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J.-B. Thorens
P. Jolliet
M. Ritz
J.-C. Chevrolet

Effects of rapid permissive hypercapnia on hemodynamics, gas exchange, and oxygen transport and consumption during mechanical ventilation for the acute respiratory distress syndrome

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J.-B. Thorens (✉) · P. Jolliet · M. Ritz · J.-C. Chevrolet
Medical ICU, Division of Pneumology, University Hospital, 1211 Geneva 14, Switzerland

Abstract *Objective:* To measure the effects of rapid permissive hypercapnia on hemodynamics and gas exchange in patients with acute respiratory distress syndrome (ARDS).
Design: Prospective study.
Setting: 18-bed, medical intensive care unit, university hospital.
Patients: 11 mechanically ventilated ARDS patients.
Intervention: Patients were sedated and ventilated in the controlled mode. Hypercapnia was induced over a 30–60 min period by decreasing tidal volume until pH decreased to 7.2 and/or P_{50} increased by 7.5 mmHg. Settings were then maintained for 2 h.
Results: Minute ventilation was reduced from 13.5±6.1 to 8.2±4.1 l/min (mean±SD), $PaCO_2$ increased (40.3±6.6 to 59.3±7.2 mmHg), pH decreased (7.40±0.05 to 7.26±0.05), and P_{50} increased (26.3±2.02 to 31.1±2.2 mmHg) ($p<0.05$). Systemic vascular resistance decreased (865±454 to 648±265 dyne·s·cm^{-5}, and cardiac index (CI) increased (4±2.4 to 4.7±2.4 l/min/m^2) ($p<0.05$). Mean systemic arterial pressure was unchanged. Pulmonary vascular resistance was unmodified, and mean pulmonary artery pressure (MPAP) increased (29±5 to 32±6 mmHg, $p<0.05$). PaO_2 remained unchanged, while saturation decreased (93±3 to 90±3%, $p<0.05$), requiring an increase in FIO_2 from 0.56 to 0.64 in order to maintain an $SaO_2>90\%$. PvO_2 increased (36.5±5.7 to 43.2±6.1 mmHg, $p<0.05$), while saturation was unmodified. The arteriovenous O_2 content difference was unaltered. Oxygen transport (DO_2) increased (545±240 to 621±274 ml/min/m^2, $p<0.05$), while the O_2 consumption and extraction ratio did not change significantly. Venous admixture (Q_{va}/Q_t) increased (26.3±12.3 to 32.8±13.2, $p<0.05$).
Conclusions: These data indicate that acute hypercapnia increases DO_2 and O_2 off-loading capacity in ARDS patients with normal plasma lactate, without increasing O_2 extraction. Whether this would be beneficial in patients with elevated lactate levels, indicating tissue hypoxia, remains to be determined. Furthermore, even though hypercapnia was well tolerated, the increase in Q_{va}/Q_t, CI, and MPAP should prompt caution in patients with severe hypoxemia, as well as in those with depressed cardiac function and/or severe pulmonary hypertension.

Key words Permissive hypercapnia · Mechanical ventilation · Alveolar hypoventilation · Oxygen transport · Oxygen consumption · DO_2/VO_2 relationship · Hemoglobin dissociation curve · ARDS

Introduction

It has been suggested that the tidal volume (V_T) should be lowered during mechanical ventilation for the acute respiratory distress syndrome (ARDS) to minimize the risk of ventilator-induced lung injury [1, 2]. This approach, known as controlled hypoventilation or permissive hypercapnia, has been associated with a decrease in mortality and fewer complications in patients with acute asthma and ARDS [3, 4]. However, even though human exposure to severe hypercapnia seems not to have serious side effects [4, 5], little is known about its consequences on hemodynamics and the various aspects of O_2 transport (DO_2) and consumption (VO_2) in ARDS patients. In fact, these effects could theoretically have a favorable impact on some patients. Indeed, hypercapnia induces a shift to the right in the oxyhemoglobin dissociation curve (ODC) [6], and has been shown in animal studies to raise cardiac output and lower systemic vascular resistance (SVR) [7, 8]. These combined effects might be beneficial if tissue hypoxia is present by increasing both DO_2 and peripheral O_2 extraction. The present study was conducted, first, to corroborate experimental data on hemodynamics and gas exchange during hypercapnia in ARDS patients, and, second, to look for a possible benefit on oxygenation should tissue hypoxia be present.

Material and methods

Patients

Patients were included in the study if they met the criteria for ARDS, were intubated and mechanically ventilated, and were equipped with pulmonary and peripheral artery catheters. ARDS was defined according to recently published guidelines [9]: sudden onset of respiratory failure, bilateral diffuse infiltrates on the chest X-ray, arterial oxygen tension/fractional inspired oxygen (PaO_2/FIO_2) ≤ 200 mmHg, and pulmonary capillary wedge pressure < 18 mmHg). Systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock were defined according to recent guidelines [10].

Patients were excluded if cerebral edema, postanoxic encephalopathy, and/or intracranial hypertension were present, or if any of the following conditions were present: systolic blood pressure ≤ 90 mmHg, arterial oxygen saturation (SaO_2) $\leq 90\%$, arterial pH ≤ 7.3.

The study was approved by the Ethics Committee of our institution. Informed consent was obtained from next of kin.

