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Effects of short-term hyperoxia on sytemic hemodynamics, oxygen transport, and microcirculation: An observational study in patients with septic shock and healthy volunteers☆

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ABSTRACT

Purpose: To characterize the microvascular effects of a brief period of hyperoxia, in patients with septic shock and in healthy volunteers.
Materials and methods: In 20 patients with septic shock, we assessed systemic hemodynamics, sublingual microcirculation by SDF-videomicroscopy, and skin perfusion by capillary refill time (CRT), central-peripheral temperature (ΔT°), and perfusion index. Measurements were performed at baseline and after 5 min of inspired oxygen fraction of 1.00. Additionally, we studied 8 healthy volunteers, in whom hyperoxia was prolonged to 30 min.
Results: In septic patients, hyperoxia increased mean arterial pressure and systemic vascular resistance, but cardiac output remained unchanged. The only significant change in sublingual microcirculation was a decreased heterogeneity flow index (1.03 [1.01–1.07] vs 1.01 [0.34–1.05], $P = .002$). Perfused vascular density (13.1 [12.0–15.0] vs 14.0 [12.2–14.8] mm/mm^2, $P = .21$) and the other sublingual microvascular variables were unmodified. CRT and ΔT° did not change but perfusion index slightly decreased. In healthy volunteers, sublingual microcirculation and skin perfusion were stable.
Conclusions: Short-term hyperoxia induced systemic cardiovascular changes but was not associated with noticeable derangement in sublingual microcirculation and skin perfusion. Nevertheless, longer exposures to hyperoxia might have produced different results.

1. Introduction

In conditions of jeopardized tissue oxygenation, high-inspired oxygen fraction (FiO_2) is often administered to critically ill patients with the goal of improving oxygen delivery. While hyperoxia increases arterial oxygen content, this effect might be offset by the induction of vasoconstriction with subsequent reduction in cardiac output, regional perfusion, and microcirculation [1]. The final effects on tissue oxygenation are thus unpredictable.

Not unexpectedly, the therapeutic use of hyperoxia in critically ill patients is controversial. Studies performed in patients after cardiac arrest showed conflicting results [2,3]. A recent randomized controlled trial performed in vasopressor-dependent septic patients, was stopped prematurely due to serious adverse events in the hyperoxia arm [4]. A post-hoc analysis of this study showed that the detrimental effects of hyperoxia were restricted to patients with arterial lactate > 2.0 mmol/L [5]. Another clinical trial also showed that an arterial PaO_2 (PaO_2) target between 70 and 100 mmHg was associated with lower ICU mortality, compared with a target up to 150 mmHg [6]. Furthermore, a systematic review and meta-analysis showed that liberal oxygen therapy increases mortality [7].

Hyperoxia has been defined as a state in which supraphysiological levels of oxygen are inspired and/or reach the arterial circulation. A formal definition for arterial hyperoxia does not exist, albeit PaO_2 > 120 mmHg has previously been characterized as mild hyperoxia and PaO_2 > 200 mmHg as severe hyperoxia [8]. Nevertheless, a recent systematic review and metaanalysis found that hyperoxia was inconstantly defined as PaO_2 ranging from >487 to >100 mmHg [9].

Arteriolar vasoconstriction with subsequent microvascular hypoperfusion is a plausible explanation for the harmful effects of hyperoxia [10,11]. Accordingly, some experimental and clinical studies found

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that microcirculation is altered after the exposure to high FiO_2 [10,12]. The evidence, however, is inconclusive. There are conflicting reports about the magnitude of the microvascular dysfunction, the extension of affected vascular beds, and the impact on tissue oxygenation [13]. Actually, protective effects of hyperoxia on microcirculation have been reported [14]. Related to sublingual microcirculation, few studies have addressed the effects of hyperoxia. Interestingly, the findings were quite different, ranging from severe alterations to subtle changes in some microvascular variables [15-17]. Nevertheless, a comprehensive assessment that includes the measurement of red blood cell (RBC) velocity in individual microvessels is lacking. This point is particularly relevant: while hyperoxia can induce vasoconstriction and decrease capillary functional density, RBC velocity and microvascular flow might increase [13]. Consequently, tissue oxygen transport could be preserved, even in the presence of microvascular alterations. A thorough evaluation of the diffusional and convective microcirculatory variables is therefore needed for understanding the effects of hyperoxia. Moreover, there are no studies focusing on patients with septic shock. These patients might be particularly vulnerable because of preexistent microvascular dysfunction.

