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ORIGINAL ARTICLE

Influence of apneic oxygenation on cardiorespiratory system homeostasis

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Abstract
Purpose The aim of this study was to elucidate the magnitude of variations in oxygenation indices and the pattern of hemodynamic changes in response to the net effect of tracheal apneic oxygenation (AO) with a view to define the safe time limit of its application.
Methods After obtaining Animal Research Ethics Committee approval, AO was applied in 12 piglets for 40 min. Arterial (a) and mixed venous (v) blood samples for oxygen (O_2) and carbon dioxide (CO_2) tension (PaO_2/PvO_2, $PaCO_2/PvCO_2$), O_2 saturation (SaO_2/SvO_2), pHa, base excess (BEa), and bicarbonate (HCO_3a) determination and for alveolar O_2 tension (PAO_2), PaO_2/FiO_2 and PaO_2/PAO_2 ratio, arterial–mixed venous O_2 content ($AVDO_2$), and O_2 extraction ratio (O_2ER) estimation were collected on anesthesia induction, 10, 20, 30, and 40 min during AO and 10 and 20 min after reconnection to the ventilator. Concomitant hemodynamic data were obtained.
Results Besides PvO_2 and PAO_2, AO adversely influenced PaO_2 (248–113 mmHg), $PaCO_2$ (35–145 mmHg), $PvCO_2$, PaO_2/FiO_2, and PaO_2/PAO_2 in a time-depended fashion, whereas SvO_2, $AVDO_2$, and O_2ER were minimally affected. $P(a-v)CO_2$ was reversed throughout AO. Acid–base status derangement, consisting of HCO_3a elevation, BEa widening, and acidemia (pH 6.9) maximized 40 min after AO. During AO, heart rate, systemic and pulmonary circulation pressures, and cardiac output were progressively elevated, whereas systemic vascular resistance was reduced. All the studied parameters reverted almost to baseline within the 20-min period of ventilator reconnection.
Conclusion Tracheal AO for 40 min ensures acceptable blood oxygenation, promotes notable hypercapnic acidosis, and consequent transient hemodynamic alterations, which are almost completely reversible after reconnection to the ventilator.

Keywords Tracheal apneic oxygenation · Hemodynamic status · Oxygenation indices · Hypercapnic acidosis

Introduction

Several clinical settings could implicate periods of apnea, which is associated by serious complications such as life-threatening hypoxemia. Apneic oxygenation (AO), that is, delivering 100 % oxygen (O_2) to the airways and lungs when spontaneous or conventional ventilatory techniques are not available or feasible, has emerged as a compensatory alternative modality ensuring adequate oxygenation for long periods mainly during tracheal, cardiothoracic [1] and airway procedures [2] or apnea testing to determine brain death [3]. In addition, AO has been shown to prolong the time to hypoxemia during endotracheal intubation [4, 5] in patients with healthy lungs [6] or those with limited respiratory reserve [7] and in morbidly obese patients in connection with anesthesia [8, 9].

Alveoli will continue to take up O_2 even without diaphragmatic movements or lung expansion. O_2 is absorbed at a

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rate of approximately 250 ml per minute in an apneic, healthy, resting, and normal-weighted adult human. The difference in O_2 and carbon dioxide (CO_2) movement across the alveolar membrane is due to the significant differences in gas solubility in the blood, as well as the affinity of hemoglobin (Hb) for O_2 [4]. This causes the net pressure in the alveoli to become slightly subatmospheric, generating a mass flow of gas from pharynx to alveoli. If O_2 is administered, it replaces the consumed alveolar O_2, so alveolar O_2 concentration remains high for a prolonged period [10]. Additional mechanisms of gas exchange, such as cardiogenic oscillations, molecular diffusion, and convection close to the exit of O_2, have also been reported [11]. Nevertheless, negligible alveolar ventilation sustained during AO is notorious for engendering retention of CO_2 in the alveoli, which leads to severe hypercapnia and acidemia development [1, 10, 12, 13].

According to the mathematical model of gas transport studied by Ingenito et al. [14], the position of the catheter tip wields notable changes in the efficacy of CO_2 elimination. The rate of O_2 flow seems to be an additional determinant not only for CO_2 elimination but for adequate oxygenation prolongation, as well [1, 12]. The more remote the location of the catheter tip within the respiratory tract and the higher the flow rate of O_2, the more adequate is CO_2 elimination, but with imminent risk of barotrauma.

