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Microvascular effects of oxygen and carbon dioxide measured by vascular occlusion test in healthy volunteers

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ABSTRACT

Background: Changes in near-infrared spectroscopy-derived regional tissue oxygen saturation (StO_2) during a vascular occlusion test (VOT; ischemic provocation of microcirculation by rapid inflation and deflation of a tourniquet) allow estimating peripheral tissue O_2 consumption (desaturation slope; DS), vascular reactivity (recovery slope; RS) and post-ischemic hyperperfusion (AUC-H). The effects of isolated alterations in the inspiratory fraction of O_2 (FiO_2) and changes in expiratory CO_2 remain to be elucidated. Therefore, in this secondary analysis we determined the effects of standardized isolated instances of hypoxia, hyperoxia, hypocapnia and hypercapnia on the VOT-induced StO_2 changes in healthy volunteers ($n = 20$) to establish reference values for future physiological studies.

Methods: StO_2 was measured on the thenar muscle. Multiple VOTs were performed in a standardized manner: i.e. at room air (baseline), during hyperoxia (FiO_2 1.0), mild hypoxia ($FiO_2 \approx 0.11$), and after a second baseline, during hypocapnia (end-tidal CO_2 ($etCO_2$) 2.5–3.0 vol%) and hypercapnia ($etCO_2$ 7.0–7.5 vol%) at room air. Differences in DS, RS, and AUC-H were tested using repeated-measures ANOVA.

Results: DS and RS remained constant during all applied conditions. AUC-H after hypoxia was smaller compared to hyperoxia (963 %*sec vs hyperoxia 1702 %*sec, $P = 0.005$), while there was no difference in AUC-H duration between hypoxia and baseline. The StO_2 peak (after tourniquet deflation) during hypoxia was lower compared to baseline and hyperoxia (92 % vs 94 % and 98 %, $P < 0.001$).

Conclusion: We conclude that in healthy volunteers at rest, common situations observed during anesthesia and intensive care such as exposure to hypoxia, hyperoxia, hypocapnia, or hypercapnia, did not affect peripheral tissue O_2 consumption and vascular reactivity as assessed by VOT-induced changes in StO_2. These observations may serve as reference values for future physiological studies.

Trial registration: This study represents a secondary analysis of an original study which has been registered at ClinicalTrials.gov nr: NCT02561052.

1. Introduction

In perioperative care, several conditions or interventions may induce changes in oxygen (O_2) and carbon dioxide (CO_2) concentrations in blood, which may eventually lead to local microcirculatory changes mainly to adapt to the metabolic cellular demands in order to maintain tissue oxygenation (Mirro et al., 1992; Laffey and Kavanagh, 2002). E.g., during hypoxia, cells form H^+ ions, lactic acid and pro-inflammatory cytokines as a by-product of metabolism may cause local vasodilation (Ely et al., 1982; Puscas et al., 2000). In contrast, hyperoxia causes local vasoconstriction (Brugniaux et al., 2018), probably resulting from the generation of reactive oxygen species (Jamieson et al., 1986). Changes in alveolar CO_2 concentrations leading to hypocapnia or hypercapnia may additionally influence local vascular tone resulting in either

Abbreviations: ABP, arterial blood pressure; AUC-H, area under the curve of the post-ischemic hyperperfusion phase; CO_2, carbon dioxide; DO_2, oxygen delivery; DS, desaturation slope; $etCO_2$, end-tidal CO_2; FiO_2, fraction of inspired O_2; IQR, interquartile range; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; O_2, oxygen; $PaCO_2$, partial arterial carbon dioxide pressure; PaO_2, partial arterial oxygen pressure; RS, recovery slope; SaO_2, arterial oxygen saturation; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; SpO_2, peripheral oxygen saturation; StO_2, tissue oxygen saturation; VOT, vascular occlusion test.

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vasoconstriction or vasodilation, respectively (Laffey and Kavanagh, 2002; Ely et al., 1982).

