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Response time of non-invasive measurement of tissue effects of lung ventilation

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Abstract:	Non-invasive techniques are routinely used for assessment of tissue effects of lung ventilation. However, comprehensive studies of response time of the methods are scarce. The aim of this study was to compare the response time of non-invasive methods for monitoring of gas exchange to sudden changes in composition of the inspired gas mixture. A prospective experimental study with 16 healthy volunteers was conducted. A ventilation circuit was designed that enabled a fast change in composition of the inspiratory gas mixture while allowing spontaneous breathing. The volunteers inhaled a hypoxic mixture, then a hypercapnic mixture, a hyperoxic mixture and finally a mixture with 0.3% CO. The parameters with the fastest response to the sudden change of O_2 in inhaled gas were peripheral capillary oxygen saturation (SpO_2) and regional tissue oxygenation (rSO_2). Transcutaneous oxygen partial pressure ($tcpO_2$) had almost the same time of reaction, but its time of relaxation was 2–3 times longer. End-tidal carbon dioxide ($EtCO_2$) response time to change of CO_2 concentration in inhaled gas was less than half in comparison with transcutaneous carbon dioxide partial pressure ($tcpCO_2$). All the examined parameters and devices reacted adequately to changes in gas

	concentration in the inspiratory gas mixture.

1. Introduction

Noninvasive monitoring of a patient's respiratory status has become common practice in critical care [1], with a special importance in neonatology. In recent two decades, promising techniques has been developed for assessment of tissue effects of lung ventilation. The most widespread noninvasive methods are based on optical sensors, following the successful development of pulse oximetry, or the peripheral capillary oxygen saturation, SpO_2. Also, near infrared spectroscopy (NIRS) showed broad clinical potential in assessing the regional tissue oxygenation rSO_2, e. g. cerebral oxygenation [2]. In addition, monitoring of carbon monoxide saturation *Sp*CO by pulse CO-oximetry has been introduced recently. Another class of noninvasive methods is transcutaneous monitoring. Transcutaneous oxygen partial pressure $tcpO_2$ can be seen as an alternative to repeated blood gas sampling and some studies suggest that it may be more reliable than SpO_2 when monitoring neonates [3]. Transcutaneous carbon dioxide partial pressure $tcpCO_2$ is a reliable and robust method [4, 5] that proved to be equally accurate or even superior to capnography, represented by end-tidal carbon dioxide $EtCO_2$ [6, 7]. Nevertheless, $EtCO_2$ was suggested to guide ventilator management during respiratory failure [8]. The noninvasive methods vary according to their indication, accuracy, reliability under different conditions and time delay [9]. Their optimal clinical application is still discussed.

One of the advantages of the noninvasive methods over periodic arterial blood sampling is the continuous monitoring that can capture fast changes in organism, developed for example as a reaction to changed settings of ventilation support. Therefore, a question arises how fast is the response of the various non-invasive monitoring methods to changes in alveolar gas composition. The aim of this study was to compare the response time of the modern diagnostic methods, which are used for non-invasive monitoring of effects of

spontaneous and mechanical ventilation and also for monitoring regional tissue parameters of gas exchange, to sudden changes in composition of the inspired gas mixture.

2. Methods

The prospective intervention study was approved by the Ethical Review Board of the Faculty of Biomedical Engineering, Czech Technical University in Prague, and was performed in laboratories of the Faculty of Biomedical Engineering in Kladno under standard laboratory conditions. Sixteen healthy volunteers (8 women and 8 men, aged 23–34, weighting 57–92 kg) participated in the study. Volunteers signed the informed consent before their enrolment into the study.

2.1 Experiment setup and realization

For the experiment, a custom-made breathing circuit was designed and assembled. The circuit enabled to deliver a prepared inspiratory gas mixture without seriously compromising spontaneous breathing activity of a volunteer. Essentially, the circuit allowed a sudden change in composition of the inspiratory gas mixture.

