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Specifics of medical equipment during field breathing experiments

Specifika použití lékařské přístrojové techniky během terénních dýchacích experimentů

Disertační práce

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Prohlašuji, že jsem disertační práci s názvem Specifika použití lékařské přístrojové techniky během terénních dýchacích experimentů vypracovala samostatně a použila k tomu úplný výčet citací použitých pramenů, které uvádím v seznamu přiloženém k disertační práci.

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ABSTRAKT

Terénní dýchací experimenty jsou důležitým podkladem pro vytváření a aktualizování mezinárodních doporučení pro záchranu a resuscitaci obětí zasypaných sněhovou lavinou. U tohoto typu experimentů ovšem byla zaznamenána celá řada medicínských i technických specifik, zvláště v použití lékařské přístrojové techniky původně určené pro monitoraci pacientů v rámci anestezie a intenzivní medicíny. Cílem této disertační práce je analyzovat specifika použití lékařské přístrojové techniky během terénních dýchacích experimentů se zaměřením na pulzní oxymetrii a související parametr – perfuzní index (*PI*).

Analyzovaná data pocházejí ze studie na 13 dobrovolnících, kteří pomocí speciálně upravené aparatury dýchali do simulovaného lavinového sněhu, nebo do materiálu, který měl takový sníh imitovat. Během tohoto dýchání došlo k rozvoji progresivní hypoxémie a hyperkapnie spolu se zvýšenou dechovou prací, což jsou i hlavní identifikovaná patofyziologická rizika těchto experimentů. Každý proband byl simultánně monitorován pomocí pěti různých sond pro pulzní oxymetrii na prstech pravé ruky. V průběhu experimentu byly pozorovány rozdíly v zobrazených hodnotách periferní saturace (SpO_2) a to jak v rychlosti nástupu desaturace, tak i v nejnižší dosažené hodnotě a návratu zpět k normálním hodnotám po ukončení experimentu. Rozdíly mezi jednotlivými pulzními oximetry v čase dosažení teoretické cílového hodnoty experimentu 75 % nebo 85 % SpO_2 byly až 50 s, respektive 90 s, což by znamenalo potenciální zkrácení experimentu až o jednu čtvrtinu času. Jeden pulzní oxymetr navíc ve 41 % případů ukazoval stereotypně nejnižší zobrazenou hodnotu ještě v době, kdy již ostatní čtyři přístroje zaznamenávaly normální saturaci probanda. Perfuzní index probandů během těchto experimentů nenaznačoval, že by problémem ve správnosti zobrazené hodnoty SpO_2 byla limitace této metody v podobě nízké perfuze monitorovaných prstů. Hodnoty *PI* probandů se výrazně nelišily od hodnot v řadě studií mimo outdoorové prostředí a během samotného dýchacího experimentu nedošlo ke statisticky významnému poklesu *PI*, a to ani během úvodní stabilizační fáze. Po odpojení probanda od aparatury ovšem došlo k dvoj- až trojnásobnému nárůstu hodnoty *PI*, což bylo pravděpodobně způsobeno vazodilatačním efektem nashromážděného oxidu uhličitého při progresivní hyperkapnii.

Na základě závěrů z této disertační práce byla vytvořena doporučení pro další podobné studie.

KLÍČOVÁ SLOVA

terénní dýchací experimenty, hypoxie, hyperkapnie, pulzní oxymetrie, perfuzní index, limitace lékařské přístrojové techniky

ABSTRACT

Field breathing experiments form an important basis for designing and updating international guidelines for the rescue and resuscitation of avalanche snow-buried victims. However, several medical and technical specifics have been identified for these experiments, especially when medical equipment designed for monitoring patients in anaesthesia and critical care is used. The aim of this doctoral thesis is to analyse the specifics of the use of medical equipment during field breathing experiments, specifically pulse oximetry and the associated parameter—perfusion index (*PI*).

The analysed data originate from a clinical trial involving 13 subjects who breathed through a specially designed breathing apparatus into simulated avalanche snow or snow model material. During the experimental breathing, progressive hypoxemia, hypercapnia, and increased work of breathing developed, which are also the main pathophysiological aspects identified in these experiments. Each subject was simultaneously monitored by five different pulse oximeters on the right-hand fingers. The peripheral oxygen saturation (SpO_2) readings differed significantly throughout the experiment. They varied in the time of desaturation onset, in the lowest measured SpO_2 value, and in the duration of the recovery phase, when the subject was already breathing ambient air and the oxygen saturation was returning to pre-experimental values. The differences among individual pulse oximeters in the time of reaching the theoretical study endpoint SpO_2 of 75% or 85% was as much as 50 s, and 90 s, respectively, which could have shortened the experimental breathing by up to one-quarter of the time. Moreover, one pulse oximeter had a tendency to show, in more than 41% of cases, the lowest measured value for a prolonged period of time, whereas the SpO_2 level was within the normal range according to the other devices. The perfusion index values during these experiments did not suggest that the error source in the displayed SpO_2 was caused by the limitation of the method, which is the low perfusion of the monitored fingers. The *PI* values did not differ significantly from the values recorded in many studies outside the outdoor environment. In the breathing experiment, there was no statistically significant decrease in *PI*, not even during the initial stabilisation phase. Following the subject disconnection from the apparatus, a two- to threefold surge in *PI* occurred, very likely due to the vasodilation effect of the accumulated carbon dioxide during progressive hypercapnia.

Based on the conclusions of this doctoral thesis, several recommendations for similar future trials were created.

KEYWORDS

field breathing experiments, hypoxia, hypercapnia, pulse oximetry, perfusion index, medical equipment limitations

Content

List of symbols and abbreviations

Notes

The capital “L” is used for “litre” throughout the thesis. This prevents confusion about the small “l” and the digit “1” in the text. This approach is preferred in respiratory care literature.

For numerical values with mathematical operations, the unit symbol belongs to all numerical values even though the brackets are omitted; e.g., instead of (3.93 ± 0.87) kPa, only 3.93 ± 0.87 kPa is used with the same meaning. This approach is more common in the cited literature.

List of symbols

Symbol	Unit	Meaning
pO_2	kPa, mmHg	partial pressure of oxygen
pCO_2	kPa, mmHg	partial pressure of carbon dioxide
PaO_2	kPa, mmHg	arterial partial pressure of oxygen
$PaCO_2$	kPa, mmHg	arterial partial pressure of carbon dioxide
FiO_2	%	Inspiratory fraction of oxygen
EtO_2	%	End-tidal fraction of oxygen
$FiCO_2$	%	Inspiratory fraction of carbon dioxide
$EtCO_2$	%, kPa, mmHg	End-tidal fraction of carbon dioxide
FiN_2O	%	Inspiratory fraction of nitrous oxide
EtN_2O	%	End-tidal fraction of nitrous oxide
Vt	mL	Tidal volume
MV	$L \cdot min^{-1}$	Minute ventilation
$I:E$	–	Inspiration to expiration time ratio
Paw	cmH_2O	Airway pressure
$FEV1$	L	Forced expiratory volume in 1s
FVC	L	Functinal vital capacity
SpO_2	%	Peripheral oxygen saturation
SaO_2	%	Arterial blood fractional oxygen saturation
ScO_2	%	cerebral oxygenation saturation
$SctO_2$	%	saturation cerebral tissue oxygenation

RR	breaths per minute	Respiratory rate
HR	beats per minute (bpm)	Heart rate
BMI	$kg \cdot m^{-2}$	Body mass index
IQR	(unit of the respect variable)	interquartile range
SEM	(unit of the respect variable)	standard error of mean
SD	(unit of the respect variable)	standard deviation

List of abbreviations

Abbreviation	Meaning
AED	Automated Eternal Defibrilator
ASA	American Society of Anaesthesiologists
ATPD	ambient temperature and pressure, dry
BTPS	body temperature, ambient pressure and saturated with water vapour
CO_2	carbon dioxide
DST	Descrete Saturation Transform
ECG	Electrocardiography
EEG	Electroencephalography
ICU	Intensive care unit
NIRS	Near-infrared spectroscopy
N_2O	Nitrous oxide
O_2	Oxygen
PD	Perlite dry
PW	Perlite wet
S	Snow
SET	Signal Extraction Technology
STPD	standard temperature and pressure, dry

1. Introduction

Avalanche burials represent one of the most dangerous risks associated with winter activities in the mountains. According to compendious statistics from the European Alps, the number of accidents has remained stable at around a hundred fatalities per year throughout the last 40 years [1], despite the broad inter-annual and inter-areal fluctuations.

The survival chances depend on multiple factors: trauma sustained during the accident, the length and depth of the snow burial, and the presence of an air pocket [2-4]. The most common cause of death in avalanche victims is suffocation. Up to 90% of the casualties die because of asphyxia [3,5-7]. This occurs as a consequence of blocked airways or due to severe hypoxia and hypercapnia resulting from rebreathing previously exhaled gas. The mechanism of gas exchange in a snow-buried avalanche victim has not yet been fully elucidated and is a subject of worldwide research.

A number of outdoor breathing trials with healthy volunteers have been conducted in order to investigate the gas exchange limitations and work of breathing effects on the probability of survival under avalanche snow. During these trials, volunteers are monitored with medical equipment in order to obtain research data and ensure the safety of the subjects. However, the monitoring equipment is challenged by the outdoor environment and physiological changes that are different from what could be seen in critically ill patients, and potential errors have already been identified [8].

2. State of the art

2.1 Breathing field experiments simulating avalanche snow burials

Breathing field experiments simulating avalanche burials and their designs vary to a great extent. The main research focus is on the gas exchange occurring in the air contained within the snow and the role of an 'air pocket' in front of the victim's airways.

The air pocket is standardly defined as any space surrounding the avalanche victim's nose and mouth, no matter how small, in the presence of the victim's patent airway. No air pocket has a victim whose mouth and nose are sealed with snow or debris [9]. Especially the question of the size of the air pocket has drawn a lot of scientific attention since the 1990s [10]. Initially, the presence and size of the air pocket appeared to be critical for survival [11]; however, Roubík *et al.* proved that breathing into snow is possible even without a formed air pocket in front of patent airways [12].

The most important risk factors have been identified, and survival chances calculated in relation to the length of burial time by Falk and Brugger, based on the data collected in the Switzerland Alps between the years 1981 and 1991. It was postulated that the plummeting survival chances, reaching 92% at the 15th minute but only 30% at the 35th minute, were caused by asphyxia due to a lack of an air pocket or free airways. The second drop from 27% at the 90th minute to just 3% at the 130th minute was presumed to be due to a slow onset of hypoxia and hypothermia [3]. The revision of the survival probability statistics, published in 2001, confirmed the previously proposed survival curve [9].

Survival statistics, together with experimental studies, contributed to the international avalanche rescue and resuscitation guidelines [13-16]. In these guidelines, the recommendations moved from the emphasis on organised rescue to the 'companion rescue' concept. It has been proved that the other group members have more chances to dig up the avalanche victim than the professional rescuers who get to the site with a significant delay [3]. This change in the concept would not be possible without the numerous studies focused on survival chances related to burial time and depth.

2.2 Field experiments studying asphyxia in avalanche victims

Asphyxia is commonly caused by the rebreathing of expired gas containing increasing partial pressure of carbon dioxide (CO_2). In obedience to the alveolar gas equation, oxygen (O_2) is replaced by this waste gas. Significant hypercapnia and hypoxemia have been observed in many

of the simulated avalanche experiments, no matter how big the artificial air pocket in the snow was [12,17,18].

For instance, Grissom *et al.* had a group of seven volunteers buried in snow and breathing into a 0.5 L air pocket. After a mean time of 10 minutes (range 5–14 minutes), the end-expiratory partial pressure of carbon dioxide ($EtCO_2$) increased from a mean value of 4.3 kPa (range 3.6–5.1 kPa) to 7.2 kPa (range 5.9–8.4 kPa) and peripheral oxygen saturation (SpO_2) decreased from a mean value of 96% (range 90–99%) to 84% (range 79–92%) [17]. Brugger and colleagues compared breathing into 1 L and 2 L air pockets. After four minutes, they recorded an increase in $EtCO_2$ from 5.1 kPa (range 3.5–6.9 kPa) to 6.8 kPa (range 5.9–8.3 kPa), and SpO_2 decreased from 99% (range 93–100%) to 88% (range 71–94%). The increase in $EtCO_2$ within the first 4 min of the experiment was affected by neither the air pocket nor the snow density. This was in contrary to the decrease of SpO_2 and suggests some CO_2 buffer capacity of the snow surrounding the air pocket [18]. An auspicious randomised prospective porcine study prepared by the same team had to be stopped prematurely due to ethical disputes [19,20].

As the accumulation of carbon dioxide seems to be one of the crucial factors limiting survival, several systems for drainage of this waste gas have been developed and tested, allowing the transition of the research outcomes to practical life. Grissom *et al.* [17] tested a device with a 500 cm^3 artificial air pocket built into a vest. This was a prototype of a device called AvaLung (Black Dimond Equipment Ltd, Salt Lake City, UT, USA). With this device, the victim breathes through a mouthpiece with an expiratory one-way valve and is allowed to inhale the air contained in the snow but to exhale carbon dioxide away from the air pocket formed in the snow, thus preventing CO_2 accumulation. The effectivity was proven in the above-mentioned study [17], and furthermore, there have been several case reports of avalanche survivors using this equipment. One of them was a skier surviving more than 20 min of avalanche burial using the AvaLung. From the group of three people affected by this particular accident, only the man equipped with this device survived. However, after using it initially, he spit it out consequently and was found buried 1.5–2.0 m deep and unconscious [21].

In the attempt to simplify the avalanche breathing device, a simple valveless tube has been tested. This ‘Snow Snorkel’ was used just to exhale while the volunteers inhaled the air around the tube from the surrounding snow. Seven out of nine subjects managed to stay buried using this equipment for the whole planned 60 min. On the other hand, the valveless design increases the expiratory resistance significantly (as was experienced by two of the abortive volunteers), and the ideal proportion of radius and length of the tube, as per the Hagen-Poiseuille equation, needs to be determined [22].

These and other technological advances were reviewed by Radwin and Grissom [23]. Some types of equipment are gaining increasing popularity among backcountry skiers. One example can be an airbag system, a backpack containing a large inflatable bag, helping the avalanche victim stay on the surface of the snow mass (using the principle of inverse segregation). There are some geographical differences in the users' preferences: North American travellers prefer AvaLung to airbag systems [24]. In the Alps, increasingly popular avalanche airbags effectively lowered the risk of critical burial. However, 20% of avalanche victims who successfully deployed their airbags ended up critically buried [25].

A recent study by McIntosh *et al.* [26] used both AvaLung and an avalanche airbag (JetForce, Black Dimond Equipment Ltd, Salt Lake City, UT, USA), which actively deflates three minutes after deployment, creating an approximately 200 L air pocket [27] posterior to victims head and backpack. During the experiment, the AvaLung was favourably placed to the artificially created air pocket, preventing effectively rebreathing of the exhaled gas. Eleven out of twelve participants managed to remain buried for the planned 60 min; one had to be extricated at 48 min due to tachycardia, hypercapnia and anxiety. In all participants, SpO_2 was well maintained, $EtCO_2$ values remained also in the target physiological range 35–45 mmHg (4.7–6.0 kPa), except in one participant reaching $EtCO_2$ of 50 mmHg (6.7 kPa) upon extrication. The authors compared their results to a study with AvaLung only [17], concluding that the oxygenation and CO_2 levels were better maintained when the subject was breathing from the air pocket created by the airbag.

2.3 Medical aspects of field breathing experiments

While conducting field breathing experiments, such as simulated avalanche burial, it is essential to minimise any medical risks posed to the subjects. This can be primarily ensured by the meticulous selection of participants. Most studies are designed for healthy volunteers, scoring ASA 1 according to the American Society of Anaesthesiologists [28], without any known moderate or severe cardio-respiratory disease and non-smokers. One study included two volunteers suffering from asthma, both treated with beta-agonist inhalers. Prior to a breathing experiment, both self-administered their usual inhalers, and no bronchoconstriction manifested [17]. In case of any emergencies, the presence of a skilled physician is crucial, along with advanced vital sign monitoring. Fortunately, only minimal medical issues have been reported in the literature during outdoor breathing experiments. On the other hand, the participants need to face the conditions seen in snow burial victims: the triad of hypoxia, hypercapnia, and hypothermia. Moreover, all these pathophysiological situations are associated with an increased risk of arrhythmias.

2.3.1 Hypoxia and hypercapnia

The main medical risks associated with rebreathing into an air pocket are the effects of hypoxia and hypercapnia, while hypercapnia has a more significant effect on haemodynamic stability compared to hypoxia [29]. In some of the trials, the end-tidal O_2 (EtO_2 in kPa, mmHg, %) and end-tidal CO_2 ($EtCO_2$ in kPa, mmHg, %) reached values that would be considered critical in an intensive care unit (ICU) setting. Other sports and outdoor experiments also documented extreme alveolar gas partial pressures.

For instance, a similar situation in terms of short-lasting, profound changes in arterial partial pressures of gases can be seen in breath-hold divers: a combination of hypoxia and hypercapnia together with a concomitant acidosis due to the cumulation of blood and tissue CO_2. For example, Willie *et al.* [30] measured the end-apnoea end-tidal partial pressure of PaO_2 and $PaCO_2$ during a static dry apnoea in breath-hold divers, reaching 29.5 ± 6.5 mmHg (3.93 ± 0.87 kPa) and 51.0 ± 6.7 mmHg (6.80 ± 0.98 kPa) respectively; arterial saturation (SaO_2) fell down to 56.7 ± 11.3%. Obviously, there is a great deal of adaptation to these derangements among elite free divers.

Another example of hypoxia observed in healthy young athletes is hypobaric hypoxia, typical for high altitude, where hypoxemia is generally accompanied by respiratory alkalosis and hypocapnia due to compensatory hyperventilation. The lowest values of arterial partial pressure of O_2 (PaO_2) recorded during a simulated high altitude ascent to 8848 m in a hypobaric chamber was 30.6 ± 1.4 mmHg (4.08 ± 0.19 kPa), with the lowest recorded values of $PaCO_2$ 11.9 ± 1.4 mmHg (1.59 ± 0.19 kPa); the lowest recorded SpO_2 measured from arterialised capillary blood was 67.9% at 8000 m above sea level [31]. During an experiment conducted on Mt. Everest in the Himalayas, arterial blood samples were obtained at the altitude of 8400 m following a successful summit ascent. Four climbers were tested while breathing ambient air. A mean PaO_2 of 24.6 mmHg (3.28 kPa) and a mean $PaCO_2$ of 13.3 mmHg (1.77 kPa) were measured by a bench-top blood gas analyser placed at 6400 m [32].

In all these experiments, conducted on mountaineers, free-divers and other healthy volunteers, there were measured short-time excursions to alarming levels of hypoxemia and hypo- or hypercapnia, mainly seen in critically ill patients. However, the recovery was always rapid back to normal.

These outstanding changes in subjects' physiology necessitate detailed monitoring. Apart from the technical means, clinical observation is a high priority. Perception of both hypoxemia and hypercapnia is highly subjective. A continuous assessment of the subject's awareness and cognition may help recognise changes in consciousness.

After their experiments [12], Roubík *et al.* conducted a short interview with each of the volunteers to evaluate their subjective perception of the changes in their consciousness (described in [33]). From the answers, it was clear that the subjective perception of the arterial gas changes differed greatly. The feeling of losing control over the situation occurred in two men out of twelve. One of them was disconnected from a zero air pocket by the supervising physician after 330 s when his $EtCO_2$ reached 8.4%. Another one described worsening dyspnoea, which suddenly started to improve, and he experienced relief. He was also disconnected at this point and reached a maximum $EtCO_2$ of 10.2%, compared to another subject, who, at the level of $EtCO_2$ of 9.5%, did not have any problems with dizziness, changes in mental state or headache.