Near-infrared spectroscopy (NIRS) is a non-invasive monitoring technique, which allows measuring tissue oxygen saturation (StO_2). NIRS monitoring is increasingly used in the perioperative and critical care setting (Biedrzycka and Lango, 2016; Scheeren et al., 2019; Vos et al., 2019a), e.g. for cerebral oxygen saturation monitoring (Lee et al., 2018; Weber and Scoones, 2019; Modestini et al., 2020) and for estimating tissue or organ perfusion by an *indirect means* (Scheeren, 2016). NIRS can be combined with a vascular occlusion test (VOT) (Vos et al., 2019a), which entails inflating a tourniquet rapidly above systolic blood pressure proximal to the NIRS StO_2 measurement site and subsequently deflating the tourniquet. This test temporarily stops blood flow to the affected extremity and produces typical changes in StO_2 (Fig. 1), in which the decreasing part (desaturation slope, DS) resembles peripheral tissue O_2 consumption after stop of blood supply (Orbegozo Cortés et al., 2015a). The recovery slope (RS) resembles vascular reactivity, i.e. the ability to vasodilate and/or recruit capillaries after tourniquet deflation and return of blood flow (Nurkiewicz et al., 2010). Subsequently, StO_2 increases following ischemia as an indication of post-ischemic hyperperfusion. The VOT StO_2 characteristics have been studied in different patient categories, e.g. after trauma (Gómez et al., 2008; Guyette et al., 2012; Domizi et al., 2019; Duret et al., 2015), perioperatively (Feldheiser et al., 2016; Bernet et al., 2011) and in critically ill patients (Orbegozo Cortés et al., 2016), and were associated with relevant clinical outcomes such as shock survival or norepinephrine dependency (Orbegozo Cortés et al., 2016; Conrad et al., 2015; Mesquida et al., 2012). Still, given that changes in respiratory concentrations of O_2 and CO_2 itself can induce local circulatory changes, it is important to assess their effects on VOT StO_2 characteristics. Therefore, we determined the effects of standardized isolated hypoxia, hyperoxia, hypocapnia, and hypercapnia on the VOT-induced changes in StO_2 in healthy volunteers, in order to provide reference values for future physiological studies.

2. Material and methods

The current study is a secondary analysis of an prospective interventional study in which the Oxygen Reserve Index was validated in healthy volunteers by collecting optical data using the Rainbow SET Pulse CO-Oximeter (Masimo Corp., Irvine, USA) (Vos et al., 2019b).

The original study was approved by the local medical ethical committee of Brabant, The Netherlands (NL52290.028.15/P 1506) and registered at ClinicalTrials.gov nr: NCT02561052.

2.1. Study procedures

A detailed description of the original study has been previously published (Vos et al., 2019b). Volunteers were connected to a standard vital signs monitor (Phillips IntelliVue MP70; Philips, Eindhoven, the Netherlands) for monitoring pulse oximetry and electrocardiography. The left radial artery was cannulated to monitor arterial blood pressure (ABP) invasively and to collect samples for arterial blood gas measurements, which were analysed using the Rapidpoint 405 Co-oximeter (Siemens, Munich, Germany). This device performs autocalibration every 6 h.

A semi-open spontaneous breathing system was used, with a tight fitted facemask that was placed on the head of the volunteers and fixed with rubber bands. Gas mixture administration was manually regulated and standardized based on the inhalation concentrations that were measured using a gas measurement module (Philips G7, Eindhoven, the Netherlands), which was calibrated on a daily basis.

2.2. Tissue oxygen saturation assessment and VOT

Measurements were performed at room temperature (20–23 °C). The InSpectra monitor (Model 650, Hutchinson Technology Inc., Hutchinson, USA) was used to measure StO_2 continuously, with the sensor placed on the thenar eminence per manufacturer instructions (Hutchinson Technology Inc., 2010). A pneumatic band was placed on the ipsilateral upper arm and was inflated when VOT started to 60 mmHg above the volunteer's own systolic blood pressure. The cuff was deflated either when StO_2 was <40 % or after 4 min of ischemia, whatever came first (Lipcsey et al., 2012).

Several VOTs (T1–T7) were performed at standardized time points during the study. At baseline (T1), the volunteers were breathing room air (fraction of inspired O_2 (FiO_2) = 0.21). After T1 a tight-fitting facemask was placed on the head of the volunteers and connected to a breathing circuit. T2 was performed during hyperoxia, with FiO_2 set at 1.0. Subsequently, T3 was performed during hypoxia, when the volunteers were breathing a mixture of nitrogen and air, in order to reach a peripheral oxygen saturation (SpO_2) level of just below 90 % as measured by pulse oximetry (approximately at an FiO_2 of 0.11). After a resting phase of approximately 5 min, a second baseline VOT was performed (T4), followed by a VOT after a second phase of hyperoxia (FiO_2

