Jakub Rafl*, Filip Kulhanek, Petr Kudrna, Vaclav Ort and Karel Roubik

Response time of indirectly accessed gas exchange depends on measurement method

https://doi.org/10.1515/bmt-2017-0070
Received December 18, 2016; accepted July 3, 2017

Abstract: Noninvasive techniques are routinely used for assessment of tissue effects of lung ventilation. However, comprehensive studies of the response time of the methods are scarce. The aim of this study was to compare the response time of noninvasive methods for monitoring of gas exchange to sudden changes in the composition of the inspired gas. A prospective experimental study with 16 healthy volunteers was conducted. A ventilation circuit was designed that enabled a fast change in the 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 0.3% CO mixture. 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.

Keywords: near infrared spectroscopy; non-invasive respiratory monitoring; pulse oximetry; transcutaneous monitoring.

***Corresponding author: Jakub Rafl,** Czech Technical University in Prague, Faculty of Biomedical Engineering, Department of Biomedical Technology, nam. Sitna 3105, 272 01 Kladno, Czech Republic, Phone: +420 728 229 991, Fax: +420 224 358 419, E-mail: rafl@fbmi.cvut.cz. http://orcid.org/0000-0001-5102-9354
Filip Kulhanek, Petr Kudrna, Vaclav Ort and Karel Roubik: Czech Technical University in Prague, Faculty of Biomedical Engineering, Department of Biomedical Technology, 272 01 Kladno, Czech Republic

Introduction

Noninvasive monitoring of a patient's respiratory status and tissue effects of gas exchange has become common practice both in adult critical care and in neonatology [4, 30]. The most widespread noninvasive methods are based on optical sensors, following the successful development of pulse oximetry. The pulse oximeter analyses absorption of two wavelengths of light in the tissue, red (660 nm) and infrared (940 nm), and calculates peripheral oxygen saturation SpO_2, which is used for estimation of arterial oxygen saturation [7]. Recently, monitoring of carbon monoxide saturation *Sp*CO by pulse CO-oximetry has been introduced [1, 14]. The principle of operation for the pulse CO-oximetry is similar to those for conventional pulse oximetry, but the *Sp*CO sensor utilizes seven or more wavelengths of near-infrared light in a range from 600 to 1200 nm. Also, near infrared spectroscopy (NIRS) showed a broad clinical potential in assessing the regional tissue oxygenation rSO_2, e.g. cerebral oxygenation. NIRS monitor estimates rSO_2 using a light source with four wavelengths (ranging from 700 to 1100 nm) and two photodetectors that capture reflected near-infrared light from different depths of the underlying tissue [7, 29]. Capnometry measures concentration of carbon dioxide in respiratory gasses utilizing chemical or spectroscopic methods. Infrared spectroscopy is based on absorption of IR radiation by CO_2 molecules, which is maximal at a wavelength of 4.26 μm. The absorbed IR light is proportional to concertation of CO_2 in the measured gas mixture. The amount of CO_2 at end-expiration is represented by end-tidal carbon dioxide ($EtCO_2$) that is usually expressed as the partial pressure or as the fractional concentration of expired CO_2 [4, 7].

Another class of noninvasive methods is transcutaneous monitoring that measures the skin surface partial pressures of oxygen and carbon dioxide by modified blood gas electrodes. Transcutaneous partial pressure of oxygen $tcpO_2$ is measured with a Clark electrode, which consists of a platinum cathode and silver anode, and transcutaneous partial pressure of carbon dioxide $tcpCO_2$ is measured by a modified Severinghaus electrode, which consists of a pH-sensitive glass and Ag/AgCl electrode. The electrodes are fixed to the skin surface with an adhesive ring and heated to 42–45°C to produce capillary vasodilation and

Rafl, J., Kulhanek, F., Kudrna, P., Ort, V. and Roubik, K., 2018. Response time of indirectly accessed gas exchange depends on measurement method. Biomedical Engineering/Biomedizinische Technik, 63(6), pp.647-655.

enhance gas diffusion through the skin. Combined O_2/CO_2 electrodes allow measuring both *tcp*O_2 and *tcp*CO_2 at the same site [4, 25].

The noninvasive methods vary according to their indication, accuracy, reliability under different conditions and time delay. Their optimal clinical application and their limitations are still discussed. Pulse oximeters generally perform well for arterial oxygen saturation greater than 80% [4, 34]. The accuracy of pulse oximeters depends on the identification of an arterial pulse that becomes difficult in cases of low perfusion. Consequently, susceptibility to motion artifacts increases. Pulse CO-oximetry is a continuous and noninvasive method of measurement of the carbon monoxide levels in the arterial blood with acceptable bias and precision. Results of several studies suggest that it can be used for fast screening of a large number of patients for occult CO poisoning, but acceptable results could be measured only when arterial oxygen saturation is more than approximately 85% [9, 27]. Cerebral NIRS provides continuous measurement of brain oxygenation for real-time management of patients at risk for compromised oxygen saturation [11]. Recent data show that NIRS reliably measures dynamic changes in cerebral tissue oxygenation and identifies successful re-saturation faster than *Sp*O_2 [8].

