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Modifications of Tissular Oxygenation and Systemic Hemodynamics after the Correction of Hypocapnia Induced by Mechanical Ventilation

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The modifications of systemic hemodynamics, oxygen transport and tissular oxygenation in mechanically-ventilated critical ARF (acute respiratory failure) patients, after the correction of its hypocapnia by addition of dead space (VD) are determined. The prospective and randomized study was carried out in a multidisciplinary ICU. Fifteen ARF patients were studied within the first 48 hours of evolution. All the patients were intubated and mechanically ventilated. Three stages were delimited: I) 30 min after the beginning of anesthesia; II) 30 min after adding 30 cm of VD; III) 30 min after replacing the previous VD with a VD of 60 cm. Similar steady states had been reached when the measurements were taken. Ventilation parameters and FiO_2 were kept stable. In stage I the patients presented a pure respiratory alkalosis and, with respect to hemodynamics, a hyperdynamic situation. In stage II the acid-base balance was normalized with a continuation of the hyperdynamic situation and an increase in mixed venous oxygen tension and saturation ($P\bar{v}O_2$ and $S\bar{v}O_2$) ($p<0.001$). Stage III was characterized by a pure hypercapnic acidosis and an increase in capillary wedge pressure (CWP) ($p<0.05$), right atrial pressure (RAP) ($p<0.001$) and cardiac output (Qt) ($p<0.001$); simultaneously, the systemic vascular resistances (SVR) decreased ($p<0.01$), the $P\bar{v}O_2$, $S\bar{v}O_2$ and oxygen delivery ($\dot{D}O_2$) increased ($p<0.001$); oxygen utilization coefficient (OUC) decreased ($p<0.01$). The results suggest that the variations in $P\bar{v}O_2$ and $S\bar{v}O_2$ are a direct consequence of the modifications in blood flow. The hemodynamic response to normocapnia and moderate hypercapnia induced by the addition of VD, in situations of previous hypocapnia, might contribute to the evaluation of myocardial and capillary reserve and of tissular oxygenation in critical patients and might facilitate early therapeutic strategies.

Key words: Tissular oxygenation, Hypo, normo and hypercapnia, Dead space, Cardiac output, Systemic vascular resistances, Extraction coefficient.

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Respiratory alkalosis, with moderate or severe hypocapnia, is frequent in sedated and relaxed patients who receive controlled mechanical ventilation (CMV) (3, 4, 8, 23, 27, 31). It is also present in patients who are treated with assisted mechanical ventilation (AMV) when they have abnormal stimuli due to propioceptive or neurogenic reflexes (12, 35).

Reductions in cardiac output ($\dot{Q}t$), in cerebral blood flow (30, 33) and in mixed venous oxygen tension ($P\bar{v}O_2$) have been attributed to respiratory alkalosis, due to the effect it causes on the shift of the haemoglobin dissociation curve (19). When $PaCO_2$ is raised or normalized, the abovementioned alterations are also normalized

Intermittent mandatory ventilation (IMV), which has been proposed to correct or avoid the situation of hyperventilation (9), has not always proven to be effective (6).

The addition of dead space (VD) has been used as a method for the correction of hypocapnia in mechanically ventilated patients (17, 20, 32).

With the present work we try to determine the modifications in systemic haemodynamics, oxygen transport and tissular oxygenation that can be observed in critical acute respiratory failure (ARF) patients receiving mechanical ventilation, when hypocapnia is corrected through the addition of VD.

Materials and Methods

This protocol study was approved by the Ethic Committee of the Hospital Gran Vía and informed consent was obtained from all patients direct relatives.

A prospective and randomized study was carried out with 15 patients within the first 48 hours of evolution in ICU. All patients presented ARF, defined as PaO_2 <60 mm/Hg with a fraction of inspired oxygen (FiO_2) >0.4, and diffuse pulmonary infiltration in the chest X-ray, with a capillary wedge pressure (CWP) <15 mm/Hg. Sixty-five percent of them also presented a documented source of infection, positive hemocultures, fever >38 °C and leukocytosis. All of them were orotracheally intubated and on CMV with an Engstrom-Erica system, which allows to continuously monitor volume minute expired ($\dot{V}E$), peak inspiratory pressure (PIP), positive expiratory end-pressure (PEEP), total pulmonary compliance (Cot), and resistance of the the airways (Raw).

