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Optimal Constant Positive Airway Pressure Assessed by Arterial Alveolar Difference for CO_2 in Hyaline Membrane Disease

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ABSTRACT. In a group of infants with hyaline membrane disease, the level of optimal constant positive airway pressure (CPAP) was assessed by raising CPAP in small steps from an initial low value, and after each change measuring the arterial alveolar difference for CO_2 ($aADCO_2$) and transmission of airway pressure to the esophagus. Below optimal CPAP there was a progressive increase in mixed alveolar partial pressure of CO_2 ($PACO_2$) and no change in arterial partial pressure of CO_2 ($PaCO_2$), so that $aADCO_2$ declined and reached a lowest value at optimal CPAP. Correspondingly, transmission of airway pressure increased progressively and reached a highest value at optimal CPAP. Between 1 step below and optimal CPAP, $PACO_2$ rose from 30.9 to 34.0 torr, and $aADCO_2$ declined from 16.6 to 12.7 torr. Between optimal and 1 step above optimal CPAP, $PaCO_2$ increased from 46.7 to 51.0 torr, $PACO_2$ rose slightly, and $aADCO_2$ increased from 12.7 to 15.6 torr. Thus, the $aADCO_2$ was an excellent index of optimal CPAP. In five patients with measurements of PaO_2 at constant fractional inspired oxygen, calculated values for arterial oxygen saturation changed from 80.8 to 91.5 to 92.2%, and calculated values for venous admixture changed from 0.61 to 0.48 to 0.46 as CPAP was raised from 1 step below through optimal to 1 step above optimal CPAP. The results are interpreted to mean a progressive improvement in perfusion of well ventilated lung units as CPAP increased to optimal levels, but a significant reduction of both ventilation and perfusion above optimal CPAP. The values for venous admixture were used to calculate ventilation-perfusion ratio (VA/Qc) in a lung model which includes three compartments, high VA/Qc, open low VA/Qc, and shunt. The calculated VA/Qc values were incorporated in O_2–CO_2 diagrams, and predicted values for $PACO_2$ were calculated for conditions 1 step below, at, and 1 step above optimal CPAP. The measured and predicted values agreed closely, validating use of the model. However, a progressive disparity, as CPAP was increased, suggests that cardiac output decreased with higher levels of CPAP. (*Pediatr Res* 20: 884–889, 1986)

Abbreviations

HMD, hyaline membrane disease
CPAP, constant positive airway pressure
Pes, esophageal pressure
Pao, pressure at airway opening
$PaCO_2$, arterial partial pressure of CO_2
$PACO_2$, mixed alveolar partial pressure of CO_2
$aADCO_2$, arterial alveolar difference for CO_2
PaO_2, arterial partial pressure of O_2
PAO_2, mixed alveolar partial pressure of O_2
SaO_2, arterial oxygen saturation
Qva/Qt, venous admixture
$C\dot{c}O_2$, pulmonary end-capillary blood O_2 content
CaO_2, arterial O_2 content
$C\bar{v}O_2$, mixed venous oxygen content
$S\bar{v}O_2$, mixed venous oxygen saturation
R, gas exchange quotient
F_{IO_2}, fractional inspired oxygen
VA/Qc, ventilation-perfusion ratio
VA, alveolar ventilation
$\dot{V}CO_2$, carbon dioxide elimination

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There has been a large decrease in mortality from HMD since the introduction of CPAP treatment. This technique is effective because it improves expansion and ventilation of poorly ventilated regions of the lung, thereby reducing regional imbalance between ventilation and perfusion, and thus decreasing venous admixture (1). A disadvantage is that it may overdistend more normal lung regions, causing depression of the circulation or pulmonary air leaks. Several investigators have suggested that changes in lung compliance, as reflected in esophageal pressure measurements, should be monitored to determine optimal levels of CPAP, so the technique may be both safe and efficacious (2, 3). However, this measurement is sensitive only to the state of lung distension, and does not reflect alterations in the circulation. Because cardiac output is difficult to measure in the newborn infant, the present investigation concerns the measurement of $PaCO_2$ and $PACO_2$ with calculation of the $aADCO_2$, a parameter which is sensitive not only to the level of ventilation, but also to changes in pulmonary perfusion (4). It was predicted that the $aADCO_2$ would decrease as CPAP was increased toward the optimal value and that it would increase as optimal CPAP was exceeded with reduction of pulmonary blood flow.