Our main goal was to characterize the effects of a brief period of hyperoxic ventilation on the sublingual microcirculation and the skin perfusion in both patients with septic shock and healthy volunteers. A secondary goal was the description of the effects of hyperoxia on systemic hemodynamics and oxygen transport.

2. Materials and methods

The study was approved by the Institutional Review Board (Comité de Ética en Investigaciones Biomédicas, Sanatorio Otamendi y Miroli, #15082015). Informed consent was obtained from the healthy volunteers and from the next of kin for all patients admitted to the study.

2.1. Setting

Intensive care unit located in a university-affiliated hospital.

2.2. Patients

We studied 8 healthy volunteers and 20 patients with septic shock [18]. All patients required norepinephrine to maintain a mean arterial blood pressure of at least 65 mmHg despite adequate fluid resuscitation, and had arterial lactate level higher than 2.0 mmol/L (3.7 [2.4–5.7] mmol/L) at diagnosis. They were assessed once the mean arterial pressure and norepinephrine infusion had changes lower than 10% for at least 2 h, and lactate decreased at rates >20% per 2 h. The length of septic shock before measurements, was 1 [1–2] days. Patients were mechanically ventilated in controlled mode and received infusions of midazolam and fentanyl. All patients had a systemic arterial catheter and a central venous catheter inserted. All patients were in regular sinus rhythm.

2.3. Measurements and derived calculations

On the day of measurements, epidemiological data (e.g., age, gender) were recorded and APACHE II (Acute-Physiology and Chronic-Health Evaluation II) [19] and SOFA (Sepsis-related Organ Failure Assessment) scores [20] calculated. We also registered the source of infection, the ICU and hospital mortality, the length of stay, the use of vasopressors, and the fluid balance. We measured heart rate, and arterial and central venous pressure. Cardiac output was measured by on pulse-contour analysis (Vigileo-FloTrac system, Edwards Lifesciences, Irvine. CA, USA). Arterial and central venous blood samples were analyzed for gases, hemoglobin, and O_2 saturation. Arterial lactate levels were also measured.

Systemic oxygen transport, consumption, and extraction ratio (DO_2, VO_2, and O_2ER, respectively) were calculated according to standard formulae. We also calculated central venous minus arterial PCO_2 difference ($P_{cv\text{-}a}CO_2$) and its ratio to arterial minus central venous O_2 content difference ($P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$).

2.4. Microvideoscopic measurements and analysis

The microcirculatory network was evaluated in the sublingual mucosa by means of a sidestream-dark-field (SDF) imaging device (Microscan, MicroVision Medical, Amsterdam, Netherlands) [21]. Different precautions were taken and steps followed to obtain images of adequate quality and to ensure satisfactory reproducibility. After careful removal of saliva by isotonic-saline-drenched gauze, the tip of the device was gently positioned in the sublingual area. There was no discomfort associated with the procedure. Steady images of at least 20 s were obtained while avoiding pressure artifacts through the use of a portable computer and an analog-to-digital video converter (ADVC110, Canopus Co., San Jose, CA, USA). The videos were recorded from three different areas. Video clips were stored as AVI files to allow computerized frame-by-frame image analysis. Files were later renumbered to allow their analysis by a well-trained researcher who was blind to the study allocation. Adequate focus and contrast adjustment were verified and images of poor quality discarded. The entire sequence was used to describe the semiquantitative characteristics of the microvascular flow and particularly the presence of stopped or intermittent flow.

We used an image-analysis software developed for the SDF-video images (Microscan analysis software®–AVA 3.0–MicroVision Medical, Amsterdam, Netherlands) [22] to determine the total vascular density (TVD). An analysis based on semiquantitative criteria that distinguished between no flow (0), intermittent flow [1], sluggish flow [2], and continuous flow [3] was performed on individual vessels [23]. The overall score, called the microvascular flow index (MFI), is the average of the individual values [24]. Quantitative RBC velocity was determined through the use of space-time diagrams [22]. We also calculated the proportion of perfused vessels (PPV) and the perfused vascular density (PVD) as the total vascular density multiplied by the PPV. The flow-heterogeneity index was calculated as the highest MFI minus the lowest MFI divided by the mean MFI [25].

