

Could hyperoxic ventilation impair oxygen delivery in septic patients?

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Summary

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Objective: In critically ill patients, a decrease in whole body oxygen consumption under hyperoxia has been reported and this could be related to hyperoxia-induced arterial changes. We investigated changes in brachial artery circulation and tone during short-term hyperoxic ventilation in septic patients.

Design and setting: Prospective clinical study in the intensive care unit of a university hospital.

Patients: Fourteen patients (severe sepsis $n = 3$ and septic shock $n = 11$) requiring mechanically controlled ventilation due to sepsis syndrome were investigated under stable clinical conditions.

Interventions: After a 20-min period of hyperoxic ventilation (inspired oxygen fraction = 100%), two-dimensional images of brachial artery cross-sectional area and brachial blood flow velocities were recorded using conventional ultrasonography and pulsed Doppler simultaneously with invasive arterial pressure measurements.

Measurements and main results: Hyperoxia did not affect heart rate, but increased mean arterial pressure and decreased cross-sectional areas both at the end of diastole and at the end of systole. Haemodynamic study showed an increase in resistance index, and a decrease in distensibility and compliance coefficients. Furthermore, a decrease in brachial artery blood flow and arterial oxygen delivery was observed during hyperoxic exposure.

Conclusions: Hyperoxia was paradoxically demonstrated to decrease oxygen delivery in upper limbs during septic shock.

Introduction

In the management of septic shock, controlled ventilation with high-inspired oxygen fraction (FiO_2) may be used to prevent hypoxemia during potential periods of hypoventilation like intubations, tracheal aspirations. Moreover, the improvement in gas alveolar exchange if FiO_2 oxygen delivery remains constant during controlled ventilation could lead to inadvertent hyperoxia even though every effort is usually made to keep FiO_2 as low as possible to protect against lung injury (Altemeier & Sinclair, 2007). There is an evidence that hyperoxia affects blood transport in both healthy subjects and critically ill patients. Several authors have previously reported in healthy subjects that a short period of hyperoxic breathing decreases heart rate (Harten et al., 2003; Waring et al., 2003; Rossi & Boussuges, 2005) and cardiac output (Harten et al., 2003; Waring et al., 2003), without affecting blood pressure (Harten

et al., 2003; Rossi & Boussuges, 2005), but increases systemic vascular resistance (Harten et al., 2003; Waring et al., 2003), and large artery stiffness (Waring et al., 2003), and decreases brachial artery compliance, cross-sectional area and blood flow (Rossi & Boussuges, 2005). There have been no reports on the effects of short-term hyperoxia on arterial vasomotor tone and its potential consequences on peripheral blood flow in septic shock. In critically ill patients, a previous study has shown a paradoxical decrease in whole-body oxygen consumption under hyperoxia, suggesting an impairment of tissue oxygenation due to impaired nutritive blood flow (Reinhart et al., 1991), and this could be due to changes in haemodynamic status. However, this investigation has been performed using catheterization, and a complete analysis of changes during normobaric hyperoxia has never been performed. In the aim to study peripheral circulation, conventional ultrasonography and Doppler may offer a reliable evaluation of peripheral arterial tonus and blood

flow by measurements of cross-sectional compliance coefficient (CC), regional output and resistance index (RI), as we have previously described in healthy men in normal condition (Rossi et al., 2004) and during normobaric hyperoxia (Rossi & Boussuges, 2005). In this study, we have assessed changes in brachial artery circulation and tone during short-term hyperoxic ventilation in septic patients, using conventional bidimensional ultrasonography and pulsed Doppler studies.