The breathing circuit is presented in Figure 1: The circuit consisted of a high-pressure part and a low-pressure part. The high pressure part served for preparation of a required inspiratory gas mixture. The part included three gas cylinders with O_2, CO_2, N_2 (1) connected into a blender (2) and a gas cylinder containing a normoxic/normocapnic CO mixture with small, yet distinctive, 0.3% concentration of CO. Following a pressure reduction valve (3), the low pressure part of the circuit served for delivering a prepared gas mixture to a volunteer. Standard medical 22mm corrugated tubing was used in the low pressure part to reduce

breathing resistance. The composition of the gas mixture from the high-pressure part was verified by a gas analyzer (4). After the required gas composition was reached, the newly prepared gas mixture flew via a three-way valve (5) and was stored in the polyethylene Douglas bag (6). Another three-way valve (7) allowed a sudden change of the inspired gas between the ambient air and the gas mixture stored in the Douglas bag. The correct direction of flow of inspired and expired gas was assured by two one-way valves (8, 9). The composition of gases was monitored by a flow orifice (10) of the Carescape B650 (GE Healthcare, United Kingdom) patient monitor. An antibacterial filter separated the volunteer from the breathing circuit.

Before the experiment, sensors of all monitoring devices were attached to the volunteer according to manufacturers' instructions. The transcutaneous pressures $tcpO_2$ and $tcpCO_2$ of Tosca TCM4 (Radiometer Medical Aps, Denmark) were measured in the left subclavian area. Pulse oximetry SpO_2 sensors of Root Radical-7 (Masimo, USA), Nellcor N-600 (Medtronic, Ireland) and Carescape B650 were placed on the left forefinger, left ring-finger and left middle-finger, respectively. Notably, carbon monoxide concentration *Sp*CO was also monitored by Root Radical-7. Regional tissue oxygenation rSO_2 was measured by an O_3 sensor of a MOC-9 module (Masimo, USA) connected to Root Radical-7. This sensor was placed on the left forehead, about 2 cm above the eyebrow. Finally, the end-tidal carbon dioxide $EtCO_2$ was measured by the orifice of Carescape B650 as described above.

Root Radical-7 was selected as a reference and the other monitoring devices were synchronized with it. Tosca TCM4 had its system time synchronized with Root Radical-7 and an event was recorded exactly 30 s after the start of recording in Root Radical-7. Then, a brief break in the pulse oximetry signal, intentionally induced by a cuff inflation, was recorded in all pulse oximeters. All monitoring devices were set to the shortest possible averaging times; specifically, Root Radical-7 averaging time was 2 seconds.

During the experiment, volunteers breathed only through the breathing circuit. The experimental protocol alternated relaxation phases and experimental phases. In a relaxation phase, a volunteer breathed the ambient air. Simultaneously, an inspiratory gas mixture was prepared for the next experimental phase. In the experimental phase, the volunteer breathed the prepared gas mixture stored in the Douglas bag. These were a hypoxic gas mixture, then a hypercapnic mixture, a hyperoxic mixture and finally the normoxic/normocapnic CO mixture with 0.3% carbon monoxide. The duration and sequence of the phases, as well as the exact composition of inspiratory gas mixtures, are summarized in Table 1. After the last relaxation phase, a volunteer was disconnected from the breathing circuit and examined for possible unwanted effects of CO inhalation.

2.2 Signal processing and data analysis

All measured signals were synchronized utilizing the recorded event time and induced break in the SpO_2 signals that was described above. Signals of SpO_2, $EtCO_2$ and rSO_2 were filtered using a sliding median filter with a window size of 20 samples to eliminate peaks caused by movement artefacts or short drop-outs. Individual experimental phases were identified in each signal as illustrated in Figure 2.

Two main parameters, the reaction time T_{20} and the relaxation time T_{80} [10], were evaluated in the signals of $tcpO_2$, $tcpCO_2$, SpO_2, $EtCO_2$ and rSO_2. The reaction time and the relaxation time are designated in Figure 3. The time T_{20} was defined as the time between the initiation of an experimental phase and the point where the signal reached 20% of the total change in amplitude caused by the change in composition of the inspiratory gas mixture. The 0% baseline was calculated as the average signal value from the last 30 s of the previous relaxation phase. Accordingly, the time T_{80} was defined as the time between the end of the

experimental phase and the point where the signal returned to the level of 20% change of amplitude.

As for the *Sp*CO signal, where the change of amplitude due to the sudden change of the inspiratory gas mixture was very slow, a different approach was applied: The reaction time was defined as the time between the initiation of the CO phase and the point where the *Sp*CO signal increased above the zone of ±2% around its mean value in the previous relaxation phase. The precision ±2% of the *Sp*CO signal was documented in [11] and this range of *Sp*CO signal swings was also rather apparent in the relaxation phase that preceded the experimental CO phase.