2.3.2 Hypothermia

Only 1–2% of avalanche victims die of hypothermia [7]. Despite careful heat protection, changes in the core temperature of outdoor breathing experiment participants may occur. Grissom *et al.* had one subject who requested an experiment termination because he was cold and shivering [17]. Another subject in Radwin's snow burial trial had to be removed from the snow, as his core body temperature dropped after 73 min below 35 °C [34].

Grissom *et al.* [11] even studied the effect of hypercapnia on the cooling rate of the avalanche victim. It can be challenging to measure the body temperature in pre-hospital medical care [35] and during the avalanche snow breathing experiments. Different means have been investigated. Rectal thermometers and skin temperature probes applied on different body sites are standardly used [11]. One study [36], assessing the effect of head and face insulation on the cooling rate of the avalanche victim's body, was also using a special remotely transmitting swallowed capsule (Vital-Sense Philips Respironics, Bend, OR), which the authors recommended in future experiments. The other mean of temperature monitoring—the oesophageal probe—can be problematic to employ in an awake subject, and in a group of 9 volunteers in this study, one subject failed to swallow the oesophageal temperature probe.

2.3.3 Arrhythmias

Different types of arrhythmias have been reported as side effects of both hypoxia and hypercapnia. In one study [17], participants were studied for haemodynamic changes at $EtCO_2$ of 7 kPa, and an increase in QT dispersion was shown [37].

As for simulated avalanche burial experiments, occasional premature ventricular beats developed during the last minute of the experimental snow burial in the AvaLung study, and the testing of the same subject had to be terminated prematurely due to hypoxia [17]. In experiments conducted by Roubík *et al.* [12], one of the volunteers had to be excluded due to frequent bigeminal

ventricular extrasystoles. The medical literature suggests frequent premature ventricular complexes can evolve into malignant ventricular arrhythmias, ventricular tachycardia, or even ventricular fibrillation [38]. These changes in electric cardiac activity have been found to increase the risk of sudden cardiac death not only in patients with structural heart disease [39] but also among young healthy athletes with concealed cardiopathy [40]. As these rhythms rank among the shockable ones, the availability of emergency equipment and drugs as per current resuscitation guidelines should be mandatory, including the Automated External Defibrillator (AED) [15].

During their study, Wik and colleagues [41] used external defibrillation pads connected to LIFEPAK 15 (LP15, Stryker, Redmond, WA, USA) to record subjects' ECG and transthoracic impedance. This approach would enable immediate treatment of a shockable rhythm but would mean significantly higher costs per subject compared to ECG electrodes.

2.4 Technical aspects of breathing experiments

Apart from the above-mentioned physiological and medical challenges of these experiments, technical aspects must be taken into account, namely the outdoor environment and the use of snow, whose properties can vary from day to day and within one day. Moreover, a specially designed breathing apparatus is often used with additional limitations.

2.4.1 Environmental conditions

As the breathing experiments to the snow are usually conducted in mountain areas, the effect of high altitude should be considered. At high altitudes, the reduced ambient pressure, compared to atmospheric pressure measured at sea level, is an important parameter to consider (Figure 2.1).

On the other hand, none of the principal field studies on breathing into simulated avalanche snow was conducted at high altitudes, commonly defined as altitudes above 2500 m [42]. The minority of the studies took place above 2000 m (2100 m [26], 2385 m [17,34]), and some studies were conducted between 1000 m and 2000 m (1499 m [43,44], 1640 m [18], 1895 m[20]), but several of them were situated even below 1000 m (660 m [41], 762 m [12,45]). As we can see from Table 2.1, the 2000 m difference from sea level in inspired moisturised pO_2 is 4.6 kPa (35 mmHg), which is a considerable difference in case we want to compare absolute numbers in the field experiment results [46].

Table 2.1 Barometric pressure and partial pressures of oxygen at altitude 0–3000 m (modified from [46]).

Altitude	Barometric pressure		Atmospheric pO_2		Inspired pO_2*	
m	kPa	mmHg	kPa	mmHg	kPa	mmHg
0	100	760	21	159	20	150
1000	90	674	18.9	142	17.4	132
2000	80	596	16.8	125	15.4	115
3000	70	526	14.7	111	13.4	100

* Inspired pO_2 is calculated as: oxygen fraction in inspired air × [barometric pressure − saturation pressure of water at 37 °C (6.3 kPa / 47 mmHg)].

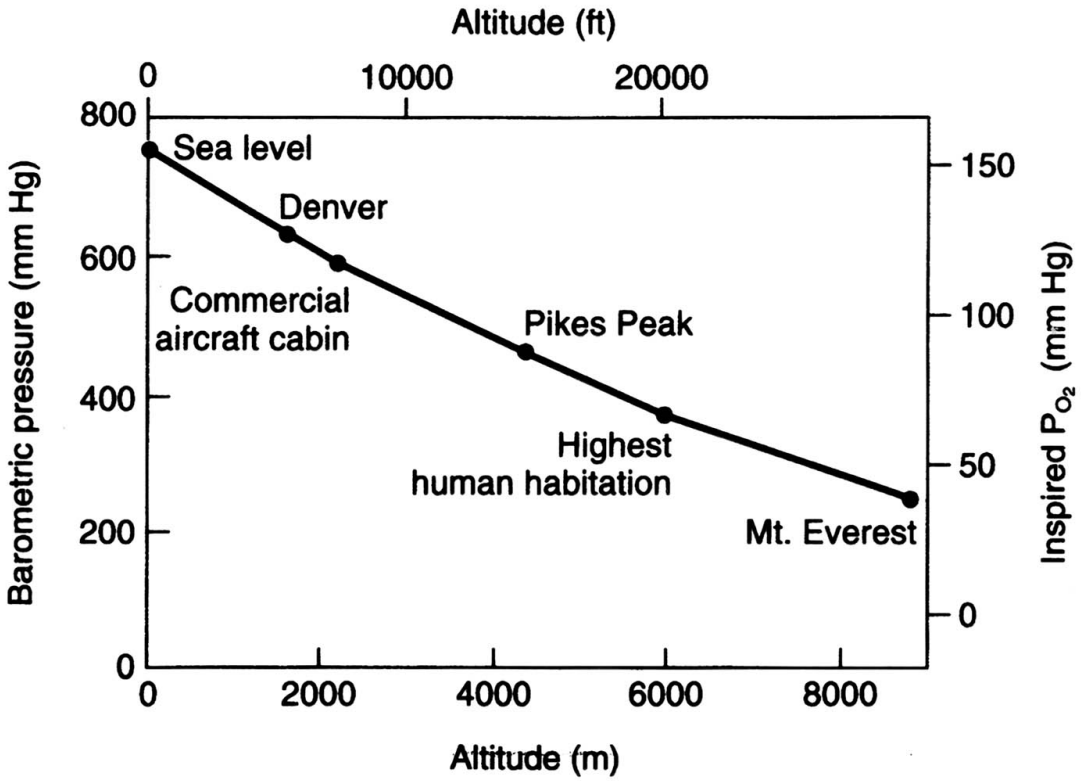

Figure 2.1 Relationship between altitude, barometric pressure and inspired pO_2 (modified from [29]).

The partial pressure may be expressed by the monitor under several conditions denoted as BTPS (body temperature, ambient pressure and saturated with water vapour), ATPD (ambient temperature and pressure, dry), or recalculated to standard conditions at a standard temperature of 0 °C and a standard pressure of 101.325 kPa (760 mmHg), denoted as STPD (standard temperature and pressure, dry). STPD makes the comparison of different subjects even from different test sites possible but is not optimal for assessment of the vital signs of the subjects, whereas the parameters expressed in BTPS describe the real physiological state of the organism optimally. A detailed description of standardised measurement conditions is presented in Table 2.2.

Table 2.2 The detailed description of standardised conditions of measurement.

Abbreviation	Meaning	Values	Comments
BTPS	Body temperature, ambient pressure, saturated with water vapour	Body temperature (estimated 37 °C), ambient barometric pressure, saturated with water vapour of 6.3 kPa (47 mmHg) at 37 °C[1]	Gas under conditions in the human body, i.e. heated to body temperature and saturated with water vapours at this temperature
ATPD	Ambient temperature and pressure, dry	Ambient temperature (estimated as room temperature 20 °C), ambient barometric pressure, dry air (not saturated with water vapour)	Gas volumes obtained during spirometry at ambient conditions
STPD	Standard temperature and pressure, dry	Standard temperature 0 °C, standard pressure 101.3 kPa (760 mmHg), dry air (not saturated with water vapour)	Gas volume under standard conditions— enables to compare results obtained under different conditions

[1]Variations in the range of 35–39 °C are of a little importance.

Furthermore, medical devices usually allow presentations of the composition of respiratory gases (FiO_2, EtO_2, $FiCO_2$ and $EtCO_2$) expressed not just as a partial pressure of the corresponding gas in the mixture (expressed in kPa or mmHg) but also as a fraction of the corresponding gas in the gas mixture (i.e., expressed in %). If, for example, the maximum allowed $EtCO_2$ value set for termination of a breathing experiment for safety reasons is 8%, it represents $EtCO_2$ of 8 kPa at sea level, whereas it is 7.2 kPa at 1000 m and only 6.4 kPa at 2000 m above sea level. Vice versa, if the set $EtCO_2$ limit is 8 kPa, it corresponds to $EtCO_2$ of 8% at sea level but to 8.9% at 1000 m and even 10% at 2000 m.

2.4.2 Snow properties

The physical properties of the snow can affect the survival of avalanche victims. Snow density showed a significant positive correlation to the decrease in oxygen saturation within the first four minutes [18] and time-to-interruption in air pocket studies [43].

The snow properties differed among the published experiments. The average avalanche snow density ranges from 200 $kg \cdot m^{-3}$ (dry snow) to 550 $kg \cdot m^{-3}$ (wet or dry) [47]. Brugger *et al.* had a median snow density in the completed tests 376 $kg \cdot m^{-3}$ (range 144–546 $kg \cdot m^{-3}$) [18], Roubík *et al.* 380 ± 14 $kg \cdot m^{-3}$ [12], Wik *et al.* 358 $kg \cdot m^{-3}$ (range 278–434 $kg \cdot m^{-3}$) [41]. Strapazzon *et al.* [43] even conducted three series of experiments, time separated, with the median snow density 364 $kg \cdot m^{-3}$ (range 155–481 $kg \cdot m^{-3}$), and then correlated the data describing the individual respiratory gas and ventilatory specifications with certain snow densities (≤250, 251–350 and >350 $kg \cdot m^{-3}$). They concluded that the snow properties directly affect the ventilation and gas exchange parameters. Furthermore, they showed a rapid decline in SpO_2 and an increase in $EtCO_2$ associated with higher snow densities. Laboratory experiments on gas distribution and absorption in snow have been proposed.

For snow-based experiments, its temperature is also important in addition to the density of snow. Weather changes often do not provide stable climate conditions for the experiment. Snow has a large heat capacity; therefore, the temperature at a depth of 50 cm and more is minimally affected by the daily changes in air temperature. Snow temperature measurement is wise to carry out during these experiments continuously (e.g., for the whole week of experiments) by a data-logger at reasonable (e.g. 5-min) time intervals. According to the international standard ISO 2533:1975/Add.2:1997 [48], the air temperature is recommended to be measured 5 cm above the snow surface and the temperature of snow at depths of 10, 20, 30, 40 and 50 cm. An example of such a record of temperature development over four days during a simulated avalanche study [12] is presented in Fig. 2.2. The graph documents that the snow temperature variability significantly decreases with the increasing snow depth.

2.4.3 Air leak during breathing experiments and its detection using nitrous oxide

Some outdoor breathing experiments investigate the gas diffusion in simulated avalanche snow. For this purpose, a meticulous separation of the simulated air pocket and ambient air is essential. Some studies use adapted breathing tubing systems with a mouthpiece [12,45] or a face mask [18,43,44], while others chose complete snow burial [17,26,34] or partial burial with the subject's head inserted into a snow pile [41]. As most of the volunteers experience hyperventilation and increased work of breathing while simulating respiration under the avalanche snow, some concerns may be raised regarding the leak tightness of some of these systems. Although the aut-

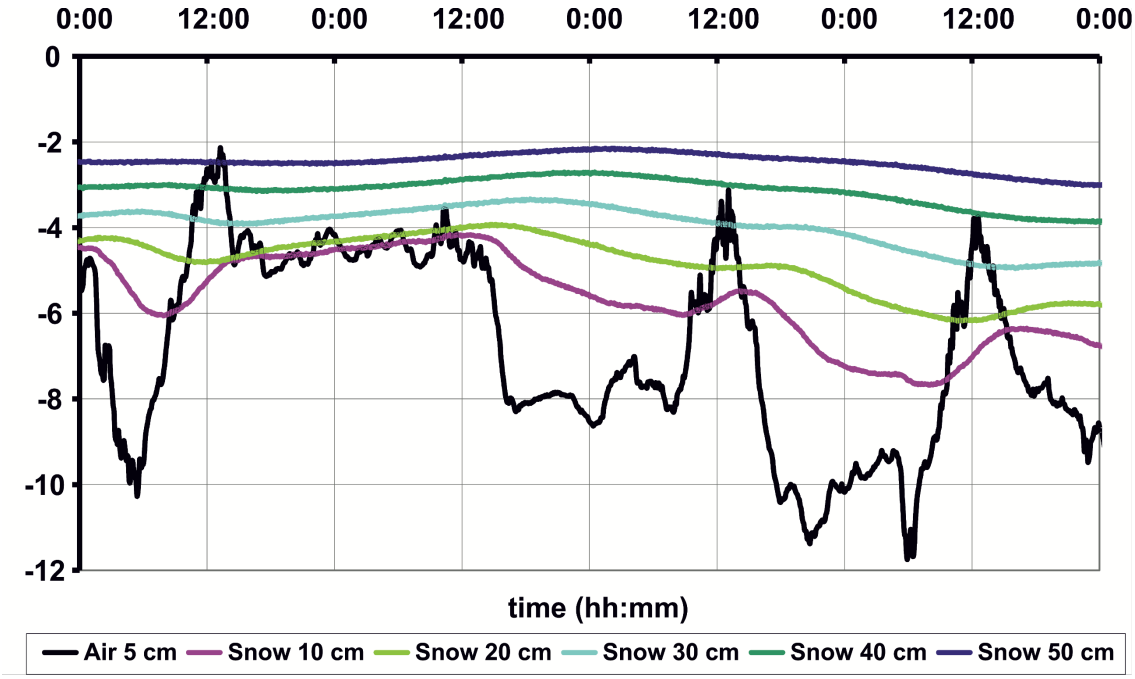

Figure 2.2 Variation of air temperature during a four day experiment measured 5 cm above the snow surface (the black line) and its effect on temperature of snow measured at different depths of 10, 20, 30, 40 and 50 cm below the surface.

hors declare an "airtight connection between the tube and artificial air pocket" and a "hermetically fitting facial mask" [18], no means of air tightness verification is mentioned in the study methodology.

Wik *et al.* [41], instead of using a breathing tubing system, inserted the whole head of the subject into a preformed air pocket in simulated avalanche snow and tried to seal it with a plywood plate and a tailor-made diving neck seal. With this setting, four out of five subjects who completed a 25-minute breathing trial without air supplementation had to be excluded from the analysis due to a leak of ambient air into the air pocket. Figure 2.3 depicts the SpO_2 and O_2 levels in the air pocket of all study subjects; the orange dashed lines are of those participants excluded due to air leaks. We can see that in these cases, the air pocket oxygen does not decrease continuously, or following some decrease, the level starts to increase again. Although not mentioned in the original paper, these observations likely indicate the mixing of air pocket gas (with low O_2 concentration) with ambient air (with normal O_2 concentration), which leaked into the pocket. Similar behaviour can be seen in SpO_2 values, which mirror this air leak in the subjects' physiology.

Roubík and colleagues [12] introduced nitrous oxide (N_2O) as a tracing gas during outdoor breathing experiments for air leak detection. Potential gas leaks can also be caused by a slipped nose clip or when the subject inhales air other than that from the prepared circuit accidentally or

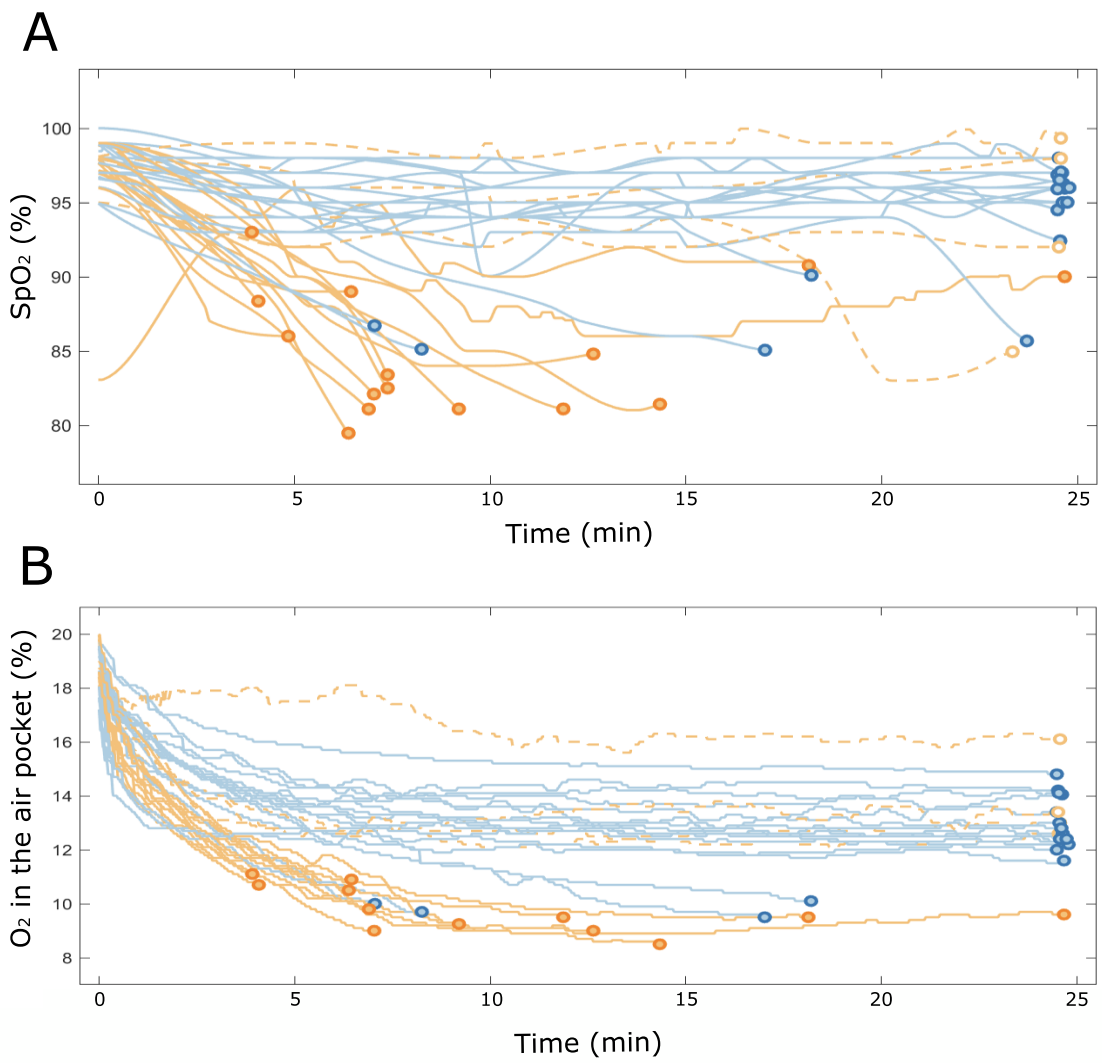

Fig. 2.3 Selected results of 20 subjects from the study by Wik et al. A. *SpO₂* values; B. O_2 levels in the air pocket. Blue lines represent treatment group receiving supplementary oxygen whilst breathing into air pocket in the snow, orange lines represent control group without supplementary oxygen. Orange dashed lines depict data excluded from the analysis due to air leak. Modified from [41].

intentionally. Even a negligible concentration of N_2O is easily detectable by the anaesthetic module of the vital sign monitor (for instance, E-CAiOVX, Datex-Ohmeda, Madison, WI, USA). Its properties should be carefully considered and tested for future use of this anaesthetic gas as a tracer in field breathing experiments.