METHODS

Subjects. Eleven infants with HMD were studied in the Neonatal Intensive Care Unit of Texas Children's Hospital in Houston. HMD was diagnosed clinically by retractions, expiratory grunting, and a typical reticulogranular pattern on the chest radiograph, and confirmed by blood gas studies and the clinical course. Infants were selected for study if an investigator was available, birth weight was above 1500 g, gestational age was 32 wk or more, postnatal age was less than 72 h, the hemoglobin and blood pressure were stable within the normal range, the clinical oxygen requirement was 60–100% without need for

mechanical ventilation and no air leak phenomena were diagnosed. All infants were considered to be in the developing rather than the recovering phase of HMD. They were managed on radiant warmers with abdominal skin temperature servo-controlled to 36.5° C. As part of routine management, all were tracheally intubated, spontaneously breathing, and receiving CPAP through a standard ventilator circuit (Bear Cub or Baby Bird) with supplemental oxygen to maintain the PaO_2 50–70 torr. Blood samples were drawn from an umbilical artery catheter with its tip in the descending aorta at the level of the fourth lumbar vertebra. These studies were approved by the Baylor Institutional Review Board for Human Research, and informed written consent was obtained from the parents before enrollment of infants. All infants did well and were subsequently discharged alive from the hospital.

Procedures. Simultaneous measurements of $PACO_2$, $PaCO_2$, PaO_2, and pH were made initially at a low level of CPAP, and subsequently at three or more levels of CPAP, the pressure being increased in arbitrary steps of 1.3 or 3 cm H_2O to a maximum of 8–16 cm H_2O. Fifteen to twenty minutes equilibration were allowed at each setting before measurements were made. In six patients the readings from the ventilator aneroid manometer were taken as the level of CPAP, in which case the increments in CPAP were 3 cm H_2O. In five patients the airway pressure was simultaneously measured with a pressure transducer (see below), in which case the increments in CPAP were much smaller, only 1.3 cm H_2O. The latter measurements were, of course, more precise, but differences were very small and not crucial for comparisons at different levels of CPAP.

F_{IO_2} was measured using a Hudson Oxygen Monitor calibrated with room air and 100% oxygen. Blood gases were measured with Radiometer equipment by standard methods.

The $PACO_2$ was measured as previously described (5) with a Godart Statham Capnograph, having a 95% response time of 0.2 s. The instrument was calibrated with the same gas mixtures used for the measurement of $PaCO_2$. CO_2 was sampled through a small T-connector interposed in the endotracheal tube at the nose. The side-arm was connected to the Capnograph, which sampled gas continuously at a rate of 60 ml/min. At the end of spontaneous expiration, the endotracheal tube was occluded with forceps between the ventilator circuit and the T-connector, and the Capnograph was allowed to sample directly from the endotracheal tube for 2 s. This maneuver resulted in easily reproducible plateaus of CO_2 concentration. Had there been leaks around the endotracheal tube, incomplete expiration or gross maldistribution of ventilation, stable plateaus could not be achieved with this method. The values were obtained in triplicate, only those agreeing within ± 1 torr were accepted, and the results averaged.