The analysis was restricted to vessels with diameters <20 μm, whereas the vessels of higher diameter were assessed only for ruling out compression artifacts. Since flow in large arterioles and venules should be always continuous, the presence of stopped or intermittent flow in those vessels was considered as an evidence of compression artifacts. In addition, compression artifacts were rule out by briefly withdrawing and then advancing the SDF while the pattern of flow was observed. Consequently, videos with such characteristics were not considered for the assessment.

2.5. Assessment of skin perfusion

We evaluated skin perfusion by means of three different approaches: capillary refill time (CRT), central-peripheral temperature difference (ΔT°), and perfusion index.

CRT was measured by applying firm pressure by means of a slide to the distal phalanx pad of the right fourth finger, for at least 5 s. Under direct visualization, a chronometer was used to measure the time from release of the pressure to the return of normal colour. Since CRT has a poor reproducibility [26], a second observer, blind to the previous measurement, repeated the procedure. CRT was considered as the mean value of both measurements.

We also measured the second finger pad temperature by a skin thermistor and the central temperature by a rectal thermistor; ΔT° was calculated as the difference.

The perfusion index was derived from the pulse oximetry signal pulse (IntelliVue MP40 monitor, Philips Medical Systems, Boblingen, Germany), in the right third fingertip. The perfusion index is the ratio between the pulsatile and the nonpulsatile component of the light

reaching the detector of the pulse oximeter. In presence of peripheral hypoperfusion the pulsatile component decreases, and because the nonpulsatile component is unchanged, the ratio decreases [27].

2.6. Procedure

After basal measurements with a FiO_2 of 0.26 ± 0.05, FiO_2 was increased to 1.00. After 5 min, measurements were repeated. The hyperoxia was restricted to 5 min because of the concerns related to a more prolonged exposure. Brief periods are considered safe; for example, FiO_2 of 1.00 is recommended as part of preoxygenation procedure during routine endotracheal suctioning [28]. Minute ventilation was kept unchanged.

Healthy volunteers were evaluated after 20 min of resting in a semirecumbent position. A nasal mask was placed and properly adjusted. The volunteers were carefully instructed to breathe only through it. The mask was initially connected to a source of humidified ambient air at a flow of 15 L/min. After basal measurements, the source was changed to 100% O_2 at the same flow. After the increase in FiO_2, measurements were performed at 5 min, and also at 30 min to study a possible delayed effect of hyperoxia. Measurements were restricted to sublingual microcirculation and CRT. In the healthy volunteers, exposure to high FiO_2 was demonstrated by the determination of arterial blood gases after 5 min of hyperoxia, at the same time of the first microcirculatory assessment.

2.7. Data analysis

Data are expressed as mean ± SD, median [0.25–0.75 IQR], and as numbers with corresponding percentages for the qualitative variables. Normality was assessed with Kolmogorov-Smirnov test. In patients with septic shock, comparisons of continuous variables in normoxia and hyperoxia were performed by paired *t*-test or Wilcoxon signed-rank test. In healthy volunteers, parametric or nonparametric (Friedman test) repeated measures ANOVA was used, followed by post hoc tests (Newman-Keuls multiple comparison or Dunns tests). According to previous results, we calculated that 20 septic patients and 8 healthy volunteers were needed to show a decrease of 20% in the PVD, with a power of 80% and a certainty of 95% [29]. A *P* value <.05 was considered significant.

Table 1
Clinical and epidemiological characteristics of the patients.

Age, years	66 ± 15
Gender male, n (%)	13 (65)
SOFA score	9 ± 3
APACHE II score	26 ± 7
Actual ICU mortality, %	25
Actual hospital mortality, %	25
APACHE II predicted mortality, %	54 ± 21
Source of sepsis, n (%)	
Intra-abdominal	6 (30)
Respiratory	5 (25)
Urinary	3 (15)
Intravascular	3 (15)
Indeterminate	2 (10)
Central nervous system	1 (5)
Norepinephrine (μg/kg/min)	0.13 [0.10–0.21]
Fluid balance on the previous 24-h, mL	3785 [1020–5395]
Mechanical ventilation, n (%)	20 (100)
Length of septic shock before measurements, days	1 [1–2]
Intensive care unit length of stay, days	13 [8–29]
Hospital length of stay, days	27 [14–44]

Data are expressed as mean ± SD, median [0.25–075 IQR], or number (percentage).