A CO_2/O_2 analyser (Engström-Erica Duo) was connected to the patient's endotracheal tube through a sampling catheter (Aridus 2.4 M) with a T adapter (22/15 mm). A humidifier by condensation (Engströn-Edith) was intercalated between the T adapter and the Y piece of the circuit. The corrugated tubing system (Intec) of the circuit had a ventilator-patient length of 72 cm and a compliance of 1.5 ml/cm of H_2O (measured at 40 cm of H_2O). The two attached water collectors had a compliance of 0.125 ml/cm of H_2O (equally measured at 40 cm of H_2O).

During the study, tidal volume (Vt), respiratory rate (RR), inspiratory/expiratory time ratio (I:E), PEEP, inspiratory flow and flow pattern were kept unmodified for each individual patient. The FiO_2 was modified after each addition of VD in order to keep measured FiO_2 stable throughout the study.

Patients were hemodynamically monitored with a triple-lumen Swan-Ganz catheter and a 4F intra-arterial (femoral) catheter (Plastimed), connected by means of Hewlett-Packard (1290A) pressure transducers to a Hewlett-Packard (78532B) monitor for the continuous reading and recording of intravascular pressures. Cardiac output ($\dot{Q}t$), determined by thermodilution techniques, was

the mean obtained from three measurements with an injection of 10 ml of cold (<8 °C) DW 5%, always started at the end of the inspiratory phase, using a Hewlett Packard system (78552B). The medial axillary line was taken as the zero reference level.

Anesthesia was induced and maintained in all patients with the combined perfusion of morphine chloride and atracurium besylate.

The period of thirty minutes that followed the beginning of anesthesia was taken as control stage (stage I). Immediately after that, 30 cm of VD were added between the condensation humidifier and the Y piece of the patient-ventilator tubing system during a period of 30 min (stage II). At the end of that period, the previous VD was replaced with a VD of 60 cm that was also kept for 30 min (stage III). The material used for VD was the same as in the previously described corrugated tubing system.

At the end of each of the three stages, while similar steady state had been reached, a sample was obtained by direct aspiration through the intra-arterial catheter, with heparinized 2 ml sterile syringes. At the same time, 2 ml of pulmonary artery blood were extracted by aspiration through the Swan-Ganz distal catheter, at a speed lower than 1 ml/2 s. A 2 ml plastic syringe was used with 1000 IU of heparin in the dead space of the syringe, having previously rejected the first 3 ml and 5 ml respectively obtained with two independent syringes.

Immediately after obtaining the samples they were analysed, in duplicate, in an automated 278 Corning analyser, subjected daily to a quality control program. All the measurements and calculations were always carried out at a temperature of 37 °C. The concentration of hemoglobin (Hb) was determined with a Stkr-Coulters Electronics system, using the first blood sample obtained from the patients at the beginning of the study. The parameters measured at the end of each stage were: RR, FiO_2, VE, PIP, PEEP, Cot, Raw, arterial blood gases and mixed venous blood gases, pH, base excess (BE), heart frequency (HR), systolic-mean-diastolic arterial pressure (s-m-dAP), CWP, right atrial pressure (RAP) and $\dot{Q}t$. In addition, arterial oxygen content (CaO_2), mixed venous oxygen content ($C\bar{v}O_2$), physiologic shunt ($\dot{Q}sp/\dot{Q}t$), systemic vascular resistances (SVR), arterio-venous oxygen content differences ($D(a-\bar{v})O_2$), oxygen consumption ($\dot{V}O_2$), delivery oxygen ($\dot{D}O_2$), oxygen utilisation coefficient (OUC) were determined, with the following formulas:

$$\dot{Q}sp/\dot{Q}t = \frac{Cc'O_2 - CaO_2}{Cc'O_2 - C\bar{v}O_2}$$

$Cc'O_2 = Hb[(1.0\text{-}HbCO)\ (1.34) + (PAO_2)\ 0.0031]$. The correction factors were: [1.0-HbCO]= 0.985, [1.0-HbCO]= 0.975, [1.0-HbCO]= 0.965 when PAO_2 was higher than 150 mm/Hg, oscillated between 150 - 125 mm/Hg or 125-100 mm/Hg, respectively.