In five infants, Pes was measured using a sterile disposable 8 French double lumen gastric tube and esophageal balloon system (American Hospital Supply). The deflated balloon was 4 cm long and 0.7 cm wide, with a radioopaque marker at the distal end, 6 cm short of the distal end of the gastric tube. Before each study the balloon had its operational volume determined by performance of a balloon pressure-volume curve according to the method of Beardsmore *et al.* (6). The balloon was then emptied under 6 cm H_2O pressure and the catheter stopcock closed. The balloon catheter was then passed through the infant's nose and advanced down the esophagus a distance of 15–18 cm, depending on the infant's size. A chest radiograph was taken as part of routine daily care, and the radioopaque marker used to adjust the position of the balloon into the exact retrocardiac position, following which the tube was secured at the nose. The catheter stopcock was then connected to an air-coupled pressure transducer (Gould-Statham PM131TC) at ambient pressure, positioned at the infant's midthoracic level. The balloon and transducer were then connected by opening the catheter stopcock. The transducer signal was amplified and recorded with an 8 channel polygraph (Grass Instruments). The operational volume of air (0.15 ml) was injected into the balloon through the stopcock, and the pressure recorded was taken as the absolute zero value. A small artifact due to cardiac pulsation was always observed. Pes at end-expiration was measured as the mean of 10 consecutive breaths during a selected, stable, and representative period when no esophageal spasms were present. The pressure transducer was calibrated with a mercury sphygmomanometer and the measurements converted to cm H_2O.

In these five infants, Pao was measured with a similar transducer using a small T-piece connected to the endotracheal tube, and the signal traced on another channel of the polygraph. CPAP was increased in small steps of 1.3 cm H_2O. At each level of CPAP preliminary end-expiratory occlusions of the airway were made and the changes of Pao and Pes recorded over a few occluded breaths. In one infant this procedure was unsatisfactory because airway occlusions caused disturbance. The ratio of change of Pes to change of Pao was calculated, and the values found to lie between 0.9 and 1.0, independent of the CPAP level. After a further 15-min interval, measurements of $aADCO_2$ and Pes at end-expiration were performed.

Calculations. SaO_2 was calculated from knowledge of PaO_2, corrected to 37° C and pH 7.4, using the oxygen dissociation curve for blood (7). PAO_2 was calculated from the alveolar gas equation (8), knowing barometric pressure and assuming the value of R to be 0.8.

The $aADCO_2$ was calculated from the equation: $aADCO_2 = PaCO_2 - PACO_2$.

The fractional transmission of airway pressure to the esophagus was calculated as the ratio Pes/Pao at end-expiration.

Statistical analysis. Results are expressed as mean ± 1 SEM unless stated otherwise. The data were analyzed by 2-factor analysis of variance, followed when appropriate by the Student-Newman-Keuls multiple range test (9).

RESULTS

In the 11 infants studied birth weight was 2311 ± 562 g (mean ± SD), gestational age was 34.3 ± 1.6 wk, postnatal age at the time of study was 31 ± 9 h, hemoglobin values were 14.7 ± 1.9 g/100 ml, F_{IO_2} was 0.81 ± 0.12 and $PaCO_2$ was 57 ± 13 torr.

In Table 1 the calculated values for $aADCO_2$ are arranged in relation to an arbitrarily defined optimal CPAP (see below), as the CPAP was increased from two or three steps below optimal to 0–2 steps above optimal CPAP. The corresponding values of CPAP for each calculation of $aADCO_2$ are given in Table 2. In all 11 studies the $aADCO_2$ decreased as CPAP was initially

Table 1. *Values for $aADCO_2$ in 11 infants with HMD during stepwise increase of CPAP**

	Steps below optimal CPAP			Optimal	Steps above optimal CPAP	
n	3	2	1	CPAP	1	2
1		27	23	19	25	
2		16	14	11	12	
3		25	22	17	17	17
4			20	19	25	27
5		13	12	10	14	
6			10	4	6	8
7			15	9	10	12
8		9	5	2		
9	12	8	5	4		
10		16	13	12		
11	17	15	9	8		

* Values for $aADCO_2$ are torr. CPAP was increased in steps from below optimal to above optimal CPAP. Optimal CPAP was the level at which serial values for $aADCO_2$ were lowest. Step changes of CPAP varied as shown in Table 2.

increased. In seven studies (Table 1, nos. 1–7), the $aADCO_2$ increased subsequently as optimal CPAP was exceeded. In another two studies (Table 1, nos. 8–9) the lowest $aADCO_2$ was below 5 torr, while in another two studies (Table 1, nos. 10–11), the values appeared to reach a plateau. Because CPAP was not further increased, these last four values were arbitrarily also called optimal CPAP. Thus, optimal CPAP in all 11 studies was defined as the CPAP having the lowest value for $aADCO_2$. The optimal level, as defined, was 8.9 ± 0.9 cm water (Table 2).