In the hypoxic phase, the hyperoxic phase and the hypercapnic phase, the response times of three parameters measuring O_2 concentration were compared: *tcp*O_2, *Sp*O_2 (Root Radical-7) and *rS*O_2. In the hypercapnic phase, the two parameters measuring CO_2 concentration were also compared: *tcp*CO_2 and *Et*CO_2. Moreover, in these three phases, the response times of the *Sp*O_2 parameter measured by various devices (Root Radical-7, Nellcor N-600 and Carescape B650) were mutually compared. Due to various artifacts and technical difficulties, all required signals were not always available for each volunteer. The exact numbers of evaluated volunteers are presented in the Results section.

The one-way repeated measures ANOVA was performed for data from each experimental phase to compare the response times of various parameters (*tcp*O_2, *Sp*O_2 and *rS*O_2) and to compare the response times of *Sp*O_2 measured by various devices to a sudden change of the inspiratory gas mixture. The reaction times and the relaxation times were evaluated separately. Normality of the data was verified by one-sampled Kolmogorov-Smirnov test. Paired t-test with Bonferroni's adjustment was used as the post test for bivariate comparisons. In all analyses, $p<0.05$ was considered statistically significant. The data were evaluated using Matlab Statistics and Machine Learning Toolbox (Mathworks, USA).

3 Results

The response time of various parameters to a sudden change of the inspiratory gas mixture, expressed as the reaction time T_{20} and the relaxation time T_{80}, is compared in Figure 4–Figure 7.

In the hypoxic phase, the reaction times of parameters *tcp*O_2, *Sp*O_2 and *rS*O_2 did not differ significantly. The *Sp*O_2 signal (Root Radical-7) showed the fastest average reaction time 52 s. Also, there was no significant difference in the relaxation times of *Sp*O_2 and *rS*O_2. However, *tcp*O_2 was slower than both *Sp*O_2 and *rS*O2 ($p<0.05$), with the relaxation time of *tcp*O_2 being 3.1 times longer on average than the relaxation time of *Sp*O_2.

Also in the hyperoxic phase, the reaction times of parameters *tcp*O_2, *Sp*O_2 and *rS*O_2 did not differ significantly. The *Sp*O_2 signal (Root Radical-7) showed the fastest average reaction time 45 s. The relaxation time of *tcp*O_2 was 1.7 times longer on average than the relaxation time of *Sp*O_2 ($p<0.05$).

In the hypercapnic phase, the reaction time of *Et*CO_2 was 2.1 times faster on average than the reaction time of *tcp*CO_2 ($p<0.05$). The reaction times of *tcp*O_2, *Sp*O_2 and *rS*O_2 did not differ significantly. The *rS*O_2 signal showed the fastest average reaction time 70 s. The relaxation time of *Et*CO_2 was 3.4 times faster on average than the relaxation time of *tcp*CO_2 ($p<0.05$). The relaxation time of *tcp*O_2 was slower than the relaxation times of *Sp*O_2 and *rS*O_2 ($p<0.05$), being 3.1 times longer on average than the relaxation time of *Sp*O_2.

In the CO phase, the average reaction time of *Sp*CO (Root Radical-7) was 203 s. Any response from other parameters and devices was not detected.

The response of *Sp*O_2 to a sudden change of the inspiratory gas mixture, measured by three various devices and expressed as the reaction time T_{20} and the relaxation time T_{80}, is

summarized in Table 2 and Table 3. Root Radical-7 showed the fastest reaction times and the fastest relaxation times on average in both the hypoxic and hyperoxic phase. In the hypercapnic phase, the reaction time of Carescape B650 and the relaxation time of Nellcor N-600 were slightly smaller than the respective times of Root Radical-7. In all the experimental phases, both Root Radical-7 and Carescape B650 exhibited very similar reaction times, but differed in the relaxation times.

4. Discussion

The study results show that all measured parameters exhibited reactions which could be expected according to the composition of the inspiratory gas mixture and a sensor cross interference was not observed.