Protocol

Patients were included as soon as possible after entry criteria were met. Sedation was maintained by a continuous infusion of either midazolam or propofol. In order to prevent all respiratory muscle activity, muscle paralysis, if necessary, was achieved by intermittent bolus injections of pancuronium bromide. All patients were ventilated in the pressure-limited controlled mode, with decelerating flow and an inspiratory : expiratory ratio between 0.5 and 2.0 (Evita respirator, Dräger Werk AG, Lübeck, Germany). FIO_2 and positive end-expiratory pressure (PEEP) were set by the clinicians in charge of the patients before measurements were taken. Hypercapnia was induced over a 30–60 min period by decreasing tidal volume (V_T). The target values for arterial CO_2 tension ($PaCO_2$) and pH were determined by an increase of 40 mmHg in $PaCO_2$ resulting in a decrease in pH of 0.2 [11], which, in turn, leads to a 7.5 mmHg increase in P_{50} [12]. The results of prior validation tests indicate that the magnitude of these expected changes was greater than the variability of the measurement techniques used (see Measurements and Discussion). Thus, V_T was reduced by increments of 100 ml until either P_{50} increased by 7.5 mmHg (four patients) or pH decreased to 7.2 (seven patients), in arterial blood gas (ABG) samples analyzed every 15 min. Subsequently, no further changes in V_T, respiratory rate, or PEEP were made during the protocol. If necessary, FIO_2 was increased to maintain an SaO_2 of $\geq 90\%$. Tracheal suctioning was withheld. No modification of vasoactive or inotropic drugs treatment or fluid administration was made during the measurements. Mean systemic arterial pressure (MAP) and SaO_2 were continuously monitored via an indwelling arterial catheter and pulse oximetry (N-200 pulse oximeter, Nellcor Inc., Hayward, Calif.), respectively. Cardiac rhythm was continuously monitored. Patients were withdrawn from the study if there was a decline in SaO_2 of $< 90\%$ not compensated for by an increase in FIO_2, a pH < 7.2, or a MAP < 60 mmHg, or if tracheal suctioning, fluid administration, or modification of vasoactive/inotropic drug treatment was required. Hypercapnia was maintained for 2 h, after which the patient was returned to baseline conditions by increasing V_T to its preprotocol level.

Measurements were performed at baseline before starting hypercapnia (baseline 1), after 1 h ($PaCO_2 = 52.2 \pm 7.0$ mmHg) and 2 h ($PaCO_2 = 59.3 \pm 7.2$ mmHg) of hypercapnia, and 1 h after returning to baseline conditions (baseline 2). As the difference between baseline and hypercapnia measurements was maximal at 2 h, only those values will be reported (henceforth referred to as hypercapnia).

Measurements

Blood gases, oxyhemoglobin saturation, and P_{50}

Arterial samples were withdrawn from the arterial catheter. Mixed venous samples were collected from the distal port of the pulmonary artery catheter. All blood gas and hemoglobin saturation measurements were performed on an ABL 520 blood gas analyzer (Radiometer, Copenhagen, Denmark). In this analyzer, PO_2, PCO_2, and pH are measured with specific electrodes, oxyhemoglobin saturation is measured by spectrophotometry, and P_{50} is calculated from pH, PO_2, and SO_2 [13]. A validation study to assess the measurement variability using this analyzer in the clinical setting had been previously conducted. Its goal was to determine if the expected changes in the various determinants of blood O_2 content could be obscured by variations due to the measurement technique. Ten sets of measurements were performed in ten patients presenting diverse blood gas and acid-base status, after appropriate calibration. The results are shown in Table 1.

Oxygen transport and consumption variables

DO_2 was computed as DO_2 (ml/min/m^2) = CI $\times$ CaO_2 $\times$ 10, where CI = cardiac index (ml/min/m^2), and CaO_2 = arterial oxygen con-

Table 1 Assessment of blood gas analyzer measurement variability. (*Sat* oxyhemoglobin saturation)

Arterial blood	Coefficient of variation (%)[a]
pH	0.4
PCO_2 (mmHg)	1.1
P_{50} (mmHg)	1.3
PO_2 (mmHg)	1.5
Sat (%)	0.2

[a] Mean coefficient of variation of ten sets of ten measurements

tent (ml/100 ml) = {[hemoglobin (g/100 ml)×1.36×arterial oxygen saturation (SaO_2)]+0.003×arterial O_2 partial pressure (PaO_2)}.

VO_2 was determined by the reverse Fick method: VO_2 (ml/min/m^2) = CI×(CaO_2-CvO_2)×10, where CvO_2 = mixed venous oxygen content (ml/100 ml) = {[hemoglobin (g/100 ml)×1.36 ×mixed venous saturation (SvO_2)]+0.003×mixed venous O_2 partial pressure (PvO_2)}.

Venous admixture (Q_{va}/Q_t) was calculated at the patients' maintenance FIO_2 as $Q_{va}/Q_t = (Cc'O_2-CaO_2)/(Cc'O_2-CvO_2)$, where $Cc'O_2$ represents the calculated O_2 content of end-capillary blood: $Cc'O_2$ = {[hemoglobin (g/100 ml)×1.36×1.0]+0.003× PcO_2}, where PcO_2, capillary O_2 partial pressure is assumed to be equal to the alveolar O_2 partial pressure (PAO_2)

The oxygen extraction ratio (O_2ER%) was computed as $O_2ER\% = (Ca-Cv)O_2/CaO_2$.

