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The Effect of Hypo-, Normo-, and Hypercapnia Induced by Mechanical Ventilation on Intrapulmonary Shunt

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The effects of hypo-, normo- and hypercapnia on the variations in arterial oxygenation and their indices in critical patients with acute respiratory failure (ARF) receiving mechanical ventilation are studied. It is a prospective and randomized study carried out in multidisciplinary ICU. Fifteen ARF patients, intubated and mechanically ventilated, were studied within the first 48 h of evolution. Three stages were delimited: I) 30 min after the beginning of anaesthesia; II) 30 min after adding 30 cm of dead space (VD); III) 30 min after replacing the previous VD with VD of 60 cm. Ventilation parameters and FiO_2 were kept stable. Stage I was characterized by respiratory alkalosis and stage II by normal acid-base balance with an increase in PaO_2 ($p<0.01$) and a decrease in intrapulmonary shunt ($\dot{Q}sp/\dot{Q}t$) ($p<0.001$); the indices alveolar to arterial oxygen tension gradient [$P(A-a)O_2$], respiratory index (R.I.) and estimated shunt (Est Shunt) also decreased significantly, whereas arterial to alveolar oxygen tension ratio (PaO_2/PAO_2) and arterial oxygen tension to inspired oxygen fraction ratio (PaO_2/FiO_2) increased significantly. In stage III there was pure hypercapnic acidosis, with decreases in PAO_2 ($p<0.001$), $P(A-a)O_2$ ($p<0.01$) and R.I. ($p<0.05$), while PaO_2, $\dot{Q}sp/\dot{Q}t$, Est Shunt, PaO_2/PAO_2 and PaO_2/FiO_2 remained stable with respect to the previous situation. The observed PaO_2 differs ($p<0.05$) from the expected PaO_2 in stage III. It is suggested that local or regional modifications of pulmonary perfusion are responsible for the observed variations. The $P(A-a)O_2$ and R.I. indices do not make it possible to differentiate the causes of arterial hypoxemia in the presence of hypercapnia.

Key words: Hypo-, normo- and hypercapnia, Oxygenation indices, Intrapulmonary shunt, Dead space, Acute respiratory failure.

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The respiratory alkalosis produced by mechanical ventilation, has been identified as a cause of hypoxemia (6, 21), which improves when $PaCO_2$ is normalized or increased (15, 19, 25). A moderate hypercapnia has been suggested for the treatment of acute respiratory failure (ARF) by the results observed in experimental animals (28).

It is now increasingly recognized that permissive hypercapnia (PerH) is a strategy for the management of patients on mechanical ventilation (MV) in several circumstances, such as severe adult respiratory distress syndrome (ARDS), infectious pneumophaties or severe airflow obstruction (1, 17, 23).

Measurement of intrapulmonary shunting ($\dot{Q}sp/\dot{Q}t$), a widely used method for monitoring disturbances of pulmonary oxygen transfer in critically ill patients, involves calculation of arterial and mixed venous oxygen contents. In circumstances where mixed venous blood samples are not readily available, oxygen tension-based indices such as the alveolar to arterial oxygen tension gradient [$P(A\text{-}a)O_2$], the arterial to alveolar oxygen tension ratio [PaO_2/PAO_2], the arterial oxygen tension to inspired oxygen fraction ratio (PaO_2/FiO_2), and Respiratory Index [$R.I. = P(A\text{-}a)O_2/PaO_2$] or oxygen content-based indices such as the Estimated Shunt (Est Shunt) (7, 12, 13, 22), are widely utilized to reflect $\dot{Q}sp/\dot{Q}t$.

The purpose of the present work is to determine the effects of hypo-, normo-, or hypercapnia on the variations in arterial oxygenation indices observed in critical ARF patients receiving mechanical ventilation.

Materials and Methods

The characteristic of the studied patients, as well as the materials and methods used in the present report have been previously described (5).