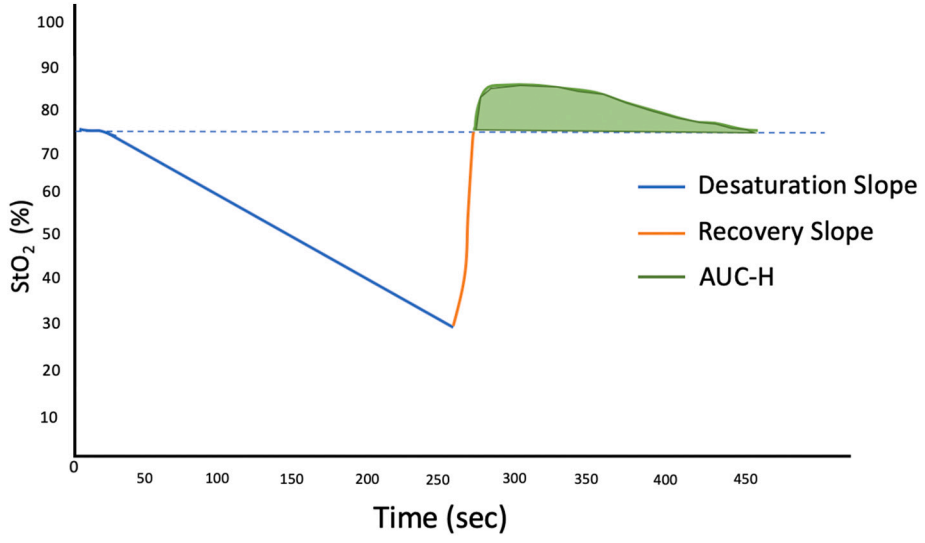

Fig. 1. Overview of StO_2 curve during a VOT, as an example of T3.
VOT: vascular occlusion test. StO_2: tissue oxygen saturation in %. Blue is the desaturation slope (i.e. tissue oxygen consumption, phase 1), orange the recovery slope (i.e. vascular reactivity, phase 2), and green the area under the curve of the post-ischemic hyperperfusion phase (phase 3).

1.0; T5). Finally, end-tidal CO_2 ($etCO_2$) was modified under normoxia: both by asking the volunteers to hyperventilate inducing hypocapnia (target $etCO_2$ 2.5–3.0 vol%; T6), and by partial rebreathing and adding external medical CO_2 to the inspiratory gas mixture (target $etCO_2$ 7.0–7.5 vol%; T7) to induce hypercapnia. The VOT was stopped in case the participants indicated discomfort. T1–3 were defined as part 1 of the experiment and T4–7 as part 2. At the end of each plateau phase (return to "resting value" StO_2), an arterial blood gas sample was drawn for measurement to determine pH, partial arterial oxygen pressure (PaO_2), partial arterial carbon dioxide pressure ($PaCO_2$), arterial oxygen saturation (SaO_2) and arterial bicarbonate concentration (HCO_3^-).

2.3. Data recording and statistical analysis

All continuous and discrete data were imported in Microsoft Excel 2018 (Microsoft, Redwood, USA) after careful synchronization. An automated algorithm was used for analysing the StO_2 changes during VOT application. Here, the VOT was divided into three phases, see Fig. 1 for an overview of the VOT StO_2 characteristics.

Phase 1 was defined as the StO_2 desaturation slope (DS; decline in %/min), which started at the beginning of inflation of the tourniquet and ended at the lowest StO_2 value before deflating the tourniquet.

Phase 2 represents the StO_2 recovery slope (RS; incline in %/sec), which started at the lowest StO_2 value after deflating the tourniquet and ended when the StO_2 reached again the pre-VOT StO_2. The area under the curve of the post-ischemic hyperperfusion phase (AUC—H, in %*sec) represents phase 3 of the VOT.

The AUC-H composed of the period of overshoot of StO_2 (started at the end of RS when StO_2 reached its "resting value" and inclined further till decrease and return to "resting value" StO_2). In case StO_2 remained above the "resting value" of that VOT for >5 min, the first closest value with an approximate deviation of 2 % of the "resting value" StO_2 was defined as the end of the post-ischemic hyperperfusion phase.

At the time of setting up the original study, Oxygen Reserve index data were not available for calculating a sample size (Vos et al., 2019b). The inclusion of 20 subjects in a repeated-measures design was then deemed sufficient for assessing the Oxygen Reserve index–PaO_2 relationship. For the present study we did not perform a sample size calculation either but included all available data from the 20 volunteers for the post-hoc analysis.