In the 7 studies (Table 1) in which values were obtained below, at, and above optimal CPAP (Fig. 1), there was a significant decrease in $aADCO_2$ between one step below and optimal CPAP ($p < 0.025$), and there was a significant increase in $aADCO_2$ between optimal and one step above optimal CPAP ($p < 0.025$). Between one step below and optimal CPAP there was a significant increase in $PACO_2$ ($p < 0.025$), but the further increase one step above optimal CPAP was not significant (Fig. 1). Between one step below and optimal CPAP there was no significant change in $PaCO_2$ (Fig. 1), but the further increase one step above optimal CPAP was accompanied by a very significant increase in $PaCO_2$ ($p < 0.001$). A secondary analysis of the eight studies in which data were obtained at optimal CPAP, and both 1 step and 2 steps below optimal CPAP (Table 1, nos. 1–3, 5, 8–11), confirmed the above suggestion that as CPAP was increased and optimal CPAP achieved, there was a progressive increase of $PACO_2$ without change of $PaCO_2$. The values were 32 ± 3 torr at 2 steps below, 35 ± 3 torr at 1 step below and 38 ± 3 torr at optimal CPAP ($p < 0.01$). During this progressive increase the values for $PaCO_2$ remained 48 ± 4 torr at all 3 steps, and $aADCO_2$ decreased correspondingly.

Due to changes in F_{IO_2} necessitated by hyperoxemia, satisfactory data for PaO_2 were obtained in only five of the seven infants who had measurements below, at and above optimal CPAP (Table 3). The values for PaO_2 and SaO_2 increased between one step below and optimal CPAP, but only the increase for SaO_2 was significant ($p < 0.025$). There was no significant change between optimal CPAP and one step above optimal CPAP, the level of oxygenation being well sustained (Table 3). The corresponding values for $aADCO_2$ were similar to those from all studies.

The measurements of Pes at end-expiration in five patients with HMD tended to increase as CPAP was increased. As expected, there was a tendency for the calculated fractional transmission of end-expiratory airway pressure to the esophagus (Pes/Pao) to increase with increased CPAP. In three infants during increase of CPAP, the values increased up to a certain critical point, defined as optimal CPAP, then decreased or remained the same before rising again with further increased CPAP. In the other two infants the values for fractional transmission continued to increase with increased CPAP, without reaching the obvious critical point described above, and in these two infants optimal CPAP was defined arbitrarily as the highest point. With optimal CPAP defined in this way for these five patients, optimal CPAP was 10.4 ± 1.7 cm H_2O, not significantly different from optimal CPAP in these five infants simultaneously determined by $aADCO_2$, which was 10.1 ± 1.5 cm H_2O. In four of these five infants, the values for optimal CPAP by Pes were exactly the same as those for optimal CPAP by $aADCO_2$. The increase of Pes/Pao as CPAP was increased to optimal CPAP in all five patients is shown in Figure 2. At 2.7 cm water below optimal

Table 2. *Values of CPAP for corresponding values of $aADCO_2$ in Table 1**

	Steps below optimal CPAP			Optimal	Steps above optimal CPAP	
n	3	2	1	CPAP	1	2
1		8.0	9.3	10.6	12.0	
2		12.0	13.3	14.6	16.0	
3		6.7	8.0	9.3	10.6	12.0
4			4.0	5.3	8.0	9.3
5		2.0	5.0	8.0	10.0	
6			2.0	5.0	8.0	11.0
7			2.0	5.0	8.0	11.0
8		2.0	5.0	8.0		
9	2.0	5.0	8.0	11.0		
10		6.7	9.3	10.6		
11	2.0	5.0	8.0	11.0		

* Values for CPAP are cm H_2O. Mean ± SEM value for optimal CPAP was 8.9 ± 0.9 cm H_2O.