Right and left ventricular stroke work indices were calculated as: RVSWI (g·m/m^2) = SI×(MPAP−CVP)×0.0136, and LVSWI (g·m/m^2) = SI×(MAP−PCWP)×0.0136, where SI = stroke index = (CI/heart rate)×1000, and MAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; MAP = mean systemic arterial pressure; CVP = central venous pressure. The factor 0.0136 corrects pressure and volume to work units.

Other measurements

Serum lactate levels were measured at baseline 1, hypercapnia, and baseline 2. 2−3 Diphosphoglycerate (2,3 DPG) was determined at baseline 1 and hypercapnia. Additional blood samples were withdrawn at baseline 1 to determine the various parameters needed to compute the Apache II score.

Statistics

All results are reported as mean±1 SD and were analyzed by a one-way analysis of variance for repeated measures (ANOVA). Significance between the three time points was determined by Fisher's protected least significance test. For 2,3 DPG, which was measured only at baseline 1 and hypercapnia, a two-tailed paired *t*-test was used. Significance for correlation tests was established by the Pearson product-moment correlation coefficient. Values of $p<0.05$ were considered significant.

Results

Thirteen patients were entered in the study. Two patients were excluded, one because of technical problems during data collection, the other because of hemodynamic instability due to the occurrence of supraventricular tachycardia and hypoxemia before the protocol had started. The clinical characteristics and outcome for the remaining 11 patients are summarized in Table 2.

Controlled hypoventilation and acute hypercapnia

Acute hypercapnia was induced by a mean reduction of minute ventilation (VE) of 40%, from 13.5±6.1 to 8.2±4.1 l/min ($p<0.05$), as shown in Table 3. $PaCO_2$ and P_{50} increased from 40.3±6.6 to 59.3±7.2 and from 26.4±2.02 to 31.2±2.18 mmHg, respectively ($p<0.05$), while arterial pH decreased from 7.40±0.05 to 7.26±0.05 ($p<0.05$). Individual data points for baseline 1, hypercapnia, and baseline 2 are shown in Fig. 1.

Table 2 Characteristics of the patients (*d* died, *Db* dobutamine, *Dp* dopamine, *NE* norepinephrine, *PCWP* pulmonary capillary wedge pressure, *s* survived, *SIRS* systemic inflammatory response syndrome)

No.	Age/sex	Diagnosis[a]	Apache II score	PaO_2/FiO_2 (mmHg)	PCWP (mmHg)	PEEP (cmH_2O)	Vasoactive drugs (μg/kg per min)	Outcome
1	48/M	Pneumonia, severe sepsis	14	130	7	5	Dp (2.9)	d
2	49/M	Pneumonia, sepsis	11	122	15	5	Dp (2.5)	s
3	83/F	Pneumonia, septic shock	17	178	10	8	NE (0.4), Dp (2.9)	s
4	37/M	Pneumonia, septic shock	19	66	12	5	NE (0.7), Dp (2.9)	s
5	58/M	Pneumonia, sepsis	19	128	14	6	NE (0.8), Dp (2.9)	s
6	67/M	Vasculitis, SIRS	11	177	16	8	NE (0.3), Db (3.9)	d
7	56/M	Sepsis	13	161	10	0	NE (0.7), Db (2.5)	s
8	73/M	Pneumonia, septic shock	19	188	17	0	NE (0.2)	s
9	73/M	Pneumonia, sepsis	15	109	9	9	–	d
10	70/M	Pneumonia, septic shock	17	109	12	9	NE (0.7), Db (2.4)	d
11	70/M	Pneumonia, sepsis	18	98	10	2	NE (0.3)	d
Mean (±SD)	62 (13)		16 (3)	133 (38)	13.2 (4.2)	5.2 (3.3)		

[a] Main diagnoses of cause of ARDS. Definitions of SIRS and various septic states from ACCP/SCCM [10]