Transcutaneous oxygen partial pressure is used in determining the adequacy of oxygenation in tissues and could be seen as an alternative to repeated blood gas sampling. Some studies suggest that it may be more reliable than *Sp*O_2 when monitoring neonates [25]; however, the validity and reliability of *tcp*O_2 measurement in adults was disputed [38]. The method cannot be used as a surrogate of the partial pressure of oxygen in arterial blood [21], but it has had relevant results even in adults, for example, in wound evaluation or detection of peripheral shock [26, 39]. Transcutaneous oxygen measurement is increasingly being used with sensors available for neonatal, pediatric and adult patients and its potential application in clinical practice is still discussed [38]. Primary clinical applications of capnometry and *tcp*CO_2 vary [15]. Transcutaneous carbon dioxide partial pressure is a reliable and robust method that can be used in infants, children and adults [32, 33, 35] and that proved to be equally accurate or even superior to capnography in nonintubated patients [18], and possibly even in intubated patients [31]. On the other hand, *Et*CO_2 was suggested to guide ventilator management during respiratory failure [37].

One of the advantages of the noninvasive methods over periodic arterial blood sampling is the continuous monitoring that can rapidly capture changes in gas redistribution in the organism, developed, for example, as a reaction to changed settings of ventilatory support. Therefore, a question arises, how fast is the response of the various noninvasive monitoring methods to the variation in gas exchange in the organism. The noninvasive methods approach the gas exchange indirectly, and their response combines the response of an organism to changes in alveolar gas composition and consequent gas redistribution with the response of the measurement methods themselves, which depends on the type and position of a sensor.

The dynamic response of an organism to changes in the alveolar gas composition has been investigated for a long time. Cherniack and colleagues studied rapid shift in partial pressure of CO_2 in first minutes after a change in ventilation and built a mathematical model that described the process [6]. Recently, Buehler et al. evaluated the equilibration time between a change in respiratory rate and achievement of a new *Et*CO_2 steady-state level [3]. The dynamics of the change between two consecutive equilibration *Et*CO_2 levels was also inspected and the study found an early prediction of the new steady-state level possible. However, the study was not focused on the method of measurement as such. The noninvasive measuring methods were evaluated rather under static conditions, such as in comparisons of *tcp*CO_2 and *Et*CO_2 in [24] or [5]. On the other hand, Redford et al. assessed absolute, but also trend accuracy of the O3 regional oximetry sensor in healthy volunteers undergoing controlled hypoxia [23]. The sensor provided absolute root-mean-squared error of 4% and relative root-mean-square error of 2.1%. Differences in desaturation response time between pulse oximeters were measured by MacLeod et al. [19]. Mild hypothermia increased the mean response time of finger oximeters from 130 to 215 s. Significant differences in desaturation response times and in resaturation response times between various pulse oximeters during induced hypoxemia were found by Trivedi et al. [34]. Kesten and colleagues tested response characteristics of a dual transcutaneous monitoring system (*tcp*O_2 and *tcp*CO_2) under induced hypercapnia, hypoxia, and hyperoxia, concluding that the response is more rapid for the CO_2 than the O_2 electrode [17]. Nevertheless, is has not been common to directly compare the dynamic response of various noninvasive methods during the same phase.

The aim of this study was to compare the response time of the modern diagnostic methods, which are used for noninvasive monitoring of effects of spontaneous and mechanical ventilation and for monitoring regional tissue parameters of gas exchange, to sudden changes in the composition of the inspired gas.

Materials and methods

The prospective interventional 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 (eight women and eight men, aged 23–34, weighing 57–92 kg) participated in the study. Volunteers signed the informed consent before their enrolment into the study.

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 to a spontaneously breathing volunteer and allowed a sudden change in the 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 the preparation of a required inspiratory gas mixture. The part included three gas cylinders with O_2, CO_2, and N_2 (1) connected to the KM 100-3MEM blender (Witt, Witten, Germany) (2) and a gas cylinder containing a normoxic/normocapnic CO mixture with a 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. The standard medical 22 mm 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 the PA 7.0 gas analyzer (Witt, Witten, Germany) (4). After the required gas composition was reached, the newly prepared gas mixture flowed 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 expired gas was monitored by a flow orifice (10) of the Carescape B650 patient monitor (GE Healthcare, Little Chalfont, UK). An antibacterial filter separated the volunteer from the breathing circuit.