3. Results

Epidemiological and clinical characteristics of patients are shown in Table 1.

3.1. Effects on systemic hemodynamics, blood gases and oxygen metabolism variables

In patients with septic shock, hyperoxia increased diastolic and mean arterial pressure, and systemic vascular resistance. Cardiac index and DO_2 remained unchanged, but VO_2 and O_2ER fell during hyperoxia (Table 2).

Arterial and central venous PO_2 and PCO_2 increased, and arterial and central venous pH decreased. Arterial lactate levels showed significant reductions. $P_{cv\text{-}a}CO_2$ and $P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$ increased (Table 2).

In healthy volunteers, arterial PO_2 reached 378 ± 77 mmHg after 5 min of hyperoxia. After 30 min of hyperoxia, systolic arterial pressure increased (119 ± 10 vs. 123 ± 9 mmHg, $P = .021$), and heart rate decreased (73 ± 3 vs. 67 ± 6 mmHg, $P < .05$) (Table 1 Supplementary material).

3.2. Effects on sublingual microcirculation

In both groups, there were no changes in the sublingual microvascular variables, except for an improvement in heterogeneity flow index in septic patients (Figs. 1 and 2).

3.3. Effects on skin perfusion

In septic patients, perfusion index (0.90 [0.21–2.00] vs. 0.53 [0.25–0.90], $P < .03$) decreased during hyperoxia whereas CRT (3.7 [2.2–5.5] vs. 4.2 [2.1–5.9] s, $P = .42$) and ΔT° were unchanged (8.5 [6.0–10.3] vs. 8.4 [6.8–10.9] °C, $P = .88$). In healthy volunteers, CRT

Table 2
Hemodynamics, arterial and central venous gases and oxygen saturations, and oxygen transport variables in normoxia and hyperoxia.

Variable	Normoxia	Hyperoxia	*P*-value
Heart rate (beats/min)	94 ± 18	89 ± 21	0.08
Systolic arterial pressure (mm Hg)	115 ± 15	111 ± 37	0.60
Diastolic arterial pressure (mm Hg)	56 ± 10	59 ± 12	<0.02
Mean arterial pressure (mm Hg)	76 ± 8	81 ± 11	<0.02
Central venous pressure (mm Hg)	10 ± 3	10 ± 3	0.11
Cardiac index (L/min/m^2)	2.98 ± 0.84	2.93 ± 0.87	0.63
Systemic vascular resistance (dynes/s/cm^{-5})	1003 ± 282	1108 ± 311	<0.001
Arterial pH	7.31 ± 0.10	7.30 ± 0.10	0.12
Arterial PCO_2 (mm Hg)	40 ± 11	41 ± 12	<0.03
Arterial PO_2 (mm Hg)	84 ± 27	329 ± 86	<0.00001
Arterial O_2 saturation	0.95 ± 0.04	0.99 ± 0.01	<0.00001
Central venous pH	7.28 ± 0.09	7.26 ± 0.08	<0.003
Central venous PCO_2 (mm Hg)	45 ± 11	47 ± 12	<0.001
Central venous PO_2 (mm Hg)	47 ± 11	76 ± 41	<0.001
Central venous O_2 saturation	76 ± 9	87 ± 11	<0.00001
Arterial lactate (mmol/L)	1.8 [1.1–2.0]	1.5 [1.0–1.8]	<0.004
Hemoglobin (g/100 mL)	9.3 ± 2.1	9.2 ± 2.1	0.27
Arterial O_2 content (mL/L)	12.1 ± 2.3	13.2 ± 2.7	<0.0001
Central venous O_2 content (mL/L)	9.7 ± 2.5	11.1 ± 3.2	<0.0001
Arterial-central venous O_2 content (mL/L)	2.3 ± 1.1	2.3 ± 1.4	0.27
O_2 transport (mL/min/m^2)	357 ± 125	386 ± 153	0.10
O_2 consumption (mL/min/m^2)	68 ± 24	59 ± 27	<0.05
O_2 extraction ratio	0.20 ± 0.10	0.18 ± 0.12	<0.01
Central venous-arterial PCO_2 (mm Hg)	6 ± 2	7 ± 2	<0.03
Central venous-arterial PCO_2/ arterial-central venous O_2 content difference	2.63 ± 1.00	4.34 ± 3.37	<0.03

Data are expressed as mean ± SD or median [0.25–075 IQR]. *P*-values are the results of paired *t*-test or Wilcoxon signed rank test.