Table 3. *Values for oxygenation and ventilation in five infants having HMD, with CPAP below, at, and above optimal levels (mean ± SEM)**

	1 step below optimal CPAP	Optimal CPAP	1 step above optimal CPAP
PaO_2 (torr)	54 ± 6	75 ± 8	81 ± 9
SaO_2 (%)	80.8 ± 4.4	91.5 ± 1.5†	92.2 ± 1.6
CPAP (cm H_2O)	4.2 ± 1.1	6.5 ± 0.9	8.9 ± 0.6
$PaCO_2$ (torr)	47.3 ± 4.7	46.1 ± 4.5	50.3 ± 4.5
$PACO_2$ (torr)	31.7 ± 2.6	34.2 ± 2.8	36.0 ± 3.1
$aADCO_2$ (torr)	15.6 ± 2.4	11.9 ± 2.7	14.3 ± 3.3

* F_{IO_2} was 0.77 ± 0.04, constant for each infant.

† Compared with 1 step below optimal CPAP, $p < 0.025$. CO_2 data not given statistical testing, see Figure 1.

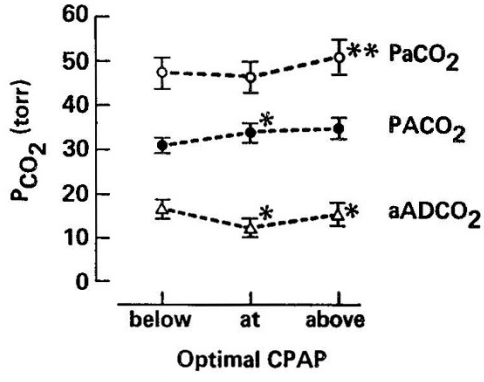

Fig. 1. Values for $PaCO_2$ (*open circles*), $PACO_2$ (*closed circles*), and $aADCO_2$ (*triangles*) in seven infants with HMD. CPAP was increased from 1 step below optimal CPAP (6.2 ± SE 1.6 cm H_2O) to optimal CPAP (8.3 ± 1.4 cm H_2O) and then 1 step above optimal CPAP (10.4 ± 1.1 cm H_2O). Compared with CPAP 1 step below, * $p < 0.025$, ** $p < 0.001$.

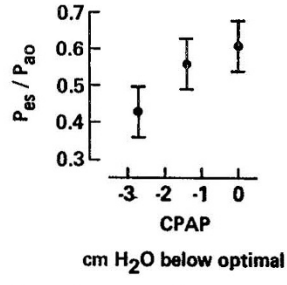

Fig. 2. Fractional transmission of airway pressure to the esophagus in five patients with HMD, as CPAP was raised from 2.7 cm H_2O below optimal to optimal CPAP (10.4 ± 0.1 cm H_2O). The increase was significant ($p < 0.01$). In the three patients who had measurements 1 step further below optimal CPAP, the mean value for transmission was 0.32.

CPAP the fractional transmission was 0.43 ± 0.07, but at optimal CPAP, this increased significantly to 0.61 ± 0.07 ($p < 0.01$).

DISCUSSION

The important finding of this study is that the $aADCO_2$, as predicted, decreased progressively with increasing CPAP (Table 1), but after a critical point was reached, namely optimal CPAP, it increased again with further increases of CPAP. At airway pressures below optimal CPAP, the $PaCO_2$ did not change with increasing CPAP, but both $PACO_2$ and SaO_2 increased (Fig. 1, Table 3), indicating more effective perfusion of the lung. This means that total ventilation actually decreased with increasing CPAP, but was progressively more effective because of the changes in perfusion, a finding consistent with previous suggestions (10). Above optimal levels of CPAP there was a sudden increase of $PaCO_2$ caused by a further decrease in ventilation (Fig. 1, Table 3) without a continuing improvement in perfusion. The accompanying slight increase in $PACO_2$ was primarily due to decreased ventilation, rather than to improved perfusion, because the accompanying change of SaO_2 was insignificant (Table 3). If the relationship between ventilation and perfusion had remained the same at 1 step above optimal CPAP, $PACO_2$ would have risen with $PaCO_2$ and the $aADCO_2$ would not have changed. Thus it would appear that not only did ventilation decrease at 1 step above optimal CPAP, but perfusion actually decreased too, even more markedly than ventilation decreased. Other investigators have defined optimal end-expiratory airway pressure as that which improves gas exchange most without reducing oxygen delivery to the tissues (11, 12). Although cardiac output was not measured in the present study, it is reasonable to believe that the decreased perfusion at 1 step above optimal CPAP, suggested by the changes of $aADCO_2$ (Fig. 1), would be the equivalent of a decrease in cardiac output at higher levels of CPAP, and hence a decrease in tissue oxygen delivery.