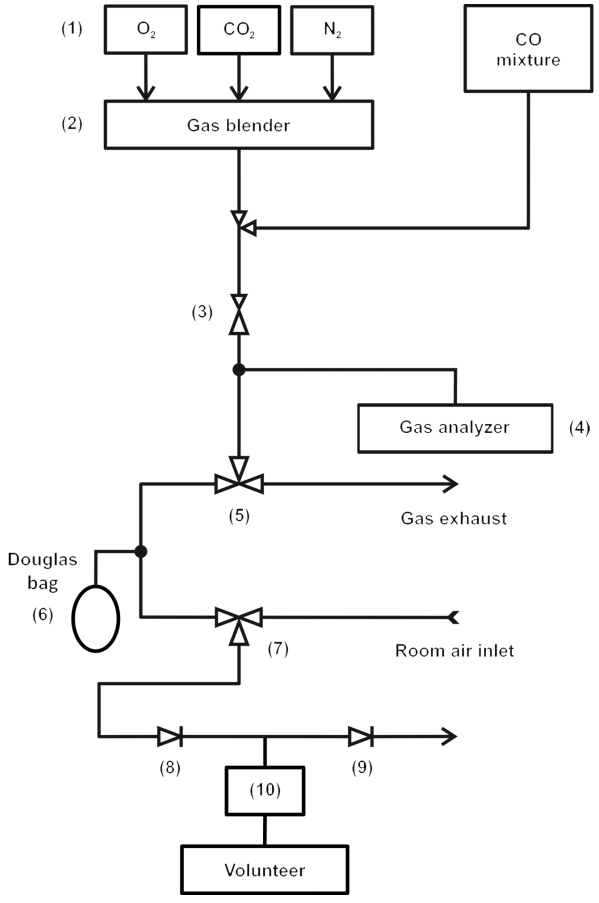

Figure 1: The breathing circuit designed and used for the experiment.
See detailed description in the main text.

Before the experiment, sensors of all monitoring devices were attached to the volunteer. The locations of the sensors were selected according to the manufacturer's recommendations. The transcutaneous pressures $tcpO_2$ and $tcpCO_2$ of Tosca TCM4 (Radiometer Medical ApS, Brønshøj, Denmark) were measured in the left subclavicular area. Pulse oximetry SpO_2 sensors of Radical-7 (Masimo Corporation, Irvine, USA), Nellcor N-600 (Medtronic, Dublin, 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 Radical-7. Regional tissue oxygenation rSO_2 was measured by the O3 sensor connected to the Root platform (Masimo Corporation, Irvine, USA). This sensor was placed on the left forehead, about 2 cm above the eyebrow. Finally, the $EtCO_2$ was measured by the orifice of Carescape B650 as described above.

Radical-7 was selected as a reference and the other monitoring devices were synchronized with it. The sampling period of the data records was 2 s in the case of Tosca TCM4, Radical-7 and Root. The sampling period of Nellcor N-600 was 4 s and the sampling period of Carescape B650 was 1 s.

During the experiment, volunteers breathed only through the breathing circuit. The experimental protocol alternated relaxation phases and experimental phases. In a relaxation phase, volunteers breathed the ambient air. Simultaneously, an inspiratory gas mixture was prepared for the next experimental phase. In the experimental phase, volunteers 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% of 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, each volunteer was disconnected from the breathing circuit and examined for possible unwanted effects of CO inhalation.

Signal processing and data analysis

Synchronized 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 artifacts 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} [36], were evaluated in the signals of $tcpO_2$, $tcpCO_2$,

Table 1: The relaxation phases and the experimental phases of the experiment.

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

The duration of relaxation phases was extended so that the measured signals reached steady values.

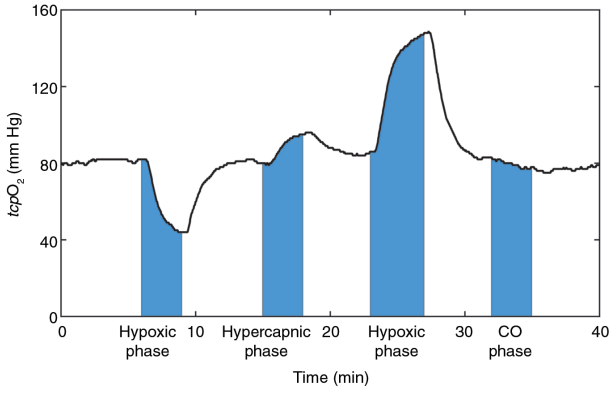

Figure 2: Recorded signal of transcutaneous oxygen pressure with the identified experimental phases.