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

$C\bar{v}O_2 = S\bar{v}O_2 \times (Hb \times 1.34) + PvO_2 \times 0.0031$

$$SVR = \frac{mAP - RAP}{\dot{Q}t} \times 80\ (dynes \cdot s \cdot cm^{-5})$$

$C(a-\bar{v})O_2 = CaO_2 - C\bar{v}O_2$ (ml/dl)

$\dot{V}O_2 = C(a-\bar{v})O_2 \times \dot{Q}t \times 10$ (ml/min)

$\dot{D}O_2 = \dot{Q}t \times CaO_2 \times 10$ (ml/min)

$OUC = \dot{V}O_2 / \dot{D}O_2$ (ml/min)

The paired Student's *t* test and the Pearson correlation analysis were utilised in the statistical analysis of the data. Once the analysis of variance about the same basic data of the three described stages was repeated, the same dintels of signifi-

cation were obtained. To favour the 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 characteristics of the patients, according to primary disease, are presented in table I, including the number of patients who died from each group (all the deceased patients died from multiorganic failure; 60.6 % of them had a documented sepsis).

As shown in table II, RR, FiO_2, VE, PIP, PEEP, Cot and Raw remained unchanged throughout the successive stages. A significant increase in $PaCO_2$ was observed in direct relation to the increment of dead space ($R=0.91$, $p<0.001$), while BE remained unchanged. Subsequent to the increase in $PaCO_2$, there was a significant decrease in pH in inverse relationship, both from stage I to stage II ($R=-0.71$,

Table I. *Characteristics of the Patients.*

Pathology	N	Sex*	Age	Deceased
Abdominal Sepsis	4	3M-1F	60 ±7.8	1
Urinary Sepsis	2	M	63-65	1
Sepsis Central Nervous System	1	F	58	1
Exogenous Intoxication	2	1M-1F	57-51	1
Multiple Traumatism	2	M	23	0
Dilated Cardiomyopathy + Community Pneumonia	2	M	48-56	2
Acute Myorcardial Infarction + Nosocomial Pneumonia (no-ICU)	1	M	70	1
Pancreatitis + Gastric Aspiration	1	M	57	1

* M = male; F = female

Table II. *Respiratory and Acid-base Parameters.*

Parameter	Stage I - Basal	Stage II - VD 30 cm	Stage III - VD 60 cm
RR (breaths/min)	14	14	14
FiO_2 (%)	39.0 ± 7.6	39.0 ± 7.4	38.07 ± 7.8
VE (L/min)	14.23 ± 1.32	14.22 ± 1.31	14.18 ± 1.29
PIP (ml/H_2O)	36.9 ± 6.3	35.9 ± 6.9	36.3 ± 7.5
PEEP (ml/H_2O)	0.7 ± 1.8	0.88 ± 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 a***	7.38 ± 0.06 b***	7.28 ± 0.06 c***
$PaCO_2$ (mm/Hg)	30.8 ± 3.35 a***	40.5 ± 5.70 b***	54.8 ± 6.67 c***
BE (mmol/L)	0.4 ± 4.4	0.6 ± 4.6	0.1 ± 5.3

a: Stage I vs II, b: Stage II vs III, c: Stage I vs III. ***$p < 0.001$.