Nitrous oxide appears to be an ideal tracing gas as it is a vapour with a long history of administration as an anaesthetic and analgesic agent. It has several favourable physical properties: it is a colourless and mostly odourless gas, moreover heavier than air (density 1,98 $kg \cdot m^{-3}$ [gas, 0 °C]). For anaesthetic purposes, N_2O is usually used in a mixture with oxygen in concentrations ranging from 50%:50% to 70%:30% N_2O:O_2. Most administering systems guarantee a minimal fraction of inspired oxygen (FiO_2) of 30% to avoid hypoxemia [49].

It is very convenient for a hospital, an outpatient clinic, or even a field use that this gas is manufactured into tanks of different sizes and stored as a vapour over liquid under pressure of 44 bar at 15°C [50]. The vapour is neither flammable nor explosive, but it can support combustion, so special storage and handling rules need to be applied. Moreover, it is relatively inexpensive compared to other volatiles or gases.

Even at concentrations used for sedation and analgesia, nitrous oxide causes minimal changes to physiological parameters. Although there was reported decreased myocardial contractility *in vitro*, *in vivo* we can see a stable cardiac output. The effects on the respiratory system are also negligible: the decrease in tidal volume is balanced by increased respiratory frequency, so minute ventilation stays the same. For patients with intracranial changes, a small increase in cerebral blood flow and, hence, cerebral oxygen consumption might be important, but this is not clinically relevant in healthy volunteers [49].

The impact on CO_2 tension may be important, especially for breathing experiments. Fortunately, this effect is minimal, although a person inhaling N_2O can express an obtunded response to hypoxia and hypercapnia. Also, the dissociation curve for haemoglobin is shifted to the left, causing greater affinity of the molecule to oxygen in pulmonary capillaries. In addition, some increase in skeletal muscle activity can be observed, which may have an unclear impact on the experiment [50].

As nitrous oxide has been used for nearly two centuries, it has a well-tested safety profile. The most commonly cited negative side effects are nausea and vomiting, dizziness, headache, tingling and euphoria. Especially the first two are dose related [51]. No allergic reaction has been registered. Besides, not many severe adverse reactions have been reported. The main worry is its neurotoxicity, which is under ongoing research interest. Mainly, the undeveloped brains of neonates or elderly people are at risk, to a large extent, following a prolonged administration of anaesthetic concentrations [52]. These effects are less of a concern in the concentrations detected while using nitrous oxide as a tracing gas.

There are just a few reports of major complications during N_2O administration, namely oxygen desaturation, aspiration or bradycardia. The incidence is influenced by age (more often in children) and also by supplementary use of other medication (e.g., benzodiazepines) [53]. On the other hand, a case report of a laryngospasm complicated by aspiration has been observed during N_2O administration as a single agent. This stresses out the importance of the reachability of a physician with airway management skills and proper equipment [54].

A classically feared event after nitrous oxide administration is diffusion hypoxia. This can happen when the N_2O/O_2 mixture administration has ceased and the patient starts to breathe air. The

diffusion of nitrous oxide from the blood back to the alveolus can dilute the alveolar oxygen and cause hypoxia. We usually try to prevent this by administering a high FiO_2 gas mixture afterwards and continuously monitoring with pulse oximetry [49].

Most of the above-mentioned effects can be seen only when anaesthetic concentrations of nitrous oxide (fraction of inspired N_2O: FiN_2O 50–70%) are administered. However, lower concentrations (FiN_2O <40%) have been also under scientific interest. Mainly, the effect on psychomotor performance and cognitive functions has been tested in several trials. If the nitrous oxide is to be used as a tracer gas, its effect on cognitive functions and mental performance should not interfere with the outdoor breathing experiment as has been investigated in several studies, determining the threshold concentration for cognitive effect between 8% and 15% FiN_2O [55-60].

From the analysis of already performed experiments [12,45,61] with breathing into simulated avalanche snow with N_2O as a tracing gas, it has been observed that even when the subject is systematically breathing gas not from the test tubing but the ambient air enriched with nitrous oxide, the maximal FiN_2O was 5% (Figure 2.4).

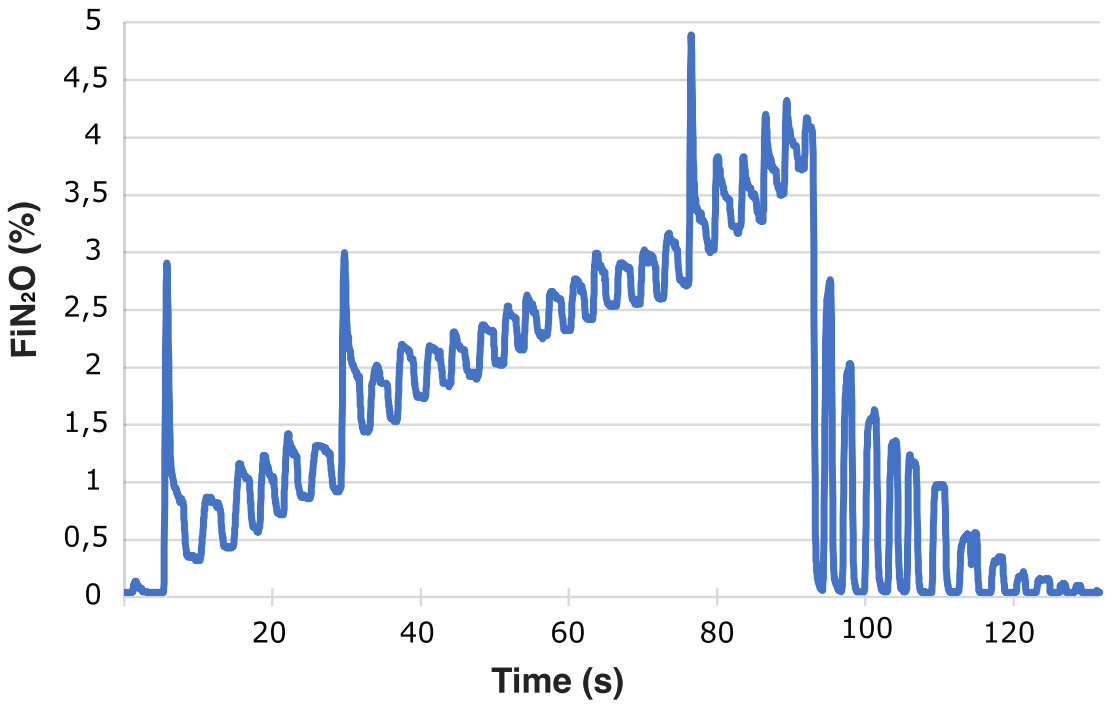

Figure 2.4 An example of a systematic breathing of a subject of an air enriched with nitrous oxide outside the test tubing during an experiment with breathing into simulated avalanche snow. The maximum FiN_2O was below 5% even after more than 90 s of breathing of the tracing gas.

The nitrous oxide delivery system has to be optimised for routine use of this tracing gas in field breathing experiments [62]. This is a subject of further research and is outside the scope of this doctoral thesis.

2.5 Monitoring of subjects during outdoor breathing experiments

Various vital sign monitors were used to monitor the subjects throughout these experiments. Frequently used monitors are originally designed for anaesthesia or critical care units [63-67]. Surprisingly, from Table 2.3, it can be seen that many of these monitors are, according to the manufacturer, suitable to operate under a wide range of environmental conditions. In some studies [26,43], monitors for emergency care have been used [68-70], but some critical care monitors have very similar environmental requirements. Apart from the temperature considerations for field experiments, the operating altitude up to 5486 m above sea level [65], or even up to 12000 m [67], covers the usual test sites well.

Table 2.3 Environmental requirements of examples of vital sign monitors [63-70].

Vital sign monitor	Operating temperature (°C)	Storage temperature (°C)	Atmospheric pressure (kPa) (altitude)	Humidity (%)
Datex-Ohmeda S/5[1]	10–35	(-10)–50	66–106	10–90 non-condensing
GE CareScape B650[1]	10–35	(-20)–60	not specified	10–90 non-condensing
Masimo Radical-7[1]	0–50	(-40)–70	50–106 (-304 m to 5486 m)	10–95 non-condensing
Nonin PalmSAT[1]	(-20)–50	(-40)–70	above 19 (up to 12000 m)	10–95 non-condensing
Edan M3B[1]	5–40	not specified	not specified	not specified
Philips HeartStart MRx[2]	0–45	(-20)–70	57–101 (0 m to 4500 m)	up to 95
LIFEPAK 15[3]	0–45	(-20)–65	57–106 (-382 m to 4572 m)	5–95 non-condensing
ZOLL X Series[4]	0–50	(-30)–70	57–103 (-170 m to 4572 m)	15–95 non-condensing

[1]Vital sign monitor used in [45], [2]vital sign monitor used in [43,44], [3]vital sign monitor used in [41], [4]vital sign monitor used in [34].

In most of the field breathing experiments, vital sign monitors are used for measuring parameters like oxygen saturation (SpO_2) [11], end-tidal CO_2 ($EtCO_2$), and inspired fraction of CO_2 ($FiCO_2$) and even these parameters often served as study endpoints [12,17,18,26,34,41,43,44]. The limits are set at different values; for pulse oximetry, SpO_2 75% [18,43,44], 80% [41], 85% [17,34], or even 88% [26] and for $EtCO_2$ at 8% [12,44], or 60 mmHg (8 kPa) [41].

However, the reliability of the monitoring during breathing experiments with considerable rebreathing has been questioned. During their laboratory experiments, Roubík and Filip [8] observed a certain discrepancy between the value of $EtCO_2$ displayed numerically on the screen and the value presented via the capnographic curve (Figure 2.4). The error in $EtCO_2$ was evaluated by the monitor incorrectly in 30–50% of the total experimental breathing time, but in one subject, this time reached up to 93%, despite regular calibrations of the system. This may be caused by imperfect software dealing with rapid changes in the exhaled gases, which are unexpected in a critical patient for whom these monitors are originally designed.

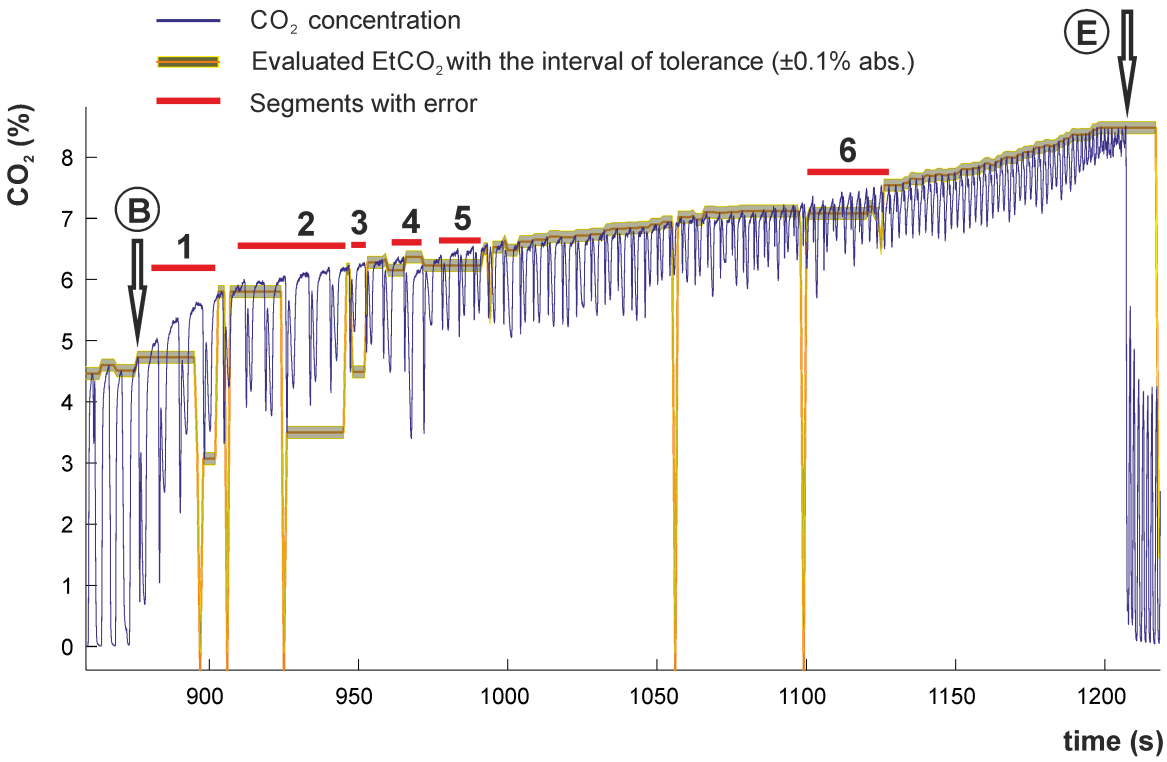

Figure 2.4 Example of a curve of measured CO_2 concentration (blue line) and the values of $EtCO_2$ (yellow line) evaluated by Datex-Ohmeda S/5 Anaesthesia Monitor. Segments where $EtCO_2$ does not correspond to the CO_2 concentration curve are marked with red horizontal lines. B—beginning of breathing trial in the simulated avalanche snow after the initial stabilisation period; E—end of the breathing trial (from [8]).

As the reliability of the other frequent vital sign parameter used as a study endpoint—SpO_2—has not been further studied, the following text concentrates mainly on this parameter and the associated perfusion index.

2.5.1 Pulse oximetry

Pulse oximetry is a standard monitoring method assessing the peripheral saturation of haemoglobin in blood with oxygen (SpO_2), including in-hospital and out-of-hospital settings. The saturation can be standardly assessed using a finger, ear, forehead, or nostril probe.

Non-invasive blood oxygen saturation monitoring is especially important in situations where rapid changes in oxygenation may occur. In clinical practice, this is crucial, for example, in airway management in anaesthesia and critical care, during which a fast drop of SpO_2—desaturation—can occur [71-74]. Rapid desaturation can also be observed in trained athletes under certain conditions, like during static apnea practised by breath-hold divers (Figure 2.5) [75]. During these voluntary apneas, the minimal achieved SpO_2 values (56.6 ± 17.7%) are much lower than the endpoints standard for hypoxic experiments. In simulated avalanche snow breathing trials, the study endpoints for desaturation are set at different values: SpO_2 75% [18,43,44], 80% [41], 85% [17,34], or even 88% [26].

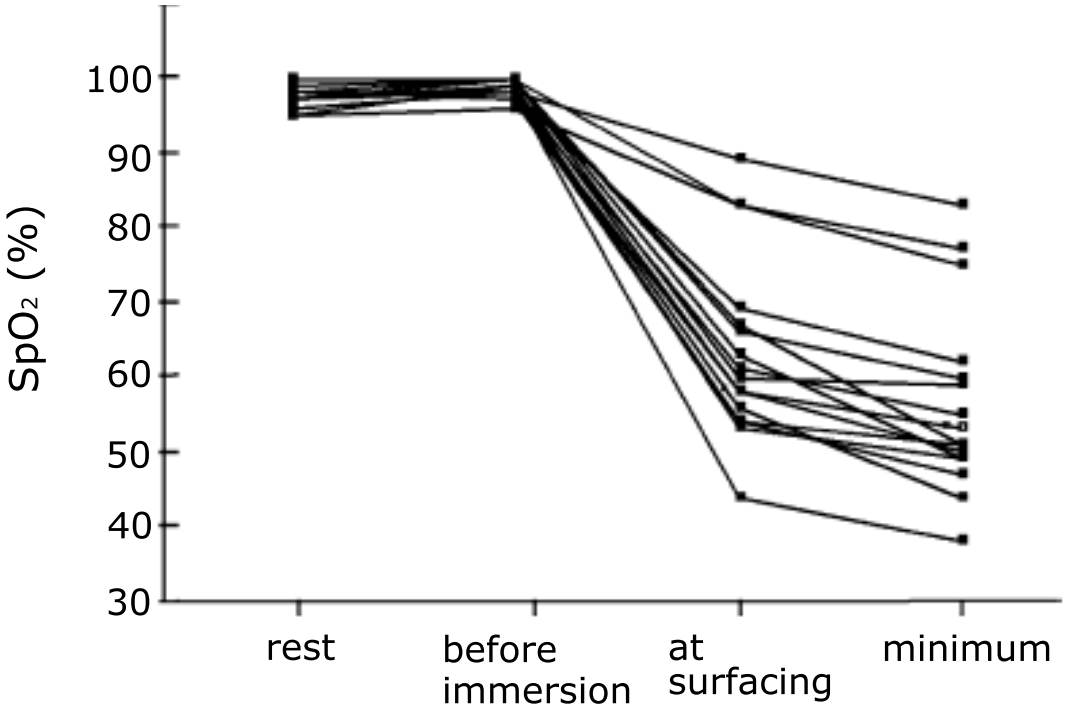

Figure 2.5 Time course of SpO_2 measured by pulse oximeter during static apnea in breath-hold divers. Each line depicts one diver monitored by one pulse oximeter (Biox 300e Pulse Oximeter, Ohmeda, Louisville, USA). Modified from [75].

Although pulse oximetry is challenged by numerous well-known limitations (Table 2.4) [76-78], it has been successfully used even in outdoor environments for the assessment of the acclimatisation process at high altitudes or the development of acute mountain sickness [79]. Factors affecting the accuracy of SpO_2 relevant in outdoor environment during monitoring of healthy volunteers are mainly low perfusion state, motion artefacts, and poor probe positioning. The ambient light effect has also been identified, but the clinical relevance seems not to be significant [80] and in field trials in the cold environments, this effect is usually suppressed by the hand placement into a glove.

Table 2.4 Factors affecting accuracy of pulse oximetry (modified from [76-78]).

Sources of error	**Effects on SpO_2**
Low perfusion state	Signal loss, underestimation
Reduced vascular pulsation	Underestimation
Venous pulsations	Underestimation
Motion artefact	Signal loss, underestimation
Poor probe positioning	Underestimation or overestimation
Ambient light	Underestimation
Dyshemoglobins	Different:
- Carboxyhemoglobin	- Overestimation
- Methemoglobin	- Underestimation
- inherited forms of abnormal hemoglobin	- Underestimation
Intravenous pigmented dyes	
- Methylene blue	- Underestimation
Hyperbilirubinemia	Overestimation
Skin pigmentation	Signal loss, underestimation
Sickle cell anemia vasooclusive crisis	Overestimation
Severe anemia (with concomitant hypoxemia)	Underestimation
Sepsis and septic shock	Underestimation or overestimation
Nail polish	Underestimation
Shape of oxygen dissociation curve	–
Limited knowledge of the technique	–

Motion artefacts caused by the measured subject's passive or active movement can challenge the accuracy of pulse oximetry measurements. Several studies have assessed the performance of different pulse oximeters used in the past 30 years under the movement of the measured hand [81-83] and found degradation in the performance of the tested pulse oximeters.