Statistical analysis was performed using Microsoft Excel 2018 (Microsoft, Redwood, USA) and SPSS (version 25 (IBM Inc., 2017, USA). Normal data distribution was assessed using the Lilliefors test. Based the normality assessment, data was either presented as mean ± SD or median (interquartile range; IQR). A paired samples *t*-test was used to determine whether heart rates or blood pressures were altered before and after each VOT. Statistical significance was set at $P < 0.05$ for the paired samples *t*-test. With the use of a Friedman test we determined the differences in the FiO_2 concentrations between T1–T3 and the different $etCO_2$ concentrations between T4, T6 and T7. We also used the Friedman test for hyperperfusion duration and peak StO_2. When this test was significant, we performed post-hoc analyses to determine which means where significantly different.

For the VOT characteristics (i.e. the pre-VOT StO_2, DS, RS and AUC—H) a one-way repeated measures ANOVA was performed to assess whether there were differences between the various alterations in FiO_2 and $etCO_2$ at timepoints T1–T3 and at timepoints T4–T7. A Greenhouse-Geisser correction was used when the assumption of sphericity was violated in the one-way repeated measures ANOVA, and when significance was found, a Bonferroni post-hoc test was used to determine which means where significantly different. To correct for multiple comparisons a Bonferroni correction was performed after the Friedman test and the one-way repeated measures ANOVA.

3. Results

Twenty healthy volunteers (5 male, 15 female) were included. The median (IQR) age of the volunteers was 22 (21–24.8) years and body mass index was 23.9 (21.4–26.0) kg^{-1} m^{-2}. A total of 133 VOTs were performed. Seven VOTs could not be finalized due to discomfort: in one subject during T3 and in six subjects during T7. The time between the VOTs of the first timepoints were: T1–T2: 32,8 min (30,6 min–40,1 min) and T2–T3: 28,8 min (28,6 min–30,5 min). The first and second set of time point had a period of 5,7 min (5,5 min–6,3 min) seconds between T3 and T4. For the second timepoints the time between the VOTs were: T4–T5: 26,9 min (26,8 min–27,3 min), T5–T6: 11,2 min (10,9 min–11,7 min), T6–T7: 6,3 min (5,8 min–6,9 min).

In general, the FiO_2 concentrations at T2 the FiO_2 concentration was higher than at T1 and T3 (both $P < 0.001$). The FiO_2 concentration at T3 was lower than at T1 ($P < 0.001$). The $etCO_2$ concentrations were significantly different between T4, T6 and T7 ($P < 0.001$), at T6 the $etCO_2$ concentrations were lower than at T4 and T7 ($P < 0.001$ and $P = 0.001$, respectively). Additionally, the $etCO_2$ concentrations at T7 were higher than at T4 ($P = 0.002$), see Table 1. During T7 the heart rate increased, while during the first baseline T1 the heart rate decreased before and after the VOT. The mean arterial pressure (MAP) only decreased during T3, while there were no changes in MAP or heart rate before and/or after each applied VOT (Table 2). We found a substantial variability in the observed DS, RS and AUC-H data for all interventions that were performed (see Additional file 1).

Baseline StO_2 at T2 was higher compared to that at T1 and T3 (86% ± 5 % vs. 82 % ± 6 % and 83 % ± 5 %, respectively, both $P < 0.001$). Neither the DS nor the RS were altered during hypoxia (T3) and hyperoxia (T2), when compared with their respective baseline values measured during normoxia (T1), Table 3. The AUC-H differed between T1–T3 ($P = 0.005$), after performing the post-hoc analyses we found that there was no difference between the AUC-H of T1 and T2 and that of T1 and T3. In contrast, the AUC-H of T3 was smaller compared to the AUC-H of T2 (AUC-H (median (IQR) T3: 963 %*sec (485–1570) vs. T2: 1702 %*sec (891 - 2459)).

The duration of the AUC-H was shorter at T6 as compared to T4 and T5 (129 s vs. both 192 s). The duration of the AUC-H at T7 was also shorter as compared to solely T4 (136 s vs. 192 s). The StO_2 peak of both T1 and T2 were higher than T3, while the StO_2 peak of T1 was lower than that of T2. The StO_2 peak of T5 was higher than those of T4, T6 and T7 (Table 4).