SpO_2, $EtCO_2$, and rSO_2. The reaction time and the relaxation time are explained 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 the composition of the inspiratory gas mixture. The 0% baseline was calculated from the last 30 s of the recorded signal in 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.

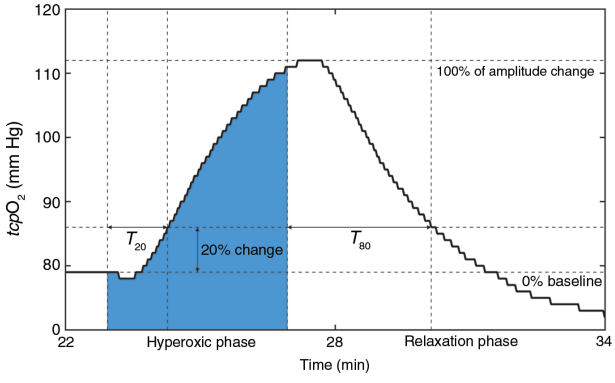

Figure 3: The reaction time and the relaxation time identified in the recorded signal of transcutaneous oxygen pressure.

As for the *Sp*CO signal, where the change in 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 [1] 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 evaluating oxygenation were compared: $tcpO_2$, SpO_2 of Radical-7 and rSO_2. In the hypercapnic phase, the two parameters measuring CO_2 concentration were also compared: $tcpCO_2$ and $EtCO_2$. Moreover, in these three phases, the response times of the SpO_2 parameter measured by various devices (Radical-7, Nellcor N-600 and Carescape B650) were mutually compared. Due to various artifacts and technical difficulties, some required signals were not always available for each volunteer and phase. In each phase, we only considered the subjects for which all the signals that were compared in the phase were available. The exact numbers of evaluated volunteers are presented in the Results section.

The one-way repeated measures analysis of variance (ANOVA) was performed for data from each experimental phase to compare the response times of various parameters ($tcpO_2$, SpO_2, and rSO_2) and to compare the response times of SpO_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, Natick, USA).

Results

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

In the hypoxic phase, the reaction times T_{20} of parameters $tcpO_2$, SpO_2 and rSO_2 did not differ significantly. The SpO_2 signal (Radical-7) showed the fastest average reaction time 52 s. Also, there was no significant difference in the relaxation times T_{80} of SpO_2 and rSO_2. However, $tcpO_2$ was slower than both SpO_2 and rSO_2 ($p < 0.05$), with the relaxation time of $tcpO_2$ being 3.1 times longer on average than the relaxation time of SpO_2.

Also in the hyperoxic phase, the reaction times T_{20} of parameters $tcpO_2$, SpO_2 and rSO_2 did not differ significantly. The SpO_2 signal (Radical-7) showed the fastest average reaction time 45 s. The relaxation time T_{80} of $tcpO_2$ was 1.7 times longer on average than the relaxation time of SpO_2 ($p < 0.05$).

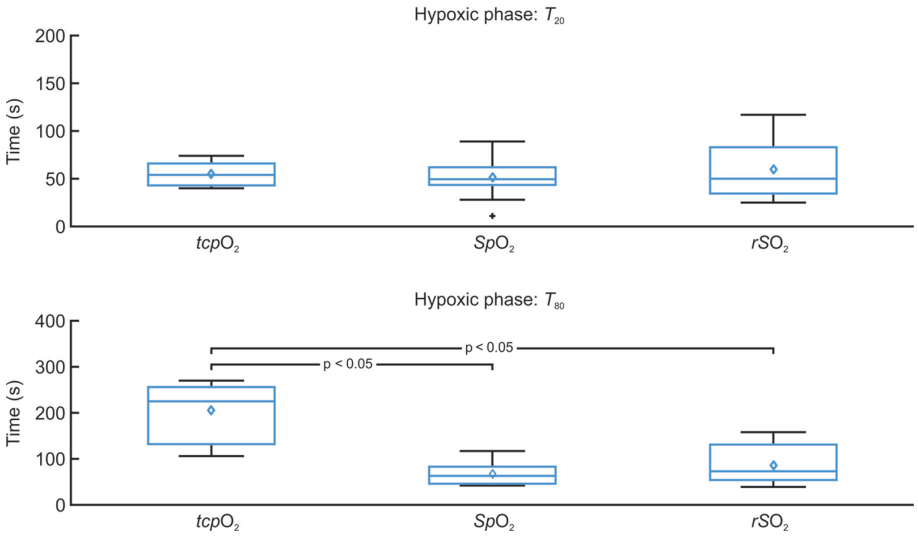

Figure 4: The reaction time T_{20} (top, 12 subjects) and the relaxation time T_{80} (bottom, 10 subjects) of various parameters measured during the hypoxic phase.
The diamonds mark the means. The cross marks an outlier.