Beyond its effect on gas exchange, AO seems to be responsible for a variety of hemodynamic sequelae, mainly attributed to the disappearance of periodic fluctuations of intrathoracic pressures caused by positive pressure ventilation discontinuation, the direct depressant effects of respiratory acidosis, and the sympathetic overdrive originating from hypercarbia [12, 13, 15, 16]. Initially, the venous return to the right heart increases rapidly, further promoting augmentation of circulating blood in the pulmonary vasculature. As a consequence of the aforementioned changes, filling pressures of the left heart are elevated, and thus an enhancement of cardiac output and systemic hemodynamic status is to be expected, which is further amplified by the concomitant catecholamine release [12, 13, 15, 17].

To our knowledge, limited published data provide a thorough assessment of the influence exerted by tracheal O_2 insufflation above the carina level on cardiorespiratory system homeostasis. Therefore, this study was designed to elucidate the magnitude of variations in oxygenation indices and the pattern of change in hemodynamic variables, both in systemic and pulmonary circulation, in response to the net effect of the AO technique with a view to define the safe time limit of its application.

Methods

The study was approved by the Animal Research Ethics Committee of Aristotle University of Thessaloniki and was performed in accordance with the most recent version of the Declaration of Helsinki.

Anesthesia setting

Twelve pigs (27–30 kg) were premedicated with midazolam 0.4–0.5 mg/kg and fentanyl 4–5 μg/kg intramuscularly (i.m.). After 5–10 min, the pig was placed supine on a table. Prior to anesthetic induction, an 18-gauge intravenous (i.v.) catheter (Venocath; Becton–Dickinson, Saõ Paulo, Brazil) was inserted into a peripheral vein located at the dorsal surface of the ear flap. Following an i.v. induction sequence consisting of thiopental 10 mg/kg, fentanyl 5 μg/kg, and rocuronium 1 mg/kg, laryngoscopy, and endotracheal intubation with a 7-mm internal-diameter (ID) endotracheal tube (Mallinckrodt Medical, Ireland) were performed. Anesthesia was maintained by continuous infusion of midazolam (1–2 mg/kg/h). The depth of the anesthesia was tested intermittently with pain stimulation of the front toes. If the anesthesia was deemed insufficient, supplemental bolus doses of fentanyl (0.1–0.2 mg) were given i.v., ensuring that anesthesia was sufficient enough to prevent responses to painful stimuli, such as large-vein catheterization. Neuromuscular blockade was achieved (according to previous experience) with 50 mg per 20 min of rocuronium. Volume control mode of mechanical ventilation (Siemens SC 9000XL, Dräger, Germany) was applied to all animals and set initially to deliver a tidal volume of 10–12 ml/kg at a rate of 12–14 beats per minute in a 50 % O_2/air mixture ($FiO_2 = 0.5$), with inspiratory:expiratory ratio (*I:E*) 1:2 and positive end-expiratory pressure (PEEP) 5 cmH_2O. Appropriate ventilator adjustments were made to maintain arterial PCO_2 at a range of 35–40 mmHg. Furthermore, 10 ml/kg/h Ringer's lactate was infused i.v. during the first hour, and then the infusion rate was altered to 5 ml/kg/h (i.v.). If the animal at this time point was unstable, it was excluded from the study.

Monitoring implementation and apneic oxygenation setup

After anesthesia induction, an open dissection of the femoral vessels was performed and an 20-gauge arterial catheter (Angiocath, Becton–Dickinson, Brasil) was inserted into the femoral artery of one site for invasive arterial blood pressure monitoring and blood sampling for blood gas analysis. In the same manner, a pulmonary artery catheter (CCOmboV; Edwards Lifesciences LLC, Irvine, CA, USA) was advanced via the contralateral femoral vein for measurements of pulmonary artery pressures, mixed venous O_2 saturation (SvO_2), and continuous cardiac output (CCO) (Vigilance monitor, Edwards Lifesciences). A

bladder catheter was inserted suprapubically to monitor urine production. Electrocardiographic monitoring was applied, and pulse oximeter (Massimo Set, Rad 8, Massimo Corporation, Irvine, CA, USA) O_2 saturation (SpO_2) was measured at the ear flap. Body temperature was monitored with CCO pulmonary artery catheter thermistor, and mild hypothermia (35–36 °C) was maintained throughout the procedure. Following application of hemodynamic monitoring, all manipulations ceased for 30 min in order to allow a steady-state condition. Then, AO was instituted by tracheal O_2 insufflation with a flow rate of 0.24 L/kg/min via a 10-F catheter advanced through the orotracheal tube until 1 cm above the carina level. AO was applied for 40 min using 100 % O_2 in order to maintain adequately high alveolar O_2 tension when alveolar CO_2 increases during the apnea.