Materials and methods

Patients

Eligible patients were aged between 18 and 70 years and presented severe sepsis or septic shock diagnosed upon or after admission to the medical intensive care unit of Sainte Marguerite University Hospital in Marseilles, France. Patients were included in this study after obtaining written informed consent from the next of kin. Study design was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale of Marseille and conducted according to the principles established in Helsinki. Sepsis was diagnosed according to the criteria proposed by Bone et al. (1992). All patients were sedated with a continuous infusion of sufentanil midazolam to tolerate endotracheal tube or mechanical ventilation, and the lungs were ventilated using conventional volume-controlled mechanical ventilation (Servo 300; Siemens, Solna, Sweden). Inspired oxygen fraction (FiO_2) required for the study was lower than 0.6 (based on a need to maintain PaO_2 above 80 mmHg). Minute ventilation was constant throughout study. All patients received conventional sepsis treatment according to the indication in each case. This treatment included antibiotics, fluid resuscitation (plasma, colloids, and/or crystalloid), surgical procedures and cardiovascular support when indicated. Respiratory and haemodynamic status had been stable for 6 h prior to inclusion. Patients with history of epilepsy, or cardiac dysrhythmia were not included in the study. The Acute Physiology and Chronic Health Evaluation (APACHE) III score was calculated at study entry (Knaus et al., 1991). The rate of administration of vasoactive agents and fluids was maintained constant throughout the study. A radial artery catheter (Seldi-cath; Plastimed, Saint-Leu-la-Forêt, France) was placed on same arm as the ultrasonographic study in all patients for continuous monitoring of systolic arterial pressure (SAP), diastolic arterial pressure (DAP).

Experimental protocol

Each subject has served as his own control. Measurements were performed during mechanical ventilation with baseline FiO_2 (lower than 60%) and after 20 min of hyperoxic ventilation ($\text{FiO}_2 = 100\%$). Each period of measurement was preceded by a 20 min of rest. In both periods, we recorded the heart rate, the arterial pressure and the blood gas by the radial artery catheter. Samples from radial blood were drawn slowly and continuously

over 20 s, and were analyzed immediately for oxygen, carbon dioxide tensions, oxygen saturation fraction, pH and haemoglobin value (Bayer M 865). Arterial oxygen content was calculated according to the following formula: (haemoglobin value $\times 1.34 \times$ oxygen saturation fraction) + (oxygen tension $\times 0.0031$).

All procedures were undertaken in silence to minimize external stimuli.

Doppler ultrasound study

The echographic-Doppler examinations were performed, as previously described (Reneman et al., 1996; Rossi et al., 2004), using a commercially available Doppler echograph (Vingmed Flex scan T57S system FIVE®, GE Medical Systems, Fairfield, CT, USA) connected to a transducer linear array of 10.5 MHz. Two trained investigators (PR, AB) carried out the examinations and were blinded to the FiO_2 . All measurements were performed at the end of expiration to minimize the effects of the mechanical ventilation on the haemodynamic parameters. The brachial artery was approached by ultrasound scan in supine position with the arm in exterior rotation and abduction. Ultrasound coupling between skin and probe was achieved using ultrasound transmission gel, avoiding direct contact the probe with the skin. Brachial artery cross-sectional areas were obtained by a transversal view with a depth of 4-cm, 15-cm upstream the antecubital fossa of the forearm. We left a mark with an indelible marker on the skin during the first measurement, in order to repeat ultrasound study at the same site.

Cross-sectional areas were measured at the end of diastole (A_{diast}) and the end of systole (A_{syst}). The end diastolic frame was selected at the peak of the R wave on the simultaneous electrocardiogram recording, and the end-systolic frame was defined as the largest vascular surface during the last half of the T wave. The systolic and diastolic artery cross-sectional areas were calculated from the values of five successive cardiac cycles.

The probe was then turned 90° to display a longitudinal view of the vessel and to measure brachial artery blood flow. Using a maximal true angle between the probe and the skin and an inclined Doppler axis of 20°, the complementary angle to align with the vessel was <60° in all cases. Brachial artery blood flow velocities were the average of the velocities on an 8-s record. We measured the maximal systolic and diastolic velocities (V_{syst} and V_{diast}), the mean velocity (V_{mean}) and velocity integral (VTI) of the blood flow. Ultrasonographic examinations were recorded on VHS video tape (Maxell Europe Ltd.).

Regional blood flow (Q_r) was obtained by the combination of the systolic artery cross-sectional areas (A_{syst}) and blood flow VTI measurements.

$$Q_r = (A_{\text{syst}}) * \text{VTI} * \text{HR}$$

Resistance index has been calculated as: $\text{RI} = (V_{\text{syst}} - V_{\text{diast}}) / V_{\text{syst}}$.