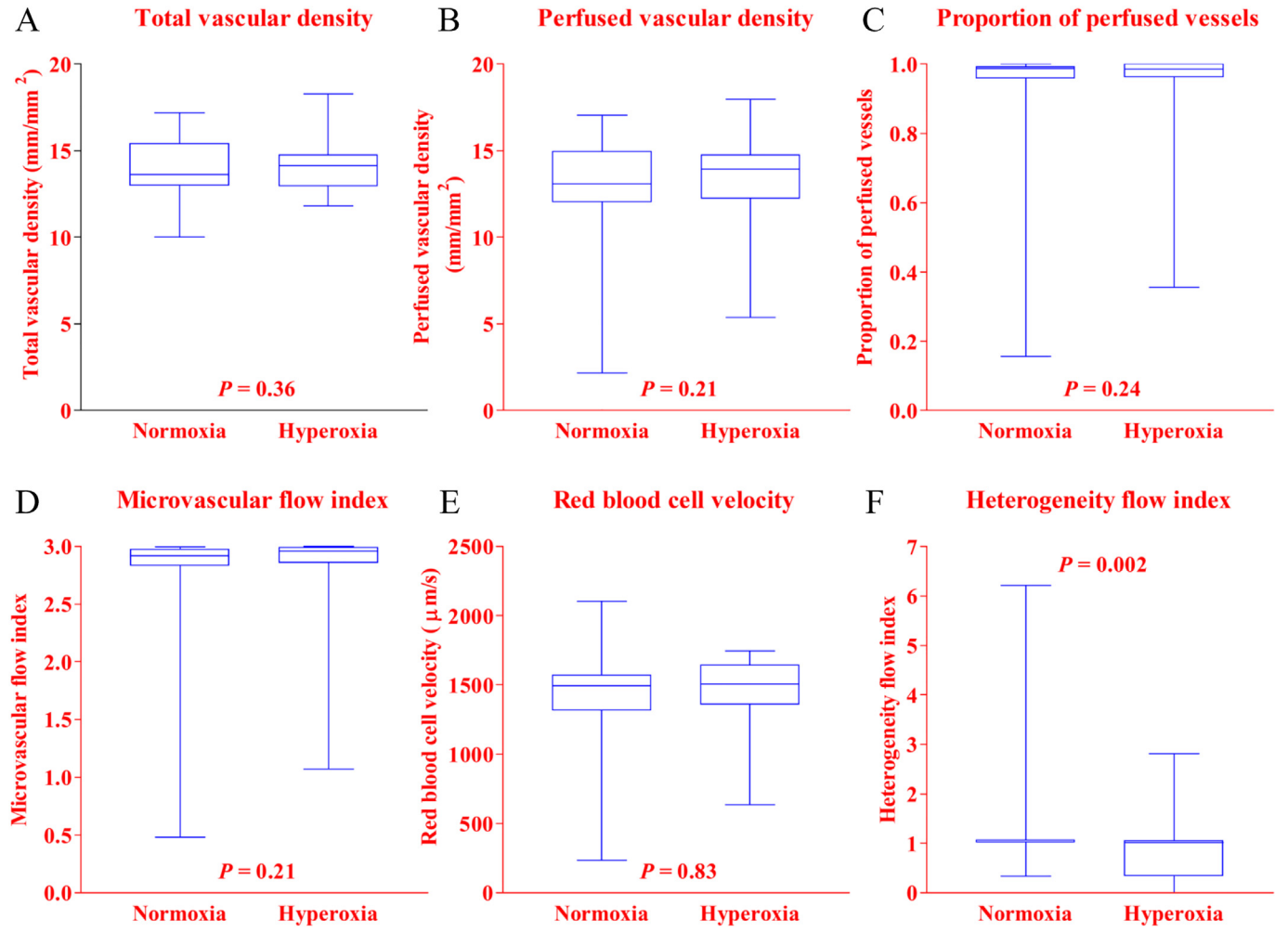

Fig. 1. Sublingual microcirculatory variables in normoxia and hyperoxia, in patients with septic shock. Panel A: Total vascular density. Panel B: Perfused vascular density. Panel C: Proportion of perfused vessels. Panel D: Microvascular flow index. Panel E: Red blood cell velocity. Panel F: Heterogeneity flow index. *P*-values are the results of Wilcoxon signed rank test. The limits of the boxes are the 25th and 75th percentiles (IQR). The line in the middle of the box is the median. The whiskers are the minimum and the maximum values.

(2.6 [1.3–3.2] vs. 1.7 [1.3–2.2] vs. 1.9 [1.3–2.4] s, $P = .62$) were also unmodified (Figs. 1 and 2 Supplementary material).

4. Discussion

The main finding of this study was that short-term hyperoxia was not associated with manifest derangements in tissue perfusion in either patients with septic shock or in healthy volunteers. Differently to previous reports on normal subjects and hemodynamically stable critically ill patients, hyperoxia did not induce any derangement in sublingual microcirculation. Concerning skin perfusion, only perfusion index decreased in septic patients, whereas CRT and ΔT° were preserved.

As shown by the high arterial PO_2 values, systemic hyperoxia was effectively reached in patients with septic shock and in healthy volunteers. Although hyperoxia duration was brief, changes in systemic hemodynamics and oxygen metabolism arose. As repeatedly shown in experimental models [10,11], hyperoxia consistently provokes arteriolar vasoconstriction. Yet the impact on systemic hemodynamics could be different, depending on several factors such as the studied species, level of anesthesia or sedation, or the underlying condition. In our septic patients, vasoconstriction resulted in increased blood pressure, unchanged cardiac output, and increased systemic vascular resistance. In healthy