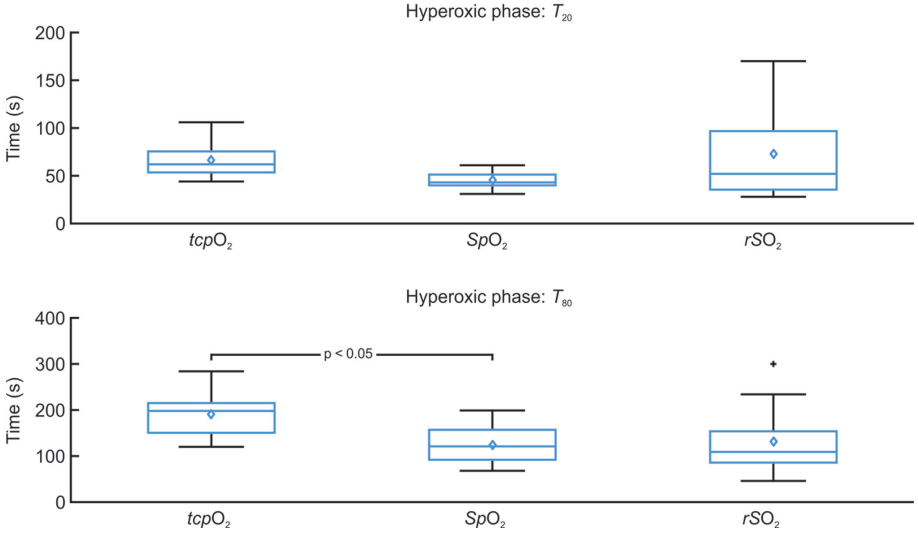

Figure 5: The reaction time T_{20} (top, nine subjects) and the relaxation time T_{80} (bottom, nine subjects) of various parameters measured during the hyperoxic phase.
The diamonds mark the means. The cross marks an outlier.

In the hypercapnic phase, the reaction time T_{20} of $EtCO_2$ was 2.1 times faster on average than the reaction time of $tcpCO_2$ ($p < 0.05$). The reaction times of $tcpO_2$, SpO_2 and rSO_2 did not differ significantly. The rSO_2 signal showed the fastest average reaction time 70 s. The relaxation time T_{80} of $EtCO_2$ was 3.4 times faster on average than the relaxation time of $tcpCO_2$ ($p < 0.05$). The relaxation time of $tcpO_2$ was slower than the relaxation times of SpO_2 and rSO_2 ($p < 0.05$), being 3.1 times longer on average than the relaxation time of SpO_2.

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

The response of SpO_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 Tables 2 and 3. 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

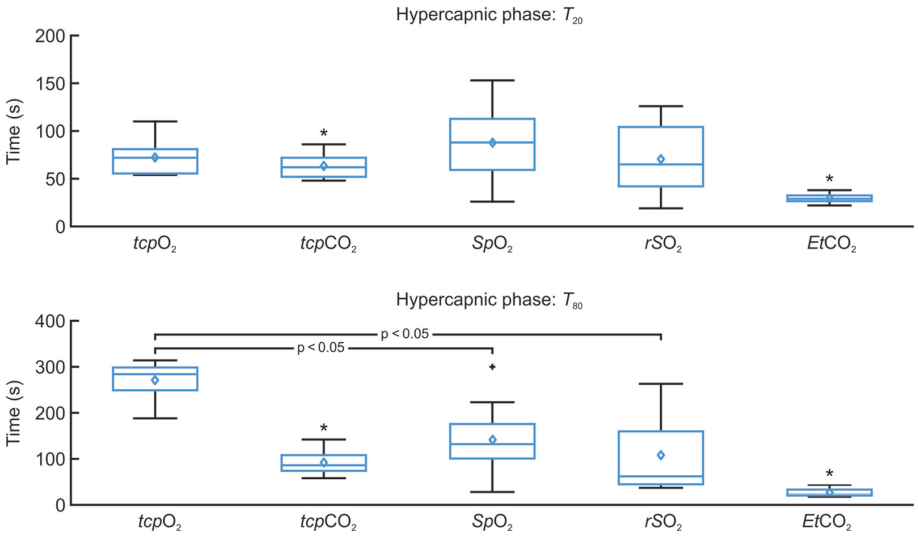

Figure 6: The reaction time T_{20} (top, nine subjects) and the relaxation time T_{80} (bottom, nine subjects) of various parameters measured during the hypercapnic phase.
The diamonds mark the means. The * marks statistical significance ($p < 0.05$) of the parameters related to CO_2. The cross marks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