3.1. Effects of alteration(s) in inspiratory or expiratory CO_2 concentration on VOT characteristics

There were no significant differences in the DS, RS or AUC-H values in T6 (hypocapnia) or T7 (hypercapnia), when compared to the respective baseline values (T4) (Table 3).

4. Discussion

In perioperative care and in the ICU, multiple clinical conditions or procedures may induce changes in a patient's alveolar O_2 and CO_2. These instances may lead to alterations in blood concentrations of O_2 (hypoxemia, hyperoxemia) or CO_2 (hypocapnia, hypercapnia), to which the microcirculation should adapt. In this study, we assessed the influence of specific interventions leading to isolated instances of hypoxia, hyperoxia, hypocapnia and hypercapnia on changes in tissue oxygenation in response to sudden ischemia by means of a VOT. Interestingly, none of these interventions affected tissue oxygen consumption or vascular reactivity as reflected by the VOT DS and RS, respectively. However, we did find that the AUC-H was smaller during hypoxia compared to hyperoxia and normoxia. Importantly, we observed substantial variability in the observed DS, RS and AUC-H data for all interventions that were performed (Additional file 1). The variability observed may limit

Table 1
Oxygen inhalation concentrations, end-tidal carbon dioxide, and the arterial blood gas values taken during the different VOTs. Data are given as median or median (IQR).

T	FiO_2	$etCO_2$	pH	PaO_2	$PaCO_2$	SaO_2	HCO_3^-
1 (1st baseline)	0.21	–	7.43 (7.42–7.44)	13.3 (13.0–13.9)	5.0 (4.7–5.3)	98.1 (97.8–98.3)	24.5 (22.6–25.1)
2 (hyperoxia)	0.98 (0.97–0.99)*	37 (35–39)	7.44 (7.43–7.44)	80.1 (77.1–82.9)	4.5 (4.2–5.8)	99.7 (99.7–99.8)	22.5 (21.2–22.9)
3 (hypoxia)	0.11 (0.11–0.11)**	36.5 (34–38)	7.44 (7.43–7.46)	6.8 (6.5–7.1)	4.7 (4.2–5.1)	87.9 (86.3–90.0)	23.1 (21.6–24.1)
4 (2nd baseline)	0.21	37 (34–40)	7.42 (7.40–7.42)	12.3 (11.2–12.9)	4.8 (4.5–5.3)	97.3 (96.6–97.7)	22.5 (21.4–24.4)
5 (hyperoxia)	0.98 (0.97–0.99)	36 (35–37)	7.43 (7.42–7.45)	82.0 (78.2–82.8)	4.5 (4.1–5.0)	99.8 (99.7–100.0)	22.0 (20.3–23.9)
6 (hypocapnia)	0.20 (0.20–0.21)	31 (29–32)#	7.48 (7.44–7.50)	16.2 (14.8–16.8)	4.1 (3.6–4.5)	98.6 (98.4–99.0)	22.2 (20.4–23.2)
7 (hypercapnia)	0.19 (0.19–0.20)	56 (53–57)##	7.32 (7.30–7.34)	17.7 (16.5–18.0)	6.8 (6.3–7.2)	98.7 (98.4–98.7)	25.0 (23.4–26.6)

VOT: vascular occlusion test. T: number of the VOT. FiO_2: fractional inspired oxygen concentration. $etCO_2$: end-tidal carbon dioxide in mmHg. PaO_2: arterial oxygen pressure in kPa. $PaCO_2$: arterial carbonic dioxide pressure in kPa. SaO_2: Arterial oxygen saturation in %. HCO_3^-: arterial bicarbonate concentration in mmol L^{-1}.
* Higher than T1 and T3 ($P < 0.001$).
** Lower than T1 ($P < 0.001$).
# Lower than T4 and T7 ($P < 0.001$ and $P = 0.001$ respectively).
Higher than at T4 ($P = 0.002$).

Table 2
Relevant hemodynamic variables of subjects before and after each VOT. Data are given as mean ± SD, rounded to whole numbers.