volunteers, there were increases in systolic blood pressure and decreases in heart rate. A systematic review and meta-analysis found that hyperoxia reduces cardiac output and increases systemic vascular resistance, and slightly increases mean arterial pressure in healthy volunteers and nonhospitalized patients with heart failure [1]. In septic patients a similar trend was observed, but the changes did not reach statistical significance [1].

Notwithstanding the comprehensive quantitative approach to sublingual microcirculation, we could not demonstrate any derangements induced by hyperoxia. Diffusional and convective determinants of microvascular oxygen transport were unaltered. Sublingual RBC velocity, which is a key perfusion variable that has not been assessed in previous studies, remained remarkably unchanged. On the contrary, patients with septic shock decreased microvascular heterogeneity during hyperoxia. Unlike our findings, some studies showed hyperoxia–associated derangements in sublingual microcirculation. In healthy volunteers, an observational study showed severe alterations, such as the decrease in the PPV from 92 to 66%, with no changes in TVD or muscle microvascular reactivity [15]. Accordingly, an experimental study found that 100% O_2 decreased PVD by 20% but did not change the PPV [30]. In healthy volunteers, a progressive increase in FiO_2 was associated with stepwise reductions in sublingual microcirculation [16]; yet the changes were subtle (i.e., the PPV fell from 0.98 to 0.93 and TVD from 8.0 to 6.9 vessels/mm). In hemodynamically stable critically ill patients, hyperoxia mildly decreased TVD but did not affect PPV [17]. After coronary artery bypass grafting, short-term hyperoxia had no noticeable effects on most of the sublingual microvascular variables [31]. Although the effects of hyperoxia have not been previously in patients with septic