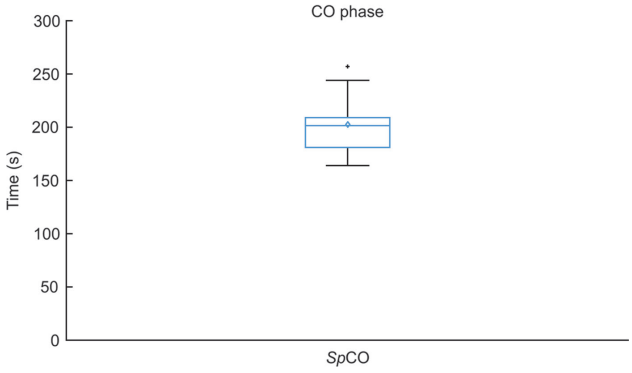

Figure 7: The reaction time (14 subjects) of peripheral oxygen saturation during the CO phase.
The diamonds mark the means. The cross marks an outlier.

and the relaxation time of Nellcor N-600 were slightly smaller than the respective times of Radical-7. In all the experimental phases, both Radical-7 and Carescape B650 exhibited very similar reaction times, but differed in the relaxation times.

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[a]	65 ± 19[a]	56 ± 15
Hyperoxic (9)	43 ± 14	55 ± 28	49 ± 15
Hypercapnic (7)	75 ± 23	119 ± 47[b]	73 ± 41[b]

Data are presented as mean ± standard deviation. [a,b]Marks 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[a]	101 ± 41	121 ± 58[a]
Hyperoxic (9)	149 ± 76[b]	156 ± 60[c]	199 ± 73[b,c]
Hypercapnic (7)	174 ± 108	168 ± 63	218 ± 55

Data are presented as mean ± standard deviation. [a–c]Marks a statistically significant difference ($p < 0.05$) of times during the same phase.

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 $tcpO_2$, spO_2 and rSO_2 which were mutually compared during the hypoxic phase with reduced fraction of O_2 in the inspiratory gas mixture, during the hyperoxic phase with increased fraction of O_2 in the inspiratory gas mixture, and during the hypercapnic phase, where increased fraction of CO_2

stimulated the central nervous system that led to hyperventilation and some increase of alveolar O_2. In the hypoxic and hyperoxic phase, the SpO_2 signal showed the fastest reaction and in the hypercapnic phase, the rSO_2 signal showed the fastest reaction. However, we did not find any significant difference in the reaction time T_{20} of the three parameters in any of the phases. The relaxation time T_{80} of SpO_2 and rSO_2 did not differ significantly in the three experimental phases. The relaxation of $tcpO_2$ was about 2–3 times slower that the relaxation of SpO_2. Slow response of transcutaneous measurement to changes in blood gas tension has been noted since the introduction of the technique into clinical practice [17]. Unlike the optical methods, the $tcpO_2$ measurement consumes oxygen and depends on O_2 diffusion into the electrode. The diffusion can be affected by interindividual dermal or physiological differences and by variations in the sensor location, and high variability of $tcpO_2$ can be expected [13, 26]. Similarly, we attribute large variations in rSO_2 data primarily to interindividual differences and variations in sensor position.

Comparison of various SpO_2 measuring devices showed almost similar reaction times of 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 $tcpCO_2$ and $EtCO_2$. During the hypercapnic phase, $tcpCO_2$ was 2.1 times slower in reaction and 3.4 times slower in relaxation than $EtCO_2$. While $EtCO_2$ can quickly react to changes in alveolar gas composition, there is a lag period for $tcpCO_2$ due to the transport of CO_2 from pulmonary capillaries to the site of the sensor [20].

The speed of reaction to the presence of carbon monoxide in the organism was evaluated during the CO phase. A detectable change in the *Sp*CO parameter of 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. The affinity of hemoglobin for carbon monoxide is 200–250 times that of oxygen and thus CO easily displaces oxygen from hemoglobin, but releases very slowly [16]. When breathing normal air, carboxyhemoglobin has a half-life in the blood of about 5 h [22]. When exposed to 0.3% CO, headache and nausea may occur in 5–10 min [12]. Therefore, the CO phase of the experiment was strictly limited to 3 min. This led to an increase of 4% in *Sp*CO at most. The volunteers were consequently further monitored. We did not observe any further adverse effects of the gas on volunteers during or after the experiment.

The custom-made breathing circuit used for the experiment could have increased breathing effort of volunteers. However, all the volunteers breathed through the same system during all experimental phases and relaxation phases, and the primary focus of the experiment was to compare the performance of various devices within the same phase.

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 towards their reference value might not affect the next experimental phase. The reduced comfort of 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 SpO_2 measurement [10] as it happened to a few volunteers in our experiment.