Barker *et al.* [82] studied devices separately during motion in normoxia (Fig. 2.6 A) and during motion in hypoxic conditions (desaturation to SpO_2 70% on the control device; Fig. 2.6 B). In normoxia, the motion artefacts can imitate desaturations, but during actual desaturation, the motion can cause errors in tracking of SpO_2; in total, up to 20% of the SpO_2 were found erroneous [82]. This behaviour is partly caused by the nature of the SpO_2 calculation, which assumes the arterial blood is the only light-absorbing pulsatile component. This classical algorithm is com-

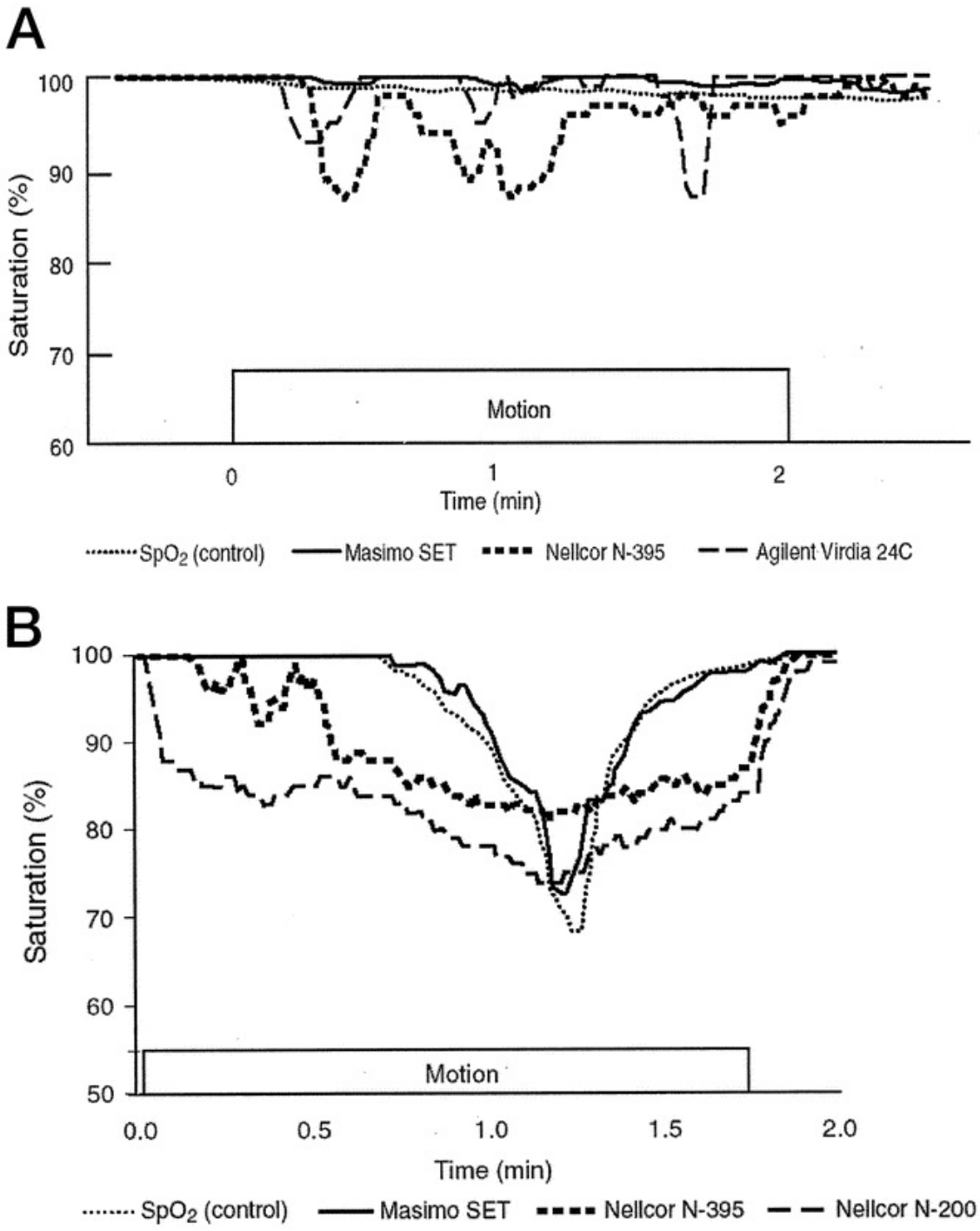

Figure 2.6 Graphs of SpO_2 from a study by Barker *et al.*, assessing pulse oximeters during hand motion with a control on a static hand. A. Normoxia with hand movement; B. Hypoxia (control SpO_2 70%) with hand movement (modified from [82]).

pletely invalid during motion, as other non-arterial components can generate pulsatile signals (e.g. venous blood). This problem can be overcome using a Discrete Saturation Transform (DST) model introduced to MASIMO devices (Masimo, Irvine, CA, USA). DST model separates individual "saturation components"—like pulsatile arterial blood vs. moving venous blood identified as pulsatile signal with low saturation—and the highest component is reported as the SpO_2 value. The DST, together with light-shielded optical sensors, digital signal processing, and adaptive filtration, form the Masimo Signal Extraction Technology (SET) [84].

Besides motion artefacts, the measurement site is of concern. Although 80% of medical staff place the probe on the index finger as their first choice [85], several studies questioned the differences in SpO_2 readings in different fingers and the effect of a dominant hand. Mizukoshi *et al.* [85] identified the middle finger as the best for monitoring SpO_2, especially in a hypoperfusion state, based on the highest perfusion index value (*PI*—more about this parameter in 2.5.2 Perfusion index). Two other studies [86,87] evaluated the best finger for probe placement solely based on the highest measured SpO_2 values, without any gold standard or additional evaluation parameter. Despite statistical differences among fingers, the clinical relevance is insignificant as the difference was smaller than the inaccuracy of the pulse oximeter declared by the manufacturer (± 2%). Similar conclusions were drawn from a study assessing differences among SpO_2 and *PI* values from all ten fingers during inhalation of a hypoxic gas mixture (12% O_2) and a gas mixture with 12% O_2 and 5% CO_2 [88]. In summary, the current knowledge has not proved a clinically significant difference among fingers for SpO_2 monitoring under normoxic or hypoxic conditions.

The peripheral placement of the probe affects the response time of the pulse oximeter as has been shown by Choi *et al.* [89]. This study compared desaturation and resaturation readings in finger transmission and forehead reflectance pulse oximeter probes. The authors speculated that the observed faster desaturation on the reflectance SpO_2 was caused by faster transport of the arterial blood to the supraorbital arteries situated underneath the probe and a smaller effect of vasoconstriction on these vessels compared to peripheries like fingers. Also, this study lacked a gold standard. An older study from 1997 [90] offered a more comprehensive experimental protocol comparing finger, ear and forehead probes of different manufacturers, and as a gold standard, they used arterial blood sample oximetry (saturation of arterial blood with oxygen, SaO_2). None of the tested oximeters displayed constant accurate values throughout the hypoxia. During a course of desaturation due to inhalation of hypoxic gas mixture (10% O_2 in nitrogen), devices with ear (Ohmeda Model 3740, Ohmeda Inc., Boulder, CO, USA) and forehead (Nellcor N-200 Reflectance Model, Nellcor, Inc., Pleasanton, CA, USA) probes showed faster desaturation times and were found superior to the finger probes of different manufacturers. The greatest difference in response time to maximal desaturation between the fastest and slowest pulse oximeter in one subject was found to be from 13 s to 29 s. The resaturation phase showed unalike results:

one of the finger probe oximeters (Novametrix Oxypleth, Novametrix, Inc., Wallingford, CT) had the fastest response time, and the interval between the slowest and fastest device in one subject increased to 15 s to 57 s. Only in 2% of recorded time the pulse oximeter failed to provide a value.

Several other studies compared different types of pulse oximeters manufactured by various companies [82,90-93]. The mean error in SaO_2 measured by pulse oximeters is 3–4% for adults. During hypoxemia with SaO_2 levels below 80% or 90%, the mean error is even more pronounced [94]. It has been hypothesised by Van de Louw *et al.* [92] that the software algorithm adopted by the particular manufacturer may affect the accuracy of the SpO_2 readings. In addition, obtaining reliable human calibration data is challenging for cases of profound hypoxemia [95].

The requirements for the safety and performance of pulse oximeters are specified in the international standard ISO 80601-2-61 [96]. This standard specifies, besides other things, the required performance of the pulse oximeter during desaturation and its accuracy. The accuracy is defined as root mean square (A_{rms}), which is required to be lower or equal to 4% for peripheral SpO_2, corresponding to SaO_2 at 70–100%. These specifications are based on controlled desaturation studies on healthy adult volunteers aged 18 to 50 years, with step-wise desaturation. Each desaturation level (60–70%, 70–80%, 80–90%) should be limited to minimal duration in order to achieve steady parameters, but should not last longer than 10 min [96]. The desaturation study protocol includes SaO_2 +3% for the lower limit and −3% of SaO_2 for the upper limit; this means for the pulse oximetry range of SaO_2 70–100%, the controlled desaturation study has to be performed at least from SaO_2 73% to SaO_2 of 97%. These requirements are limiting for the declared device accuracy as the study needs to involve a step-wise lowering of SaO_2 to levels down to 60–70%. Lower limits would need to involve controlled profound desaturation below SaO_2 of 60%. Although the international standard states the risk of even mild adverse effects lower to 0.03% in over 10000 clinical studies performed in the past 30 years [96], testing the accuracy of pulse oximeters at lower SpO_2 levels would be ethically challenging, and we have to rely on extrapolation of the calibration curve to the lower values.

There is contradicting evidence regarding under-reporting or over-reporting of SaO_2 by different pulse oximetry devices. The tendency of underestimation was found in the interval of SpO_2 82–93% [91], or even below 75% [90], which was expected by Trivedi and colleagues [90] to be a safety measure intentionally adopted by the manufacturers. Other studies have revealed an opposite tendency to display higher values, for instance, due to the specifics of the calibration curve used by the software [97]. The difference between SpO_2 and SaO_2 in paediatric data reached the greatest bias in the range of SpO_2 81–85% (mean 6.6%) [98], exceeding the guaranteed accuracy of the two types of examined devices, in neonates the median size of the bias climbed to 5% in SpO_2 75–93% [99]. However, to date, no study has examined the bias in adult subjects

during field breathing experiments, so the tendency of the pulse oximeters in this scenario is unknown. Also, no study investigated the SpO_2 monitoring response to hypoxia associated with increased work of breathing—a frequent combination of pathological factors seen in volunteers undergoing outdoor studies assessing the gas exchange in avalanche snow. Additionally, a cold environment and poor peripheral perfusion are expected to be an issue. For this reason, the perfusion index can be considered an auxiliary parameter.

2.5.2 Perfusion index

Perfusion index (*PI*) derived from pulse oximetry is a parameter for the assessment of perfusion changes in peripheral tissues. *PI* is calculated as the ratio of the pulsatile to the non-pulsatile signal amplitude of the infrared signal of the plethysmography waveform (Figure 2.7), from the equation:

$$PI = \frac{I_p}{I_{np}}, \tag{1}$$

where I_p is the absorbance of the pulsatile and I_{np} of the non-pulsatile signal [100].

The *PI* can reach values 0.02–20; the higher the *PI*, the better the perfusion. The parameter *PI* is calculated as a ratio of 3–5 s pulse amplitude to the non-pulsatile 30 s average [101], so this averaging could mask the very rapid changes in perfusion.

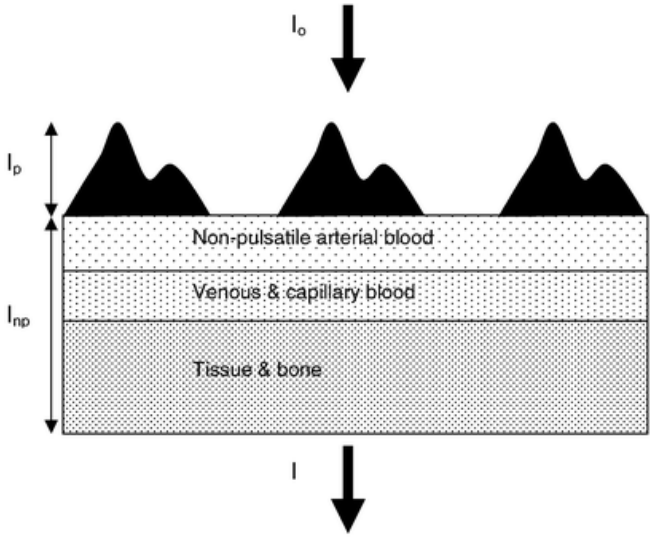

Figure 2.7 Pletysmografic waveform and the absorbance of the pulsatile (I_p) and non-pulsatile (I_{np}) signal. I_0 source light intensity, I light intensity at the detector [100].

Overall, the perfusion index is mainly used as a trend parameter. The values differ among individual subjects, the site of probe placement and the clinical situation [102]. Lima *et al.* [103]

observed *PI* 1.4 [0.7–3.0] (expressed as median [*IQR*]) in healthy volunteers. Chu *et al*. [104] assessed the perfusion index before and after administration of analgesics. Before the administration, the *PI* was 1.3 ± 1.2; following the administration, the index raised to 1.7 ± 1.6. Another study [105] in urology patients observed baseline *PI* from 1.6 ± 1.1 to 2.0 ± 1.2, depending on the grade of the patient's hydronephrosis. Slightly higher values at rest were measured in patients in the post-operative unit, 2.2 (0.97–3.6), but this value dropped to 1.0 [0.5–1.9] (expressed as median [*IQR*]) after positioning [106]. In paediatric patients, prior to induction to anaesthesia, the *PI* was 1.25 ± 0.13 (mean ± *SEM*) [107]. However, in some studies, the perfusion index values at rest were much higher. In a Japanese study in a laboratory environment in men, the baseline value was 4.99 ± 0.45 (mean ± *SEM*), and after painful stimuli, 3.20 ± 0.37 [108]. Attempts to categorise the *PI* values have been made, for instance, by Thijssen *et al.* [109], who sorted out the *PI* values in critically ill patients into three bins: low *PI* ($PI < 1.0$), intermediate *PI* ($1.0 \leq PI \leq 2.5$), and high *PI* ($PI > 2.5$).

Monitoring of the perfusion index is mainly used in anaesthesia, where increasing *PI* is associated with vasodilation due to the effect of anaesthetics, and a decrease in *PI* suggests inadequate analgesia accompanied by vasoconstriction [104,106,108]. During regional anaesthesia, the vasodilation caused by the local anaesthetics can be identified in changes in the perfusion index [110-112]. Systemic hypoxia stimulates sympathetic nerve activity and, besides other reactions, causes acral skin vasoconstriction [113,114].

The perfusion index changes during hypoperfusion due to low ambient temperature in combination with motion artefacts, as assessed by Shah *et al.* [115]. In a laboratory tempered to 16 °C–18 °C, the resulting average fingertip temperature was 21.4 °C ± 3.3 °C, and the median perfusion index was 0.95 (0.63 at the first quartile) in the control hand and 1.16 (0.873 at the first quartile) in the motion hand during non-motion conditions. Under these conditions, the SpO_2 failure rate (proportion of time when the device failed to display SpO_2 value to total test time) was 0% for Masimo Radical, 1.3% Datex-Ohmeda TruSat, and 9.3% for Nellcor N-600.

Attempts to assess the finger perfusion in order to estimate the reliability of the pulse oximetry have already been made, but only in a few studies. Thijssen and colleagues studied critically ill patients. In this cohort, the higher *PI* was not associated with an improved correlation between SpO_2 and SaO_2 [109]. However, in these patients, numerous factors affected the vasomotor activity (e.g., acidosis, vasoactive drugs, systemic inflammatory response). In a study by Hummler *et al.* [116] on rabbits with induced sepsis, they observed a bias between SpO_2 and SaO_2 exceeding the declared 3% limit when the perfusion index was below 0.5.

A study by Mizukoshi *et al.* [85] assessing the difference among fingers in SpO_2 measurement found that the middle finger had the highest *PI* value, but the available results in the published study abstract do not provide any more details.

Walzel, in his study [88], measured *PI* under laboratory conditions during breathing of a hypoxic (12% O_2, 88% N_2) and hypoxic-hypercapnic (5% CO_2, 12% O_2, 83% N_2) gas mixture that imitated rebreathing. The highest PI was measured in the thumb, and the median baseline *PI* was 3.5. No correlation between changes in SpO_2 and *PI* was found.

A study by Louie and colleagues [83] compared the performance of four types of pulse oximeters during motion and used *PI* as one of the assessing parameters. They concluded that PI < 2 is associated with a decreased precision of SpO_2 readings. They also found significant differences in *PI* between male and female volunteers. Female subjects tended to have baseline much lower, usually *PI* below 2.0.

2.5.3 Cerebral oxygenation measurement during field experiments

Some studies included monitoring of cerebral oxygenation using the near-infrared spectrometry (NIRS) technology [41,43,44]. Assessing cerebral oxygen saturation (ScO_2) addresses the issue of potential vasoconstriction when measuring saturation of acral parts of the body. However, this method has several limitations. Near-infrared light emitted from the NIRS optode must penetrate extracranial perfused tissues before reaching the cerebral tissue beneath. Manufacturers attempt to distinguish the signal from extracranial tissues through modifications to the optodes, such as adjusting the emitter-to-detector distance or utilising additional infrared light wavelengths. Despite these efforts, the residual effect persists, as evidenced by pharmacological [117] and ischaemic experiments [118].

The first study on cerebral oxygen saturation in avalanche burial was conducted by Strapazzon and colleagues [44]. They found a preserved ScO_2 despite decreasing oxygen supply and carbon dioxide removal and decreased ScO_2. This effect was observed in subjects breathing into the snow of medium to low density (<350 $kg \cdot m^{-3}$), but high snow densities led to a rapid decrease of ScO_2. These findings are in agreement with laboratory desaturation experiments, which also showed preservation of cerebral oxygenation despite peripheral desaturation below SpO_2 of 80% [119].

Wik *et al.* [41] used ForeSight (Casmed, Branford, CT, USA), a NIRS device emitting five different wavelengths and two detectors, to remove scalp oxygenation from the brain tissue signal—saturation cerebral tissue oxygenation ($SctO_2$) [120]. The authors reported that subjects

breathing into an air pocket without access to supplemental air dropped their $SctO_2$ below values that are standardly reported as normal ($SctO_2$ 66–80%).

NIRS technology has been successfully used in out-of-hospital settings during cardiopulmonary resuscitation [121]. The authors tried to prevent the effect of skin vasoconstriction on the NIRS measurement by covering the probes on the forehead [44].

2.6 Topical issues in field breathing experiments

The presented literature review shows that breathing field experiments are a topical subject due to constantly evolving guidelines for the rescue and resuscitation of avalanche victims [9,13-16]. This research also affected the development of safety equipment for people in danger of avalanche snow burial. Numerous questions remain that have not been answered by the already published studies. However, the few already conducted studies have different methodologies, with specific medical and technical aspects, and some of the conclusions are very challenging to compare.

The medical concerns mainly arise from the concomitant hypoxia and hypercapnia experienced by the study subjects. This necessitates a meticulous monitoring of the subjects—for their safety, as study endpoints, but also in order to obtain data for further analysis.

The field breathing experiments are affected by many technical aspects, like the properties of the material (simulated avalanche snow or a snow model material), the breathing apparatus used and its tightness, and other environmental conditions (hypobaric hypoxia, ambient temperature, etc.) that can interfere with the subject's physiology. Moreover, some issues with vital sign monitoring and limitations of standardly used medical equipment have been reported during these experiments.

An attempt to standardise clinical research at high altitude resulted in recently published international ‘STAR guidelines’ [122]. These guidelines yet cover individual risk parameters, symptoms, and scores of acute mountain sickness but not other aspects.

3. Aims of the thesis

The aim of this thesis is to analyse the medical and technical issues in outdoor breathing experiments, especially in simulated avalanche snow, which can potentially affect the results of the studies and pose safety hazards to study subjects.

As documented in the State of the art, there are some errors in displaying data by monitoring medical equipment. The aim is to assess the performance of one of the main monitoring means in field breathing experiments—pulse oximetry. Pulse oximetry is used in these experiments frequently as a study endpoint with a great degree of variability among studies and also as a safety limit for monitoring the subjects.

The perfusion index has been used to assess pulse oximetry performance under a low perfusion state. Another aim is to assess the dynamic changes in the perfusion index during outdoor breathing experiments with concurrent worsening hypercapnia and hypoxemia due to rebreathing.

The final aim is to assess the possible implications of these findings for clinical practice, including emergency medicine, resuscitation recommendations, and intensive care.

4. Outdoor breathing experiment in simulated avalanche snow

Data from the clinical trial described below have been used for this study. This thesis includes only a partial analysis of this trial; the complex analysis of the results is the subject of a different study and has been published in [45].