Previous work has shown that the lung in HMD may be described in terms of a three compartment model (5). The high VA/Qc compartment receives virtually all the ventilation, reflected in the measured $PACO_2$, and all the perfusion which is not venous admixture. The open low VA/Qc compartment, representing at least 20% of the lung, receives virtually no ventilation and only a small part of the venous admixture, about 3% of the cardiac output (1). This compartment makes no contribution to the measured $PACO_2$ because it is so poorly ventilated. The remaining venous admixture is attributed to the shunt compartment, possibly collapsed alveoli, but more likely vessels without developed alveoli. It is thought that CPAP expands open low VA/Qc airspaces into the high VA/Qc compartment, and replaces the open low VA/Qc compartment by recruitment of collapsed airspaces (1). The above described changes of ventilation and perfusion with increasing CPAP (Fig. 1) may be further analyzed in a semiquantitative fashion with use of this model (Fig. 3).

The measurements of PaO_2 (Table 3) make it possible to estimate values for venous admixture (see Appendix A) and so assign values for perfusion in the three compartment model, but it is necessary to assume constant cardiac output. The calculated values 1 step below optimal CPAP, at optimal CPAP and 1 step above optimal CPAP are shown in Figure 3. It can be seen that between 1 step below and optimal CPAP, perfusion of the well-ventilated lung compartment increased from 0.39 to 0.52 of cardiac output, whereas there was not real improvement of perfusion at 1 step above optimal CPAP.

In addition, if it is assumed that steady state conditions were obtained below, at, and above optimal CPAP, and that CO_2 elimination was the same at each steady state, then relative changes of ventilation in the high VA/Qc compartment can be calculated from values of $PACO_2$ (see Appendix B, equation 1). Compared with 1 step below optimal CPAP, there was a 7% reduction of ventilation at optimal CPAP, and a further 5%

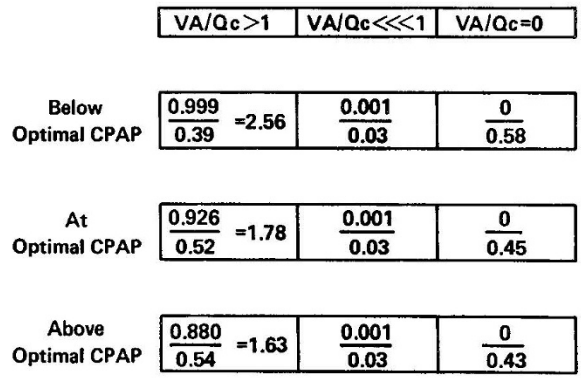

Fig. 3. Three compartment lung model in HMD showing estimated values for VA/Qc under three conditions, below, at, and above optimal CPAP. The calculated mean values for Qva/Qt, derived from PaO_2 values in Table 3 and the shunt equation in Appendix A, were 0.61 at 1 step below, 0.48 at optimal CPAP, and 0.46 at 1 step above optimal CPAP. Therefore, values for perfusion in the well-ventilated high VA/Qc compartment (1 − Qva/Qt) were 0.39, 0.52, and 0.54, respectively. Constant cardiac output was assumed. Values for perfusion in the open low VA/Qc compartment were taken to be 0.03 of cardiac output and not to change with CPAP (1), and thus perfusion in the shunt compartment could also be estimated. Ventilation in the open low VA/Qc compartment was assigned a negligible value, and in the shunt compartment it was 0. Changes in ventilation, derived from the measured $PACO_2$ values in Table 3 and equation 1 of Appendix B, are incorporated in the values assigned for ventilation in the high VA/Qc compartment, and hence in the calculations of VA/Qc.