After a basal period (Stage I) of induced hypocapnia by mechanical ventilation, the $PaCO_2$ is normalized (Stage II) and increased (Stage III) by the addition of dead space (VD) (2, 18, 29, 31). At the end of each of the three stages, simultaneous arterial and mixed venous blood samples were obtained and analyzed.

In addition, tension oxygen alveolar (PAO_2), $P(A\text{-}a)O_2$, PaO_2/PAO_2, PaO_2/FiO_2, R.I., Est Shunt and physiologic shunt ($\dot{Q}sp/\dot{Q}t$), were determined by:

$$PAO_2 = FiO_2\,(PB\text{-}PH_2O)\text{-}(1.25\ PaCO_2)$$

$$\text{Est Shunt} = \frac{CcO_2 - CaO_2}{CcO_2 - CaO_2 + 3.5}$$

$$\dot{Q}sp/\dot{Q}t = \frac{CcO_2 - CaO}{CcO_2 - CvO_2}$$

$CcO_2 = Hb[(1\text{-}HbCO)\ 1.34 + 0.0031\ PAO_2]$. The correction factors [1.0 - HbCO] were: 0.985, 0.975 and 0.965 when PAO_2 was higher than 150 mm/Hg, oscillated between 150 - 125 mm/Hg or 125-100 mm/Hg, respectively.

$$CaO_2 = SaO_2\ (1.34\ Hb) + 0.0031\ PaO_2$$

$$CvO_2 = SvO_2\ (1.34\ Hb) + 0.0031\ PvO_2$$

The expected PaO_2 values of each one of the patients were obtained after correcting their observed PaO_2 values with respect to the acid-base variations, by Kelman's formula, using a program with the original subrutine written in Fortram (16).

The paired Student's *t* test and the Pearson correlation analysis were utilized in the statistical analysis of the data. After repeating the analysis of variance about the same basic data of the three stages described, the same dintels of significance were obtained. To favour simplicity the values of Fisher's F are eluded. All values are reported as mean ± SD. Values of $p < 0.05$ were considered significant.

Results

The parameters FiO_2, VE, PEEP, Cot and Raw were kept unmodified in the three stages. The initial situation of pure respiratory alkalosis in the acid-base balance evolves to normality in stage II, and of pure hypercapnic acidosis in stage III, after the significant increase in $PaCO_2$ subsequent to the augmentation in dead space (R = 0.91, p<0.001) (table I). The addition of a 30 cm VD caused a significant improvement in PaO_2 (table II), as it also did in the tension indices ($P(A\text{-}a)O_2$, PaO_2/PAO_2, PaO_2/FiO_2 and R.I.) and in the content of O_2 (Est Shunt and $\dot{Q}sp/\dot{Q}t$). The PAO_2 dropped significantly. With the addition of 60 cm VD, PaO_2 and the indices $Pa\dot{Q}v/P\dot{A}O_2$, PaO_2/FiO_2, Est Shunt and $\dot{Q}sp/\dot{Q}t$ remained stable with respect to stage II; however, a further decrease was produced in PAO_2, as well as in $P(A\text{-}a)O_2$ and R.I. Table II also shows the significant correlation found between PAO_2 and the $P(A\text{-}a)O_2$ and R.I. indices. Such a relationship does not exist with all the other indices, except for PaO_2/PAO_2 after the addition of the 60 cm VD.

The figure 1 shows the observed PaO_2 values and the expected PaO_2 for the Bohr effect; adverting their similiarities during the stage II but underlining their significant difference ($p < 0.05$) in stage III (observed PaO_2 = 105 + 36.9 and expected PaO_2 = 117.6 + 47.7 mmHg).

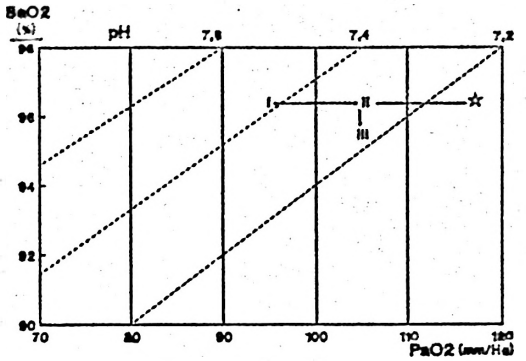

Fig. 1. *Detail of the fixation curves of PaO_2 in human blood Bohr pH 7.2; 7.4; 7.6 (37 °C).* Operative sequence Bohr effect. * Awaited effect that does not take place.