The monitored parameters reacting to the concentration of oxygen in the organism were *tcp*O_2, *sp*O_2 and *rS*O_2. The reaction times of the three parameters were very similar during the hypoxic phase (reduced fraction of O_2 in the inspiratory gas mixture), the hyperoxic phase (increased fraction of O_2) and the hypercapnic phase (increased CO_2 fraction that also stimulated hyperventilation and thus some increase of alveolar O_2). In the hypoxic and hyperoxic phase, the *Sp*O_2 signal showed the fastest reaction and in the hypercapnic phase the *rS*O_2 signal showed the fastest reaction. The relaxation time of *Sp*O_2 and *rS*O_2 did not differ significantly in the three experimental phases. The relaxation of *tcp*O_2 was about 2–3 times slower that the relaxation of *Sp*O_2. Comparison of various *Sp*O_2 measuring devices showed almost similar reaction times of Root Radical-7 and Carescape B650. Carescape B650, on the other hand, was slower in relaxation.

The monitored parameters reacting to the concentration of carbon dioxide in the organism were *tcp*CO_2 and *Et*CO_2. During the hypercapnic phase, *tcp*CO_2 was 2.1 times slower in reaction and 3.4 times slower in relaxation than *Et*CO_2.

The speed of reaction to presence of carbon monoxide in the organism was evaluated during the CO phase. A detectable change in the *Sp*CO parameter of Root Radical-7 appeared in about 200 s.

The main limitation of the study is the impossibility to clearly separate the reaction of a measuring device from the reaction of a volunteer's organism. Also, there was a time gap between the start of an experimental phase, i.e. the valve opening, and the first full breath of a new inspiratory gas mixture. The time gap of about 5 s is determined by the dead space of the breathing apparatus between the Douglas bag and a volunteer's airways opening, which is approximately 1 L. Some concern had been raised about the safety of volunteers breathing 0.3% CO during the CO phase of the experiment. Nevertheless, we did not observe any adverse effect of the gas on volunteers during or after the experiment.

As for the further development of the experiment we recommend to extend the relaxation phases between the experimental phases so that the incomplete relaxation of signals might not affect the next experimental phase. The reduced comfort a volunteer should be compensated by introducing breaks after the end of a relaxation phase that would also prevent reduction of peripheral perfusion in arms and hands. The reduced perfusion affects *Sp*O_2 measurement [12] as it happened to a few volunteers in our experiment.

In this paper we were able to compare time response of methods for non-invasive respiratory monitoring. Although the results show some differences in the time responses between various methods and even between various devices that utilize the same method of measurement, the detected differences do not seem important for clinical practice. However, they could be interesting for planning and evaluation of experimental measurements where

the fast changes of physiological parameters are expected, such as while breathing under extreme conditions of snow burial [13, 14], etc.

5. Conclusions

In this experimental study we designed a breathing circuit which allows sudden changes in composition of the inspiration gas mixture and does not restrict spontaneous breathing excessively. The response time of non-invasive methods for monitoring of gas exchange were compared in a study on healthy volunteers. After a change of oxygen concentration in inhaled gas mixture against the normal air, signals of the peripheral capillary oxygen saturation, the regional tissue oxygenation and the transcutaneous oxygen partial pressure reacted with approximately the same speed. Transcutaneous measurement detected the return to normoxemia with about 2–3 times longer relaxation time than the other methods. During the hypercapnic phase, the transcutaneous carbon dioxide partial pressure was more than 2 times slower in reaction and more than 3 times slower in relaxation than end-tidal carbon dioxide. The measured data showed that all the examined parameters and devices reacted adequately to changes in gas concentration in the inspiratory gas mixture. The differences between the device reaction times should be considered during physiological experiments when a rapid change of those parameters is expected.