Data collection

Simultaneous blood samples from the arterial (a) and pulmonary artery (v) catheters were collected on seven clearly predefined occasions for blood gas analysis: after 30 min of mechanical ventilation (baseline), 10 min after AO was commenced (time point 10) and thereafter every 10 min until the procedure had been carried out for 40 min (time points 20, 30, and 40), and 10 and 20 min after discontinuation of AO and mechanical ventilation reestablishment (time points 50 and 60 min). Blood gas analysis was performed using an ABL 700 blood gas machine (Radiometer, Medical ApS, Copenhagen, Denmark). At each time point, the following parameters were determined: pH (pHa), O_2 tension (PaO_2/PvO_2), CO_2 tension ($PaCO_2$/$PvCO_2$), base excess (BEa), bicarbonate (HCO_3a/HCO_3v), and O_2 saturation of arterial (SaO_2) and SvO_2. Furthermore, O_2 content for both circulations (CaO_2/CvO_2, respectively) and PaO_2/FiO_2 (P/F) ratio were estimated, whereas arteriovenous O_2 content ($AVDO_2$), O_2 extraction ratio (O_2ER), and PAO_2 were calculated as follows: $AVDO_2 = CaO_2 - CvO_2 = [(SaO_2 - SvO_2) \times Hb \times 1.36] + (PaO_2 - PvO_2)$, $O_2ER = (SaO_2 - SvO_2/SaO_2)$ % and $PAO_2 = [FiO_2 \times (P_{ATM} - P_{H_2O})] - (PaCO_2 \times 1.25)$.

At the same time points, Hb concentration and hemodynamic data, including heart rate (HR), mean arterial pressure (MAP), right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), pulmonary wedge pressure (PCWP), stroke volume (SV), systemic and pulmonary vascular resistance (SVR and PVR, respectively), as well as readings of cardiac output (CO) determinations, were also recorded. Inotropic or vasoactive drugs were not used, so hemodynamics were purely influenced by AO. At the end of the experiment, the animals were killed by an overdose of potassium chloride (20 mEq i.v.).

Statistics

For P values of 0.05 and a power of 0.8 for the primary outcome variable of time to life-threatening hypoxemia (SpO_2 <60 %), eight animals were considered sufficient. Normality of data was assessed by Kolmogorov–Smirnov test. Analysis of variance (ANOVA) for repeated measures with Greenhouse–Geisser correction was conducted to analyze continuous variables over time. Spearman correlation coefficient was estimated to evaluate the strength of agreement between $PaCO_2$ changes and hemodynamic response. Values are presented as mean and standard deviation (SD) unless otherwise stated. For all statistical procedures, a P value <0.05 was considered significant. Statistical Package for Social Sciences (SPSS, version 16.0; SPSS Inc., Chicago, IL, USA) was used for all calculations.

Results

Initially, 12 animals were enrolled in this study. One was excluded because of sustained hemodynamic deterioration 5 min after AO, which led to ventricular fibrillation, and another due to serious hypoxemia necessitating early AO discontinuation. Thus, a total of ten piglets were included in the final analysis. Regarding systemic oxygenation status, PaO_2, $PaCO_2$, $PvCO_2$, and PaO_2/FiO_2 ratio were influenced adversely in a time-depended fashion by AO application (Table 1). The higher rate of PaO_2 and $PaCO_2$ derangement was recorded 10 min after AO initiation (6.6 and 3.81 mmHg/min, respectively), whereas in the subsequent phases (T20, T30, and T40) of AO, the sequence of change was less pronounced (4.26, 0.56, and 2.26 mmHg/min for PaO_2 and 2.41, 1.94 and 2.56 mmHg/min for $PaCO_2$). Three animals presented a PaO_2 value <70 mmHg after 30 min following AO establishment. The highest individual $PaCO_2$ measurement was 180 mmHg and was recorded 40 min after AO; at the same phase, three piglets presented $PaCO_2$ values >150 mmHg.