T	HR		*P*	MAP		*P*
	Before	After		Before	After	
1 (1st baseline)	76 ± 13	73 ± 15	0.006*	84 ± 9	87 ± 10	0.61
2 (hyperoxia)	69 ± 13	70 ± 13	0.11	91 ± 19	87 ± 10	0.21
3 (hypoxia)	83 ± 15	84 ± 16	0.31	88 ± 10	85 ± 10	0.05*
4 (2nd baseline)	69 ± 12	70 ± 13	0.92	86 ± 10	85 ± 10	0.67
5 (hyperoxia)	70 ± 14	68 ± 13	0.25	87 ± 11	88 ± 11	0.53
6 (hypocapnia)	84 ± 18	81 ± 17	0.053	91 ± 13	92 ± 10	0.62
7 (hypercapnia)	78 ± 16	85 ± 17	0.006*	104 ± 12	105 ± 10	0.85

VOT: vascular occlusion test. T: number of the VOT. HR: heart rate (beats/min). MAP: mean arterial pressure (mmHg).
Effects of alteration(s) in inspiratory O_2 concentration on VOT characteristics.
* Significant difference in value before and after VOT.

the use of VOT should it be used for clinical decision-making. The observed data may serve as reference values for future physiological studies.

4.1. Tissue oxygen consumption

The DS (as a marker of tissue oxygen consumption) did not change during hypoxia in our study. In high-altitude conditions, i.e. in subjects receiving hypobaric hypoxia, DS remained unaltered as well (Martin et al., 2013). An explanation for an absence of any effect of hypoxia on the DS might be that the 'critical' oxygen delivery (DO_2) value (which is the cut-off value below which O_2 delivery fails to satisfy metabolic demands) (Sharma et al., n.d.; Lieberman et al., 2000) was not reached during our interventional study in healthy volunteers. In other words, O_2 supply to the thenar muscle remained above the critical DO_2 threshold despite moderate hypoxic challenge, as volunteers were healthy with good cardiopulmonary function and remained at rest during the experiments. Importantly, it must also be considered that the VOT during hypoxia was performed after the baseline VOT and hyperoxia VOT (Krumschnabel et al., 2000; Buttgereit and Brandt, 1995). Due to multiple consecutive hypoxic events, a process called 'ischemic preconditioning' (Orbegozo Cortés et al., 2015a) could develop in the peripheral muscular tissues. In this case the muscle cells protect themselves from apoptosis by requiring less oxygen, due to a decrease in the production of non-essential proteins (Krumschnabel et al., 2000; Buttgereit and Brandt, 1995). We speculate that, next to not reaching the critical DO_2 threshold, this process of ischemic preconditioning could be a reason for not finding an effect of hypoxia on the DA since the baseline

Table 4
Overview of duration of the post-ischemic hyperperfusion phase and the peak StO_2 for each performed VOT. Data are given as median (IQR).

T	Post-ischemic hyperperfusion phase (sec)	Peak StO_2 (%)
1 (1st baseline)	206 (161–364)	94 (92–69)
2 (hyperoxia)	277 (188–415)	98 (95–99)#
3 (hypoxia)	212 (116–282)	92 (88–93)##
4 (2nd baseline)	192 (154–306)	95 (94–96)
5 (hyperoxia)	192 (146–255)	98 (97–99)###
6 (hypocapnia)	129 (105–143)*	95 (94–97)
7 (hypercapnia)	136 (111–195)**	95 (93–97)

VOT: Vascular occlusion test. T: number of the VOT.
* Shorter duration compared to T4 ($P = 0.01$) and T5 (P0.014).
** Shorter duration compared to T4 ($P = 0.015$).
# Higher peak compared to T1 ($P < 0.001$).
Lower peak compared to both T1 and T2 (both $P < 0.001$).
Higher peak compared to T4 and T6 (both $P < 0.001$), and T7 ($P = 0.001$).

Table 3
Overview of the VOT StO_2 characteristics of each performed VOT. Data are given as mean ± SD.

T	Pre-VOT StO_2 (%)	Desaturation slope (decline in %/min)	Recovery slope (incline in %/sec)	AUC-H (%*sec)
1 (1st baseline)	82 ± 6	12.6 ± 3.8	1.82 ± 0.58	1667 ± 1081
2 (hyperoxia)	86 ± 5*	11.9 ± 2.5	1.82 ± 0.56	1670 ± 776
3 (hypoxia)	83 ± 5	12.4 ± 3.4	1.59 ± 0.64	979 ± 662**
4 (2nd baseline)	85 ± 4	12.8 ± 2.6	2.23 ± 0.81	1172 ± 565
5 (hyperoxia)	90 ± 4	12.0 ± 3.1	1.93 ± 0.70	1016 ± 748
6 (hypocapnia)	87 ± 5	14.6 ± 4.7	2.41 ± 0.80	749 ± 639
7 (hypercapnia)	87 ± 5	14.8 ± 7.6	2.43 ± 1.32	919 ± 515

VOT: vascular occlusion test. T: number of the VOT. StO_2: tissue oxygen saturation. AUC—H: area under the curve of the post-ischemic hyperperfusion phase.
* $P < 0.001$ difference with T1 and T3.
** $P = 0.005$ difference with T1 and T2.

and hyperoxia VOT already induced a short period of ischemia.