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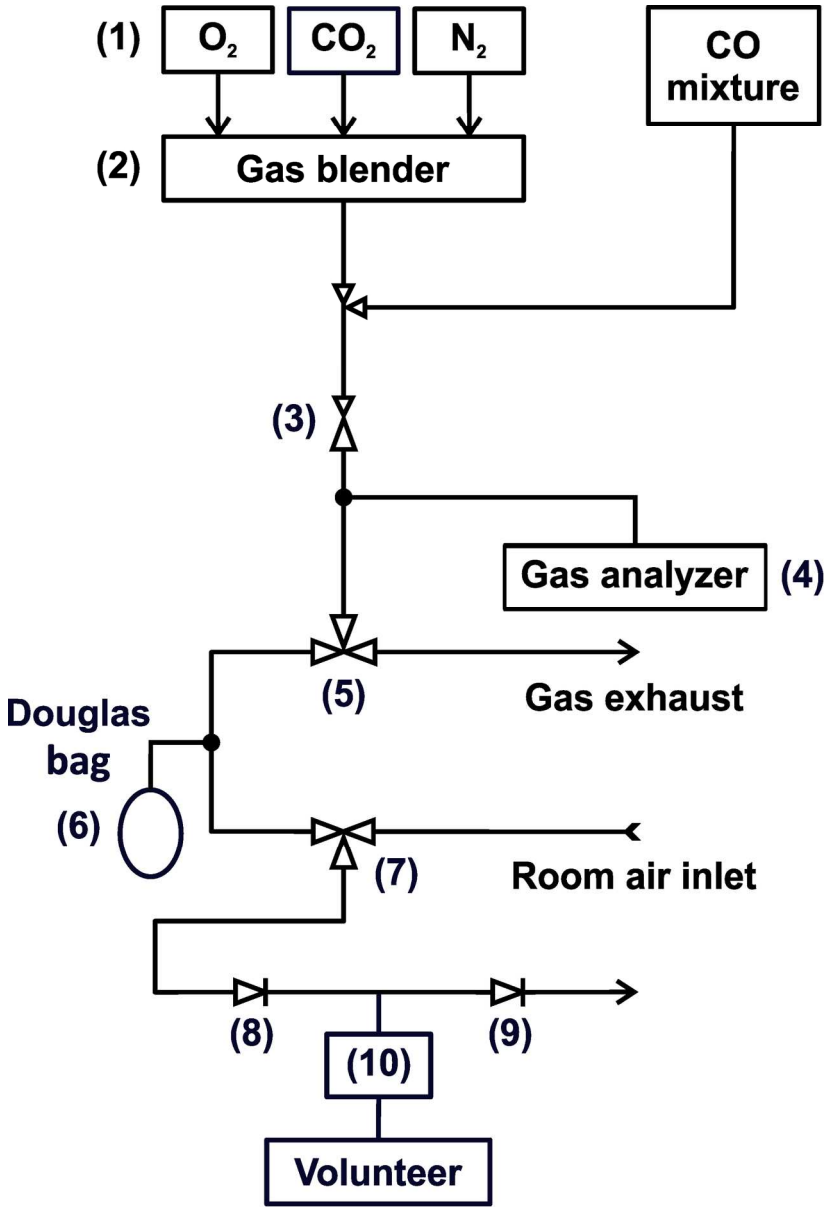

Figure 1: The breathing circuit designed and used for the experiment. See detailed description in the main text.
Figure 1
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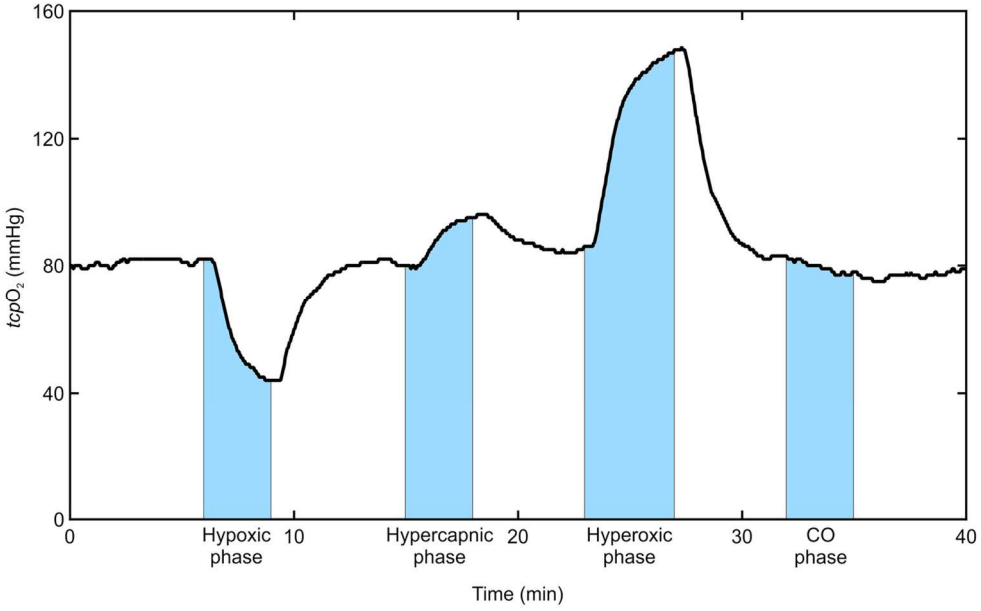