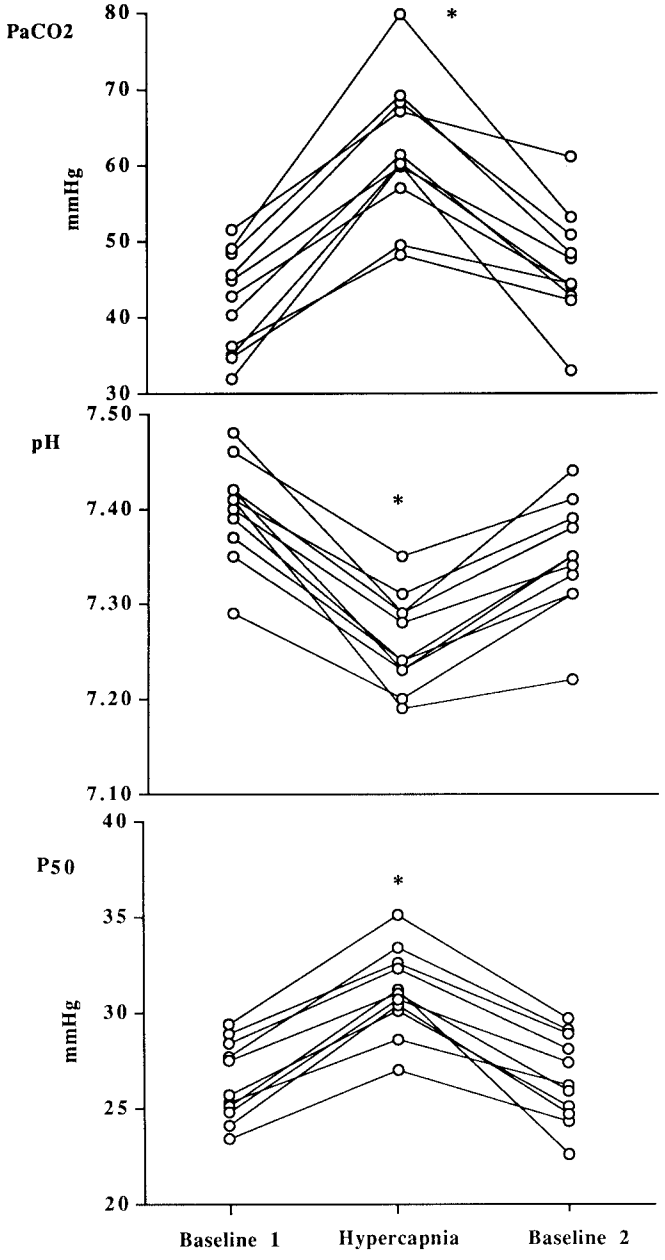

Fig. 1 Individual data points for $PaCO_2$, pH, and P_{50} at baseline 1, during hypercapnia, and at baseline 2. Each *open circle* represents one patient. $*p<0.0001$, ANOVA

Controlled hypoventilation resulted in a small but significant decrease in peak (P_{peak}) and mean (P_{awm}) airway pressures (Table 3).

Gas exchange (Table 4)

Baseline FIO_2 was $56\pm14\%$ (mean $\pm$ SD). FIO_2 had to be increased in five patients (patients 1–4 and 6), by an average of 13%. During hypercapnia, despite the increase in FIO_2 in five patients, mean SaO_2 decreased ($p<0.05$), while PaO_2 remained unchanged. PvO_2 increased ($p<0.05$), without any change in SvO_2. These were unaccompanied by a significant change in CaO_2, CvO_2, and $Ca-CvO_2$.

Q_{va}/Q_t increased significantly ($p<0.05$). There was a significant correlation between CI and Q_{va}/Q_t, both at baseline and during hypercapnia ($r=0.84$ and 0.78, $p<0.001$ and <0.004, respectively). For all patients except one, the increase in CI was paralleled by an increase in Q_{va}/Q_t (Fig. 2).

Table 3 Controlled hypoventilation and respiratory mechanics (P_{peak} peak airway pressure, P_{awm} mean airway pressure, *VE* minute ventilation)

Parameters	Baseline 1	Hypercapnia	Baseline 2	ANOVA
VE (l/min)	13.5 (6.1)	8.2* (4.1)	12.1** (4.6)	0.001
P_{peak} (cmH_2O)	32.5 (7.0)	30.6* (6.7)	32.8** (7.3)	0.03
P_{awm} (cmH_2O)	15.4 (4.9)	13.7* (4.5)	15.1** (4.8)	0.03

Results expressed as mean ($\pm$ SD)
* $p<0.05$ vs baseline 1; ** $p<0.05$ vs hypercapnia

Table 4 Gas exchange and venous admixture. (CaO_2 arterial oxygen content, CvO_2 mixed venous oxygen content, $Ca-CvO_2$ arteriovenous oxygen content difference, PaO_2 arterial oxygen tension, PvO_2 mixed venous oxygen tension, Q_{va}/Q_t venous admixture, SaO_2 arterial oxygen saturation, SvO_2 mixed venous oxygen saturation). Results expressed as mean ($\pm$ SD)

Parameters	Baseline 1	Hypercapnia	Baseline 2	ANOVA
PaO_2 (mmHg)	70.5 (7.6)	74.1 (12)	71.8 (9.3)	0.51
SaO_2 (%)	93 (3)	90* (3)	92** (3)	0.015
PvO_2 (mmHg)	36.5 (5.7)	43.2* (6.1)	38.6** (3)	0.0001
SvO_2 (%)	63 (5)	64 (6)	64 (5)	0.8
CaO_2 (ml/%)	14.5 (2.7)	14.2 (2.8)	14.4 (2.5)	0.4
CvO_2 (ml/%)	9.8 (1.9)	9.9 (1.8)	10.1 (2.1)	0.35
$Ca-CvO_2$ (ml/%)	4.7 (1.4)	4.2 (1.5)	4.3 (0.9)	0.09
Q_{va}/Q_t (%)	26.3 (12.3)	32.8* (13.2)	28.6** (10.9)	0.003

* $p<0.05$ vs baseline 1; ** $p<0.05$ vs hypercapnia

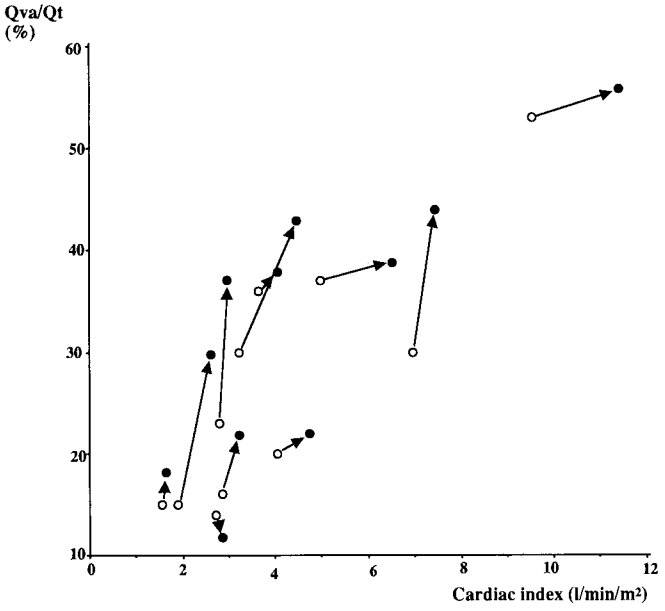

Fig. 2 Venous admixture (Q_{va}/Q_t) as a function of cardiac index (CI) for the 11 patients, at baseline 1 (*open circles*) and during hypercapnia (*filled circles*). In all but one patient, the increase in CI was accompanied by an increase in Q_{va}/Q_t. For further explanation, see text