4.1 Methods

Following approval by the Institutional Review Board of the Faculty of Biomedical Engineering, Czech Technical University (No. A001/018, issued on 22 January 2018) and registration under ClinicalTrials.gov (NCT03413878, last updated: 25 February 2021), the prospective randomised double-blind crossover breathing experiment was conducted between 29 January and 1 February 2018 in Spindleruv Mlyn, Krkonose Mountains, Czech Republic (altitude 762 meters above sea level). Written informed consent was obtained from all volunteers before entering the study.

4.1.1 Subjects

Thirteen male volunteers participated in this study, and all of them completed the study protocol. The characteristics of the study group are shown in Table 4.1. All volunteers were members of the Czech Army forces and students at the Military Department of the Faculty of Physical Education and Sport, Charles University in Prague.

Table 4.1. The characteristics of the group of volunteers involved in the breathing experiment.

Parameter	Volunteers (n=13)
Age (years)	22.8 ± 4.1 (20–35)
Weight (kg)	80.8 ± 8.8 (66–103)
Height (cm)	179.5 ± 5.0 (172–187)
BMI ($kg \cdot m^{-2}$)	25.1 ± 2.6 (22.3–33.3)
FEV1 (L)	4.6 ± 0.6 (3.3–5.4)
FVC (L)	5.0 ± 0.8 (3.3–6.0)
FEV1/FVC	0.93 ± 0.05 (0.84–0.96)

The values are presented as mean ± standard deviation and range (minimum–maximum). Abbreviations: *BMI*—Body Mass Index; *FEV1*—Forced Expiratory Volume in 1 second; *FVC*—Forced Vital Capacity.

All study subjects were fit and well. They underwent an entrance examination performed by an experienced physician, which included an assessment of past medical history, smoking history, physical examination, and spirometry. The exclusion criteria were a Tiffeneau Index (*FEV1*/*FVC* ratio) less than 0.70, any acute respiratory infection, and a history of moderate or severe cardiovascular or respiratory disease.

4.1.2 Study design

Each volunteer underwent three phases of the experiment: phase "S"—breathing into snow, phase "PD"—breathing into dry perlite, and phase "PW"—breathing into wet perlite. CONSORT flowchart is in Fig. 4.1. The volunteers were randomly divided into six equal groups in two steps. In the first step, the volunteers were divided into three groups, each starting the experiment with one of the three tested materials. In the second step, the volunteers were randomly assigned an order of the two remaining tested materials. As a result, every subject underwent all three experimental phases (S, PD and PW), but in randomised orders, i.e., 39 individual breathing experiments were performed. The allocation was made using computerised random numbers by an assistant who did not participate in further research. The volunteers and the investigators directly conducting the experiment did not know whether the prepared experiment involved S, PD or PW breathing. At least an 8-h recovery interval was included between each subject's breathing phases.

4.1.3 Equipment

Continuous monitoring of all study subjects was performed throughout the whole experiment. Before the initiation of each breathing experiment, the subject was attached to vital sign monitors. Datex-Ohmeda S/5 (Datex-Ohmeda, Madison, WI, USA) [63] served as a primary monitor, which monitored and recorded the following physiological parameters: electrocardiography (ECG), heart rate (*HR*), non-invasive blood pressure (*NIBP*—intermittently in two-minute intervals), and peripheral blood oxygen saturation (SpO_2). Using a respiratory sensor D-Lite (Datex-Ohmeda, Madison, WI, USA), connected between the mouthpiece and the tubing leading to the cone (Fig. 4.2), ventilation parameters were obtained, namely: breathing frequency (*BF*), tidal volume (*VT*), airway pressure (*Paw*) and airflow (*Qaw*) measured at the airway opening. The spirometry sensor D-Lite also provided a gas sampling port for the Datex-Ohmeda S/5 monitor measuring inspiratory and end-tidal fractions of oxygen (FiO_2, EtO_2), carbon dioxide ($FiCO_2$, $EtCO_2$), and nitrous oxide (FiN_2O, EtN_2O), using an E-CAiOVX (Datex-Ohmeda, Madison, WI, USA) anaesthesia and spirometry module. The analyser was calibrated before each experimental day using a standard calibration gas. Apart from the monitor Datex-Ohmeda S/5, there was another vital sign monitor, CareScape B650 (GE Healthcare, Helsinki, Finland) [66], used as a backup SpO_2 and *HR* monitor of the subjects.

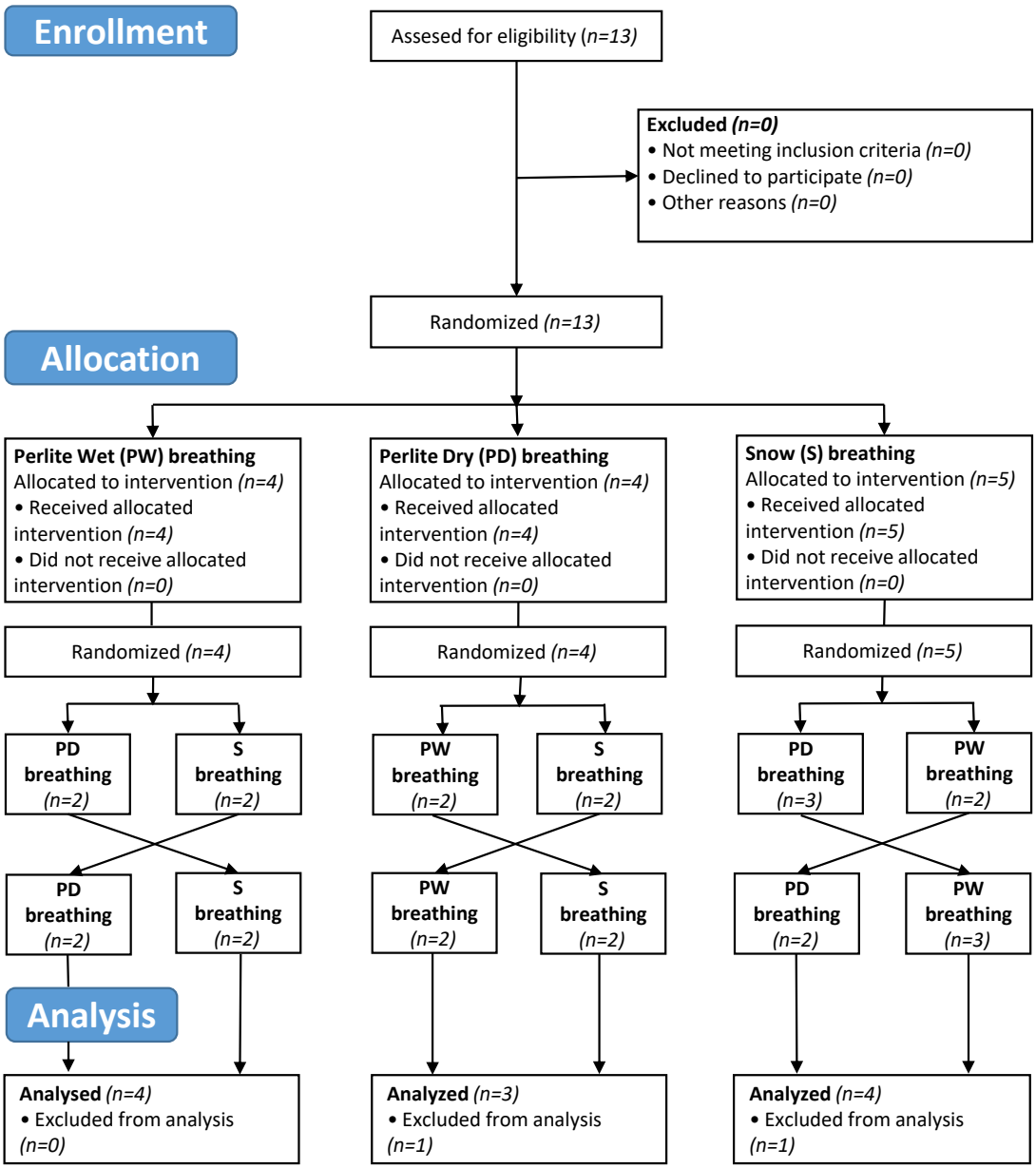

Figure 4.1 Flow diagram of study enrolment, allocation and analysis.

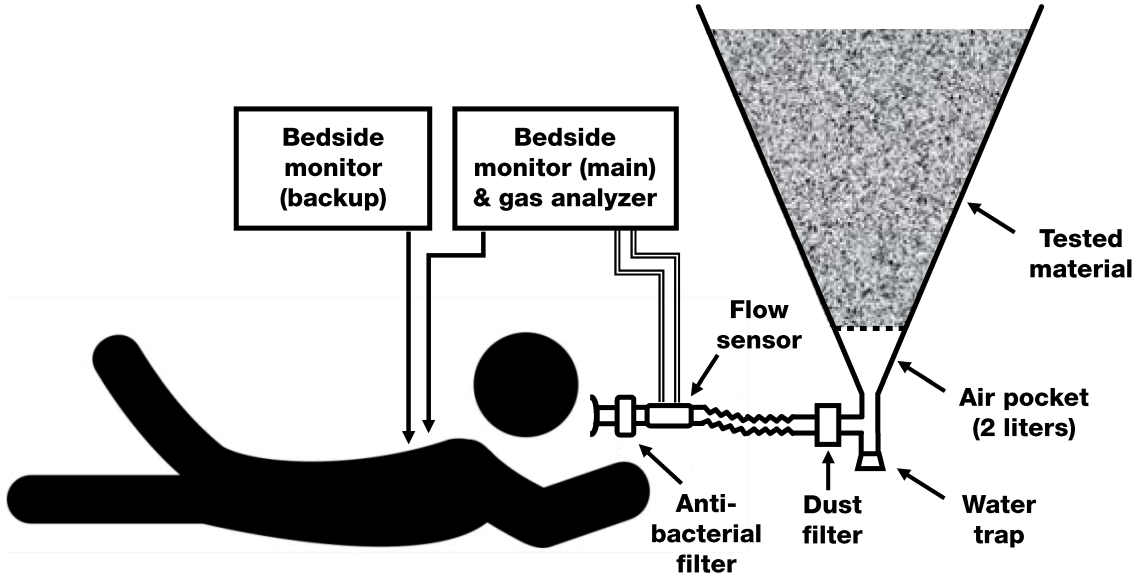

Figure 4.2 Study setting and equipment.

For simultaneous monitoring of SpO_2 levels, five different finger oxygen saturation probes were placed on the subject's right-hand fingers in a standardised manner, presented in Table 4.2 and Figure 4.3. The position of the finger probe was not randomised.

Table 4.2 A list of used pulse oximetry devices, their standardized placement on subjects' right-hand fingers, the manufacturer guaranteed accuracy in the defined measurement intervals of peripheral saturation and the minimal response time set [65-67].

Pulse oximeter	Finger	Interval of SpO_2 measurement	Accuracy in adults (no motion)	Response Time (minimal)
Datex-Ohmeda S/5	V.	40–100 %	80–100 % ± 2 % 50–80 % ± 3 %	beat-to-beat
Masimo Radical-7	IV.	0–100 %	70–100 % ± 2%	2 to 4 s
CareScape B650	III.	40–100 %	80–100 % ± 2 % 50–80 % ± 3 %	3 s
Edan M3B	II.	0–100 %	70–100 % ± 2 % 0–69 % undefined	not adjustable
Nonin PalmSAT 2500	I.	0–100 %	70–100 % ± 2%	not adjustable

Figure 4.3 Subject's right hand with finger probes of five different pulse oximeters. The hand was placed in preheated insulated glove (in the assistant' s hand on the photo).

Besides the two anaesthetic monitors (Datex-Ohmeda S/5 and CareScape B650) serving as main vital sign monitors during the experiment, SpO_2 was measured by three other monitoring devices: Edan M3B (Edan Instruments, Nanshan, Shenzhen, China) [64], Masimo Radical-7 Pulse CO-Oximeter (Masimo, Irvine, CA, USA) [65] and a hand-held pulse oximeter Nonin PalmSAT 2500 (Nonin Medical Inc., Plymouth, MN, USA) [67]. All devices are certified for medical use, they had valid periodic safety and technical checks (including validation on a pulse oximeter tester) and were a property of the Faculty of Biomedical Engineering, Czech Technical University in Prague.

To eliminate possible erroneous readings due to low perfusion or motion artefacts, the volunteer's hand with all probes was placed into a preheated insulated glove, and the participants were instructed to minimise hand and finger movements during the experiments.

The data from all pulse oximeters and monitors were logged, and the monitor screens were simultaneously filmed to document the SpO_2 values displayed by all oximeters at the same time. The response times of the individual oximeters were set to the minimal possible averaging (in Table 4.2); this parameter is used in clinical practice to minimise false alarms, but during rapid changes in SpO_2, its minimal setting prevents erroneous readings.

For data logging from Datex-Ohmeda S/5 and CareScape 650, laptop computers with software for data collection (S/5 Collect software, Madison, WI, USA) were used. For data from Masimo

Radical-7, special software MICT (Masimo Instrument Configuration Tool, Masimo Corporation, Irvine, CA, USA) was used for data collection. All the devices were placed in a tent equipped with an electric heater. The gas sampling lines were wrapped in polyurethane foil for insulation and supplemented with a heated wire to prevent condensation and freezing of water in the tubing.

The experiments were recorded on three independent camcorders; the first continuously recorded the vital sign monitor screens, the second recorded the study subject, and the third the overall situation on the site. The video and audio recording was intended as a backup of the data recorded by the laptop computer and written protocols. This enabled reviewing the situation on the site later during the data processing and evaluation. The investigators communicated via private mobile radio strictly adhering to the protocol, protecting the double-blind design of the study.

4.1.4 Study protocol

During each experimental breathing (S, PD, PW), the study subject was in a prone position, lying on an insulated mat, connected to all sensors of the above-mentioned vital sign monitors (study setting depicted in Figure 4.2). At the initiation of the stabilisation phase (Fig. 4.4), the subject was connected to the mouthpiece with a nose clip, breathing the ambient air; ventilation parameters with the gas analysis results were recorded. After five minutes, the customised tubing was attached to a cone-shaped container filled with the tested material (snow or perlite) and the main part—the breathing phase—was initiated.

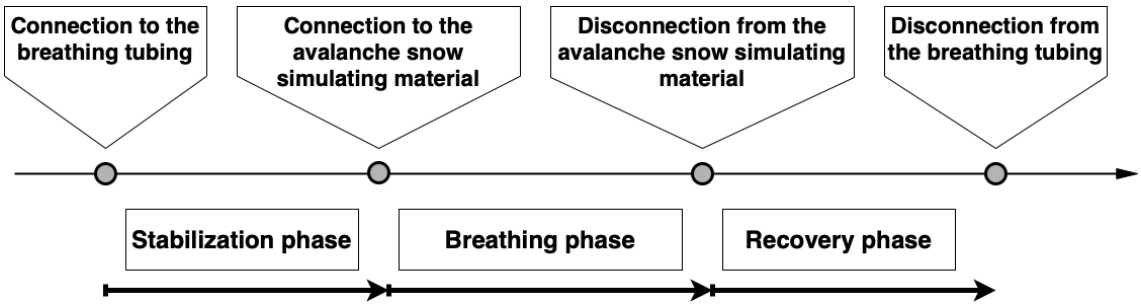

Figure 4.4 Phases of the experiment.

The custom-made apparatus allowing fast exchange of the breathing media (Fig. 4.2) consisted of a stiff metal inverse cone with volume of 65 L. The height of the cone was 1 m, and the apex angle was 28 degrees. The inner wall of the cone was lined with a 1 mm thick polypropylene foil, which prevented freezing and heat conduction. At the bottom part of the cone, a two-litre air pocket was created using a sieve placed perpendicularly to the cone axis at an appropriate position. The rest of the cone was filled with a tested material. The cone was filled 5 cm below

the upper edge, which corresponds to a volume of 56 L. After subtracting 2 L of air pocket at the entrance to the cone, the total volume of tested material was 54 L. A dust filter, a piece of corrugated tube 12 cm long, a flow sensor with a gas sampling port, a bacterial filter and a mouthpiece were connected to the air pocket at the cone tip.

All parts of the breathing circuit were designed in an attempt to minimise the equipment dead space and resistance to breathing effort. The dead space of the whole breathing circuit was 220 mL, and its airflow resistance was 475 $Pa \cdot s \cdot L^{-1}$ measured at the flow rate of 60 $L \cdot min^{-1}$ according to EN ISO 8835–2. Owing to the fact that some components of standard anaesthetic tubing were modified for this experiment, it posed a risk of leaks of the gas from the system. As it is a standard practice to check for leaks of breathing systems in anaesthesiology and intensive care, also in this experiment, a system for leak detection was used, utilising nitrous oxide (N_2O) as a 'tracing gas'. This technique has already been used during previous studies [12,61]. This easily detectable gas was administered via a 6 mm flexible tube into the vicinity of the participant's airways, breathing mouthpiece and along the breathing tubing. The gas source was a 50 L N_2O gas cylinder equipped with a pressure-reducing valve and a gas flow regulator, set at a flow of 20 $L \cdot min^{-1}$. The gas analysers of two anaesthetic monitors, Datex-Ohmeda S/5 (Datex-Ohmeda, Madison, WI, USA) and CareScape B650 (GE Healthcare, Helsinki, Finland), were sampling the gas from inside the tubing and from the air pocket in the cone and thus were able to detect even a minimal concentration of nitrous oxide. The presence of nitrous oxide in the system suggested either a leak in the tubing system or an occasion when the test subject inhaled gas not directly from the mouthpiece but around the mouthpiece or through the nose, which was not properly sealed by the nose clip. The positive detection of N_2O in the system served as one of the study endpoints.

Throughout the experiment, a supervising physician performed a clinical assessment of the volunteer's consciousness level: the physician asked the subject to calculate simple mathematical operations and show the result using their fingers, which were not attached to the pulse oximeter probes.

The breathing into the test material was terminated by a subject's request, by the supervising physician's command, when the study safety limit $EtCO_2$ 62.5 mmHg (8.3 kPa) was reached, or when a gas leak from the tubing was detected using a tracing gas (N_2O). The participant was then disconnected from the test material and allowed to breathe ambient air through the mouthpiece with the respiratory sensor still attached (recovery phase). When all parameters stabilised and returned close to the baseline values, the subject was detached from the mouthpiece, and the experiment was ceased.

4.1.5 Tested snow model material

As a snow model material, perlite was used based on a pilot study with several other materials [61]. Perlite is an amorphous volcanic glass, an industrial mineral, and a commercial product. It is useful for its low density and ability to bear a relatively high amount of water. The grain size of the perlite specified by the manufacturer was 1–3 mm ("Expandovany perlit EP AGRO"; Perlit ltd., Senov u N. Jicina, Czech Republic). It is a non-toxic material, and perlite dust is listed as a "nuisance dust" in most countries [123]. However, as a special precaution, an extra High-Efficiency Particulate Air (HEPA) filter (Servo Duo Guard, MAQUET, Solna, Sweden) was inserted between the cone filled with the tested material and the rest of the breathing apparatus (as shown in Fig. 4.2).

The material was used in two forms—dry and moisturised. The moisturised perlite was a mixture of dry perlite and water in the proportion of 100:20 by volume. The mixture was then left to settle and mixed several times a day to ensure a uniform composition.

The cone was filled with snow gradually by adding and compacting small portions of homogeneous snow collected from a depth of 20–50 cm from the surface. The snow was identical throughout the depths. Both dry and wet perlite are non-clogging materials; thanks to this, they could be poured into the cone at once. The density of all materials was measured by weighing the whole cone filled with the tested material (54 L) before every experimental phase. The porosity of the snow was then derived from the knowledge of the ice density [124]. The porosity of perlite was quantified by filling a calibrated cylinder (1.6 L) full of the tested material and topping it up with water, and then the whole cylinder was weighed on the scales. Porosity was then calculated as:

$$porosity = 1 - \frac{m_m - m_0}{m_t - m_0}, \tag{2}$$

where m_m is the weight of the cylinder filled with the tested material, m_0 is the weight of the empty cylinder, and m_t is the weight of the cylinder filled with the tested material and then flooded fully by water. The density and porosity of the wet and dry perlite were experimentally measured before every breathing experiment of the volunteers.