Among oxygenation variables, only PvO_2 and PAO_2 were favorably affected by AO. In detail, PvO_2 presented a gradual elevation, which peaked by the end of AO application, whereas PAO_2 was heightened 10 min after AO and thereafter remained at these levels up to AO completion. Unlike the aforementioned indices, SvO_2, $AVDO_2$, and O_2ER were affected in a minor way and remained within acceptable limits throughout the study period. Corresponding to the rising $PaCO_2$, acid-base status showed a notable derangement characterized by a significant increase in HCO_3 and widening of BEa with concomitant severe acidemia, which peaked 40 min after AO initiation. Systemic oxygenation and acid–base status

Table 1 Time course of oxygenation parameters and related factors

Variables	Baseline	T10	T20	T30	T40	T50	T60
PaO_2 (mmHg)	248 ± 87	182 ± 103	140 ± 77**	135 ± 67**	113 ± 57***	159 ± 55**	178 ± 64*
PaO_2/FiO_2 (mmHg)	489 ± 187	182 ± 103***	140 ± 77***	135 ± 67***	113 ± 57***	312 ± 118*	352 ± 138*
$PaCO_2$ (mmHg)	35 ± 8.4	74 ± 19***	97 ± 23***	119 ± 29***	145 ± 27***	66 ± 12***	55 ± 8.7***
PvO_2 (mmHg)	52 ± 6	78 ± 24*	82 ± 19**	83 ± 17**	84 ± 23**	74 ± 24*	69 ± 23
$PvCO_2$ (mmHg)	43 ± 4	75 ± 18***	90 ± 23***	113 ± 27***	136 ± 29***	75 ± 13***	65 ± 13***
PAO_2 (mmHg)	344 ± 16	618 ± 7***	587 ± 9***	563 ± 11***	553 ± 20***	285 ± 17*	305 ± 16
PaO_2/PAO_2	0.75 ± 0.2	0.29 ± 0.2***	0.23 ± 0.1***	0.24 ± 0.1***	0.20 ± 0.1***	0.54 ± 0.2*	0.65 ± 0.2
$AVDO_2$	2.9 ± 0.7	2.1 ± 1.1	2.4 ± 1.6	1.7 ± 1.3**	1.3 ± 1.3***	1.8 ± 0.7**	2.0 ± 0.8
O_2ER (%)	20.6 ± 6	18.9 ± 5.7	20.1 ± 1.5	18.1 ± 3.4	15.5 ± 3.8**	17.4 ± 4.7	17.7 ± 3.7
SaO_2 (%)	98.2 ± 0.8	95.1 ± 3.6	94.3 ± 2.5	94.1 ± 3.1	96.6 ± 6.3	96.9 ± 2.8	96.4 ± 1.5
SvO_2 (%)	77.9 ± 2.11	76 ± 4.3	75.1 ± 4.1	77 ± 9.1	82 ± 9.2	80 ± 9.9	79.3 ± 1.5
HCO_3a (mEq/L)	21 ± 3.2	27 ± 4.9***	29 ± 3.7***	29 ± 3.9***	30 ± 3.2***	26 ± 3.2***	25 ± 2.8***
BEa (mmol/L)	−2.7 ± 3.8	−3.2 ± 3.2	−4.2 ± 3.4*	−4.8 ± 4.4*	−8.2 ± 2.9***	−2.8 ± 3.2	−1.7 ± 3.4
pHa	7.4 ± 0.09	7.2 ± 0.07***	7.1 ± 0.08***	7 ± 0.06***	6.9 ± 0.06***	7.2 ± 0.07***	7.3 ± 0.06**

Data are expressed as mean ± standard deviation. Asterisks indicate statistical significance of each setup versus baseline

PaO_2 partial pressure of oxygen in arterial blood, *PaO_2/FiO_2* partial pressure of oxygen in arterial blood/inspired oxygen fraction, *$PaCO_2$* partial pressure of carbon dioxide in arterial blood, *PvO_2* partial pressure of oxygen in mixed venous blood, *$PvCO_2$* partial pressure of carbon dioxide in mixed venous blood, *PAO_2* partial pressure of oxygen in alveoli, *$AVDO_2$* arterio-mixed venous oxygen difference, *O_2ER* oxygen extraction ratio *SaO_2* arterial oxygen saturation, *SvO_2* mixed venous oxygen saturation, *HCO_3a* bicarbonate in arterial blood, *BEa* base excess in arterial blood, *pHa* pH in arterial blood

* $P < 0.05$

** $P < 0.01$

*** $P < 0.001$

deterioration began to normalize as soon as mechanical ventilation was reestablished and reverted almost to baseline values within the 20-min period of reconnection to the ventilator.

