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Mechanical Ventilation of Newborn Infants:

II. Effects of Independent Variation of Rate and Pressure on Arterial Oxygenation of Infants with Respiratory Distress Syndrome

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Respiratory rate and peak airway pressure were independently varied during controlled mechanical ventilation of infants with severe respiratory distress syndrome. During the first five days of mechanical ventilation five newborn infants were studied four times each. Each study consisted of six predetermined rate and/or pressure changes. Pressures ranged from 21 to 53 cm H_2O and rates from 8 to 40 breaths/min. Changes in Pa_{O_2}, Pa_{CO_2} and pH_a, the dependent variables, were correlated with changes in the independent variables, rate and pressure. When pressure is increased, Pa_{O_2} and pH_a increase and Pa_{CO_2} decreases. When rate is increased, Pa_{O_2} and Pa_{CO_2} decrease and pH_a increases. The magnitudes of the changes in dependent variables for unit changes in rate and pressure are given. Specific variations of rate and/or pressure during controlled mechanical ventilation of infants with respiratory distress syndrome do result in changes in Pa_{O_2}, Pa_{CO_2} and pH_a which are predictable in magnitude and direction. (Key words: Prolonged mechanical ventilation; IPPV/I; Respiratory rate; Airway pressure; Newborn infants; Respiratory distress syndrome.)

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WE HAVE DEMONSTRATED that arterial oxygenation of infants with respiratory distress syndrome (RDS) can be increased during intermittent positive-pressure ventilation (IPPV/I) by simultaneously increasing peak airway pressure (P_{aw}) and decreasing respiratory rate/min (f) in a manner which does not significantly alter Pa_{CO_2} or pH_a.[1] We observed that the changes we found in Pa_{O_2} while keeping alveolar ventilation almost constant might have been influenced by the sequence ("path") of concomitant rate and pressure changes. The present study was designed to eliminate this "path" effect and to determine the effects of independent variations of rate and pressure on Pa_{O_2}, Pa_{CO_2}, and pH_a.

Methods

Five infants with respiratory distress syndrome (RDS) of sufficient severity to necessitate mechanical ventilation of the lungs were studied (table 1). The diagnosis of RDS was made when grunting, nasal flaring, and sternal or subcostal retraction were present together with a radiograph of the chest showing reticulogranularity and an air bronchogram. The initial care of the newborn infants and the method of selection for IPPV/I have been described.[2] This method of selection ensured that all babies studied were in a similar clinical condition.

For the present investigation any one study of one infant consisted of a sequence of four sets of measurements which were designed to eliminate the "path" influence on the dependent variables. For each of five infants a series of four substudies was designed to assess the influence of the independent (controlled) variables, rate and pressure, on the dependent variables, Pa_{O_2}, Pa_{CO_2}, and pH_a. To investigate the effect of each controlled variable separately,

TABLE 1. Preventilation Data for the Five Infants

	Sex, Weight (g)	Time of Blood Sampling (Min before IPPV/I)	Age at Onset of IPPV/I (Hours)	Blood-Gas Values and Score Prior to Initiation of Mechanical Ventilation*					Outcome
				Pa_{O_2}	Pa_{CO_2}	pH_a	Other	Score	
Infant 1	M, 2,098	300	74	96	100	7.19	Apnea	8	Survived
Infant 2	M, 2,400	10	62	35	115	7.28	—	7	Survived
Infant 3	M, 2,500	30	55	30	71	7.24	Apnea	9	Survived
Infant 4	F, 1,503	—	3	—	—	—	Apnea	3	Died
Infant 5	M, 3,510	60	41	34	40	7.29	—	4	Survived
MEAN	2,402.2	100	47	48.75	81.5	7.25			

* Arterial blood-gas values and *p*H obtained after administration of sodium bicarbonate with the infants breathing 100 per cent oxygen. Infants were scored according to the system for selection for mechanical ventilation previously reported.[2]

a scheme was chosen such that for each level of one controlled variable the other one was balanced to make the correlation between them ideally equal to zero. The actual correlation coefficients between rate and pressure for the five infants are presented in table 2.