In this paper, we were able to compare time response of methods for noninvasive 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 [2, 28], etc.

Conclusion

The response times of noninvasive 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 SpO_2, rSO_2 and $tcpO_2$ reacted with approximately the same speed. The transcutaneous measurement detected the return to normoxia with about 2–3 times longer relaxation time than the other methods. During the hypercapnic

phase, *tcp*CO_2 was more than two times slower in reaction and more than three times slower in relaxation than *Et*CO_2. 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.

Acknowledgment: The authors thank Markéta Masopustová for her assistance during the preparation and realization of the experiment.
Funding: The work was supported by grant SGS17/203/OHK4/3T/17 of the Czech Technical University in Prague and by project reg.no. CZ.2.16/3.1.00/21564 from OP Prague Competitiveness.
Conflict of interest statement: The authors state no conflict of interest.

References

[1] Barker SJ, Curry J, Redford D, Morgan S. Measurement of carboxyhemoglobin and methemoglobin by pulse oximetry: a human volunteer study. Anesthesiology 2006; 105: 892–897.
[2] Brugger H, Sumann G, Meister R, et al. Hypoxia and hypercapnia during respiration into an artificial air pocket in snow: implications for avalanche survival. Resuscitation 2003; 58: 81–88.
[3] Buehler S, Jensen MC, Lozano-Zahonero S, et al. The dynamics of carbon dioxide equilibration after alterations in the respiratory rate. Physiol Meas 2013; 34: 1151–1161.
[4] Cairo JM, Pilbeam SP. Mechanical ventilation: physiological and clinical applications. 5th ed. St. Louis: Elsevier 2012.
[5] Casati A, Squicciarini G, Malagutti G, Baciarello M, Putzu M, Fanelli A. Transcutaneous monitoring of partial pressure of carbon dioxide in the elderly patient: a prospective, clinical comparison with end-tidal monitoring. J Clin Anesth 2006; 18: 436–440.
[6] Cherniack NS, Longobardo GS, Staw I, Heymann M. Dynamics of carbon dioxide stores changes following an alteration in ventilation. J Appl Physiol 1966; 21: 785–793.
[7] Ehrenfeld JM, Cannesson M, editors. Monitoring technologies in acute care environments: a comprehensive guide to patient monitoring technology. New York: Springer 2014.
[8] Eichhorn L, Erdfelder F, Kessler F, et al. Evaluation of near-infrared spectroscopy under apnea-dependent hypoxia in humans. J Clin Monit Comput 2015; 29: 749–757.
[9] Feiner JR, Rollins MD, Sall JW, Eilers H, Au P, Bickler PE. Accuracy of carboxyhemoglobin detection by pulse CO-oximetry during hypoxemia. Anesthesia 2013; 117: 847–858.
[10] Gehring H, Hornberger C, Matz H, Konecny E, Schmucker P. The effects of motion artifact and low perfusion on the performance of a new generation of pulse oximeters in volunteers undergoing hypoxemia. Resp Care 2002; 47: 48–60.
[11] Genbrugge C, Dens J, Meex I, et al. Regional cerebral oximetry during cardiopulmonary resuscitation: useful or useless? J Emerg Med 2016; 50: 198–207.
[12] Goldstein M. Carbon monoxide poisoning. J Emerg Nurs 2008; 34: 538–542.
[13] Górska K, Korczyński P, Maskey-Warzęchowska M, Chazan R, Krenke R. Variability of transcutaneous oxygen and carbon dioxide pressure measurements associated with sensor location. Adv Exp Med Biol 2015; 858: 39–46.
[14] Hampson NB. Noninvasive pulse CO-oximetry expedites evaluation and management of patients with carbon monoxide poisoning. Am J Emerg Med 2012; 30: 2021–2024.
[15] Huttmann SE, Windisch W, Storre JH. Techniques for the measurement and monitoring of carbon dioxide in the blood. Ann Am Thorac Soc 2014; 11: 645–652.
[16] Kaymak C, Basar H. Carbon monoxide intoxication – Review. Fabad J Pharm Sci 2010; 35: 163–172.
[17] Kesten S, Chapman KR, Rebuck AS. Response characteristics of a dual transcutaneous oxygen/carbon dioxide monitoring system. Chest 1991; 99: 1211–1215.
[18] Lermuzeaux M, Meric H, Sauneuf B, et al. Superiority of transcutaneous CO_2 over end-tidal CO_2 measurement for monitoring respiratory failure in nonintubated patients: a pilot study. J Crit Care 2016; 31: 150–156.
[19] MacLeod DB, Cortinez LI, Keifer JC, et al. The desaturation response time of finger pulse oximeters during mild hypothermia. Anaesthesia 2005; 60: 65–71.
[20] Nishiyama T, Nakamura S, Yamashita K. Effects of the electrode temperature of a new monitor, TCM4, on the measurement of transcutaneous oxygen and carbon dioxide tension. J Anesth 2006; 20: 331–334.
[21] Nishiyama T, Nakamura S, Yamashita K. Comparison of the transcutaneous oxygen and carbon dioxide tension in different electrode locations during general anaesthesia. Eur J Anaesth 2006; 23: 1049–1054.
[22] Prockop LD, Chichkova RI. Carbon monoxide intoxication: an updated review. J Neurol Sci 2007; 262: 122–130.
[23] Redford D, Paidy S, Kashif F. Absolute and trend accuracy of a new regional oximeter in healthy volunteers during controlled hypoxia. Anesthesia 2014; 119: 1315–1319.
[24] Reid CW, Martineau RJ, Miller DR, Hull KA, Baines J, Sullivan PJ. A comparison of transcutaneous, end-tidal and arterial measurements of carbon dioxide during general anaesthesia. Can J Anaesth 1992; 39: 31–36.
[25] Restrepo RD, Hirst KR, Wittnebel L, Wettstein R. AARC clinical practice guideline: transcutaneous monitoring of carbon dioxide and oxygen: 2012. Resp Care 2012; 57: 1955–1962.
[26] Rich K. Transcutaneous oxygen measurements: implications for nursing. J Vasc Nurs 2001; 19: 55–59.
[27] Roth D, Herkner H, Schreiber W, et al. Accuracy of noninvasive multiwave pulse oximetry compared with carboxyhemoglobin from blood gas analysis in unselected emergency department patients. Ann Emerg Med 2011; 58: 74–79.
[28] Roubik K, Sieger L, Sykora K. Work of breathing into snow in the presence versus absence of an artificial air pocket affects hypoxia and hypercapnia of a victim covered with avalanche snow: a randomized double blind crossover study. PLoS One 2015; 10: e0144332.
[29] Scheeren TWL, Schober P, Schwarte LA. Monitoring tissue oxygenation be near infrared spectroscopy (NIRS): background