reduction 1 step above optimal CPAP (Table 3). Thus, values for ventilation may also be assigned in the model (Fig. 3) and values for VA/Qc in the well-ventilated lung compartment calculated.

With the same assumptions used for calculating Qva/Qt (see Appendix A), and making the additional assumption that $P\bar{v}CO_2$ is 6 torr greater than $PaCO_2$, we have constructed O_2–CO_2 diagrams (Fig. 4), using a standard procedure (8). Estimates for VA/Qc in the high VA/Qc compartment, at various values of R, are calculated from a modification of the standard VA/Qc equation (see Appendix B, equation 3). The VA/Qc line obtained gives a close approximation of the only VA/Qc possible at any given value for $PACO_2$. Using the calculated values for VA/Qc in the well-ventilated lung compartment (Fig. 3), we have estimated expected values for $PACO_2$, and hence $aADCO_2$. Comparison of these values with the measured values (Table 4) reveals a generally close agreement, especially at 1 step below optimal CPAP, thus justifying the use of this model. In addition however, it can be seen that there was a small but progressive disparity between measured and predicted values as CPAP was increased, with predicted $PACO_2$ tending to be too high. As changes of ventilation have been taken into account, this may be due to a corresponding decline in cardiac output, which would directly increase the VA/Qc and so reduce the predicted values for $PACO_2$. However, in this model small changes of cardiac output have relatively little effect on predicted $PACO_2$. This is because, as shown previously (4), changes of $P\bar{v}CO_2$ and $S\bar{v}O_2$ on the one hand, and changes of perfusion in the high VA/Qc compartment on the other hand, all due to changes of cardiac output, tend to balance each other in the estimate of VA/Qc and $PACO_2$. A conservative analysis indicates that a minimal reduction of cardiac output at optimal CPAP, and a 25% reduction at 1 step above optimal CPAP, would be required to bring the disparity between measured and predicted $PACO_2$ to within 2 torr, a more reasonable level of agreement. Although this suggests that CPAP above optimal levels reduces cardiac output, it is not known what happens to cardiac output with CPAP below optimal levels. There may be a substantial increase. But, compared with levels

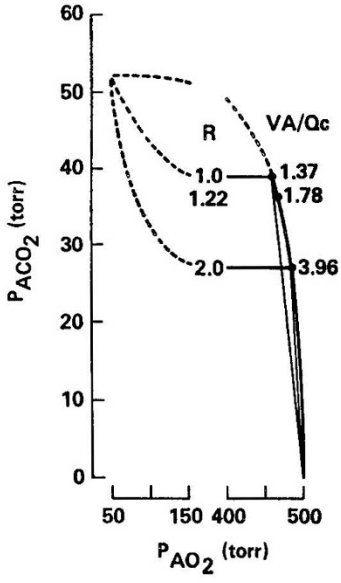

Fig. 4. O_2–CO_2 diagram for predicting $PACO_2$ at optimal CPAP, derived from mean values in Table 3, with inspired oxygen point 500 torr and $P\bar{v}CO_2$ 52 torr. Blood and gas R lines for R values of 1 and 2 were drawn, the points of intersection indicating alveolar gas composition in the high VA/Qc compartment. Then appropriate values for R and $PACO_2$ were repeatedly calculated in the VA/Qc equation (see Appendix B, equation 3). At VA/Qc 1.78 (Fig. 3) the $PACO_2$ was 36.4 (Table 4). *Broken lines* are diagrammatic.