Cross-sectional CC ($10^{-3}\text{mm}^2\text{kPa}^{-1}$) was calculated as $(A_{\text{syst}}-A_{\text{diast}})/\text{PP}$ and distensibility coefficient (DC 10^{-6}kPa^{-1}) was calculated as $[(A_{\text{syst}}-A_{\text{diast}})/A_{\text{syst}}]/\text{PP}$ where PP is the pulse pressure.

The brachial delivery of O_2 (D_{O_2}) was calculated as the product of the regional blood flow and the arterial O_2 content.

To assess reproducibility of measurements, our laboratory has previously studied their intraobserver and interobserver variabilities in healthy men. The coefficient of variation for intra and interoperator was respectively 2.3% and 4.4% for A_{syst} , 3.1% and 5.8% for A_{diast} , 5.2% and 6.3% for VTI, 5.2% and 8.5% for Q_r , 5.7% and 4.2% for V_{syst} , 6.5% and 6.9% for V_{mean} , 7.9% and 9.9% for V_{diast} , 5.2% and 9% for CC, 3.4% and 2.7% for RI (Rossi et al., 2004).

Statistical analysis

Statistical tests were run on Sigma Stat software (Jandel Scientific Software, San Rafael, CA, USA). Two series of measurements were obtained: the first in baseline FiO_2 and the second in hyperoxia. We analyzed the data distribution using a Kolmogorov–Smirnov test. We used a t-test for paired data because data's distribution reflected a normal distribution. Data are expressed as mean \pm SD. P-values <0.05 were considered significant.

Results

Patients

The study included fourteen consecutive patients (seven men and seven women; mean age 52 ± 20 years) treated for sepsis between September 2001 and December 2001. At study entry, 11 patients were in septic shock. Baseline FiO_2 was $47 \pm 8\%$. Mean baseline APACHE III score was 57.2 ± 18.3 . The largest number of infections originated in the lung ($n = 8$). The next largest group had urinary tract infections ($n = 4$) followed by abdominal tract infections ($n = 2$). Vasoconstrictor agents were administered in 11 patients (noradrenalin in eight patients and adrenalin in three patients). All patients required controlled mechanical ventilation support because of underlying lung disease (pneumonia or acute respiratory distress syndrome) or as adjunctive management for shock.

Oxygen-transport variables

The PaO_2 in baseline FiO_2 rose up after 20 min of $\text{FiO}_2 = 1$, inducing arterial oxygen content increased (Table 1; $P < 0.001$). The PaCO_2 and the pH remained stable during hyperoxia exposure (Table 1).

Haemodynamic modifications in hyperoxia

Systolic arterial pressure and mean arterial pressure (MAP) were increased significantly in 20 min of hyperoxic ventila-

Table 1 Oxygen-transport variables and haemodynamic modifications in hyperoxia.

	Baseline FiO_2 (mean \pm SD)	$\text{FiO}_2 = 1$ (mean \pm SD)	P-value
pH	7.37 ± 0.07	7.37 ± 0.07	0.5
PaO_2	102 ± 33	$350 \pm 76^*$	<0.001
PaCO_2	43 ± 7	42 ± 10	0.5
SaO_2	0.97 ± 0.02	$0.99 \pm 0.03^*$	<0.001
CaO_2 , ml dl^{-1}	13.9 ± 1.3	$15.1 \pm 1.4^*$	<0.001
SAP, mmHg	110 ± 16	$117 \pm 18^*$	0.02
MAP, mmHg	69 ± 14	$74 \pm 15^*$	0.02
DAP, mmHg	54 ± 14	55 ± 14	0.7
PP, mmHg	56 ± 13	$62 \pm 13^*$	0.008
HR, beats min^{-1}	93 ± 15	91 ± 16	0.06

PaO_2 , arterial partial pressure of O_2 ; PaCO_2 , arterial partial pressure of CO_2 ; SaO_2 , arterial O_2 saturation; SAP, systolic artery pressure; MAP, mean artery pressure; DAP, diastolic artery pressure; PP, pulse artery pressure; HR, heart rate.

* $P < 0.05$.

tion, and DAP remained stable. Pulse pressure increased significantly. Furthermore, heart rate remained unchanged (Table 1).