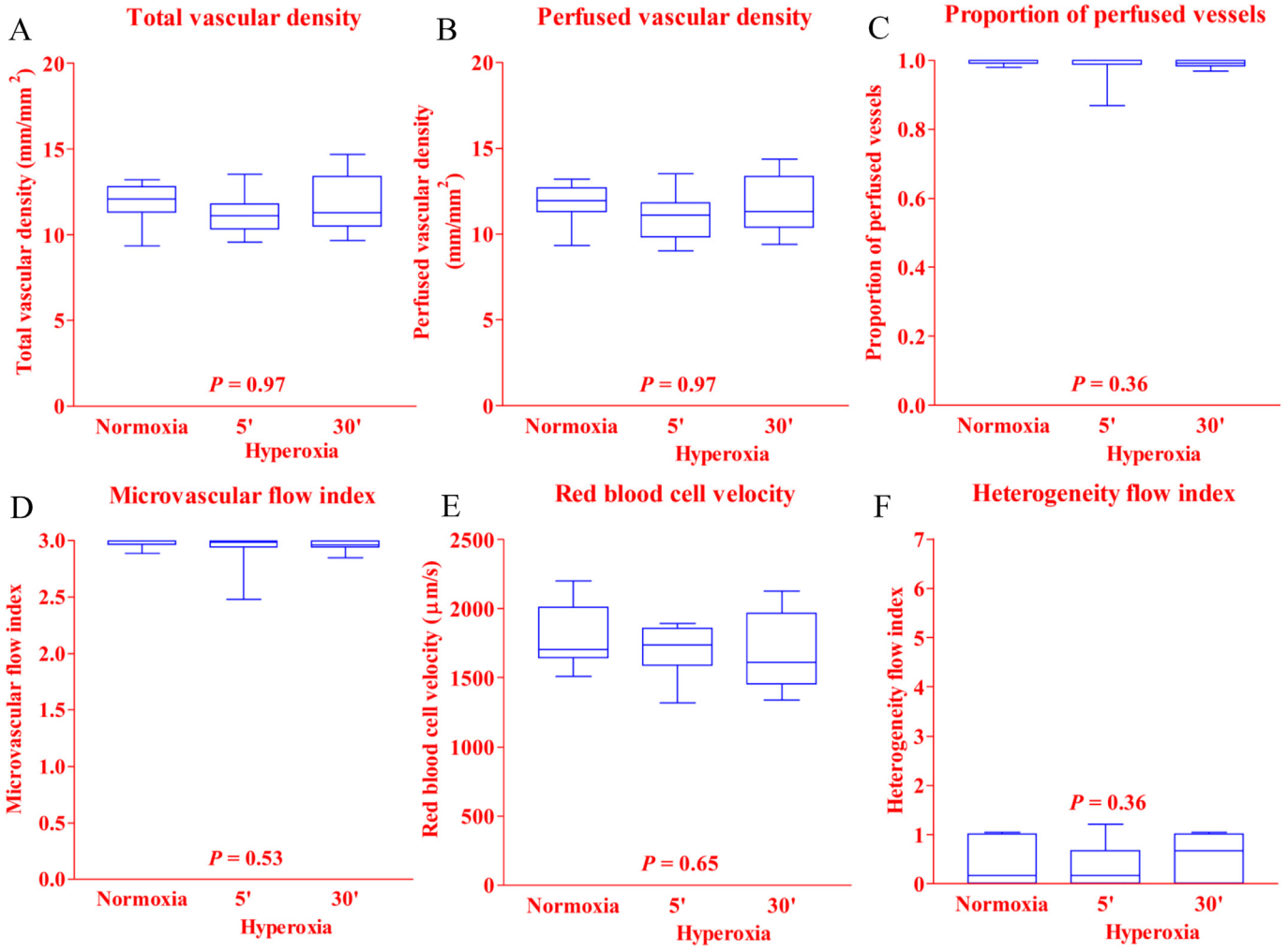

Fig. 2. Sublingual microcirculatory variables in normoxia and hyperoxia, in healthy volunteers. Panel A: Total vascular density. Panel B: Perfused vascular density. Panel C: Proportion of perfused vessels. Panel D: Microvascular flow index. Panel E: Red blood cell velocity. Panel F: Heterogeneity flow index. *P*-values are the results of nonparametric repeated measures ANOVA (Friedman test). The limits of the boxes are the 25th and 75th percentiles (IQR). The line in the middle of the box is the median. The whiskers are the minimum and the maximum values.

shock, an experimental found beneficial effects on sublingual perfusion [32]. In the setting of reperfusion injury, hyperoxia elicits favorable actions on mesenteric and pleural microcirculation [14]. To sum up, the varied reported effects of hyperoxia on microcirculation might be dependent on the underlying condition. The most striking difference with the previous studies, however, was the short-term exposure to hyperoxia in our study. It can be argue that a longer period of hyperoxia might have induced different effects. Nevertheless, experimental models showed that vasoconstriction begins within 2 min from the start of 100% O_2 inspiration [33]. Likewise, a clinical study demonstrated that the first 2 min of hyperoxia were associated with early and consistent changes [17]. Also, a continuous assessment of retinal perfusion in normal subjects showed that vascular derangements completely developed in the first 4 min while there were no further modifications in the following 21 min [12]. In addition, a longer period of hyperoxia also failed to modify sublingual microcirculation in healthy volunteers. Consequently, our results do not seem dependent on the short time of observation.