Significant change over time was detected for PaO_2 ($P = 0.008$), *P/F* ratio ($P = 0.000$), $PaCO_2$ ($P = 0.000$), PvO_2 ($P = 0.027$), $PvCO_2$ ($P = 0.000$), PAO_2 ($P = 0.000$), PaO_2/PAO_2 ratio ($P = 0.000$), pHa ($P = 0.000$), HCO_3 ($P = 0.000$), and BEa ($P = 0.002$), but not for SvO_2 ($P = 0.173$), O_2ER ($P = 0.221$), and $AVDO_2$ ($P = 0.107$). Furthermore, $PaCO_2$ before AO was lower than the $PvCO_2$, but this relationship was reversed 10 min after AO establishment and was maintained throughout the AO application. The level of this derangement was almost equivalent to baseline values and was restored after mechanical ventilation reestablishment (Fig. 1).

Hemodynamic data for each time point are given in Table 2. Significant change over time was detected for HR ($P = 0.033$), MAP ($P = 0.005$), CO ($P = 0.000$), SV ($P = 0.000$), RAP ($P = 0.032$), mPAP ($P = 0.000$), PCWP ($P = 0.018$), SVR ($P = 0.002$), and PVR ($P = 0.000$). All animals were hemodynamically stable at baseline. During the 40-min period of AO, a tendency toward increased values was noted for HR, MAP, CO, SV, MAP, RAP, mPAP, and PCWP, which peaked 40 min after AO establishment. After reconnection to the ventilator, these parameters began to decline; by the end of the experimental period, they returned almost to baseline values, with the exception of HR and CO, which remained in statistically significant higher levels compared with baseline ($P < 0.05$). The noteworthy elevation of mPAP and PVR suggests that AO affects the right ventricular afterload in an adverse manner. The only hemodynamic variable that presented reduction by AO application was SVR, reaching a maximum level 40 min after AO establishment.

When the effect of $PaCO_2$ changes to hemodynamic response was tested, a significant intraclass correlation coefficient with CO ($R = 0.396$, $P = 0.001$), mPAP ($R = 0.642$, $P = 0.000$), CVP ($R = 0.349$, $P = 0.003$), PVR ($R = 0.462$, $P = 0.003$), and SVR ($R = -0.245$, $P = 0.043$) occurred.

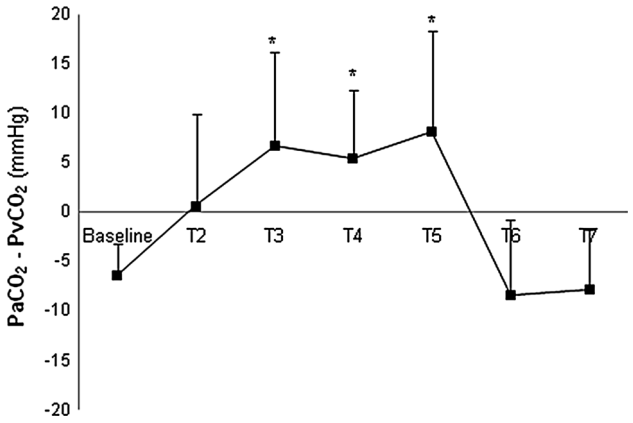

Fig. 1 Alterations in mean difference of partial pressure of carbon dioxide in arterial blood – partial pressure of carbon dioxide in mixed venous blood ($PaCO_2 - PvCO_2$) over time. Data are expressed as mean ± standard deviation. *Asterisk* statistical significance of each setup versus baseline; *$P < 0.05$

Discussion

This porcine study showed that application of AO for 40 min achieved by administering O_2 with a flow of 0.24 L/kg/min via an endotracheal catheter does not affect oxygenation parameters at levels that are clinically dangerous and incompatible for life and so constitutes a safe option for substantial prolongation of time to life-threatening hypoxemia. This benefit is achieved at the expense of noteworthy gradual hypercarbia and acid-base balance-status derangement, which are responsible for hemodynamic changes. This was transient, however, and is almost fully reversed with reestablished mechanical ventilation.