Figure 2: Recorded signal of transcutaneous oxygen pressure with identified experimental phases.
Figure 2
128x79mm (300 x 300 DPI)

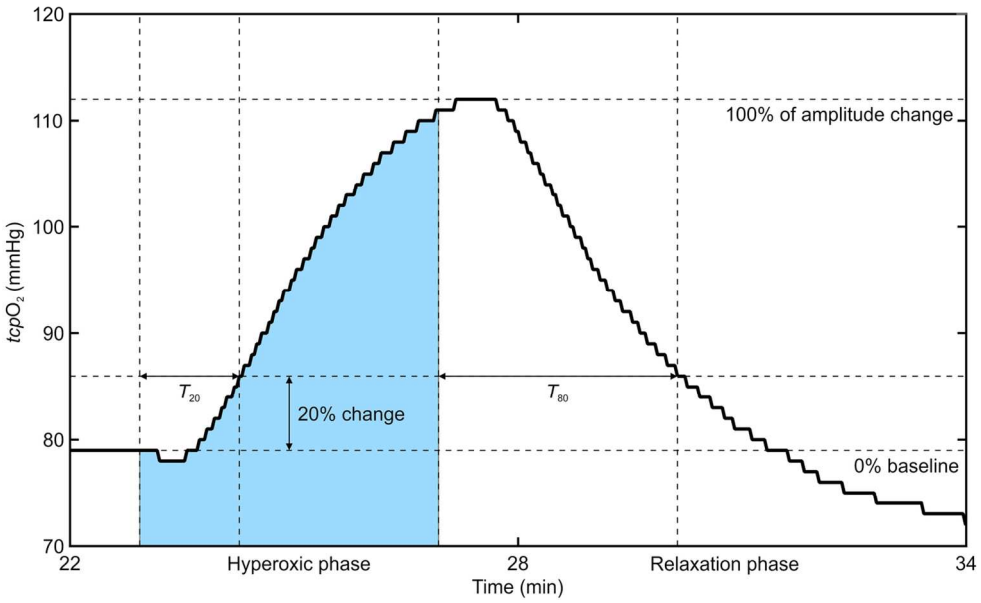

Figure 3: The reaction time and relaxation time identified in a recorded signal of transcutaneous oxygen pressure.
Figure 3
128x79mm (300 x 300 DPI)

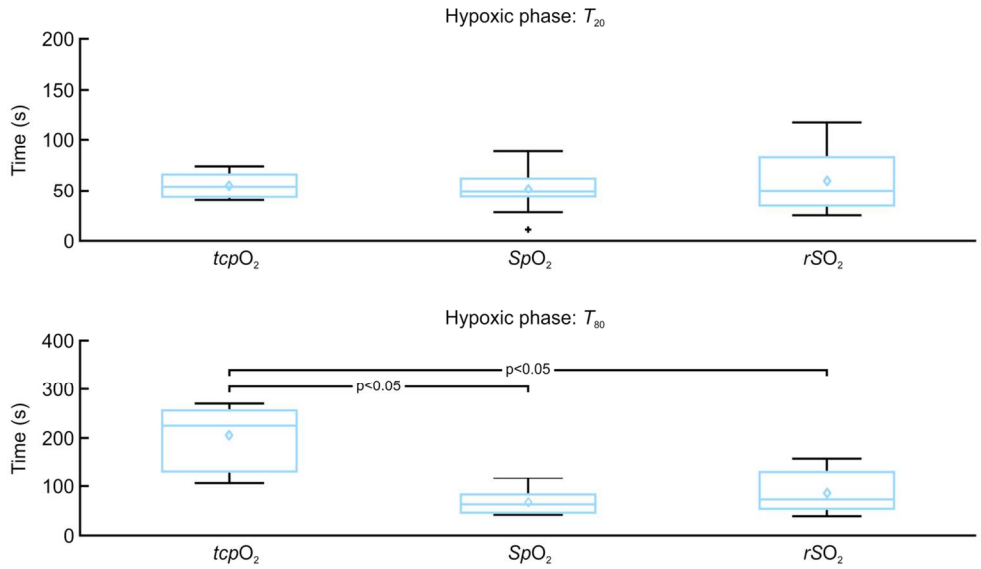

Figure 4: The reaction time T_{20} (top, 12 subjects) and the relaxation time T_{80} (bottom, 10 subjects) of various parameters measured during the hypoxic phase. The diamonds mark the means. The cross marks an outlier.