Concerning hyperoxia, we neither found any effect on the DS. We speculate that the difference in effect of hyperoxia on the DS compared to two other studies might be caused by the relatively short period of hyperoxia in our study: 6 min, compared to 30 min (Orbegozo Cortés et al., 2015b) and even 2 h (Donati et al., 2017). The first study reported that the administration of 30 min of normobaric hyperoxia in healthy volunteers led to a decrease in the DS (i.e. implying less tissue O_2 consumption) (Orbegozo Cortés et al., 2015b). Their explanation for this finding was a reduced tissue oxygen consumption during hyperoxia as found in critically ill patients, speculating that a maldistribution of blood flow and functional shunting arose to protect the tissues during hyperoxia (Reinhart et al., 1991). The second study found no effect on the DS directly after hyperoxia in critically ill patients (Donati et al., 2017). This finding was in contrast to an increased central venous O_2 saturation (Donati et al., 2017). However, the DS did increase 2 h after hyperoxia (Donati et al., 2017), giving an indication that healthy volunteers should not be compared to critically ill patients because of their difference in timing of regulation mechanisms and adaption of microvasculature (Donati et al., 2017).

Finally, we neither found an effect of hypocapnia or hypercapnia on the DS, which complies with a study in healthy volunteers who were subjected to both conditions (Morel et al., 2017).

The DS can also be altered during other instances than different O_2 and CO_2 conditions, and has shown to be a strong predictor for the need of blood transfusion, emergency surgery, and ICU admission in trauma patients (Guyette et al., 2012). It also served as a predictor of less organ failure and ultimately survival in the critically ill patient (Orbegozo Cortés et al., 2015a; Haertel et al., 2019). In contrast, in other studies a correlation between the DS and survival after (septic) shock (Lima et al., 2011), evolution of Acute Respiratory Distress Syndrome (Orbegozo Cortés et al., 2016; Salgado et al., 2010) or successful weaning from ventilation was not found (Poriazi et al., 2014).

4.2. Vascular reactivity

Vascular reactivity after an ischemic provocation is reflected by the RS after release of the tourniquet. In our study we did not find changes in RS during standardized hypoxia, hyperoxia, hypocapnia and hypercapnia. This is in contrast to a high-altitude study, where hypobaric hypoxia was associated with a decreased RS, although this result was independent from the absolute degree of arterial hypoxemia (Martin et al., 2013). Possible explanations for the difference in result might be that our healthy volunteers were not subjected to low ambient temperatures or acclimatization to high altitude, factors that affect vascular reactivity (Martin et al., 2013). We did not find an effect of hyperoxia on the RS, which is in agreement to a previous study in healthy volunteers (Orbegozo Cortés et al., 2015b).

We neither found an effect of hypocapnia or hypercapnia on the RS. This result is partly comparable to a study in 15 healthy male volunteers under hypocapnia conditions (Morel et al., 2017). The same study also found an increased RS in during hypercapnic conditions, which indicates a vasodilatory response on CO_2 in their volunteers (Morel et al., 2017). We speculate that in our study, volunteers were subjected to more stressful stimuli (i.e., hypoxia, hyperoxia, and hypocapnia) before induction of hypercapnia (as also visible by an increase in heart rate), causing activation of the sympathetic nervous system, which may "overshadow" or underemphasize the vasodilatory effect of hypercapnia on the microvasculature by vasoconstriction. Apart from the possible effects of different O_2 and CO_2 concentrations, the RS proved to be a strong predictor of mortality as reflected by higher Sequential Organ Failure Assessment (SOFA) scores and higher injury severity scores (Guyette et al., 2012; Domizi et al., 2019). Furthermore, in high risk surgery patients correcting effective intravascular volume caused an increase in the RS, without causing changes in the systemic hemodynamics (Futier et al., 2011). Also, in patients with sepsis the RS decreased earlier than markers of tissue hypoperfusion such as muscle pyruvate or muscle lactate concentrations, indicating tissue hypoxia/microvascular impairment, which could alert the clinician to resuscitate the patient in an earlier phase (Orbegozo et al., 2018).