The technique of AO is not a new concept, as it was described in the medical literature almost a century ago, referred to as apneic diffusion oxygenation, diffusion respiration, or mass-flow ventilation [18, 19]. A considerable body of evidence both in experimental and clinical settings deals with the safe time interval of AO application, with divergent results. Under optimal circumstances, it seems that O_2 flow rates of approximately 0.1 L/kg/min ensure an acceptable oxygenation status for up to 45 min [2, 4–8, 13, 17, 19, 20], although the negligible ventilation will eventually cause marked hypercapnia and significant acidosis, which constitute the main limitations of this technique [1, 10, 12, 21]. On the basis of these findings, we chose to apply AO for up to 40 min; in order to ensure adequate oxygenation prolongation, it was applied by insufflation of 100 % O_2. If this gas contains nitrogen (N_2), which is not absorbed, N_2 will be accumulated/concentrated in the alveolar compartment with no space for O_2 replenishment [22]. This phenomenon is well known and, as early as 1944, Draper and Whitehead [18] proposed not only the use of $FiO_2 = 1$ during apnea but denitrogenation before AO as essential maneuvers. Also, this practice promotes toxic concentrations of O_2 in alveolar gas, and it seems that even when N_2 has been entirely washed out of the alveoli by ventilation with pure O_2, the N_2 that is dissolved in blood diffuses across the alveolar capillary membrane due to the partial pressure gradient between blood and alveolus, resulting in a PAO_2 decline [17]. In addition, recent data show that when the lungs are ventilated with an FiO_2 <1 before applying AO, the N_2 will remain there, and no new N_2 is delivered to the lungs [23]. These findings support the notion that AO can be performed without denitrogenation and that it is possible to predict and keep alveolar N_2

Table 2 Time course of hemodynamic parameters and related factors

Parameters	Baseline	T10	T20	T30	T40	T50	T60
HR (beats/min)	95 ± 18	112 ± 16*	109 ± 21*	109 ± 18*	121 ± 27**	119 ± 22**	114 ± 11*
MAP (mmHg)	93 ± 17	109 ± 8	107 ± 11	111 ± 16*	123 ± 12***	109 ± 14	104 ± 12
CO (L/min)	5 ± 1.6	5.9 ± 1.2*	5.7 ± 1.2*	6.3 ± 1.3**	7.2 ± 0.9**	6.1 ± 0.8**	5.8 ± 1.3*
SV (ml)	45 ± 11	57 ± 16	55 ± 16	60 ± 18*	65 ± 13**	53 ± 11	55 ± 15
RAP (mmHg)	4.1 ± 1.6	5.1 ± 3.8	5.7 ± 4.3	5.6 ± 4.6	6.5 ± 3.8*	4.9 ± 2.1	4.5 ± 2.5
mPAP (mmHg)	19.1 ± 6.4	24.8 ± 7.9	27.1 ± 8.9*	27.7 ± 9*	28.6 ± 6.5**	22.5 ± 7.8	20.4 ± 7.7
PCWP (mmHg)	6.6 ± 2.2	6.8 ± 2.8	8.2 ± 4.5	8.6 ± 4.5	9.4 ± 1.9*	7.7 ± 2.3	7.2 ± 2.4
SVR (dyn/s)	1412 ± 514	1427 ± 304	1622 ± 408	1534 ± 455	1012 ± 306*	1107 ± 409*	1319 ± 384
PVR (dyn/s)	111 ± 19	138 ± 31*	175 ± 38**	202 ± 65**	215 ± 23***	176 ± 34**	141 ± 34*

Data are expressed as mean ± standard deviation. Asterisks indicate statistical significance of each setup versus baseline

HR heart rate, *MAP* mean arterial pressure, *CO* cardiac output, *SV* stroke volume, *RAP* right atrial pressure, *mPAP* mean pulmonary arterial pressure, *PCWP* pulmonary wedge pressure, *SVR* systemic vascular resistance, *PVR* pulmonary vascular resistance

* $P < 0.05$

** $P < 0.01$

*** $P < 0.001$

concentration at a desired level during a 10-min AO period [23]. This enables the delivery of nontoxic concentrations of alveolar O_2 with maintained adequate blood oxygenation [23]. Before instituting AO, all animals in our setting were ventilated with a $FiO_2 = 0.5$ in order to avoid both O_2 toxicity and the development of shunt due to absorption atelectasis [23–25].

