pediatrics, *35:* 662 (1965).
24. Roberton, N. R. C., And Dahlenburg, G. W.: Ductus arteriosus shunts in the respiratory distress syndrome. Pediatr. Res., *3:* 149 (1969).
25. Rudolph, A. M., Auld, P. A. M., Golinko, R. J., And Paul, M. H.: Pulmonary vascular adjustments in the neonatal period. Pediatrics, *28:* 28 (1961).
26. Rudolph, A. M., Drorbaugh, J. E., Auld, P. A. M., Rudolph, A. J., Nadas, A. S., Smith, C. A., and Hubbell, J. P.: Studies on the circulation in the respiratory distress syndrome. Pediatrics, *27:* 551 (1961).
27. Severinghaus, J. W., and Stupfel, M.: Alveolar dead space as an index of distribution of blood flow in pulmonary capillaries. J. Appl. Physiol., *10:* 325 (1957).
28. Sinclair, J. C., Engel, K., and Silverman, W. A.: Early correction of hypoxemia and acidemia in infants of low birthweight: a controlled trial of oxygen breathing, rapid alkali infusion, and assisted ventilation. Pediatrics, *42:* 565 (1968).
29. Strang, L. B., and McLeish, M. H.: Ventilation failure and right-to-left shunt in newborn infants with respiratory distress. Pediatrics, *28:* 17 (1961).
30. Swyer, P. R., Murdock, A. I., Llewellyn, M. A., and Bryan, M. H.: Right-to-left shunting in the respiratory distress syndrome of the newborn. Bull. Physio-Path. Resp., *9:* 1495 (1973).
31. Tori, C. A., Krauss, A. N., and Auld, P. A. M.: Serial studies of lung volume and $\dot{V}A/\dot{Q}$ in hyaline membrane disease. Pediatr. Res., *7:* 82 (1973).
32. Wagner, P. D., and West, J. B.: Effects of diffusion impairment on O_2 and CO_2 time courses in pulmonary capillaries. J. Appl. Physiol., *33:* 62 (1972).
33. Watts, J. L., Ariagno, R. L., and Brady, J. P.: Chronic pulmonary disease in neonates after artificial ventilation: distribution of ventilation and pulmonary interstitial emphysema. Pediatrics, *60:* 273 (1977).
34. West, J. B.: Ventilation-perfusion inequality and overall gas exchange in computer models of the lung. Resp. Physiol., *7:* 88 (1969).
35. West, J. B.: Ventilation Blood Flow and Gas Exchange. p. 107–110 (Oxford, Blackwell Scientific Publication, 1972).
36. Whitehorn, W. Y., Edelman, A., and Hitchcock, F. A.: Cardiovascular response to 100% oxygen breathing at normal barometric pressure. Am. J. Physiol., *146:* 61 (1946).
37. Woodrum, D. E., Oliver, T. K., and Hodson, W. A.: The effect of prematurity and hyaline membrane disease on oxygen exchange in the lung. Pediatrics, *50:* 380 (1972).
38. The present address of Dr. A. J. S. Corbet is: Department of Pediatrics, Flinders Medical Center, Adelaide, Australia 5042.
39. This research was supported by a grant from the Public Health Service, General Research Support RR-05425.
40. Requests for reprints should be addressed to: Dr.. Thomas Hansen, Department of Pediatrics, Texas Children's Hospital, Texas Medical Center, Houston, TX 77030 (USA).
41. Received for publication April 18, 1978.
42. Accepted for publication November 15, 1978.

0031-3998/79/1310-1167$02.00/0

Printed in U.S.A.