Hemodynamics (Table 5)

Heart rate remained unchanged. CI increased during hypercapnia ($p<0.05$). SVR decreased ($p<0.05$), while pulmonary vascular resistance (PVR) remained unchanged. There was a significant correlation between the drop in SVR and the rise in CI ($p<0.04$). MAP decreased slightly. There was an increase in mean pulmonary artery pressure (MPAP) ($p<0.05$). PCWP and CVP remained unchanged. RVSWI increased by 25% ($p<0.05$), whereas LVSWI was unchanged.

O_2 transport and consumption (Table 6)

The mean DO_2 increased from 545 to 621 ml/min per m^2 ($p<0.05$). VO_2 (from 165 to 172 ml/min per m^2) and O_2ER (from 32 to 30%) did not change significantly. Serum lactate and 2,3 DPG levels did not change.

Adverse effects

Hypercapnia was well tolerated. In no instance did the drop in MAP require the administration of fluids or an increase in the dosage regimen of vasoactive or inotropic drugs. No arrhythmia was documented. Although FIO_2 had to be increased in five patients, no protocol was discontinued because an $SaO_2\% \geq 90\%$, could not be maintained.

Discussion

The results of the present study show that in mechanically ventilated ARDS patients, controlled hypoventilation

Table 5 Hemodynamic parameters. (*CI* cardiac index, *CVP* central venous pressure, *HR* heart rate, *LVSWI* left ventricular stroke work index, *MAP* mean arterial pressure, *MPAP* mean pulmonary arterial pressure, *PCWP* pulmonary capillary wedge pressure, *PVR* pulmonary vascular resistance, *RVSWI* right ventricular stroke work index, SVR systemic vascular resistance). All results expressed as mean (± SD)

Parameters	Baseline 1	Hypercapnia	Baseline 2	ANOVA
HR (beats/min)	104 (16)	108 (12)	103 (16)	0.23
CI ($l/min/m^2$)	4 (2.4)	4.7* (2.7)	4.3** (2.6)	0.003
PCWP (mmHg)	13.3 (4.3)	13.6 (4)	12.5 (3.9)	0.59
CVP (cmH_2O)	9.3 (1)	9.8 (2.1)	8.5 (2.9)	0.29
SVR ($dyne \cdot s \cdot cm^{-5}$)	865 (454)	648* (265)	739 (313)	0.012
MAP (mmHg)	74 (10)	67 (11)	66 (6)	0.07
LVSWI ($g \cdot m/m^2$)	323 (178)	335 (221)	310 (176)	0.65
PVR $dyne \cdot s \cdot cm^{-5}$)	208 (115)	209 (114)	191 (89)	0.66
RVSWI ($g \cdot m/m^2$)	101 (57)	127* (73)	106** (48)	0.02
MPAP (mmHg)	29 (5)	32* (6)	28** (5)	0.04

*$p<0.05$ vs baseline 1;
** $p<0.05$ vs hypercapnia

Table 6 Oxygen transport and consumption. (DO_2 oxygen delivery, VO_2 oxygen consumption, O_2 *ER* oxygen extraction ratio, *2,3 DPG* 2-3diphosphoglycerate). All results expressed as mean ± SD

Parameters	Baseline 1	Hypercapnia	Baseline 2	ANOVA
DO_2 (ml/min per m^2)	545 (240)	621* (274)	586 (286)	0.014
VO_2 (ml/min per m^2)	165 (50)	172 (55)	170 (67)	0.62
O_2ER (%)	32 (6)	30 (7)	30 (5)	0.2
Lactate (mmol/l)	2.3 (1.2)	1.9 (0.8)	2.1 (1)	0.31
2,3 DPG (mmol/l)	1.84 (0.48)	1.91 (0.44)	–	0.22[a]

* $p<0.05$ vs baseline
[a] Paired *t*-test

leading to acute hypercapnia and a shift to the right in the ODC, had the following measurable effects:

1. Hemodynamic changes consisting of an increase in CI and a lowered SVR with no change in MAP and LVSWI, an unchanged PVR with an increase in MPAP and RVSWI, and an unmodified HR
2. A decrease in SaO_2 requiring an increase in FIO_2, an unchanged PaO_2; an increased PvO_2 with SvO_2 unchanged
3. An increase in Q_{va}/Q_t
4. A significant increase in DO_2, with no significant change in VO_2, and O_2ER
5. A modest decrease in P_{peak} and P_{awm}.