Ultrasound scan data modifications in hyperoxia

The cross-sectional areas at peak systole and end diastole were reduced significantly. We didn't note modifications about V_{syst} and V_{diast} , however V_{mean} and VTI were significantly reduced, and brachial artery blood flow decreased significantly (Table 2). As a result, O_2 delivery was paradoxically decreased after 20 min of 100% breathing oxygen (Table 2).

Table 2 Ultrasound scan data and vasomotor parameter variations in hyperoxia.

	Baseline FiO_2 (mean \pm SD)	$\text{FiO}_2 = 1$ (mean \pm SD)	P-value
A_{syst} , mm^2	16.4 ± 5.5	$14.5 \pm 6.0^*$	0.005
A_{diast} , mm^2	14.1 ± 4.7	$12.5 \pm 5.7^*$	0.03
VTI, cm	96.2 ± 36.0	$82.8 \pm 35.8^*$	0.04
V_{syst} , cm s^{-1}	58.9 ± 18.6	51.6 ± 16.6	0.2
V_{mean} , cm s^{-1}	18.5 ± 8.2	$15.9 \pm 8.0^*$	0.04
V_{diast} , cm s^{-1}	8.0 ± 5.3	6.8 ± 5.5	0.06
Q_r , ml min^{-1}	144.6 ± 72.6	$112.3 \pm 67.4^*$	0.04
D_{O_2} , ml min^{-1}	198.6 ± 96.9	$166.6 \pm 96^*$	0.01
CC, $10^{-3}\text{mm}^2\text{kPa}^{-1}$	31.6 ± 19.5	$23.3 \pm 14.3^*$	0.04
DC, 10^{-6}kPa^{-1}	36.8 ± 20.3	$21.1 \pm 11.3^*$	0.02
RI	0.85 ± 0.11	$0.89 \pm 0.09^*$	0.04

A_{syst} , brachial artery end-systolic surface; A_{diast} , brachial artery end-diastolic surface; VTI, velocity time integral; V_{syst} , systolic velocity; V_{mean} , mean velocity; V_{diast} , diastolic velocity; Q_r , brachial output; D_{O_2} , oxygen delivery; CC, cross-sectional compliance coefficient; DC, distensibility coefficient; RI, resistance index.

* $P < 0.05$.

Vasomotor indices variations in hyperoxia

Distensibility coefficient and cross-sectional compliance coefficient decreased significantly (Table 2; $P < 0.05$). RI was increased (Table 2; $P < 0.05$).

Discussion

In our study, normobaric hyperoxia was obtained using short-term breathing of 100% oxygen. The hyperoxic ventilation used increased the PaO_2 to approximately 350 mmHg, without any modifications in pH or PaCO_2 . Vasoconstrictor agents were administered in most of patients for restoring haemodynamic parameters, and thus may influence their absolute values. However, we attribute the modifications observed mainly to hyperoxia because haemodynamic status of the patients had been stable and vasoconstrictor agents' dose had been maintained for 6 h prior to inclusion and throughout the study. The analysis was based on the evolution of haemodynamic data as observed with ultrasound that is a reference tool in the non-invasive evaluation of the mechanical arterial properties. The authors have focused on the brachial artery because this artery is non-atheromatous and easy accessible to ultrasound. Moreover, changes in brachial artery might mirror changes in peripheral muscular arteries, thus could be extrapolated to the peripheral arterial circulation. We obtained satisfactory and complete echocardiographic and Doppler examinations in all patients. We have previously used this technique during experiments in healthy subjects (Rossi et al., 2004; Rossi & Boussuges, 2005). Hyperoxic ventilation was administered in a sequential rather than a randomized design because of the lack of data available in the literature about the lasting effects of hyperoxia on peripheral circulation. Moreover, as there have been no reports about how long breathing of 100% oxygen takes to obtain changes in cardiovascular status in septic patients, we chose a 20-min exposure to FiO_2 of one because it seems to be sufficient in healthy subjects to induce changes in heart rate and cardiac index (Harten et al., 2003) and in brachial vasomotor tone (Rossi & Boussuges, 2005).