It is obvious that a rise in $PaCO_2$ levels during prolonged apnea causes alveolar O_2 to be reduced according to the alveolar gas equation [7]. In a similar experimental setting, Hostman et al. [23] applied AO for 10 min using 100 % O_2 with flow of 2 L/min with concomitant continuous positive airway pressure at 5 cmH_2O. Although AO duration in our setting was four times longer compared with the previous experimental setting, oxygenation parameter changes were similar. A possible explanation could be the approximately threefold higher flow of O_2 used in our study, promoting more effective O_2 replenishment and CO_2 elimination [1]. Nielsen et al. [24] previously found in pigs with healthy lungs that AO at zero end-expiratory pressure could maintain a high PaO_2 for at least 10 min. Therefore, we assume that the initial drop in PaO_2 (6.6 mmHg/min) seen after 10 min of AO in our study was caused by a rapid collapse of lung regions induced by the abrupt removal of PEEP.

Progressive hypercapnia induced by AO is typically expressed by an increase in $PaCO_2$ of 6 mmHg in the first minute, as this corresponds to normal human mixed venous–arterial $PaCO_2$ difference, so at least that degree of $PaCO_2$ increase should occur in the first minute of apnea [26]. During the following minutes, alveolar CO_2 does not increase more than about 3–4 mmHg/min, because only 8–20 ml/min of CO_2 moves into the alveoli during apnea, with the remainder being buffered in the bloodstream by erythrocytes and dissociated in the tissue [26, 27]. In our study, the increase in $PaCO_2$ was most pronounced during the first 10 min of AO (3.81 mmHg/min) and thereafter ranged from 1.94 to 2.56 mmHg/min. After 40 min of total duration of AO, $PaCO_2$ was 145 mmHg, approximating the threshold of supercarbia in humans (150 mmHg), and pH was diminished to 6.9. Considering that CO_2 production increases at 6–8 % per 1 °C, body temperature was kept at 35–36 °C throughout the experimental procedure, with a view to maintain $PaCO_2$ levels as low as possible [21, 28]. Furthermore, a reversal of the $PaCO_2$ minus $PvCO_2$ relationship throughout AO application was revealed in our experimenting setting. This finding was previously reported in arterial and mixed-venous samples by Rigg and Cruickshank [29], who investigated CO_2 kinetics in two patients undergoing apnea testing for brain death. They postulated that reversal of the normal $PaCO_2$ and $PvCO_2$ relationship during apnea was a consequence of the Haldane effect; the CO_2 dissociation curves are different in reduced and oxygenated hemoglobin. As apnea testing was performed without oxygenation, it was concluded that reduced hemoglobin was able to carry more CO_2 than carbamino compounds, thus explaining how the rise in $PaCO_2$ was greater than that in $PvCO_2$. Considering their results, we reached same findings by using AO, and it can be assumed that reversal of the arterial and mixed-venous PCO_2 relationship is independent of the absence of O_2. There may be an alteration in CO_2 transportation from its dissolved form (corresponding to 7 % of the total CO_2 transported) to transportation linked to the HCO_3a ion or carbamino compounds [30]. Another possible explanation is that the lung parenchyma continues producing CO_2 and consuming O_2 via the bronchial arteries that empty the bronchial veins into the left auricle. However, in view of a reversed $PvCO_2$ and $PaCO_2$ gradient, we may have to consider modifying our practice, assessing $PvCO_2$ rather than $PaCO_2$.

Respiratory acidosis induced a compensatory gradual elevation of plasma HCO_3a levels, which peaked (30 mEq/L) by the end of AO application, due to cellular buffering. Likewise, Blaze et al. [31], in an experimental setting involving 30 min of tracheal O_2 insufflation above the carina level in ponies or horses, confirmed acid–base status derangement.