Throughout the whole study, the snow temperature was between −0.8 and 0 °C in the snow profile from the surface to the depth of 20 cm (not used for the experiments), and the temperature of snow was stable at 0 °C between 20 and 50 cm below the surface (this snow was used for the experiments). The snow used during the experiment was classified according to the International classification for seasonal snow on the ground [125] as wet snow without any impurities. Snow density was 542 ± 32 kg·m^{-3}, grain size was 'very coarse' (2–3 mm), snow hardness cor-

responded to ‘soft snow’ (4F), and grain shape was classified as ‘melted forms’ (clustered rounded grains).

The average ambient temperature during the breathing experiments varied from 0 to 3 °C. The minimum temperature during nights was −5.4 °C. Atmospheric pressure was 91.8 ± 1.2 kPa (range from 90.5 to 93.0 kPa).

4.1.6 Data processing and statistics

This thesis analyses the performance of five pulse oximeters and the behaviour of the perfusion index derived from pulse oximetry during the experiment of breathing into materials simulating avalanche snow.

The data from pulse oximetry measurements were obtained from simultaneous video recordings of the screens of all the pulse oximeters in 10-s intervals. Data were processed in MATLAB R2019a (MathWorks, Natick, MA, USA) and R (R Project for Statistical Computing, Lucent Technologies, Murray Hill, NJ, USA). Data from all breathing experiments (S, PD, PW) were analysed together because the differences among the tested materials were not the subject of this analysis.

For the analysis, firstly, graphs for all five pulse oximeters measurements in all breathing experiments of all subjects were constructed. Secondly, the graphs were complemented with the interval of accuracy [96,126] stated by the individual manufacturers (as summarised in Table 4.2). Then, the agreement among the pulse oximeters, including their declared accuracy intervals, was assessed using an algorithm programmed in MATLAB.

The algorithm divided each graph into congruent and incongruent parts. The SpO_2 signals were evaluated as congruent only when the signals of all five pulse oximeters were present, and the SpO_2 values displayed by all five pulse oximeters lay within the accuracy intervals of all pulse oximeters. If the measured SpO_2 value was out of the interval for which the manufacturer stated the accuracy, the algorithm used the accuracy stated for the previous interval of peripheral oxygen saturation values. For example, if the accuracy ±2% was declared for the interval of SpO_2 70% to 100%, but there was no declared accuracy for values below 70%, the same accuracy was used for these lower values as no other figure was available.

Finally, all five pulse oximeters were assessed together. Every 60 s, starting at the point when the subject was connected to the breathing circuit (time 0 s), the average value from all SpO_2 measurements from all five pulse oximeters in all subjects was calculated and formed the baseline value. Afterwards, the average for each pulse oximeter for all subjects in all experiments

was calculated every 60 s and depicted in the graph with error bars representing standard deviation (*SD*).

For the analysis of the behaviour of perfusion index during the experiment, the synchronised data of end-tidal carbon dioxide and peripheral oxygen saturation with perfusion index values were used.

For the analysis of *PI*, each phase (stabilisation, breathing and recovery phase) was divided into one-minute intervals in order to analyse also the changes in *PI* within the phases. The stabilisation and breathing phases were divided into four one-minute segments (A1–A4, B1–B4, respectively), and the final recovery phase was divided only into three phases (C1–C3), as in most of the subjects, the physiological parameters returned to the pre-test baseline values within 2.5 to 3 min and hence the subjects were disconnected from the breathing apparatus. In the breathing phase, only the first 240 s were included in the analysis as most subjects completed this period.

The changes of *PI* with time were assessed. The statistical significance of the difference was tested by the ANOVA for repeated measures with Fisher's post-hoc test; the normality was tested using the Shapiro-Wilk test. $P < 0.05$ was considered as statistically significant.

Data are presented as mean ± standard deviation and medians with the 25th and 75th percentiles unless otherwise indicated.

5. Results

The results section presents data from pulse oximetry and perfusion index analysis. A complete evaluation of the clinical trial has been published in [45] and is not a subject of this thesis. The results were published in [127-129].

5.1 Performance of pulse oximeters during field breathing experiments

All 13 recruited subjects completed all breathing experiments (S, PD, PW) and were included in the data analysis; in total, 39 breathing experiments were analysed. The predominant reason for termination (Fig. 5.1, Table 5.1) of the breathing experiment was the subject's request (n = 24). Identically, in five cases, the breathing experiment was terminated due to accidental disconnection of the breathing circuit due to a detection of the 'tracing gas'—nitrous oxide in the breathing gas—and in the same number of cases, the experiment was ceased upon the physician's decision. No harm occurred to any of the subjects of the experiment. The length of the breathing experiment differed among subjects and materials; the total length of recorded data in one breathing experiment was 419.5 ± 92.4 (230–620) s. A photo from the experiment is in Figure 5.2.

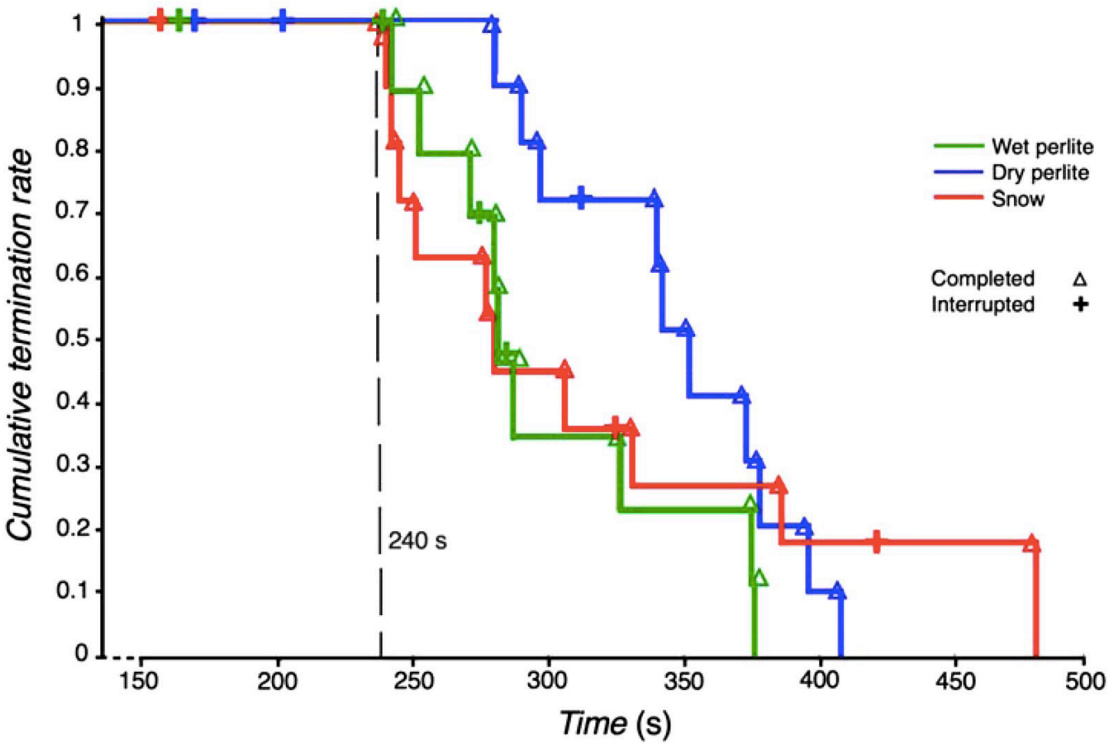

Figure 5.1 Time to breathing experiment termination for the three different materials: snow (S), dry perlite (PD) and moisturised perlite (PW). The term "completed" means that the subject terminated the experiment upon his own request, or the experiment was terminated by the supervising physician based on the clinical assessment of the subject. The term "interrupted" means that the experiment was terminated due to accidental disconnection, or detection of N_2O in the breathing circuit.

Table 5.1. Reasons for termination of the breathing experiments and their frequency.

Termination of the breathing experiment	Termination status	Frequency
N_2O in breathing circuit	Interrupted	5
Accidental disconnection	Interrupted	5
Supervising physician	Completed	5
Subject's request	Completed	24

Figure 5.2 A photo from the stabilisation phase of the experiment. Subject is in a prone position, lying on an insulated mat, breathing through a mouthpiece connected to a monitor. The specially designed tubing is ready to be connected to the cone-shaped container filled with material simulating avalanche snow. The subject is monitored closely by the physician.

Figures 5.3 and 5.4 provide the heart rate and respiratory rate analysis during the first 240 s of all phases in all subjects. Figure 5.5 presents the mean SpO_2 values measured by the five pulse oximeters during the first 240 s of all phases in all subjects.

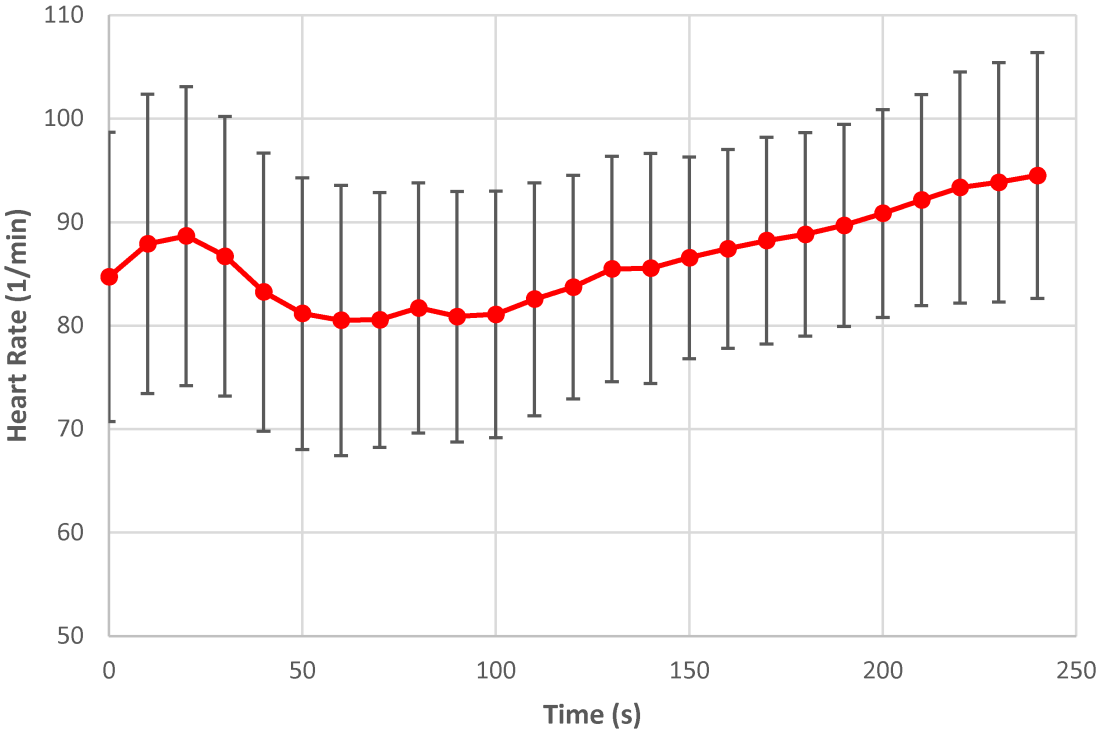

Figure 5.3 The mean heart rate in all subjects during all breathing experiments in the first 240 s, error bars show standard deviation.

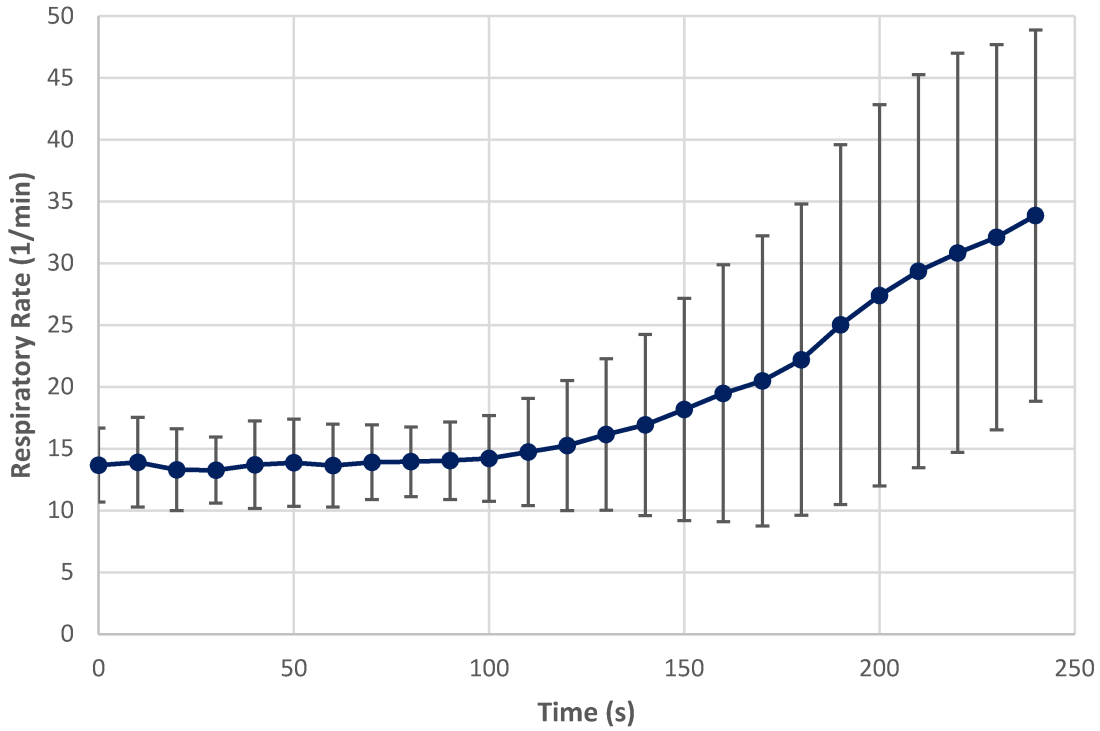

Figure 5.4 The mean respiratory rate in all subjects during all breathing experiments in the first 240 s, error bars show standard deviation.

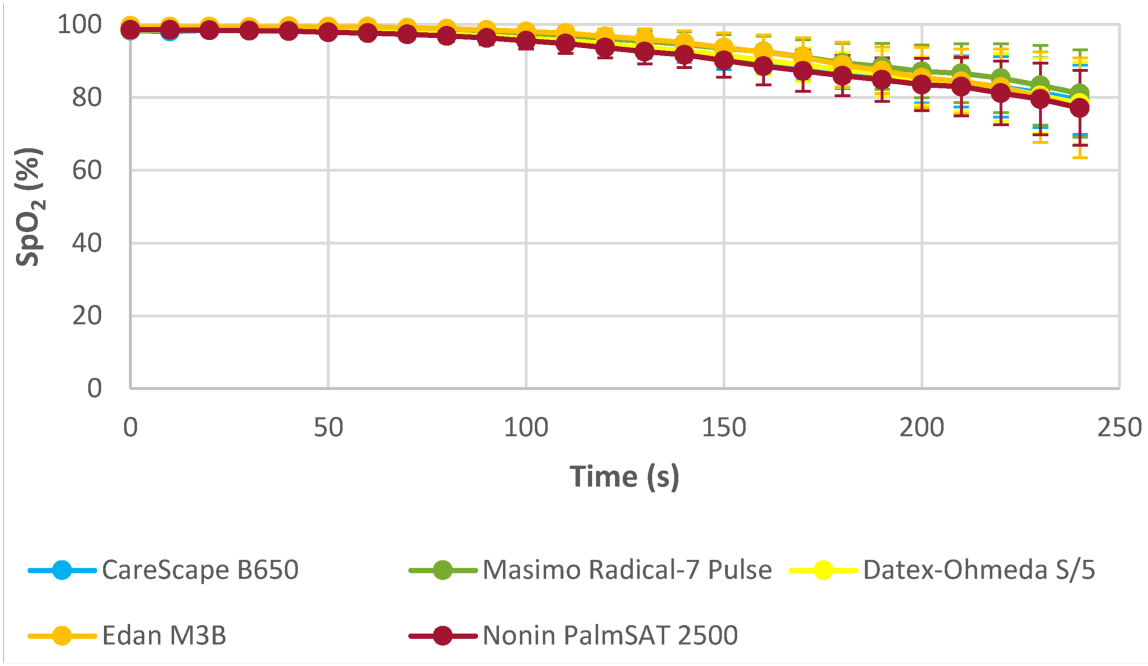

Figure 5.5 The mean peripheral saturation of blood with oxygen (SpO_2) measured by five different pulse oximeters in all subjects during all breathing experiments in the first 240 s, error bars show standard deviation.

The individual oxygen saturation readings displayed by the five different pulse oximeter devices used in this experiment were found to be variable. They varied at the time of onset of desaturation, in the lowest SpO_2 value, and in the duration of the recovery phase, i.e., the period after the subject was disconnected from the test material, breathing ambient air and the oxygen saturation values were returning to baseline.

An example of changes in SpO_2 over time in one subject during breathing into simulated avalanche snow is presented in Figure 5.6. The time difference between the moment when the first (Nonin PalmSAT 2500) and the last pulse oximeter (CareScape B650) showed the SpO_2 value of 85% was 90 s. A similar situation occurred at SpO_2 75%, where the difference was 50 s. The lowest recorded values varied from 69% (CareScape B650) to 43% (Edan M3B), and the screen of Edan M3B displayed the lowest value constantly for 70 s.

In the whole dataset of all breathing experiments, the time difference between the moment when the first and the last pulse oximeter showed the theoretical study endpoint value of SpO_2 85% or 75% was 32.1 ± 23.6 s and 24.7 ± 19.3 s, respectively. Moreover, the pulse oximeter embedded in the Edan M3B vital sign monitor had a tendency to show the lowest detected SpO_2 value for a prolonged period of time, despite the fact that four other devices were already displaying normal SpO_2 values (as shown in Figure 5.6). This behaviour was observed in 16 out of 39 breathing experiments (in 41% of cases).