Table III. *Arterial and Tissular Oxygenation and Oxygen Transport.*

Parameter	Stage I - Basal	Stage II - VD 30 cm	Stage III - VD 60 cm
$\dot{Q}sp/\dot{Q}t$ (%)	9.58 ± 14.4 a*	5.83 ± 12.6	6.54 ± 22.0
PaO_2 (mm/Hg)	96.1 ± 39.8 a**	106.8 ± 41.9	105.2 ± 36.92
SaO_2 (%)	96.1 ± 2.2	96.5 ± 2.1 b*	95.7 ± 2.5
CaO_2 (ml/dl)	15.6 ± 3.6	15.3 ± 3.7	15.1 ± 3.7
$P\bar{v}O_2$ (mm/Hg)	40.4 ± 5.5 a***	45.4 ± 6.4 b***	51.7 ± 7.8 c***
$S\bar{v}O_2$ (%)	75.0 ± 7.5 a**	77.5 ± 6.6 b*	79.2 ± 6.3 c**
$C\bar{v}O_2$ (ml/dl)	11.8 ± 3.4 a***	12.3 ± 3.4 b*	12.5 ± 3.6 c**
$D(a\text{-}\bar{v})O_2$ (ml/dl)	3.2 ± 1.1	3.0 ± 0.9 b**	2.6 ± 0.9 c*
$\dot{V}O_2$ (ml/min)	187.7 ± 75.0	202.4 ± 82.6	215.9 ± 100
$\dot{D}O_2$ (mm/Hg)	958.4 ± 465	1066.2 ± 527 b***	1293 ± 647 c***
OUC (ml/min)	0.22 ± 0.8	0.20 ± 0.6 b**	0.18 ± 0.6 c*

a: Stage I vs II, b: Stage II vs III, c: Stage I vs III.
*p<0.05, **p<0.01, ***p<0.001.

Table IV. *R values between the studied paramters.*

Parameter	Stage I Basal	Stage II VD 30 cm	Stage III VD 60 cm
$P\bar{v}O_2$-OUC	−0.64 a**	−0.92 b***	
$P\bar{v}O_2$-$\dot{Q}t$	−0.21	−0.23	
$D(a\text{-}\bar{v})O_2$-$\dot{Q}t$	−0.74 a***	−0.50 b*	
$D(a\text{-}\bar{v})O_2$-OUC	−0.53 a*	−0.70 b**	
$\dot{V}O_2$-$\dot{D}O_2$	−0.78 a***	−0.17	

a: Stage I vs II, b: Stage II vs III.
*p<0.05, **p<0.01, ***p<0.001.

p<0.01) and from stage II to stage III (R= −0.64, p<0.01). This is reflected, into the acid-base balance, by an initial situation of pure respiratory alkalosis in stage I, of acid-base normality in stage II, and of pure hypercapnic acidosis in stage III.

The data presented in table III show that the addition of 30 cm of VD produced a decrease in $\dot{Q}sp/\dot{Q}t$ and an increase in PaO_2, both significant, while SaO_2 remained unchanged. The addition of 60 cm (stage III) did not introduce any new variations with respect to those values. The $P\bar{v}O_2$, $S\bar{v}O_2$ and $C\bar{v}O_2$ increased with each addition of VD; $D(a\text{-}\bar{v})O_2$ decreased significantly between stages II and III only. There were no significant changes in $\dot{V}O_2$, whereas both a significant increase in $\dot{D}O_2$ and a decrease in OUC were observed between stages II and III.

The correlation data are shown in table IV. It can be observed that $P\bar{v}O_2$ maintains a significant inverse correlation with OUC, but not with $\dot{Q}t$, whereas $D(a\text{-}\bar{v})O_2$ maintains an inverse correlation with Qt and a direct correlation with OUC.

The hemodynamic profile in the three stages is presented in table V. The hyperdynamic situation is maintained, with tachycardia, and increases in $\dot{Q}t$ and RAP. Only the addition of 60 cm of VD produces significant increases in CWP, RAP and $\dot{Q}t$, as well as a decrease in SVR, with respect to stage I.

Discussion

The increase in PaO_2 and reduction in $\dot{Q}sp/\dot{Q}t$, in the conditions mentioned above, had been previously considered as secondary to changes of the $\dot{V}A/\dot{Q}$ due to modifications in pulmonary local or regional flow (2).