In relation to skin perfusion, we only found a small reduction in the perfusion index but not in CRT and ΔT°. An investigation that used laser Doppler imaging in normal volunteers found that vasoconstriction only developed in high flow vessels [34]. Thus, the skin seems to be a vascular territory insensitive to hyperoxia.

The effects of hyperoxia on other microvascular beds, as well as the magnitude of the involvement are controversial. Experimental studies found substantial microcirculatory derangements in the skin muscle [13,34]. Although a 48% reduction in the PVD has been described [33], slighter decreases (26%) were found in the same experimental preparation [13]. On the other hand, thenar near-infrared spectroscopy along with a vascular occlusion test showed preserved muscle microvascular oxygenation and reactivity in healthy volunteers and critically ill patients [15,17].

Hyperoxia reduced O_2ER and VO_2 and did not affect DO_2. Since VO_2 was calculated from central instead mixed venous blood, absolute values should be cautiously interpreted. In spite of this, its behavior, together with the decrease in O_2ER, is consistent with previous reports [35]. Contrasting with a previous experimental study that showed an increased hyperlactatemia in response to hyperoxia [32], we found small but significant decreases in blood lactate levels. Although this effect might be attributed to improved tissue oxygenation, a direct effect on glycolysis could also be present. Hyperoxia decreases muscle glycogenolysis, lactate production, and lactate efflux during steady-state exercise, resulting in lower arterial lactate levels [36]. In normal subjects, hyperoxia was associated with reductions in lactate levels from 1.0 to 0.7 mmol/L [16].

Despite the fact that cardiac output, DO_2, and tissue perfusion were not impaired, and lactate levels decreased during hyperoxia, $P_{cv\text{-}a}CO_2$ and $P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$ increased. It has been suggested that $P_{cv\text{-}a}CO_2$ reflects microvascular flow [37] and $P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$ is a surrogate for

respiratory quotient and tissue oxygenation [38,39]. In our study, however, these increases might be completely explained by Haldane effect [40]. Since the increment in central venous O_2 saturation was almost 3 times those of arterial O_2 saturation, the increases in central venous PCO_2 were higher than those of arterial PCO_2, resulting in elevations in $P_{cv\text{-}a}CO_2$ and $P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$. Although hyperoxia might actually increase the respiratory quotient measured by expired gases, this effect probably results from metabolic changes, and not from tissue hypoxia [41]. Therefore, our results give additional support for the compelling experimental and clinical evidence that show that such variables are misleading indicators of tissue perfusion and oxygenation [42,43].

Our study has limitations. As previously discussed, the duration of the hyperoxia period was brief; longer exposures might have produced different results. Another limitation is that the assessment of tissue perfusion was limited to the sublingual and skin territories. Since each vascular bed can display a distinctive microcirculatory pattern [44], the presence of hypoperfusion cannot be ruled out in other territories. Besides, hemodynamic measurements in healthy volunteers were limited to blood pressure and heart rate. Also, septic patients only exhibited mild sublingual microcirculatory disturbances. This was a probable consequence of measurements taken after 24-h of successful resuscitation [45]. Hence, different effects of hyperoxia on a more severe disrupted microcirculation cannot be ruled out. Finally, the calculation of VO_2 by means of central venous blood could be misleading. Central venous O_2 saturation not only is systematically higher than mixed venous O_2 saturation but also can change in an opposite direction [46].

5. Conclusions

In response to hyperoxia, sublingual microcirculation and skin perfusion did not show overt abnormalities and were globally preserved. Since some degree of arteriolar vasoconstriction developed in patients with septic shock, as highlighted by the increase in systemic vascular resistance, microvascular hypoperfusion might have been present in other vascular beds.

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Availability of data and material

The datasets used during the current study are available from the corresponding author on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.05.021.

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