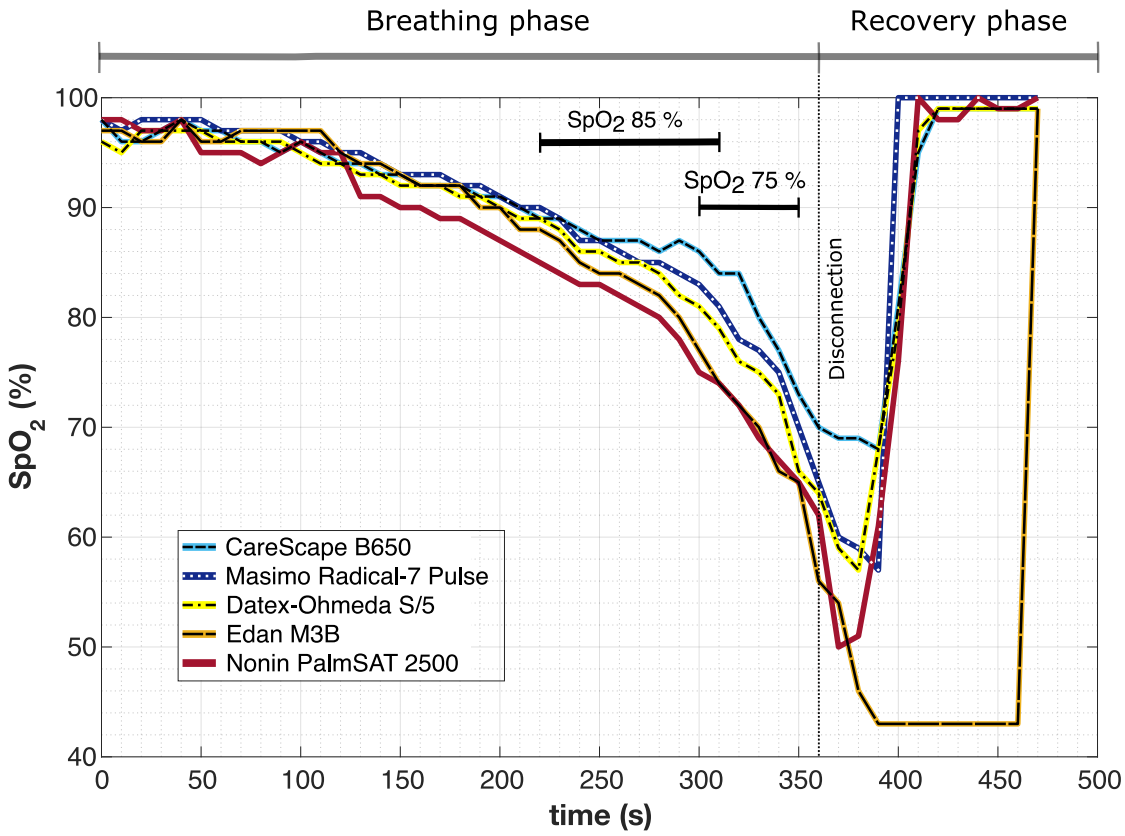

Figure 5.6 An example of SpO_2 waveforms simultaneously presented by five different pulse oximeters. The time difference between the point when the first and the last pulse oximeter showed the typical study endpoints SpO_2 85% and 75% is depicted as the black horizontal line. The pulse oximeter Edan M3B showed a stereotypical value of 43% for 70 s after the end of the breathing phase even though other devices presented values within the physiological range already.

When the declared accuracy of the individual pulse oximeter devices was considered (values for each device are in Table 4.2), in none of the experimental phases did the pulse oximeters show identical values throughout the entirety of the recorded time. Eleven experiments (28.2%) showed no time period when signals from all five pulse oximeters were congruent. Only in one case did the devices agree in 86.7% of the recorded time. However, on average, the congruent periods formed 30.5 ± 26.4 (5.5–86.7) per cent of the recorded time. The total duration of the congruent signals was 115.6 ± 94.0 (30–290) s, with the length of individual segments lasting from 10 s to 260 s. The signal often had two or three separated congruent segments (both n = 8); seven signals had only one of these segments. The maximum number of observed congruent segments was four in four cases. The duration of incongruent segments was 303.9 ± 152.8 (40–620) s (complete data in Supplementary table S1 in Appendix A).

Three examples of evaluation of the congruent segments using an automated algorithm are shown in Figure 5.7. In Figure 5.7a, the signals are incongruent most of the time; however, there

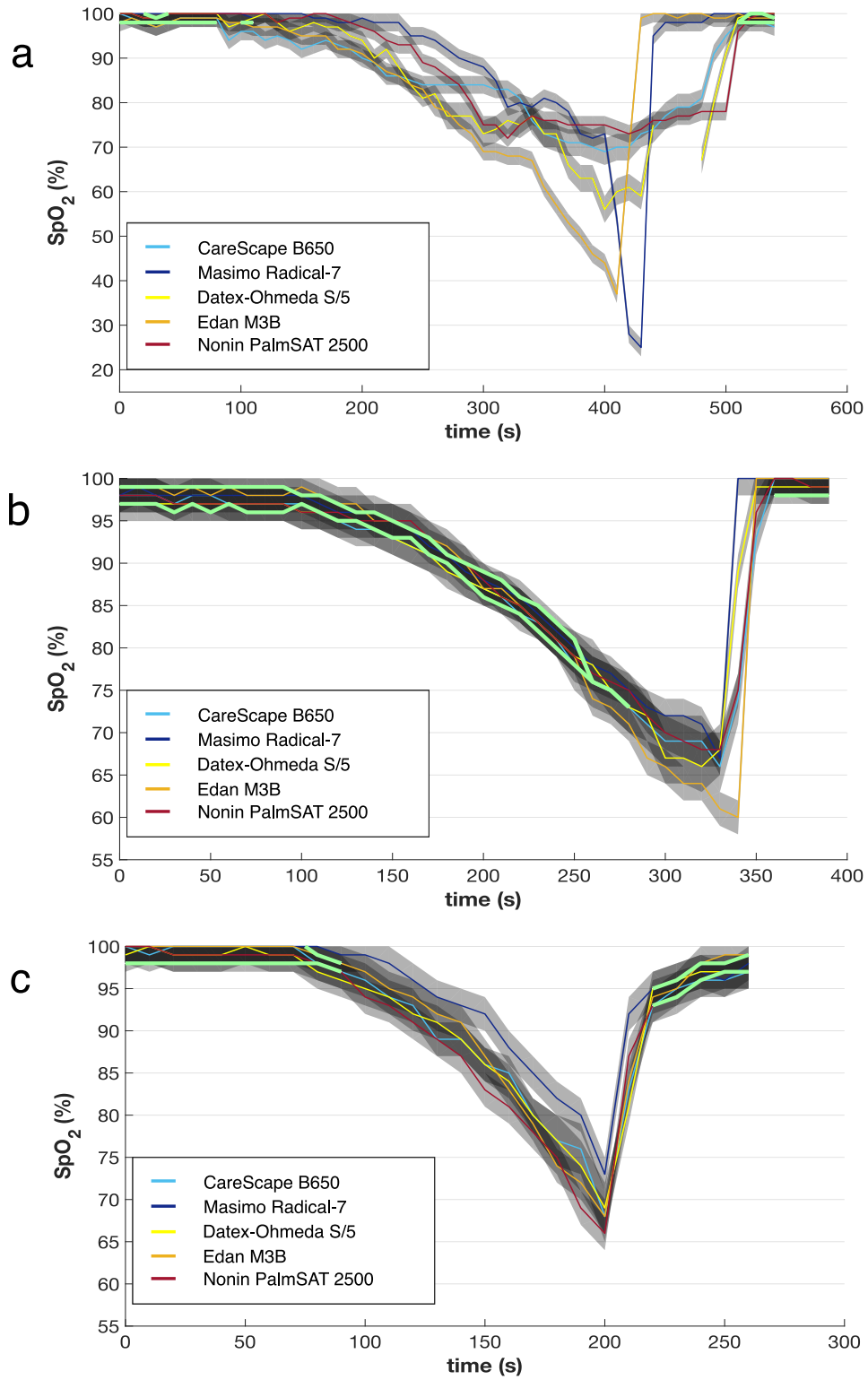

Figure 5.7 Examples of three individual breathing experiments underwent by three different subjects. The SpO_2 values measured by five different pulse oximeters are presented by colour lines. A grey stripe around each line represents the accuracy range of the respective oximeter guaranteed by the manufacturer. Green thick lines represent periods when all five grey stripes overlap, that means all five pulse oximeters showed a value consistent with the others when respecting the accuracies guaranteed by the manufacturer. (**a**) Very short congruent periods; (**b**) long congruent periods lasting 74.4% of experimental time; (**c**) ostensibly long congruent periods were proved to be congruent only in 50% of time; moreover, the congruent segments were present outside the period of rapid changes of SpO_2.

are three short congruent segments (depicted as bright green lines)—two segments at the beginning of the breathing phase and one at the end of the resaturation. The graph in Figure 5.7b shows the longest uninterrupted congruent segment lasting 260 s with an additional 30 s segment at the end of the recovery phase, which forms nearly three-quarters of the total recorded time (74.4%). The graph in Figure 5.7c shows another breathing experiment, where the signals seem congruent; however, following the analysis, only two congruent segments, lasting only 50% of the time, were identified. Moreover, these congruent segments were present outside periods of rapid changes in SpO_2.

In Figure 5.8, all breathing phases were analysed together, and the global difference among the individual pulse oximetry devices is presented. For every 60 s, the difference between the average value displayed by the particular device in all breathing phases and the average value across all the devices is shown. This graph shows that with the time course of desaturation, the variance among the devices increased.

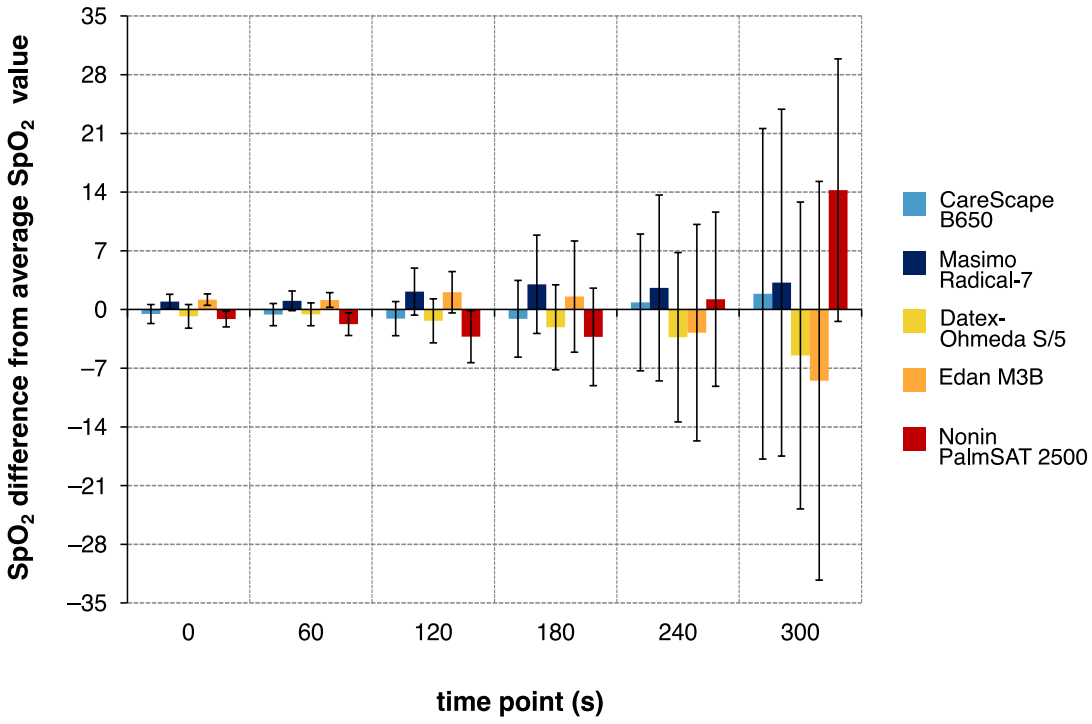

Figure 5.8 The difference of average SpO_2 value displayed by individual pulse oximetry devices and the average value of all pulse oximeters which represents '0' on the *y*-axis. The difference is displayed at the beginning of the breathing experiment (0 s), and at 60, 120, 180, 240 and 300 s. The error bars depict the standard deviation (*SD*). For example, at 300 s the Nonin PalmSAT on average read 14% higher than the average pulse oximeter reading with a *SD* 15%.

5.2 Perfusion index derived from pulse oximetry during the breathing experiments

Although all thirteen volunteers completed the three breathing experiments from the protocol (39 breathing experiments in total), due to technical issues with data recording, only 33 complete sets of perfusion index data were eligible for analysis; the other 6 data sets were excluded due to long periods of corrupted or missing data. A minimal duration of the breathing phase was set at 240 s, and for insufficiently short experimental breathing, all three breathing experiments of one subject and two of another subject were excluded. In total, 29 breathing experiments of 12 subjects were included in the final analysis of *PI* (in Supplementary table S2 in Appendix A).

The baseline perfusion index value of all 33 experimental breathings during the stabilisation phase of the experimental protocol was, on average, 1.54 ± 1.01 (mean ± *SD*). The perfusion indices of the 29 experimental breathings included in the final analysis during all three experimental phases are presented in Table 5.2.

Table 5.2 The perfusion index of all subjects during the experimental breathings included in the analysis.

Perfusion index	**Experimental phase**		
	Stabilisation phase	***Breathing phase***	***Recovery phase***
Mean ± SD	1.58 ± 1.34	1.25 ± 0.71	3.92 ± 3.36
Median (IQR)	1.20 (0.85–1.80)	1.1 (0.78 – 1.50)	3.00 (1.50 – 6.20)

Figure 5.9 shows an example of experimental breathing with its phases and corresponding changes in perfusion index, peripheral saturation of blood with oxygen, and end-tidal concentration of carbon dioxide. The slow onset of hypoxemia and hypercapnia due to re-breathing of the exhaled gas is apparent. When the breathing phase is ceased, the rapid increase of SpO_2 back to the pre-test values is accompanied by a slower restoration of the concentration of carbon dioxide in the organism.

Figure 5.10 presents box plots of the individuals' *PI* values to document the variability of perfusion indices among the tested subjects. Even in the stabilisation phase, the subjects reached different baseline perfusion index values. The recovery phase is characterised by a surge in *PI* values and an increase in *PI* value variability.

The changes in *PI* values assessed over one-minute intervals for all subjects are presented in Figure 5.11. A statistically significant difference exists between the recovery phase and all segments of the stabilisation and breathing phases. Within the stabilisation and breathing phases, the segments are not significantly different, so there is no detectable change in the perfusion index prior to disconnection of the subject from the tested material when hypoxemia and hypercapnia develop. However, in the second minute of the recovery phase, the subjects reached higher *PI* values compared to the other two segments of this phase.

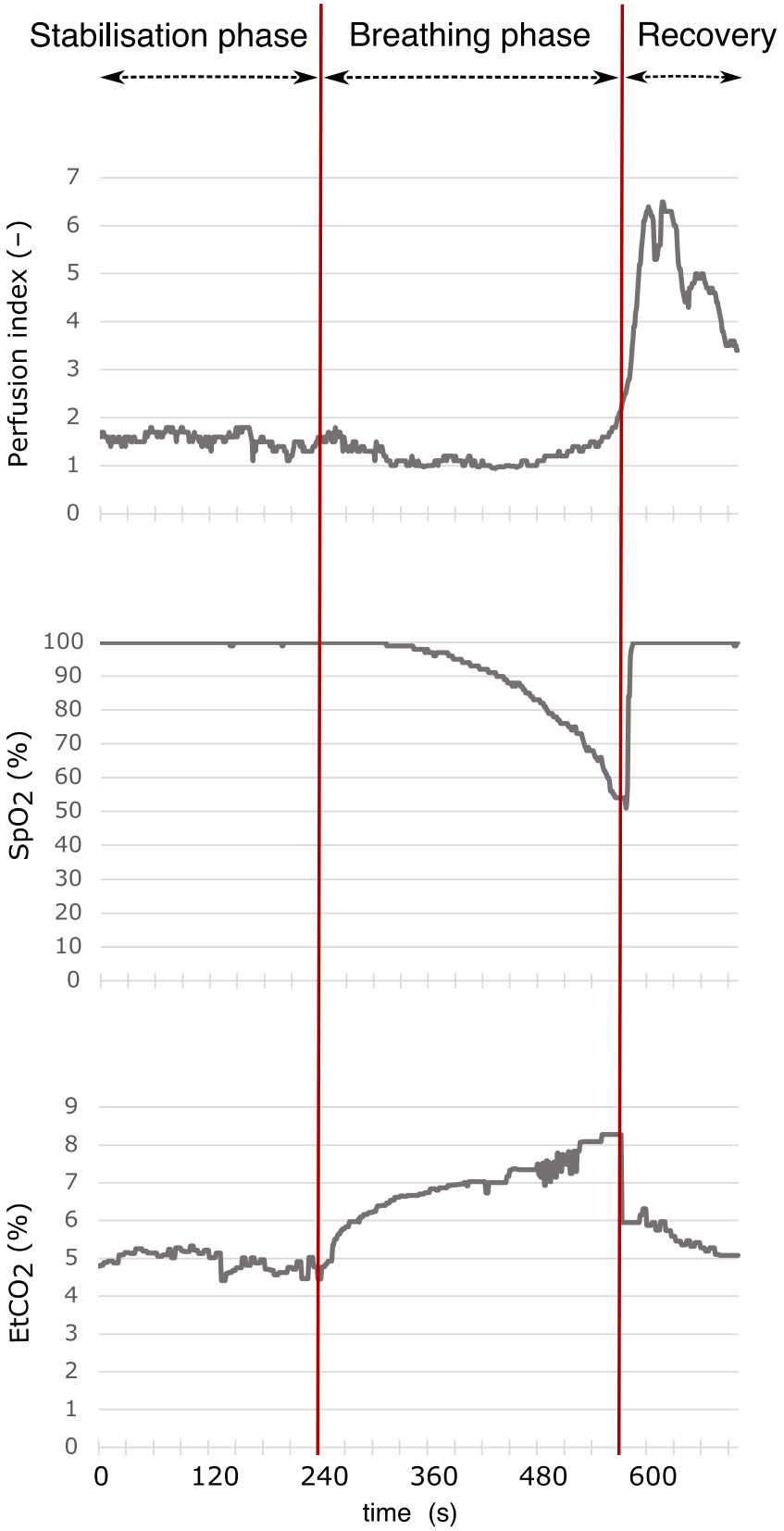

Figure 5.9 An example of recorded physiological parameters during experimental breathing of one of the subjects. The graphs show simultaneous measurements of perfusion index (*PI*), peripheral saturation of blood with oxygen (SpO_2) and end-tidal carbon dioxide concentrations ($EtCO_2$). The experimental phases are labeled: stabilisation, breathing and recovery phase.

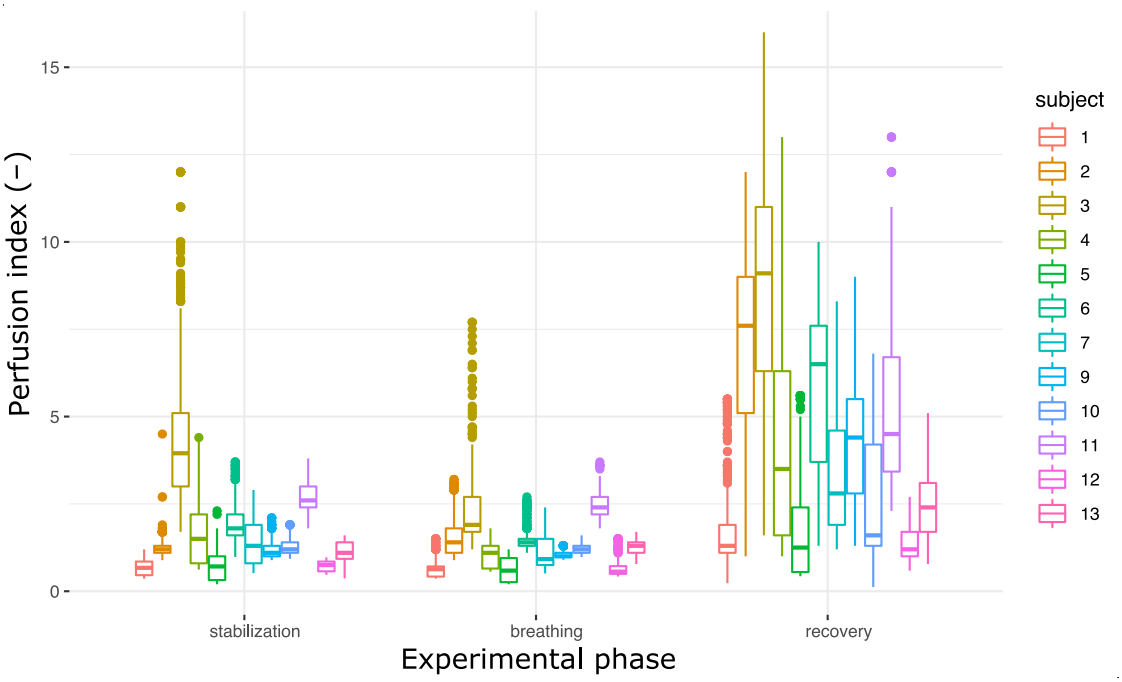

Figure 5.10 The *PI* values of individual subjects 1–13 (subject number 8 excluded) in the experimental phases. The box plots are made from the one-second raw data, the dots represent outlying values.