Each infant was studied four times during the first five days of IPPV/I, approximately 24 hours apart. As an example, the sequence and increments of rate and pressure and the actual rates and pressures used for each of the four studies designed for *one* infant are shown in table 3. Study designs for the other infants followed the same principles, but were not identical to the one shown.

Bennett PR2 ventilators with infant minimum-deadspace circles and polyvinyl nasotracheal tubes § were used. Peak airway pressure and respiratory frequency were adjusted at the start of IPPV/I so that Pa_{CO_2} was between 30 and 40 torr. The I:E ratio of the Bennett PR2 ventilators was fixed at 1:1.2 and the end-inspiratory flow rate was less than 0.1 l/sec. The airway-pressure curve was recorded on a Brush direct-writing oscillograph. An 18-gauge needle was inserted near the endotracheal tube on the inspiratory limb of the circle, and attached to it was a stiff catheter which led to a Statham PM5 strain gauge. Peak airway pressure in cm H_2O (P_{aw}) was measured directly, and respiratory rate in breaths/min (f) was measured by counting the number of pressure peaks from the chart recordings. Rate and pressure settings on the ventilator were changed every half hour, and aortic blood samples were drawn after 25 minutes of undisturbed IPPV/I. The nasotracheal tubes were cleared by suction with a polyethylene catheter ¶ before the change to the next levels of P_{aw} and f. Catheters placed via an umbilical artery into the aorta were used routinely for blood sampling and fluid infusion. The tip was stationed above the diaphragm and distal to the ductus arteriosus. The position was verified by radiography. It has been shown that in infants with RDS and a patent ductus arteriosus Pa_{O_2} often is lower in the aorta than in the right radial artery.[3] Throughout this report, Pa_{O_2}, Pa_{CO_2}, and pH_a refer to values in aortic blood samples. All samples were drawn into heparinized 1-ml plastic syringes °° sealed immediately with mercury-filled

TABLE 2. Correlation Coefficients for Independent Variables, Respiratory Rate and Airway Pressure

	Correlation Coefficient
Infant 1	−.06
Infant 2	.44*
Infant 3	−.06
Infant 4	.11
Infant 5	−.04

* The protocol could not be strictly adhered to for four of the 28 settings.

§ Foregger For-Clear.
¶ Intramedic PE 205.
°° Tomac.

TABLE 3A. Protocol for the Magnitudes and Sequence of Rate and Pressure Changes To Be Made in the Four Studies of Infant 4*

	Study 1		Study 2		Study 3		Study 4	
	ΔP	ΔR	ΔP	ΔR	ΔP	ΔR	ΔP	ΔR
1)	Starting measurements at onset of Study 1		Starting measurements at onset of Study 2		Starting measurements at onset of Study 3		Starting measurements at onset of Study 4	
2)	+5	−10	−5	+10	−5	+10	+5	+10
3)	−5	Same	+5	Same	Same	−10	Same	−10
4)	−5	Same	+5	Same	Same	−10	Same	−10
5)	+10	+20	−10	−20	+10	+20	−10	+20
6)	−5	Same	+5	Same	Same	−10	Same	−10
7)	−5	Same	+5	Same	Same	−10	Same	−10

TABLE 3B. Actual Rate and Pressure Settings Used in the Four Studies of Infant 4†

	Study 1		Study 2		Study 3		Study 4	
	P	R	P	R	P	R	P	R
1)	35	40	40	32	45	35	38	25
2)	40	30	35	42	40	45	43	35
3)	35	30	40	42	40	35	43	25
4)	30	30	45	42	40	25	48	15
5)	40	50	35	22	50	45	33	35
6)	35	50	40	22	50	35	33	25
7)	30	50	45	22	50	25	33	15

* ΔP = change in peak airway pressure in cm H_2O from previous setting; ΔR = change in respiratory rate in breaths/min from previous setting; "same" indicates no change from previous setting.