In septic patients exposed to hyperoxic ventilation, we observe a reduction in brachial cross-sectional areas and an increase in MAP of about 7%. We also observe vasomotor-index variations such as an increase in pulse pressure and in RI, and a decrease in DC and in CC, showing that vasomotor tone increases. Interestingly, these results are consistent with hyperoxia-induced vasoconstriction, as we already shown in healthy subjects (Rossi & Boussuges, 2005), and with the decreased systemic vascular resistance observed after 30-min recovery at baseline FiO_2 (< 0.4) in 20 critically ill patients, septic or not, ventilated at $\text{FiO}_2 = 1$ for 30 min (Reinhart et al., 1991). In our study, brachial blood flow decreases significantly during hyperoxic exposure in agreement with the hyperoxic-induced decrease in blood flow at renal (Aber et al., 1964) and myocardial (Ganz et al., 1972) levels in humans, and at liver level in rats (Torbati et al., 1979). In haemorrhagic shock on

anaesthetized rats, inhalation of 100% oxygen has been shown to significantly increase mean arterial blood pressure and vascular resistance in the hindquarters, with a concomitant decrease in blood flow in the distal aorta and biceps femoris muscle (Bitterman et al., 1996). This may be related both to the hyperoxia-induced vasoconstriction and to an impairment of the cardiac function as suggested by the decrease in VTI we observe in the brachial artery. Hyperoxia-induced bradycardia and decreased cardiac output have been well documented in healthy subjects and in animals and have been attributed to an increase in parasympathetic tone (Lodato, 1989; Lund et al., 1999). However in our study, hyperoxia exposure does not significantly modify heart rate, which is in good accordance with a previous study (Reinhart et al., 1991). During the sepsis syndrome, sympathetically mediated heart rate variability is lower (Garrard et al., 1993), which could explain why the decrease in heart rate under hyperoxia exposure is limited. Moreover, the cardiac index of septic patients was not modified by hyperoxia exposure, but increased 10% after the end of exposure without an increase in heart rate (Reinhart et al., 1991). In subjects with normal left ventricle function, hyperoxic-induced impairment of cardiac relaxation and increment of left ventricle filling pressures have been previously reported (Mak et al., 2002). A simultaneous study of these cardiac functions in a population of septic patients may be interesting to better understand their role in reduction in hyperoxia-induced blood flow.

A significant decrease in brachial oxygen delivery is demonstrated in septic patients exposed to 20 min of hyperoxic ventilation. Thus, a hyperoxic-induced increase in arterial oxygen content does not counterbalance the decrease in brachial blood flow. This study did not address tissue oxygen utilization, and cannot derive any conclusions in regards to whole body oxygen delivery; it only provides an estimate of brachial oxygen delivery. However, the paradoxical decrease in brachial D_{O_2} is consistent with previous evidence that brief hyperoxic ventilation can substantially decrease both regional and whole body oxygen consumption in various conditions. Hyperoxic ventilation depressed in a reversible manner both the whole body and hind limb oxygen consumption during acute anaemia, or after β blocker treatment or vagotomy, in anaesthetized (Chapler et al., 1984; Persad et al., 1998) or in healthy conscious dogs (Lodato, 1989). In the same way, the decrease in V_{O_2} following a brief hyperoxic exposure has been demonstrated on myocardial (Ganz et al., 1972) and cerebral (Lambersten et al., 1959) levels in healthy subjects. This decreased V_{O_2} could be related to the decrease in D_{O_2} or to more local phenomena due to sepsis, such as disturbances in microcirculatory flow, in nutrient exchange, and mitochondrial metabolism involved by production of reactive oxygen species, acidosis, increase in tissue partial pressure of CO_2 , or hyperthermia (Chierago et al., 2006).

In this study, we show that hyperoxia induces a vasopressive response of the brachial artery during sepsis. In spite of increased arterial partial pressure of oxygen, vasoconstriction as a response to hyperoxia seems to result in a paradoxical decrease

in arterial oxygen delivery, due to an impaired arterial blood flow, at least for the upper limbs. Because of the lack of homogeneity of perfusion in vascular regions during septic shock, a full evaluation of systemic circulation is needed to confirm whether hyperoxic ventilation could impair whole oxygen delivery.

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