Table V: *Arterial and Tissular Oxygenation and Oxygen Transport.*

Parameter	Stage I - Basal	Stage II - VD 30 cm	Stage III - VD 60 cm
HR	111 ± 21	111 ± 20	117 ± 22
sAP (mm/Hg)	116 ± 17	113.8 ± 17.9	123.1 ± 24
mAP (mm/Hg)	79.7 ± 11	78.8 ± 11.5	83.2 ± 20.3
dAP (mm/Hg)	63.5 ± 9.5	61.2 ± 9.3	65.2 ± 17.6
CWP (mm/Hg)	13.3 ± 4.1	12.8 ± 3.4 b*	15.4 ± 4.7 c*
RAP (mm/Hg)	8.0 ± 2.7	8.6 ± 2.6 b***	11.1 ± 3.5 c***
$\dot{Q}t$	116 ± 3.6	7.1 ± 3.5 b***	8.8 ± 4.5 c***
SVR (dynes • s • cm^{-5})	1137.3 ± 722	1041.1 ± 755	862.1 ± 563 c**

a: Stage I vs II, b: Stage II vs III, c: Stage I vs III.
*p<0.05, **p<0.01, ***p<0.001.

Such an increase in PaO_2 should not be sufficient to modify CaO_2, since Hb was stable and SaO_2 in our patients was found to be at levels in which the Hb dissociation curve is flat and the variations produced by changes in pH and/or in $PaCO_2$ are very small. The increase in PaO_2 under such circumstances should not be significant enough to cause any modifications on CaO_2.

In our patients, the addition of VD (either 30 or 60 cm) produced an increase in $P\bar{v}O_2$, $S\bar{v}O_2$ and $C\bar{v}O_2$ with constant CaO_2 values and with no changes between stages I and II in the values of $D(a\text{-}v)O_2$, $\dot{V}O_2$, $\dot{D}O_2$ and OUC. According to BLACKBURN *et al.* (1) all the hemodynamic parameters also remained stable in two stages. The increase in PvO_2 and SvO_2 in stage II does not seem to be the consequence of a greater $\dot{Q}t$, which does not change significantly and is confirmed by the lack of a $P\bar{v}O_2$–$\dot{Q}t$ relation; this cannot be a consequence of modifications in the initial hyperdynamic situation, since it also remains stable; and it cannot be explained by a decrease in $\dot{V}O_2$; therefore the increase in PvO_2 between these two stages might well be explained by the Bohr effect on the oxyhemoglobin dissociation curve as the $PaCO_2$ increases, but $S\bar{v}O_2$ and $C\bar{v}O_2$ also changes. A "tendency" to a reduction in SVR was, however, found, which becomes significant in stage III, after the addition of a greater dead space (1), and the highly significant correlation $P\bar{v}O_2$-OUC. This might suggest that tissular oxygenation, in these patients, is maintained at the expense of a hyperdynamic situation, with an abnormal flow distribution (22, 26). In other words, this increment in $P\bar{v}O_2$ and SvO_2 could be the first manifestation of a lack of equilibrium between the delivery and the O_2 uptake. As CaO_2 and $\dot{Q}t$ ($\dot{D}O_2$) do not change, the hemodynamic parameters are also similar, $\dot{V}O_2$ remains unchanged and OUC is the same. In this situation, only the increase in $P\bar{v}O_2$ and $S\bar{v}O_2$, would possibly reflect, a very early process of impaired oxygen used during capillary transit (5, 29, 34).