Hemodynamics

The most marked hemodynamic change was a substantial increase in CI. In the absence of an increase in heart rate, this probably resulted from an increased ventricular ejection fraction stemming from peripheral vasodilatation, as evidenced by the fall in SVR. This finding is consistent with data from animal studies showing that CO_2 is a potent vasodilator [14, 15]. Hypercapnia has been shown to reduce myocardial contractility, both in isolated rabbit myocardium preparations [16] and in intact dogs [7]. We did not assess myocardial function through cardiac ultrasound or gated radionuclide ventriculography and thus cannot exclude such an effect in our patients. However, judging from the magnitude of the rise in CI, any such effect would probably have been minimal, and largely offset by the lowered afterload. Furthermore, when this occurs in intact animals, it is usually additionally compensated for by an increased heart rate due to the release of endogenous catecholamines [8]. We did not measure plasma levels of catecholamines, but there was no increase in heart rate in our patients. A possible contribution to the increase in CI might be an improvement in venous return due to the reduction in P_{awm}. However, this seems unlikely or quantitatively insignificant, as the reduction in P_{awm} was quite small (2 cm H_2O), and as there were not significant variations in either right or left heart filling pressures.

It is noteworthy that while SVR decreased substantially PVR remained unchanged. This led to a significant, albeit moderate, increase in MPAP due to the rise in CI. Furthermore, while LVSWI remained unchanged, RVSWI increased during hypercapnia. This confirms findings from studies performed both in normal subjects [17, 18] and in patients after-cardiac surgery [19], suggesting that hypercapnia exerts different effects on the systemic and pulmonary circulations.

Gas exchange

A complex interaction between the consequences of hypoventilation and hypercapnia probably affected the changes in gas exchange. Even though this is an oversimplification, four major events were most likely determinant, which we will briefly discuss. First, the decrease in VE from 13 to 8 l/min should entail a decrease in PaO_2 [20]. The impact of hypoventilation alone on PaO_2 in our patients can be computed: if we assume the same alveolar-arterial oxygen tension difference ($DA-aO_2$) and in view the increase in $PaCO_2$, mean PaO_2 during hypercapnia, computed from the alveolar gas equation, would have been 52 mmHg, which is a decrease of 19 mmHg. However, hypoventilation entails a small decrease in PAO_2, which in turn lowers the $DA-aO_2$. This decrease in PAO_2, computed from the alveolar gas equation, and from the mean $PaCO_2$ at baseline 1 and during hypercapnia, is equal to 3.2 kPa (from 48.5 to 45.3 kPa). Furthermore, during hypercapnia, we had to increase the FIO_2 in five patients to maintain an $SaO_2 \geq 90\%$. As mean FIO_2 increased from 56 to 64%, this should have raised PAO_2 from 41.9 to 49.3 kPa if the other parameters were unchanged. Thus, mean PAO_2 probably increased in this study as well as $DA-aO_2$.

Second, in animal studies an increase in CI has been shown to entail a concomitant increase in Q_{va}/Q_t [20,

21]. A recent study using the multiple inert gas elimination technique in ARDS patients demonstrated an increase in VA/Q mismatching with a concomitant rise in Q_{va}/Q_t during hypercapnia [22]. By extrapolating the findings from animal data to predict the increase in Q_{va}/Q_t from the mean 0.7 l/min/m^2 rise in CI in our patients, a mean increase in Q_{va}/Q_t from 26 to 36% could be expected [21]. This is in the order of magnitude of the observed change from 26 to 33% in our patients. This hypothesis is further substantiated by the significant correlation between the increases in CI and Q_{va}/Q_t. Had this change in Q_{va}/Q_t been isolated, this should have led to a mean decrease in PaO_2 of approximately 10 mmHg [23].

Third, PvO_2 rose during hypercapnia. Indeed, in the presence of significant Q_{va}/Q_t and/or inequalities in VA/Q, PaO_2 becomes more sensitive to the variations in PvO_2 [20]. Extrapolating from published diagrams, the rise in PvO_2 in our patients should have been accompanied, with a baseline shunt fraction of 26%, by a 10 mmHg increase in PaO_2 [20].

Finally, the small but significant reduction in airway pressure (Table 3) could be associated with a further decrease in PaO_2 due to the derecruitment of some alveoli [24, 25], although this is difficult to quantitate.

Taken together, these four events would have led to a net decrease in PaO_2 of approximately 20 mmHg. In fact, PaO_2 did not change significantly during hypercapnia. FIO_2 was increased in five patients, but if that had not been the case, their PaO_2 would have been lower. By using PaO_2 values for these patients corrected for the increase in FIO_2, to compute the group's mean PaO_2, the latter would be 52 mmHg, which corresponds approximately to the estimated drop of 20 mmHg mentioned above. Thus, hypoventilation led to a decrease in PaO_2, the rise in CI to an increase in Q_{va}/Q_t, and the increase in PvO_2 to a rise in PaO_2. The net result would have been a decrease in PaO_2, which was offset by an increase in FIO_2 in five patients.

Oxygen transport, consumption, and extraction

The changes in arterial and mixed venous O_2 partial pressures, saturation, and content are in line with expectations in a rightward shift in the ODC. When initial SaO_2 is $\geq 90\%$, if PaO_2 remains constant, a displacement to the right will result in a modest decrease in SaO_2 because of the flat shape of this portion of the ODC. Different responses in terms of O_2 extraction and mixed venous PO_2 (PvO_2) might ensue, as illustrated in Fig. 3A. If $Ca-CvO_2$ does not vary, PvO_2 should increase maximally (line a). If, at the other extreme, mixed venous PO_2 remains unchanged, the arteriovenous O_2 content $(Ca-Cv)O_2$ should increase maximally (line c). All intermediate possibilities are summarized by line b. The response of our patients is illustrated in Fig. 3B.