Discussion

The respiratory alkalosis observed in patients receiving mechanical ventilation has been identified as the cause of hypoxemia (6, 25); its origin has been attributed to variable and imprecise physiopathological mechanisms (7, 9, 14).

The genesis of a hypoxemia, excluding some special circumstances (a decrease of FiO_2, intracardiac right-left shunt, etc.) that were not present in our patients, stem from an imbalance in $\dot{V}A/\dot{Q}$; depending on different pathologies, the prevalent alterations are either in ventilation or in perfusion.

Table I. *Respiratory and Acid-base Balance Parameters.*

Parameter	(Stage I) BASAL	(Stage II) VD 30 cm	(Stage III) VD 60 cm
FiO_2 (%)	39.0 ± 7.6	39.0 ± 7.4	38.0 ± 7.8
$\dot{V}E$ (L/min)	14.23 ± 1.32	14.22 ± 1.31	14.18 ± 1.29
PEEP (ml/H_2O)	0.7 ± 1.8	0.8 ± 1.7	0.7 ± 1.8
Cot ($ml/cm\ H_2O$)	37.7 ± 10.4	35.8 ± 9.4	35.9 ± 12.4
Raw ($ml/\ H_2O$)	12.3 ± 6.1	10.0 ± 5.3	11.4 ± 6.6
pH	7.46 ± 0.06***	7.38 ± 0.06	7.28 ± 0.06***
$PaCO_2$ (mm/Hg)	30.8 ± 3.35***	40.5 ± 5.70	54.8 ± 6.67***

*** p<0.001, vs II. n = 15.

Table II. *Oxygen-content and oxygen-tension indices and their correlation (r values) between them.* Correlation (r values) with PAO_2 respectively and PaO_2 are indicated.

	(Stage I) Basal			(Stage II) VD 30 cm			(Stage III) VD 60 cm		
Parameter	$\bar{x}$ ± SEM	r		$\bar{x}$ ± SEM	r		$\bar{x}$ ± SEM	r	
PAO_2 (mmHg)	245.0 ± 54.3***			230.1 ± 53.9			208.4 ± 54.32***		
PaO_2 (mmHg)	96.1 ± 39.8**			106.8 ± 41.9			105.2 ± 36.92		
$P(A\text{-}a)O_2$	148.4 ± 53.1***	0.71^{++}	−0.39	123.5 ± 59.8	0.74^{+++}	-0.51^{+}	103.4 ± 58.2**	0.79^{+++}	−0.37
PaO_2/PAO_2	0.4 ± 0.15***	−0.26	0.77^{++}	0.48 ± 0.18	−0.47	0.73^{++}	0.53 ± 0.19	-0.59^{+}	0.56^{+}
PaO_2/FiO_2	244.7 ± 89.0***	−0.17	0.83^{+++}	278.0 ± 102.9	−0.36	0.82^{+++}	276.9 ± 89.0	−0.33	0.80^{+++}
R.I.	1.86 ± 1.06***	0.34	-0.73^{++}	1.44 ± 1.06	0.53^{+}	-0.70^{++}	1.18 ± 0.96*	0.59^{+}	-0.59^{+}
Est Shunt	9.83 ± 12.3**	0.15	-0.70^{++}	4.67 ± 19.2	0.45	-0.64^{++}	6.23 ± 13.9	0.39	-0.61^{+}
Qsp/Qt	9.58 ± 14.4*	0.16	-0.73^{++}	5.83 ± 12.6	0.46	-0.62^{++}	6.54 ± 22.0	0.42	-0.55^{+}

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ respect to the stage II. n= 15.
+ $p < 0.05$, ++ $p < 0.01$, +++ $p < 0.001$ respect to the r values. n = 15.