† P = peak airway pressure in cm H_2O; R = respiratory rate in breaths /min.

caps, mixed, and placed in ice, and analyzed for pH_a, Pa_{CO_2}, and Pa_{O_2} within 15 minutes. Corrections were made to accommodate the difference between the temperature of the electrode (38 C) and the rectal temperature of the infant.

Pearson product-moment correlation coefficients [4] were computed for Pa_{O_2}, Pa_{CO_2}, and pH_a with rate and pressure for all studies of each infant. Since these coefficients varied from infant to infant, only their means are reported. Multiple correlation coefficients, calculated for Pa_{O_2}, Pa_{CO_2}, and pH_a with rate and pressure, were also computed.

Regression coefficients and their standard deviations for each pair of a controlled and an independent variable were obtained for all four studies of each of the five infants. These coefficients were then tested for significance (t test), resulting in five (one for each baby) *P* values for each pair of independent and dependent variables. In order to obtain a summary statement about the whole data set, one overall regression analysis was performed for all five infants, and confidence limits for the resulting regression coefficients were computed.

Results

The range of respiratory rates used was 8–40 breaths/min and that of peak airway pressures was 21–53 cm H_2O. Pa_{O_2}'s ranged from 1 to 104 torr, Pa_{CO_2}'s from 18 to 51 torr, and pH_a's from 7.30 to 7.62.

The relationships between the independent variables, f and P_{aw}, and the dependent variables, Pa_{O_2}, Pa_{CO_2}, and pH_a, were found to be significant. The directions and the magnitudes of the relationships between the two types of variables are summarized in table 4. When pressure is increased independently of a rate change, Pa_{O_2} and pH_a increase and Pa_{CO_2} decreases. When rate is increased independently

of an airway-pressure change, Pa_{O_2} and Pa_{CO_2} decrease, while pH_a increases. Pa_{O_2} increases when the rate is decreased and peak airway pressure is increased simultaneously. The effects of such a change on Pa_{CO_2} and pH_a depend on the relative weights of the independent variables. Similarly, if pressure and rate are increased at the same time, the result is a decrease in Pa_{CO_2} and an increase in pH_a, while the ultimate effect on Pa_{O_2} will depend on the relative weights given to rate and pressure.

The 99 per cent confidence limits for the regression coefficients are given in table 5. Owing to the small number of infants studied, these confidence limits are somewhat wide.

Average simple and multiple correlation coefficients obtained for the independent and dependent variables are given in table 6. The simple correlation coefficients relating either one or the other of the independent variables to the dependent variables agree in sign with the data presented in table 4. The multiple correlation coefficients illustrate the degree to which rate and pressure combined are correlated with the three dependent variables, Pa_{O_2}, Pa_{CO_2} and pH_a.

Discussion

During controlled IPPV/I of infants with respiratory distress syndrome, aortic P_{O_2} can be increased without significant alteration of Pa_{CO_2} or pH_a when, concomitantly, airway pressure is increased and respiratory rate decreased.[1] Alteration of inspiratory flow rate and of the inspiration–expiration ratio during assisted IPPV/I has also been shown to influence oxygenation of infants with RDS significantly.[5] These observations suggest that specific determinants of IPPV/I significantly and predictably influence arterial oxygen tension. The data also indicate that adequate alveolar ventilation (Pa_{CO_2}) can be achieved during IPPV/I of infants in severe respiratory distress and that oxygenation of these infants can be influenced independently of alveolar ventilation.

That an incremental increase in pressure, and thus tidal volume (V_T), increases alveolar ventilation and oxygenation more than an incremental increase in rate is not surprising. An increase in V_T would not alter the deadspace significantly, but would encroach upon the reserve volumes, probably enlarging FRC, thus enabling better oxygenation and alveolar ventilation.