In terms of DO_2 and VO_2, the slight lowering of CaO_2, from the decrease in SaO_2, was largely offset by the increase in CI. Thus, hypercapnia increased both DO_2 and the capillary O_2 off-loading capacity of hemoglobin. However, VO_2 remained the same. Consequently, O_2ER tended to decrease, though not significantly, probably because of the small sample size. These modifications merit some comment, as many investigators have reported that in at least some ARDS patients VO_2 could be limited by O_2 availability, even when DO_2 is within its normal range, a situation termed "pathological supply dependency" [26–28]. When this is present, raising DO_2 should entail an increase in VO_2 [29, 30], which was not the case in our patients. This could be due to the numerous methodological problems in determining VO_2 by the indirect method [31–34]. Another possibility is that the rightward shift in the ODC was insufficient to entail a significant detectable increase in O_2 extraction. P_{50} increased from 26.4 mmHg (which corresponds to the normal P_{50} of hemoglobin [6]) to 31.2 mmHg. If we hypothesize that extraction were to increase maximally in response to this increased off-loading capacity, as illustrated in Fig. 3A, it is reasonable to assume that PvO_2 would have remained unchanged (36.5 mmHg). Using standard nomograms correcting for the increased P_{50}, this would have resulted in an SvO_2 of 58% [6]. Calculations of the O_2 content of mixed venous blood would then yield a CvO_2 of 8.9 ml/dl, with represents an increase in the CaO_2-CvO_2 difference of 5.4 ml/dl from the baseline of 4.7 ml/dl, a 15% potential increase in O_2 extraction. As indicated in Table 1, coefficient of variation was 0.2% for SO_2 with a variance of 0.047. PaO_2 can be disregarded, as it plays a minor part in the O_2 content of the blood. The coefficient of variation for hemoglobin was 2.5% with a variance of 0.118. Using theoretical calculations to find approximate variance and standard deviation, the coefficient of variation of CaO_2-CvO_2 difference = 3.1% [35]. This is far below the expected maximum extraction of 15%. It can thus be assumed that the induced shift would have been sufficient to entail a measurable increase in peripheral O_2 extraction. It could also be hypothesized that insufficient time was available for an increase in O_2 extraction. However, this seems unlikely, as the increase in O_2 extraction in response to a shift to the right in the ODC in animal models is very rapid and can be measured in a few minutes [36]. Likewise, ARDS patients will respond to an increase in DO_2 by a rise in VO_2 in approximately 30 min [29, 30]. In our patients, hypercapnia was maintained for 2 h, probably sufficient to observe a change in VO_2. The most likely explanation for the absence of any increase in O_2 extraction is that our patients did not have tissue hypoxia and thus responded to the increase in DO_2 and to the rightward shift in the ODC by decreasing extraction. An obvious caveat to this assumption is that it reflects global phenomena, and that areas of regional hypoxia may have been present.