It has been shown, moreover, that hypoxemia secondary to hypocapnia, in patients receiving mechanical ventilation, improves when $PaCO_2$ is normalized, and that one of the $PaCO_2$ increase with the addition of VD (8, 10, 15, 18, 28). In all our patients, with ARF and anesthetized, there was a basal situation of respiratory alkalosis. They also presented a relative hypoxemia as a function of the FiO_2 employed (39 %), which is reflected in PaO_2 and the gas exchange indices ($P(A-a)O_2$, PaO_2/PAO_2, PaO_2/FiO_2, R.I., Est Shunt and $\dot{Q}sp/\dot{Q}t$).

The addition of 30 cm of VD produces a significant improvement of PaO_2, an increase in PaO_2/PAO_2 and PaO_2/FiO_2 and a decrease in $P(A-a)O_2$, R.I., Est Shunt and $\dot{Q}sp/\dot{Q}t$. Such modifications are produced while the ventilatory parameters FiO_2, VE, PEEP, Cot and Raw remain stable. Therefore, they cannot be attributed to variations in the characteristics of mechanical ventilation or in the "quantity" of alveolar ventilation, although its "quality" is modified by reinhalation of expired CO_2 (27, 28), which increases $PaCO_2$ and normalizes blood pH.

The improvement of PaO_2 and of the PaO_2/FiO_2 index cannot be explained by modifications in ventilation or in FiO_2 since it always remained stable; neither can it be explained by an increase in PAO_2, which actually decreased.

Nevertheless, there is a decrease in $P(A-a)O_2$, reflecting an improvement in $\dot{V}A/\dot{Q}$, that matches the significant decrease in both $\dot{Q}sp/\dot{Q}t$ and Est Shunt.

It can be deduced that if the numerator of the $\dot{V}A/\dot{Q}$ balance is quantitatively maintained, which is reflected in an improvement at the clinical level, then either qualitative changes (Bohr effect) are produced or there are regional or general changes in perfusion (20, 24, 26, 30), which depend only on the increase in $PaCO_2$ and/or the normalization of the pH (3, 4, 11). The similarity in the observed PaO_2 increment with respect to the expected PaO_2, suggests that the Bohr effect is responsible for this change in stage II.

With the addition of 60 cm of VD, the levels of PaO_2, the PaO_2/PAO_2 and PaO_2/FiO_2 indices, as well as the Est Shunt and $\dot{Q}sp/\dot{Q}t$, are maintained at similar values with respect to the previous stage. A further decrease is observed in PAO_2, $P(A-a)O_2$ and R.I. Such changes are interpreted as a direct function of the increase in $PaCO_2$, since $\dot{V}A/\dot{Q}$ is maintained as the stability factor in the mentioned parameters.

The increase in $PaCO_2$, i.e. in $PACO_2$, entails a decrease in PAO_2 which subsequently decreases $P(A-a)O_2$ and R.I., since FiO_2 has remained unchanged. The absence of significant variations in the PaO_2/PAO_2 index, in contrast to those observed in $P(A-a)O_2$ and R.I., reflects the greater sensitivity of these two with respect to variations in $PaCO_2$. Nevertheless, it should be emphasized that the PaO_2/PAO_2 index shows a correlation with PAO_2 when 60 cm of VD are added. This suggests that, to some extent and according to the reasons pointed out previously, the PaO_2/PAO_2 index might be related to the changes in $PaCO_2$. The apparent relations observed between PaO_2 and the PaO_2/PAO_2 and PaO_2/FiO_2 indices, as well as between PAO_2 and the indices $P(A-a)O_2$ and R.I., led to their verification. The data presented in table II to a great extent allow us to confirm them in the present study. The systematic correlation of the Est shunt and $\dot{Q}sp/\dot{Q}t$ with PaO_2 is also particularly apparent as well as the absence of such a correlation with PAO_2. Nevertheless, a direct correlation is repeatedly observed between PAO_2 and $P(A-a)O_2$ which decrease simultaneously (improve), whereas $P(A-a)O_2$ and PaO_2 are correlated only between stages I and II.