Table 4. *Comparison of predicted values for $aADCO_2$, based on three compartment lung model and O_2-CO_2 diagram, with measured values from Table 4**

	Predictions			Measured	
Condition	VA/Qc	$PACO_2$	$aADCO_2$	$PACO_2$	$aADCO_2$
Below optimal CPAP	2.56	32.4	14.9	31.7 ± 2.6	15.6 ± 2.4
At optimal CPAP	1.78	36.4	9.7	34.2 ± 2.8	11.9 ± 2.7
Above optimal CPAP	1.63	39.0	11.3	36.0 ± 3.1	14.3 ± 3.3

* Predicted values for VA/Qc based on three compartment lung model (Fig. 3). Predicted $PACO_2$ derived from calculated VA/Qc and the appropriate O_2-CO_2 diagram based on data from Table 3.

just below optimal CPAP, the present data suggest a possible small reduction of cardiac output at optimal CPAP, and a probable large reduction of cardiac output at higher levels.

Previously optimal CPAP has been defined by other workers using measurements of Pes (3). The rationale is that Pes is a good reflection of pleural pressure. This is thought to be true when the ratio of change of Pes to change of Pao is near unity during breathing efforts with an obstructed proximal airway (15). In our subjects this condition was found present at all levels of CPAP (see "Methods"), and so gives confidence in the method. Although cyclical changes in Pes may not accurately reflect cyclical changes of pleural pressure at all levels of the lung in premature infants (16), the present measurements are a good reflection of pleural pressure at the level of the heart.

As a result of previous work (2, 3), the concept has arisen that fractional transmission of airway pressure to the esophagus is small, and at optimal CPAP it suddenly increases to about 0.6. Although the present data are consistent with this concept, examination of Figure 2 shows that in our infants transmission of airway pressure rose more gradually to high levels at optimal CPAP. In general there was close agreement between the two methods for estimating optimal CPAP, namely $aADCO_2$ and Pes/Pao, but the changes in fractional transmission were in some cases small, and the critical point sometimes difficult to define. As indicated by the concurrent $aADCO_2$ measurements, this difficulty was not because all measurements were made below or above optimal CPAP.

The observation of high fractional transmission of airway pressure to the esophagus provides a good explanation for why CPAP might decrease the cardiac output by impairment of the venous return due to a high pleural pressure at the level of the heart. In HMD, many airspaces are completely collapsed (possibly 40%), and many others are very nearly collapsed (at least 20%). Since these airspaces would have poor compliance, they would not favor transmission of airway pressure to the esophagus. However, the remaining airspaces, in the high VA/Qc compartment, must be sufficiently compliant to sustain a level of ventilation which is higher than normal, which suggests they would transmit airway pressure well. As increasing CPAP progressively recruits more airspaces into the high VA/Qc compartment, there should be a progressive increase in the transmission of airway pressure to the esophagus, rather than a sudden increase. This would be consistent with the present findings.

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APPENDIX A

Venous admixture 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 oxygen content values were derived using a value of 1.34 ml oxygen for each gram of hemoglobin, a value of 0.003 ml/torr for oxygen dissolved in plasma, and assuming that the difference between SaO_2 and $S\bar{v}O_2$ was 0.15 (13) and constant.

APPENDIX B

CO_2 elimination can be calculated in terms of ventilation (14). Thus,

$$\dot{V}CO_2 = \frac{VA \cdot PACO_2}{0.863} \quad 1)$$

CO_2 can also be calculated in terms of perfusion (14). If only the high VA/Qc compartment is involved in gas exchange, as in our model, and it is the VA/Qc of this compartment which is being calculated, then $C\mathring{c}O_2$ must be substituted for CaO_2, and $C\dot{c}CO_2$ must be substituted for $CaCO_2$.

Thus, from first principles,

$$\dot{V}CO_2 = Qc \cdot (C\dot{c}O_2 - C\bar{v}O_2) \cdot R \quad 2)$$

After eliminating $\dot{V}CO_2$ in these two expressions,

$$VA/Qc = \frac{R \cdot (C\dot{c}O_2 - C\bar{v}O_2) \cdot 0.863}{PACO_2} \quad 3)$$