Figure 4
119x67mm (300 x 300 DPI)

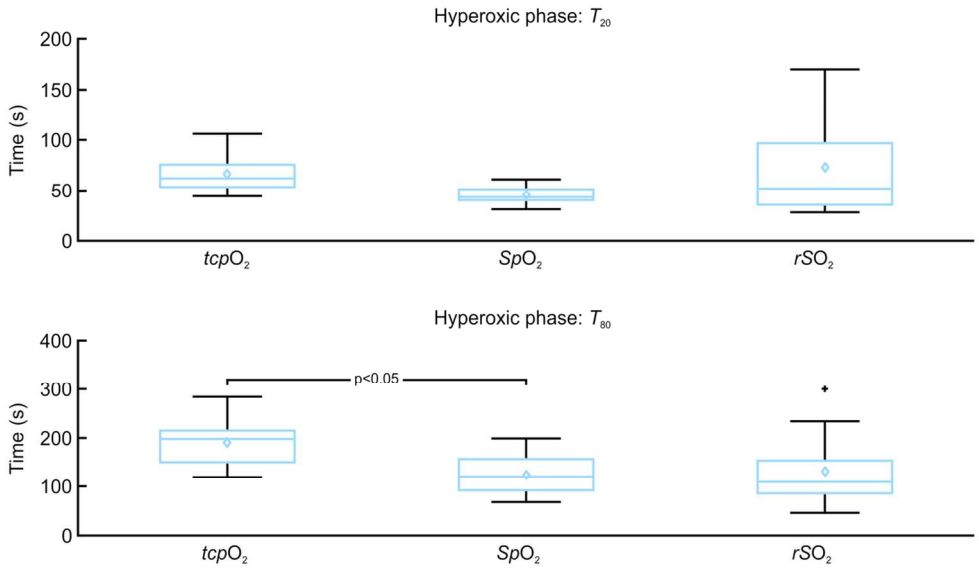

Figure 5: The reaction time T_{20} (top, 9 subjects) and the relaxation time T_{80} (bottom, 9 subjects) of various parameters measured during the hyperoxic phase. The diamonds mark the means. The cross marks an outlier.

Figure 5
119x67mm (300 x 300 DPI)

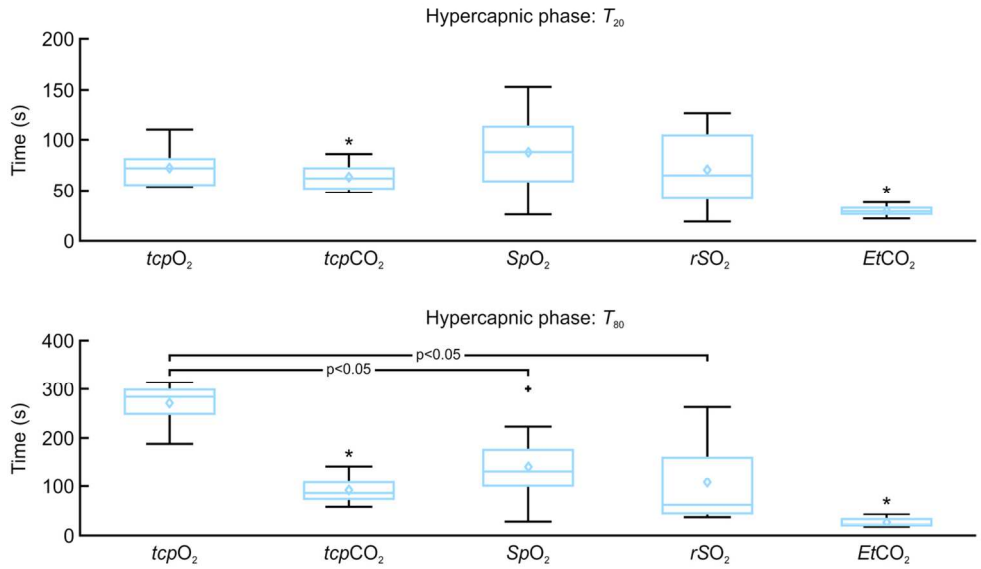

Figure 6: The reaction time T_{20} (top, 9 subjects) and the relaxation time T_{80} (bottom, 9 subjects) of various parameters measured during the hypercapnic phase. The diamonds mark the means. The * marks statistical significance ($p<0.05$) of the parameters related to CO_2. The cross marks an outlier.