and current applications. J Clin Monit Comput 2012; 26: 279–287.
[30] Sivarajan VB, Bohn D. Monitoring of standard hemodynamic parameters: heart rate, systemic blood pressure, atrial pressure, pulse oximetry, and end-tidal CO_2. Pediatr Crit Care Med 2011; 12: S2–11.
[31] Spelten O, Fiedler F, Schier R, Wetsch WA, Hinkelbein J. Transcutaneous $PtcCO_2$ measurement in combination with arterial blood gas analysis provides superior accuracy and reliability in ICU patients. J Clin Monit Comput 2017; 31: 153–158.
[32] Storre JH, Magnet FS, Dreher M, Windisch W. Transcutaneous monitoring as a replacement for arterial PCO_2 monitoring during nocturnal non-invasive ventilation. Resp Med 2011; 105: 143–150.
[33] Tobias JD. Transcutaneous carbon dioxide monitoring in infants and children. Pediatr Anesth 2009; 19: 434–444.
[34] Trivedi NS, Ghouri AF, Shah NK, Lai E, Barker SJ. Pulse oximeter performance during desaturation and resaturation: a comparison of seven models. J Clin Anesth 1997; 9: 184–188.
[35] van Oppen JD, Daniel PS, Sovani MP. What is the potential role of transcutaneous carbon dioxide in guiding acute noninvasive ventilation? Resp Care 2015; 60: 484–491.
[36] Vazquez AL, Fukuda M, Tasker ML, Masamoto K, Kim SG. Changes in cerebral arterial, tissue and venous oxygenation with evoked neural stimulation: implications for hemoglobin-based functional neuroimaging. J Cereb Blood Flow Metab 2010; 30: 428–439.
[37] Walsh BK, Crotwell DN, Restrepo RD. Capnography/capnometry during mechanical ventilation: 2011. Resp Care 2011; 56: 503–509.
[38] Yip WL. Evaluation of the clinimetrics of transcutaneous oxygen measurement and its application in wound care. Int Wound J 2015; 12: 625–629.
[39] Yu M, Morita SY, Daniel SR, Chapital A, Waxman K, Severino R. Transcutaneous pressure of oxygen: a noninvasive and early detector of peripheral shock and outcome. Shock 2006; 26: 450–456.

Rafl, J., Kulhanek, F., Kudrna, P., Ort, V. and Roubik, K., 2018. Response time of indirectly accessed gas exchange depends on measurement method. Biomedical Engineering/ Biomedizinische Technik, 63(6), pp.647-655.