The addition, in these circumstances, of a 60 cm VD (stage III) results in a new increase in PVO_2 and SVO_2. There are also increases in $\dot{Q}t$, RAP, and CWP with respect to stage II, while SVR decreases with respect to the basal stage and coinciding with OUC decrease; $\dot{D}O_2$ increases, clearly following the Fick principle ($\dot{Q}t$ increases in the presence of stable CaO_2), with a stable $\dot{V}O_2$. All these factors together can be interpreted as the extreme ineffective hemodynamic effort, already

with limitations in the myocardial reserve (13, 14, 16, 21) to provide a sufficient amount of O_2 to the tissues. Under such circumstances, the increase in $P\bar{v}O_2$ and $S\bar{v}O_2$ could be justified by the lack of utilization of the O_2 at the cellular level, as the highly significant, inverse correlation $P\bar{v}O_2$-OUC seems to confirm. It could be physiopathologically explained by changes in microcirculation, with reductions in SVR and a deviation of blood flow from nutritive capillary channels to non-nutritive ones (7, 10, 18); as a consequence, some tissues receive more than sufficient blood but there is tissular hypoxia in hypoperfused areas (11, 15, 25, 28).

All the previous considerations lead to the conclusion that the hemodynamic response to normocapnia and moderate hypercapnia, both produced by the addition of VD, in a situation of hypocapnia after mechanical ventilation might constitute a test to evaluate myocardial and capillary reserves and tissular oxygenation in critical patients, similar to the low dobutamine dose test (34). Such a test, in turn, would allow us to determine early therapeutic strategies and could help recognize the uptake/supply dependency phenomenon. The increase in $P\bar{v}O_2$ and $S\bar{v}O_2$, when the other hemodynamic parameters remain stable, might represent one of the earliest indices of the imbalance in oxygen supply/demand. Therapeutically, the dead space that normalizes the acid-base ballance should be considered as the optimal one.

J. H. BOIX, J. MARIN, E. ENRIQUE, J. MONFERRER, A. BATALLER y E. SERVERA. *Modificaciones de la oxigenación tisular y hemodinámica sistémica tras la corrección de la hipocapnia inducida por la ventilación mecánica.* Rev. esp. Fisiol. (J. Physiol. Biochem.), 50 (1), 19-26, 1994

Se determinan las modificaciones de la hemodinámica sistémica, del transporte de oxígeno y de la oxigenación tisular en 15 pacientes críticos ventilados mecánicamente por fallo respiratorio agudo (FRA), tras corregir su hipocapnia por la adición de espacio muerto (VD). El estudio prospectivo y aleatorio se realiza en una UCI multidisciplinaria. Se inicia dentro de las 48 primeras horas de evolución. con los pacientes intubados y ventilados mecánicamente. Se delimitan 3 estadios: I) a los 30 min de iniciar la anestesia; II) a los 30 min de añadir 30 cm VD y III) a los 30 min de substituir el VD previo por 60 cm. Se obtienen medidas similares y los parámetros de ventilación y la FiO_2 no se modificaron. Los pacientes en el estadio I presentan una alcalosis respiratoria pura y, hemodinámicamente, una situación hiperdinámica. En el estadio II se normaliza el equilibrio ácido-base y se incrementa la $P\bar{v}O_2$ y $S\bar{v}O_2$ ($p<0,001$). El estadio III se caracteriza por una acidosis hipercápnica pura e incremento de la presión cuña pulmonar (CWP) ($p<0,05$), presión auricular derecha (RAP) ($p<0,001$) y gasto cardíaco ($\dot{Q}t$) ($p<0,001$); simultáneamente, las resistencias vasculares sistémicas (SVR) y el descendieron ($p<0,01$) y la $P\bar{v}O_2$, $S\bar{v}O_2$ y el transporte de oxígeno (DO_2) se elevan ($p<0,001$); el coeficiente de extracción de oxígeno (OUC) descendió en ($p<0,01$). Estos resultados permiten suponer que las variaciones de la $P\bar{v}O_2$ y $S\bar{v}O_2$ son consecuencia directa de las modificaciones del flujo sanguíneo. La respuesta hemodinámica a la normo e hipercapnia moderada inducidas por la adición de VD, en situaciones de hipocapnia previa, podría ayudar a valorar la reserva miocárdica, la capilar y la oxigenación tisular en pacientes críticos y facilitar estrategias terapéuticas de forma precoz.

Palabras clave: Oxigenación tisular, Hipo, normo e hipercapnia, Espacio muerto, Gasto cardíaco, Resistencias vasculares periféricas, Coeficiente de extracción.

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