The disassociation between the observed PaO_2 and the expected PaO_2 incapacitates the operative sequence of the Bohr effect and makes the pulmonar vas-

cular changes responsible for the absence of the awaited change in stage III (fig 1).

At the same time, the levels reached in the cases studied (pH 7.28 and $PaCO_2$ 54 mm/Hg), given their magnitude, might have any adverse effects on pulmonary perfusion in general.

All this suggests that "extra-alveolar" modifications, due to changes in pulmonary local or regional flow, are responsible for the improvement in $\dot{V}A/\dot{Q}$ that occurs with normocapnia (8, 10, 15, 20, 26, 30). The modifications produced in the $P(A\text{-}a)O_2$ and R.I. indices, would be justified by hypercapnia, although this might not entail an improvement of the pulmonary function under the circumstances of the present study.

J. H. BOIX, F. ÁLVAREZ, M. TEJEDA, E. PEYDRO, D. OLIVARES y A. ARNAU. *Efectos de la hipo, normo e hipercapnia inducidas por la ventilación mecánica sobre el Shunt intrapulmonar.* Rev. esp. Fisiol. (J. Physiol. Biochem.), 50 (2), 89-96, 1994.

Se estudia el efecto de la hipo, normo e hipercapia sobre las variaciones de la oxigenación arterial y sus índices en 15 pacientes críticos, con fallo respiratorio agudo (FRA) que reciben ventilación mecánica desde las primeras 48 horas de evolución. El estudio es prospectivo y aleatorio y se realiza en UCI multidisciplinaria. Se delimitan tres estadios: I) a los 30 min de iniciar la anestesia; II) a los 30 min de añadir 30 cm de espacio muerto (VD); y III) a los 30 min de la substitución del VD anterior por otros 60 cm. Los parámetros de ventilación no se alteran y la fracción inspirada de oxígeno (FiO_2) es estable. El estadio I se caracteriza por una alcalosis respiratoria y el II por un equilibrio ácido-base normal con incremento de la PaO_2 ($p < 0,01$) y descenso del shunt intrapulmonar ($\dot{Q}sp/\dot{Q}t$) ($p<0,05$). La diferencia alveolo arterial de oxígeno $P(A\text{-}a)O_2$, indice respiratorio (R. I.) y shunt estimado (Est Shunt) muestran descensos significativos, mientras que el cociente arterio alveolar de oxígeno (PaO_2/PAO_2) y la fracción entre la tension arterial y la fracción inspirada de oxígeno PaO_2/FiO_2 se incrementan significativamente. El estadio III muestra una acidosis hipercápnica pura, con descensos en la tension alveolar (PAO_2) ($p<0,001$), $PO_2(A\text{-}a)$ ($p<0,01$) y R.I. ($p<0,05$) mientras que la PaO_2, $\dot{Q}sp/\dot{Q}t$, Est Shunt, a/A y PaO_2/FiO_2 permanecen estables con respecto a la situacion anterior. La PaO_2 observada es diferente ($p<0,05$) de la esperada. Todo ello sugiere que las modificaciones extra-alveolares locales o regionales de la perfusión pulmonar son responsables de estas variaciones. Los índices PO_2 (A-a) y R.I. no permiten diferenciar las causas de hipoxemia arterial en presencia de hipercapnia.

Palabras clave: Hipo-, normo-, e hipercapnia, Indices de oxigenación, Shunt intrapulmonar, Espacio muerto, Fallo respiratorio agudo.