Figure 6
119x67mm (300 x 300 DPI)

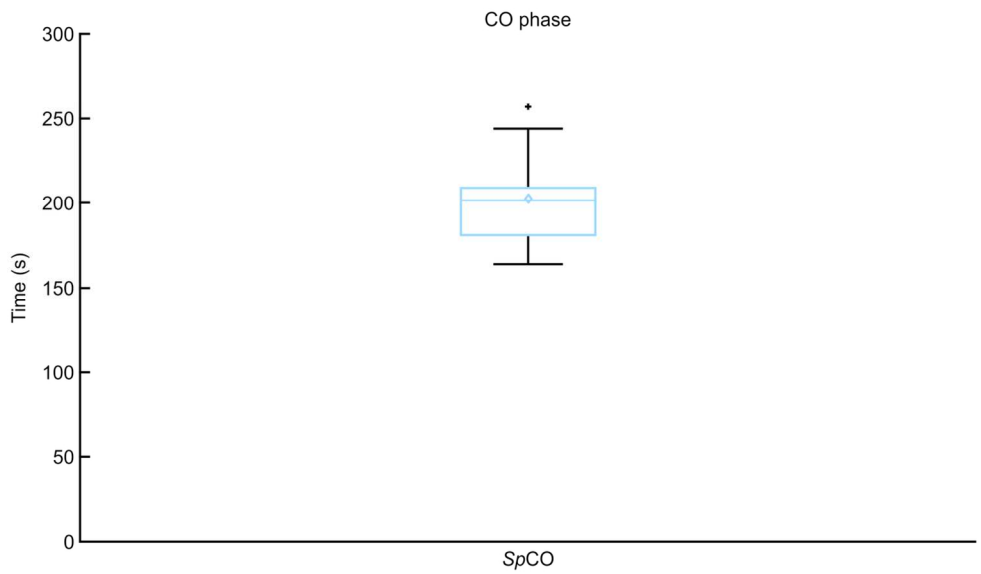

Figure 7: The reaction time (14 subjects) of peripheral oxygen saturation during the CO phase. The diamonds mark the means. The cross marks an outlier.
Figure 7
124x73mm (300 x 300 DPI)

Table 1: The relaxation phases and the experimental phases of the experiment. The duration of relaxation phases was extended so that the measured values returned to the pre-experiment "reference" values.

Phase	Inspired gas composition	Duration
Relaxation	ambient air	6 min
Hypoxic	0% CO_2, 15.0% O_2, 85.0% N_2	3 min
Relaxation	ambient air	reference
Hypercapnic	5.0% CO_2, 20.0% O_2, 75.0% N_2	3 min
Relaxation	ambient air	reference
Hyperoxic	0% CO_2, 40.0% O_2, 60.0% N_2	4 min
Relaxation	ambient air	reference
CO phase	0.3% CO, 0.3% CH_4, 21.0% O_2, 78.4% N_2	3 min
Relaxation	ambient air	reference

Table 2: The reaction time T_{20} of the peripheral oxygen saturation, SpO_2, measured by three different devices.

Phase (Subjects)	T_{20} (s)		
	Root Radical-7	Nellcor N-600	Carescape B650
Hypoxic (14)	52±15*	65±19*	56±15
Hyperoxic (9)	43±14	55±28	49±15
Hypercapnic (7)	75±23	119±47#	73±41#

Data are presented as mean ± standard deviation. Symbols * and # mark a statistically significant difference ($p<0.05$) of times during the same phase.

Table 3: The relaxation time T_{80} of the peripheral oxygen saturation, SpO_2, measured by three different devices.

Phase (Subjects)	T_{80} (s)		
	Root Radical-7	Nellcor N-600	Carescape B650
Hypoxic (14)	76±34*	101±41	121±58*
Hyperoxic (9)	149±76#	156±60$	199±73#,$
Hypercapnic (7)	174±108	168±63	218±55

Data are presented as mean ± standard deviation. Symbols *, # and $ mark a statistically significant difference ($p<0.05$) of times during the same phase.