4.3. Post-ischemic hyperperfusion

The AUC-H represents the local capillary recruitment in the post-ischemic hyperperfusion phase. This results in an increase of blood flow to the tissues affected by ischemia (Rosenberry and Nelson, 2020). In our study we found a subtle effect of hypoxia, causing a smaller AUC-H when compared to hyperoxia. No study investigated the effects of changing respiratory O_2 or CO_2 concentrations on the AUC-H measured by NIRS after a VOT. One of the previous mentioned studies (Martin et al., 2013) found a lower peak StO_2 after deflation of the tourniquet during hypoxia. This might be comparable with our study, although they measured during hypobaric hypoxia at altitude and did not measure the area under the curve of the post-ischemic hyperperfusion phase. Other studies investigating various patient categories and circumstances reported a lower AUC-H in patients who had a complicated postoperative course after cardiac bypass surgery (Bernet et al., 2011) or had to be reintubated after weaning from ventilation (Mesquida et al., 2020). One study in healthy volunteers investigating the effect of ingestion of glucose showed that the AUC-H is also correlated with the RS (Soares et al., 2017). Since our healthy volunteers had fasted and the RS in our study was not altered by changing FiO_2 or $etCO_2$ we speculate that the post-ischemic hyperperfusion phase in our study was mainly affected by the (lack of) availability of O_2 and perhaps less through the cellular mechanisms causing local capillary recruitment (Rosenberry and Nelson, 2020).

4.4. Limitations

First, the 'critical' DO_2 threshold (Sharma et al., n.d.; Lieberman et al., 2000) of the thenar muscle might not have been met during hypoxia, i.e. the healthy volunteers were still administered sufficient FiO_2 to maintain DO_2 above their individual critical threshold at all times. Therefore, in patients in whom the critical DO_2 threshold was reached, VOT-associated changes in StO_2 may be of clinical relevance. Second, the period of hyperoxia and possibly hypoxia might have been too short to show changes in DS and RS. Third, our volunteers were predominantly female, however due to the post-hoc nature of this study we were not able to correct our data for the effect of the menstrual cycle on the microvasculature (Adkisson et al., 2010).

Fourth, since the data in this healthy volunteer study were gathered in a systematic manner with a fixed order of FiO_2 and $etCO_2$ instances, it cannot be ruled out that some form of systemic bias exists, possibly influencing DS and RS values to a certain extent. Fifth, this study was performed in healthy volunteers, limiting conclusions from our findings to different types of patients and diseases, e.g. critically ill patients with (multiple) organ failure, and moreover, only short-term interventions and observations were done. Finally, since we have not performed an a priory sample size calculation specifically for VOT-derived variables, the risk of a type II statistical error is increased. Together with the observed substantial variability in the DS and RS between the different FiO_2 and $etCO_2$ concentrations (more than expected beforehand), this may implicate – on top of the increased type II error risk – a limited clinical use of a VOT as a tool for clinical decision-making as it already appears to have substantial variability in healthy volunteers that were exposed to tightly controlled alterations in FiO_2 and CO_2 only.

5. Conclusion

In healthy volunteers at rest, common situations observed during anesthesia and intensive care such as exposure to hypoxia, hyperoxia, hypocapnia, or hypercapnia did not affect peripheral tissue O_2

consumption and vascular reactivity as derived from vascular occlusion tests. These observations may serve as reference values for future physiological studies.

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CRediT authorship contribution statement

C.K. Niezen: Writing – Original Draft, Visualization, Formal analysis.

J.J. Vos: Software, Data Curation, Formal analysis, Writing – Review & Editing.

A.F. Bos: Writing – Review & Editing, Supervision.

T.W.L. Scheeren: Methodology, Writing – Review & Editing, Supervision.

All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: T.W.L. Scheeren received research grants and honoraria from Edwards Lifesciences (Irvine, CA, USA) and Masimo Inc. (Irvine, CA, USA) for consulting and lecturing (payments made to institution). The other authors declare no conflicts of interest.

Data availability

Data will be made available on request.

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Ethics approval

The original study was approved by the local medical ethical committee of Brabant, The Netherlands (NL52290.028.15/P 1506). All methods were carried out in accordance with relevant guidelines and regulations.

Availability of data and material

The data that support the findings of this study are available from the sponsor (Masimo Corp, Irvine, CA, USA) but restrictions apply to the availability of these data, which were used under license for the original study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the sponsor (Masimo Corp, Irvine, CA, USA).

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