References

1. Albelda, S. M., Gefter, W. B. and Kelley, M. A. (1983): *Am. Rev. Respir. Dis.*, 127, 360-365.
2. Askitopoulou, H., Chakrabarti, M. K. and Morgan, M. (1984): *Acta Anaesthesiol. Scand.*, 28, 348-350.
3. Barer, G. R., McCurrie, J. R. and Shaw, J. W. (1971): *Cardiovasc. Res.*, 5, 490-497.
4. Benumof, J. L., Mathers, J. M. and Wahrenbrock, E. A. (1976): *J. Appl. Physiol.*, 41, 466-469.
5. Boix, J. H., Marín, J., Enrique, E., Monferrer, J., Bataller, A. and Servera, E. (1994): *Rev. esp. Fisiol.*, 50, 19-26.
6. Breivick, H., Grenvick, A., Milllen, E. and Safar, P. (1973): *Chest*, 63, 525-531.
7. Cane, R. D., Shapiro, B. A., Templin, R. and Walther, K. (1988): *Crit. Care Med.*, 16, 1243-1245.
8. Culpepper, J. A., Rinaldo, J. E. and Rogers, R. M. (1985): *Am. Rev. Respir. Dis.*, 132, 1075-1077.
9. Cherniack, R. M. and Cherniack, L. (1983): Respiration in health and disease (3rd ed.). W. B. Saunders Co. Philadelphia.
10. Downs, J. B., Perkins, H. M. and Modell, J. H. (1974): *Arch Surg.*, 109, 519-523.
11. Enson, Y., Giuntini, C. and Lewis, M.L.(1964): *J. Clin. Invest.*, 43, 1146-1151.
12. Hess, D. and Maxwell, C.(1985): *Crit. Care Med.*, 30, 961-963.

13. Hoffstein, V., Duguid, N. and Zamel, N. (1984): *J. Lab. Clin. Med.*, 104, 685-690.
14. Hurlow, R. S., Hudson, L. D., Pierson, D. J., Craig, K. C. and Albert, R. K. (1982): *Chest*, 82, 211.
15. Johansen, S. H. and Mourkidou, S. (1969): *Acta Anaesth. Scand.*, 13, 241-246.
16. Kelman, G. R., (1966): *J. Appl. Physiol.*, 21, 1375-1376.
17. Marinii, J. J. (1990): *Clin. Chest. Med.*, 11, 673-690.
18. Martz, K. V., Joiner, J. and Shepherd, R. M. (1979): Management of the patient-ventilator system. C. V. Mosby Co. St. Louis.
19. Michenfelder, J. D., Fowler, W. S. and Theye, R. A. (1966): *J. Appl. Physiol.*, 21, 1471-1476.
20. Monkcom, W. and Patterson, R. (1972): *J. Thorac. Cardiovasc. Surg.*, 63, 577 584.
21. Nunn, J. F. (1977): Applied Respiratory Physiology (2nd ed.). Butterworths, Boston.
22. Peris, L. V., Boix, J. H., Salom., J., Segura, V. and Arnau, A. (1983): *Crit. Care Med.*, 11, 888-891.
23. Perret, C. and Feihl, F. (1992): Respiratory failure in asthma (2nd ed.). Springer-Verlag, Berlin.
24. Prys-Roberst, C., Kelman, G. R. and Greenbaum, R. (1967): *Anesthesia*, 22, 257-275.
25. Prys-Roberts, C. and Kelman, G. R. (1968): *J. Appl. Physiol.*, 25, 80-87.
26. Severinghaus, J. W., Swenson, E. W., Finley, M. T., Lategola, M. T. and Willians J. (1961): *J. Appl. Physiol.*, 16, 53-60.
27. Shapiro, B. A., Harrison, R. A., Kacmareck, R. M. and Cane, R. D. (1985): Clinical application of respiratory care (3th. ed.). Year Book Medical Publishers. Chicago.
28. Slotman, G. J., Machiedo, G. W., Novack, R. T. and Rush, B. F. (1983): *Circ. Shock*, 11, 187-194.
29. Suwa, K. and Bendixen, H.H. (1968): *J. Appl. Physiol.*, 24, 556-562.
30. Swenson, E. W., Finley, T. N. and Guzman, S. V. (1961): *J. Clin. Invest.*, 40, 828-835.
31. Sykes, M. K. Young, W. E. and Robinson, B. E. (1965): *Br. J. Anesth.*, 37, 314-325.