The principal effects of hypercapnia and subsequent acidosis include decreased myocardial contractility and suppression of smooth-muscle fibers [32]. These seem to be counteracted by increased sympathetic nervous system activity due to an indirect effect of hypercapnia on the vasomotor center in the brain, which induces a notable secretion of catecholamine, causing vasoconstriction of blood vessels and elevation of systemic vascular resistance and blood pressure [12, 13, 15–17, 33]. From direct measurements of catecholamine levels occurred that, sympathoadrenal response mainly involves norepinephrine release [16]. In our case, the degree of hypercapnic acidosis (pH 6.9) did not compromise circulation. On the contrary, HR, MAP, CO, SV, RAP, mPAP, and PCWP were gradually elevated in an important manner. Our results further validate, by assessing HR, MAP, and CO, what has been illustrated by the groups of Engstrom [7] and Hostman [23] in similar experimental settings. The early increase of cardiac output and pressures of pulmonary circulation during the first half of AO could be attributed to increased venous return due to mechanical ventilation discontinuation, whereas the further notable increase during the second half of AO could be due to increased sympathetic nervous system activity. Data support the fact that catecholamine release becomes important when $PaCO_2$ levels >100 mmHg [33]. This effect of catecholamine release was maintained during the immediate period following reestablishment of mechanical ventilation and began to normalize 20 min after AO withdrawal. The impact of

increased sympathetic nervous system activity on the aforementioned hemodynamic changes is further supported by studies of AO application with the concomitant use of extracorporeal CO_2 removal ($ECCO_2R$), showing that hemodynamic status both in systemic and pulmonary circulation remained unchanged [21, 24]. It should be emphasized that the advanced circulatory status during AO encourages a state of enhanced aerobic metabolism, which in our setting was reflected by a slight narrowing of $AVDO_2$ owing to the compensatory decrease in O_2ER. Nevertheless, these changes were rather negligible for inducing a significant alteration in SvO_2 values. Furthermore, hypoxia- and hypercapnia-induced acidosis triggers hypoxic pulmonary vasoconstriction, causing an increase in PVR, which also could have contributed to the increased pressures in pulmonary circulation [34]. Data indicate that hypercapnia causes constriction of the pulmonary vessels, which is related to the endothelium and the reduced production of nitric oxide (NO) [35]. However, as acidosis becomes more excessive and concentration of hydrogen (H^+) and potassium (K^+) increase, the main effect is dilatation of blood vessels and decrease in SVR [32]. When AO is applied for a prolonged time period (>20 min), there is a significant possibility that it will be necessary to support the circulation with vasoconstrictors (such as phenylephrine or norepinephrine). This is in accordance with our findings, as SVR increased during the first 20 min after the initiation of AO, then decreased and reached lower levels than before AO was commenced. SVR remained low, even after the piglets were reconnected to the ventilator. By the end of the experiment, as acid–base homeostasis was restored, SVR returned almost to baseline values. Although hypercapnia and acidosis are responsible for an increased tendency to fibrillation and other arrhythmias, this did not occur in our study. However, both experimental [36] and clinical [13] studies have shown that at $PaCO_2$ levels up to 170 mmHg, cardiac dysrhythmias rarely occur. Despite the known adverse effects of hypercarbia—mainly attributed to the alteration of intracellular pH, which interferes with enzymatic systems and resulting in a variety of organ-specific dysfunction—high serum levels of CO_2 itself are not thought to be cytotoxic [4]. Nunn described normal physiologic responses during periods of $PaCO_2$ >400 mmHg, suggesting that vital organs can tolerate both high $PaCO_2$ levels and concomitant low intracellular pH [32].

Our study has several limitations. It was carried out in pigs weighting approximately 30 kg. Thus, the ratio between end-expiratory lung volume, representing O_2 debt, and O_2 consumption is low, making the apneic period before desaturation shorter than in adult patients. Although the pig is considered to be an excellent model for studying respiratory physiology, these results might not be thoroughly translated to human adults.

Conclusions

In conclusion, the findings of this porcine study indicate that AO for 40 min through endotracheal insufflation with a flow of 0.24 L/kg/min does not significantly perturb blood oxygenation, enabling satisfactory tissue oxygenation, which is prerequisite for the body's viability. However, this is achieved at the expense of significant hypercapnic acidosis. Although progressive hypercapnia and derangement of acid–base status induced hemodynamic alterations, these were transient, ranged within normal or near-normal limits, and were almost fully reversed after mechanical ventilation was reestablished. It makes intuitive sense that this temporizing maneuver could be useful in several clinical situations by resolving hypoxia without the morbidity associated with more invasive procedures.

Conflict of interest None.

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