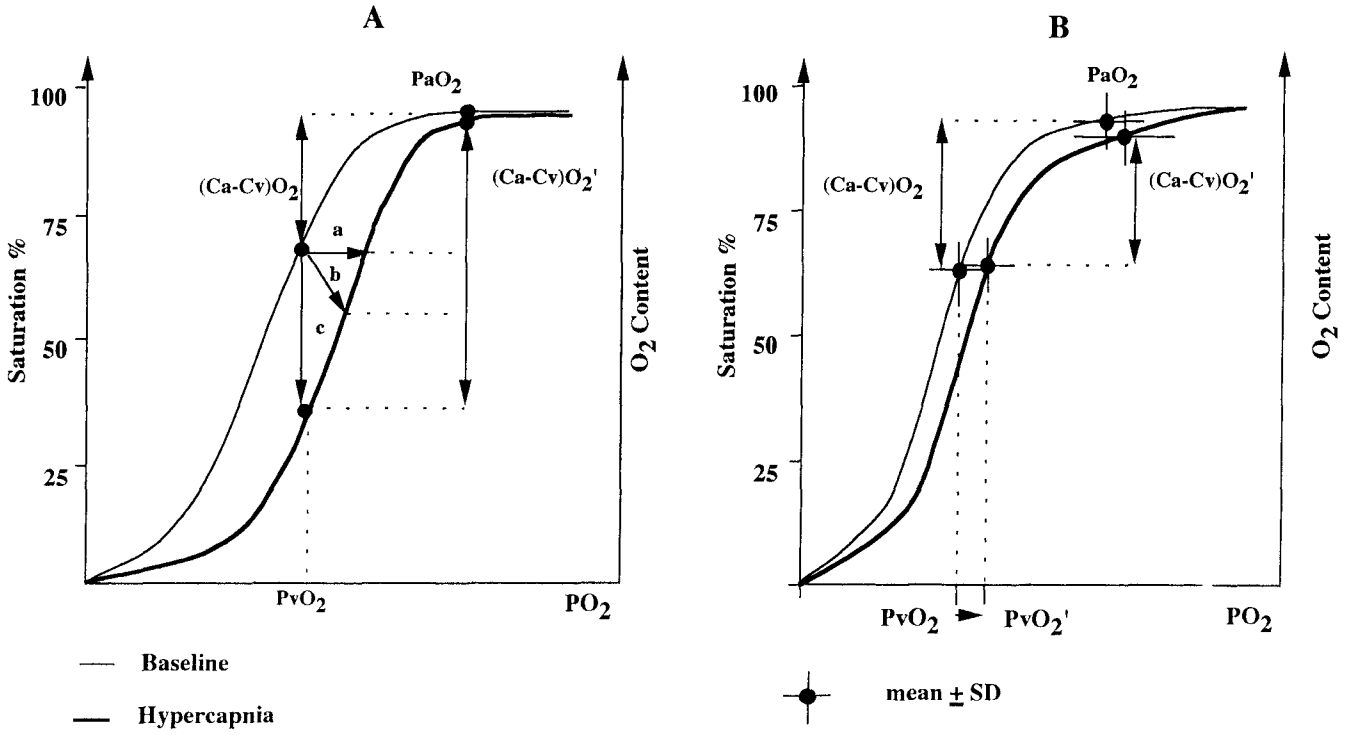

Fig. 3 A Conceptual plot of the oxyhemoglobin dissociation curve (ODC), with PO_2 on the abscissa, O_2 saturation and content on the left and right ordinates, respectively. The standard ODC is represented by the *thin line*, with *points* representing the normal values of arterial (PaO_2) and mixed venous (PvO_2) pressures, as well as the arteriovenous O_2 content difference ($Ca-CvO_2$). The displacement of the ODC to the right is indicated by the *thick line*. It can be seen that PaO_2 remains unchanged, while SaO_2 decreases, although only slightly due to the flat aspect of this portion of the ODC. *Lines a, b,* and *c* represent the possible responses in terms of O_2 extraction, expressed as $Ca-CvO_2$ and PvO_2. *Line a* illustrates unvarying O_2 extraction, and a maximal increase in PvO_2. *Line c* exemplifies a maximal increase in extraction, with an unchanged PvO_2. *Line b* represents one of the many intermediate possibilities between these extremes, i.e., a certain degree of increase in both O_2 extraction and PvO_2. **B** Plot of the observed response in our patients, using the same axes and line thickness for baseline and hypercapnia ODC. *Data points* represent mean ± SD. It can be seen that the patients in this study responded in a manner similar to *line a* in the conceptual diagram

Nonetheless, it should be noted that PvO_2 is considered to be representative of whole-body end-capillary PO_2, which in turn approximates the minimal driving pressure for the diffusion of O_2 from the capillaries to the tissues [37]. The increase in our patients suggests that hypercapnia could lead to an "O_2 extraction reserve," which might be beneficial when tissue hypoxia is present.

Airway pressures

Reducing airway pressure was not an end-point of this study, and thus the reduction in VE was titrated on the target P_{50} and pH change, and not on P_{peak} and P_{awm}. Nonetheless, a small but significant reduction was recorded in these parameters, in line with what might be expected from the changes in the ventilator settings.

Side effects

Even though hypercapnia was well tolerated and no side effects were observed in our patients, some words of caution are in order. First, the drop in SVR during hypercapnia was compensated for by an increase in CI, thus leading to a moderate lowering of MAP. However, all our patients had high initial CIs, and although myocardial function was not directly assessed, they did not have overt heart failure. Should myocardial function be sufficiently depressed, a sharp drop in MAP could result. Permissive hypercapnia might thus be deleterious in patients in whom cardiac function is severely depressed. Second, there was an increase in both MPAP and RVSWI, which might be of concern in patients with severe pulmonary hypertension and/or right ventricular dysfunction. Third, the complex interplay of hypoventilation, increased Q_{va}/Q_t, and reduction in airway pressure led to hypoxemia, which was insufficiently compensated for by the rise in PvO_2 and required an increase in FIO_2 to maintain SaO_2 in five patients. These effects could be a limiting factor in severely hypoxemic patients, while added toxicity from a higher FIO_2 is a theoretical possibility, although difficult to quantitate [38].

Limitations of the study

Two limitations should be outlined. First, even though hypercapnia led to an increase in DO_2 and extraction reserve, the hypothesis that it might be beneficial could not be tested in our patients, as tissue hypoxia seemed to be absent. Patients with low initial values of DO_2, and/or increased serum lactate levels, should be studied, although an excessive decrease in pH could prove limiting. Second, hypercapnia was maintained for only 2 h. Chronic hypercapnia induces compensatory changes in the cerebral circulation [39, 40], as well as in other regions. Consequently, the possible favorable effects on tissue oxygenation might pogressively wear off over time. Alternatively, the side effects such as a drop in MAP, increase in MPAP, and decrease in PaO_2 might also be progressively attenuated.

In conclusion, acute permissive hypercapnia in mechanically ventilated ARDS patients was well tolerated and led to an increase in oxygen transport as a result of a rise in cardiac output, and to an increase in the capillary oxygen off-loading capacity through a shift to the right in the ODC. O_2 consumption remained unchanged in response to these modifications, and O_2 extraction tended to decrease, most likely because of an absence of tissue hypoxia in these patients. The increased O_2 transport and extraction reserves accompanying hypercapnia could be beneficial in patients with tissue hypoxia. However, because of the shift to the right in the ODC, FIO_2 had to be increased by 13% to maintain an SaO_2 of >90%. Finally, caution should be exercised in patients with depressed myocardial function, severe hypoxemia, preexisting acidosis, pulmonary hypertension, and depressed right ventricular function.

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