TABLE 4. Regression Coefficients of Peak Airway Pressure and Respiratory Rate for the Three Dependent Variables*

Dependent Variables	Independent Variables	
	Peak Airway Pressure (cm H_2O)	Respiratory Rate (Breaths/Min)
Pa_{O_2} (torr)	+1.84	−1.37
Pa_{CO_2} (torr)	−0.40	−0.20
pH_a	+0.007	+0.003

* Values consist of slopes of regression lines when rate or pressure is increased by one unit. Since prior to analysis the data were adjusted for each infant, intercepts of these lines are close to zero and have no importance for this analysis.

TABLE 5. The 99 Per Cent Confidence Limits for the Regression Coefficients of Rate and Pressure for Pa_{O_2}, Pa_{CO_2}, and pH_a*

Dependent Variables	99 Per Cent Confidence Limits	
	Independent Variable, Pressure (P_{aw})	Independent Variable, Rate (f)
Pa_{O_2}	$0.16 \leqq \beta_{11} \leqq 3.52$	$-2.24 \leqq \beta_{21} \leqq -0.50$
Pa_{CO_2}	$-0.76 \leqq \beta_{12} \leqq -0.04$	$-0.38 \leqq \beta_{22} \leqq -0.02$
pH_a	$0.004 \leqq \beta_{13} \leqq 0.010$	$0.0013 \leqq \beta_{23} \leqq 0.0045$

* β_{11} = regression coefficient of pressure on Pa_{O_2}.
β_{12} = regression coefficient of pressure on Pa_{CO_2}.
β_{13} = regression coefficient of pressure on pH_a.
β_{21} = regression coefficient of rate on Pa_{O_2}.
β_{22} = regression coefficient of rate on Pa_{CO_2}.
β_{23} = regression coefficient of rate on pH_a.

TABLE 6. Average Simple and Multiple Correlation Coefficients between Independent and Dependent Variables

Dependent Variables	Simple Correlation Coefficients, Independent Variables*		Multiple Coefficients
	P_{aw}	f	
Pa_{O_2}	.36	−.25	.52
Pa_{CO_2}	−.05	−.24	.44
pH_a	.10	.36	.50

* P_{aw} = peak airway pressure in cm H_2O; f = respiratory rate in breaths/min.

Our studies do not explain the mechanism for the negative correlation of Pa_{O_2} with rate and its positive correlation with pressure. Hypercarbia and acidosis both cause constriction of pulmonary vessels, which would alter the ventilation/perfusion relationship. Thus, when rate is increased Pa_{CO_2} decreases (see table 4), and the alkalosis produced would decrease pulmonary vascular resistance. The expected improvement in oxygenation does not occur, whether or not the subject was originally hypoxic or hyperoxic. Thus, it must be that the slow rates and high pressures lead to a ventilation–perfusion relationship that is more nearly normal and a decrease in left-to-right shunt.

Analysis of previous data suggested that the order in which rate and pressure were changed ("path") could have influenced the results obtained. The present study was designed to eliminate such "path" dependencies and to determine whether rate and pressure influenced pH_a, Pa_{O_2}, and Pa_{CO_2} independently. The results demonstrated that variations of either rate alone or pressure alone exert effects on aortic P_{O_2}, P_{CO_2}, and pH. Whether this holds true for normal infants or those who have respiratory failure from causes other than RDS has not been investigated. A study of a group of infants, some with RDS and others with normal lungs ventilated with the Hammersmith ventilator, comparing rates and pressures with tidal volume and alveolar ventilation, has been reported.[6] Optimal rates and pressures for maximal alveolar ventilation were found, but correlations with blood–gas tensions or pH were not reported.

In our study an increase in respiratory rate and/or an increase in airway pressure resulted in a decrease in pH_a. Increasing pressure and/or decreasing rate increased Pa_{O_2}. However, when rate and pressure were simultaneously changed in the same direction, the direction of change in Pa_{O_2} depended on the relative weights given to rate and pressure. This underlines the absolute necessity for measuring Pa_{O_2}, Pa_{CO_2}, and pH_a whenever determinants of minute ventilation are adjusted. Our data suggest that during IPPV/I of infants with severe RDS, specific alterations of variables of ventilation should result in more adequate and continuous control of oxygenation and better treatment of respiratory failure.

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