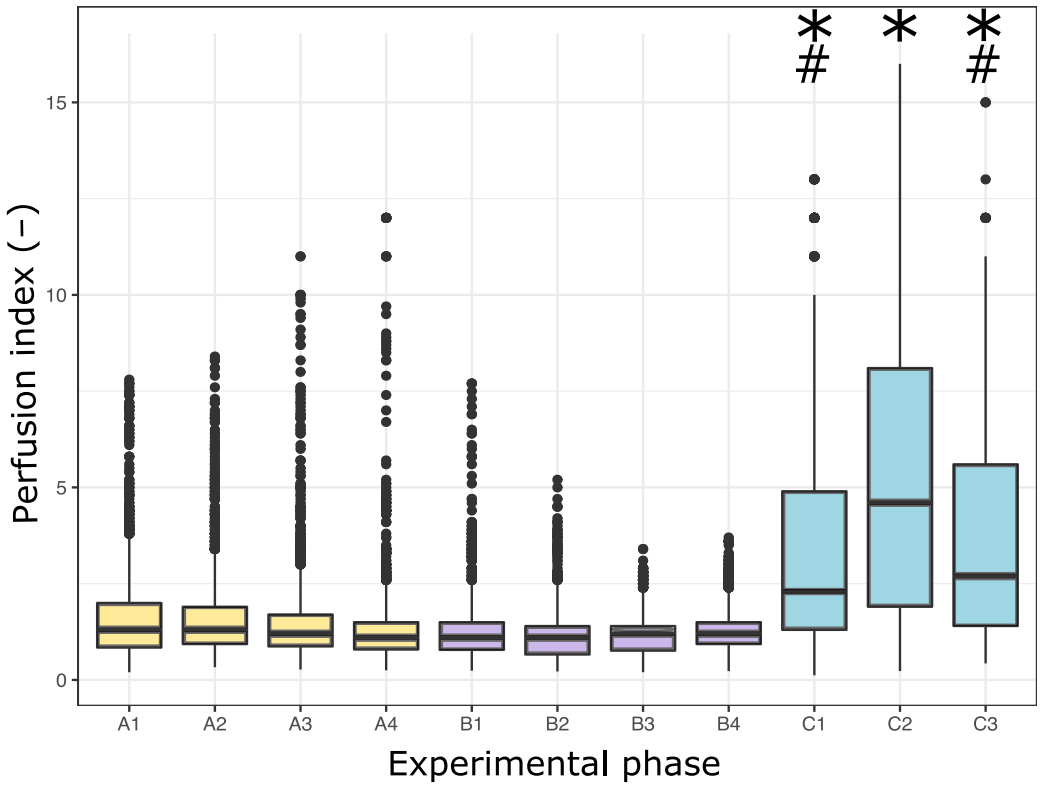

Figure 5.11 The changes in *PI* values in the experimental phases. The phases are divided in one-minute segments: four segments of stabilisation phase (A1–A4), four segments of breathing phase (B1–B4) and three segments of recovery phase (C1–C3). In the breathing phase, only the first 4 minutes are included in the analysis. The symbol * represents statistically significant difference of the segment from all segments of the stabilisation and breathing phases, the symbol # represents statistically significant difference from the segment C2.

Finally, in Figure 5.12, the relationship between the mean perfusion index and the proportion of the congruent segments of SpO_2 values from the total length of recorded data during the stabilisation and breathing phase is presented. The linear regression model was insignificant in both phases, with p = 0.62 for the stabilisation phase and p = 0.35 for the breathing phase.

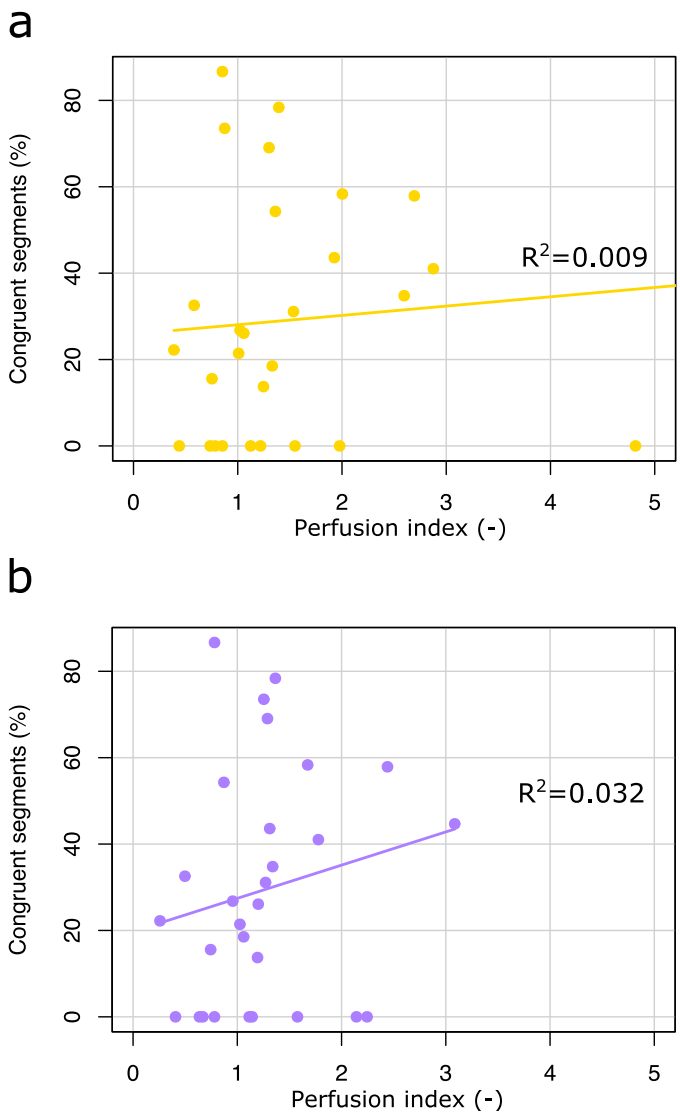

Figure 5.12 The relationship between the mean perfusion index and the proportion of congruent segments of SpO_2 values from the total length of recorded data during stabilisation (a) and breathing (b) phase of the experiment in all analysed subjects. R^2 – coefficient of determination of the linear regression model.

6. Discussion

6.1 Medical and technical aspects of the field breathing experiments

The findings presented in this thesis offer novel insights crucial for the design and conduction of field breathing experiments, particularly experiments in simulated avalanche snow. These findings primarily address the interaction between subjects and medical equipment, as well as the performance of medical equipment during experiments involving physiological parameter changes due to factors such as rebreathing of exhaled gas, progressive hypoxia, hypercapnia, increased work of breathing, and nonstandard environmental conditions. Understanding these medical and technical aspects is paramount not only for effective study designs and accuratel data analysis but also for ensuring the safety of the subjects involved.

Field breathing experiments' technical and medical aspects are directly related to the vital sign monitors and their functionality in specific environmental conditions, as discussed in [33]. While errors in $EtCO_2$ display during simulated avalanche breathing experiments have been reported [8], the performance of pulse oximetry—the commonly monitored parameter and endpoint in such studies—remains unexplored to the best of my knowledge. Additionally, despite its potential clinical significance, the behaviour of the perfusion index under these specific conditions has not been thoroughly investigated.

Within my thesis, I have focused on examining these two aspects: the performance of pulse oximeters and the behaviour of the perfusion index. The subsequent discussion will explore these topics further.

Despite some level of hypoxia and hypercapnia developed in the study subjects, no adverse effects were observed. No arrhythmia was detected during the presented study, although in the past, the exclusion of subjects from studies due to ventricular extrasystoles has been reported [12,17]. Figure 5.3 shows initial tachycardia shortly after the connection of the apparatus to the material simulating avalanche snow. This phenomenon can be attributed to a stress reaction. The second increase in heart rate following approximately two minutes of the experiment might be due to worsening hypoxemia and hypercapnia, which are known to increase sympathetic nerve activity [130-132].

6.2 Performance of pulse oximeters during field breathing experiments

The main finding is that oxygen saturation readings displayed by the five pulse oximeter devices during short periods of rapid onset hypoxemia and hypercapnia were significantly different. They varied in the time of desaturation onset, in the lowest measured SpO_2 value, and in the

duration of the recovery phase, when the subject was already breathing ambient air and the oxygen saturation was returning to pre-experimental values.

The results suggest that if SpO_2 is chosen as a study endpoint for a field breathing trial, the selection of a particular device can prolong or shorten the trial by tens of seconds (Figure 5.6). If we consider that most of the volunteers in this study managed to complete 240 s to 300 s of breathing into the material simulating avalanche snow, the change in the testing period by, e.g., 50 s is a significant intrusion into the course of the clinical trial.

Not only the rate of the SpO_2 changes but also the minimal values reached following the disconnection from the test material can pose a significant drawback. Manufacturers usually guarantee the accuracy ±2% in the interval of SpO_2 70% to 100% (Masimo Radical-7, Edan M3B, Nonin PalmSAT 2500 [64,65,67]), anaesthetic monitors Datex-Ohmeda S/5 and CareScape B650 have declared the accuracy ±3% in the range between 50% and 80% [63,66] (Table 4.2). However, even when the declared accuracy of the devices was considered (Figure 5.7), the values from the pulse oximeters were often not comparable. In fact, in 28.2% of the breathing experiments (n = 11), there was no congruent signal identified, and in the rest of the experiments, the congruent intervals covered, on average, only less than a third of the total recorded time (30.5 ± 26.4%). The intervals of congruent signals were observed mainly at the beginning of the breathing phase and at the end, during the recovery phase. However, in the course of the desaturation, which is the potentially risky experimental phase, the congruity among the devices was infrequent.

The resaturation phase also exhibited considerable differences among the pulse oximeters. Moreover, one device (Edan M3B) had a tendency to show the lowest measured value for a prolonged period of time, whereas the SpO_2 level was within the normal range according to the other devices (as in Figure 5.6). This behaviour can be potentially dangerous because the displayed low value could spur the physician to undertake unnecessary measures.

Under laboratory conditions, a comparison of four pulse oximetry devices during desaturation was studied by Gehring *et al.* [133]. They studied mainly the effect of motion and low perfusion state, but without both of these limiting factors, the SpO_2 differences of all four pulse oximeters were within ± 3%. In the same study, when a low perfusion state due to brachial artery compression was introduced, there was still a very good agreement among the pulse oximeters and in comparison to the reference hand (Figure 6.1). The time course in Figure 6.1 is similar to desaturations observed during our study with long congruent parts (like in Figure 5.7 b); however, full congruency of all SpO_2 values was not observed in our study. Also, Trivedi and colleagues [81] did not recognise the superiority of any of the five tested pulse oximeters during desatura-

tion and resaturation. At the same time, none of the pulse oximeters displayed a SpO_2 value differing from the SaO_2 by more than 3%.

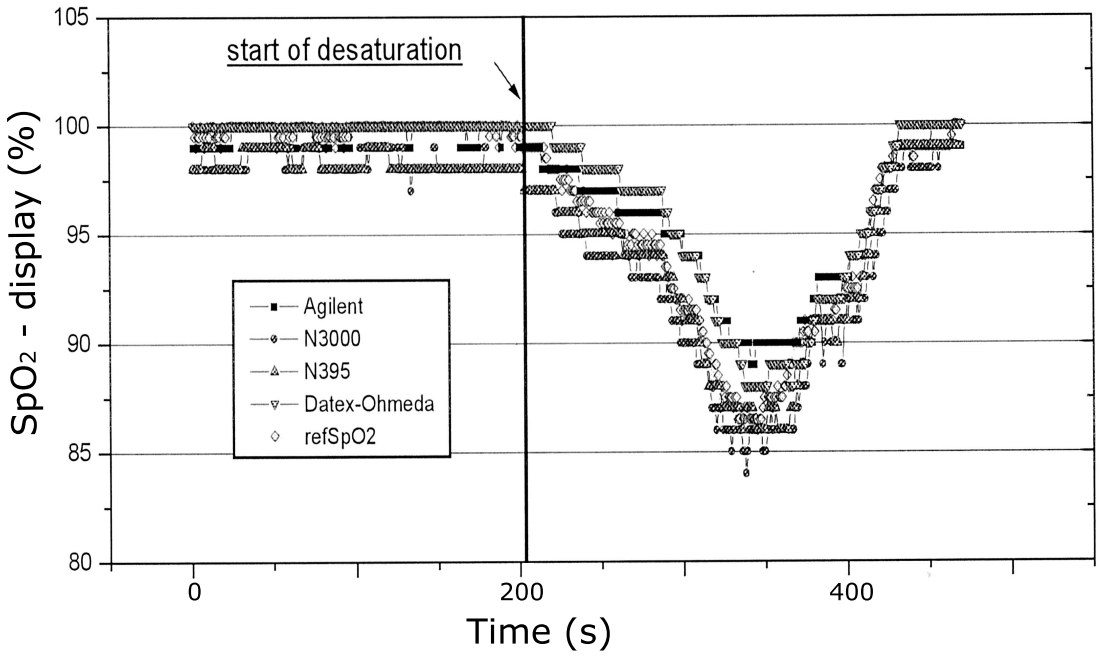

Figure 6.1 Example of pulse oximetry devices in a good agreement during a desaturation study with no motion and low perfusion state secondary to a brachial artery compression compared to SpO_2 displayed on the reference hand (refSpO2). Modified from [130]).

As a part of the settings of each device, it is possible to select data averaging and display refreshment time, usually referred to as 'response'. This equates to the speed at which the displayed value appears following the measurement of the parameter. For SpO_2, the monitor can display the values beat-to-beat or present an average of results from the set time period, e.g., 20 s. The latter is a default setting for Datex-Ohmeda S/5 monitors because, in anaesthesia, it helps to eliminate distracting artefacts and false alarms. However, in breathing experiments, we may observe changes in volunteers' physiological parameters within a couple of seconds, and this averaging can give us incorrect information about the subject's state and inaccurate experimental data. In addition, this can present safety risks to the volunteers [33]. In this current study, the 'response' was set to the minimal option available, so it was different for each device (also listed in Table 4.2): for Datex-Ohmeda S/5, it was set to beat-to-beat, for CareScape B650 to minimum 3 s. In Masimo Radical-7, the values are recorded every 2 s, and the response time can be set to a minimum of 2 to 4 s. The other two devices, Edan M3B and Nonin PalmSAT 2500 do not offer the option of adjustable response time. The difference in the device response times may have affected the simultaneously displayed SpO_2 values (Fig. 6.2) [96]. Trivedi *et al.* [81] documented the largest difference in response time within a single subject between the fastest and slowest oximeter, ranging from 13 to 29 seconds.

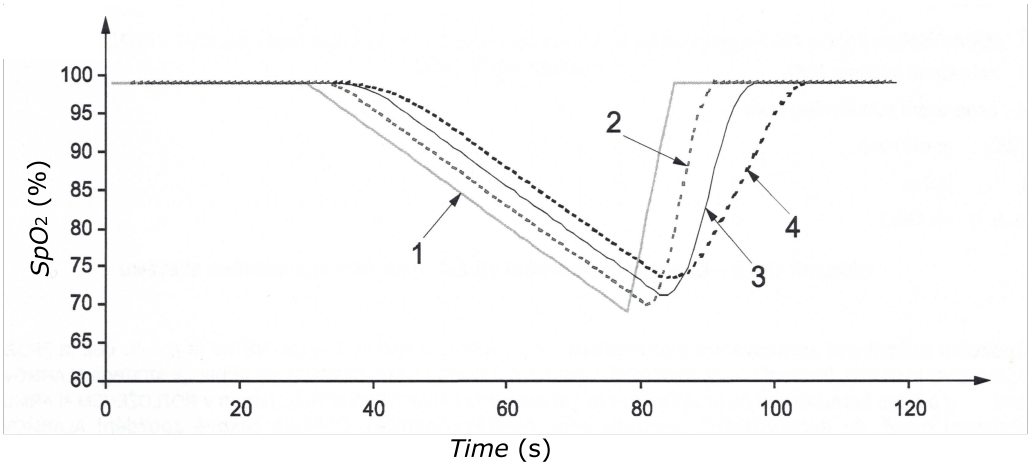

Figure 6.2 Example of fidelity of pulse oximetry device during changes of SaO_2 in time. 1. SaO_2 during desaturation, 2. displayed SpO_2 with faster averaging, 3. displayed SpO_2 with normal averaging, 4. displayed SpO_2 with slower averaging (modified from [96]).

The effect of the SpO_2 averaging time on the detection of desaturation events and their duration has already been investigated [134,135]. The study by McClure and colleagues [135] documents well that the change in averaging time from 2 s to 16 s causes a significant smoothing of the SpO_2 curves during desaturation periods (Figure 6.3). The evidence suggests that in experiments with expected rapid changes of SpO_2, devices with minimal response time are preferable to reduce inaccuracy in data acquisition.

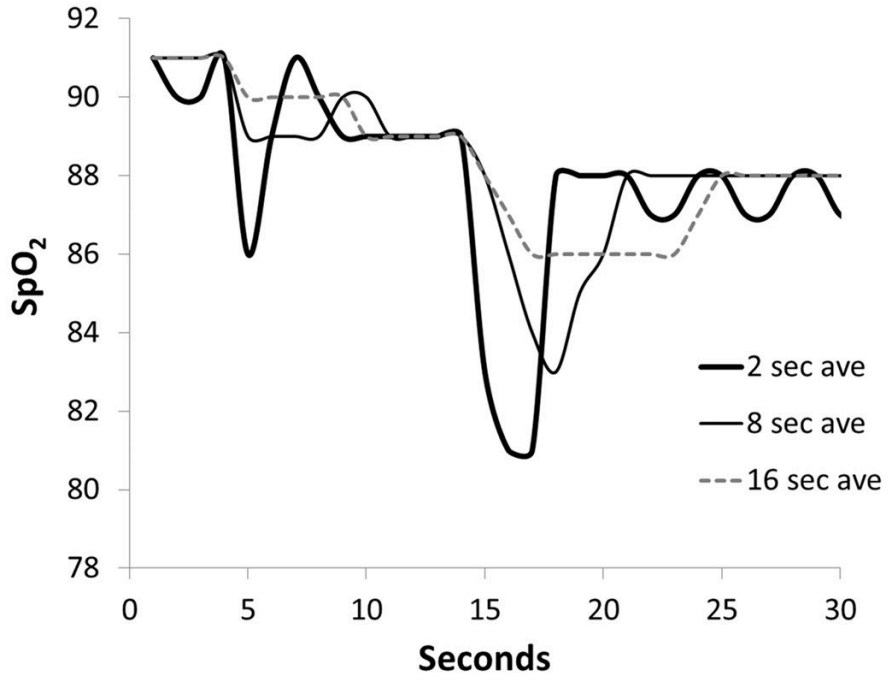

Figure 6.3 Example of impact of SpO_2 averaging time on detection of desaturation events in a preterm very low birth weight infant with SpO_2 averaging time at the shortest setting (2–4 s), and calculated SpO_2 for the same 30 s time period if the oximeter had been set to 8 or 16 s SpO_2 (from [132]).

Although pulse oximetry is a widely used means of monitoring with upgraded algorithms [84], it has well-known limitations [78], and its use outside the hospital environment is challenging [79]. The peripheral low perfusion state, typically associated with cold conditions, can alter the pulse oximetry readings. However, during all breathing experiments, a maximum effort was made to prevent this effect: the subjects had their hand placed in a warmed glove, and the perfusion of the fingers was monitored by perfusion index—*PI* [65]. No significant decrease in the perfusion index was observed throughout the breathing experiments (Fig. 5.11), and no significant relationship between the low *PI* and an increased proportion of incongruent segments was identified (Fig. 5.12). More discussion about the effect on *PI* can be found in chapter 6.3 Perfusion index during field breathing experiments. We can speculate that the low perfusion state was not a crucial limiting factor for the performance of the pulse oximeters and, hence, an important source of the incongruity in the displayed SpO_2 values.

Additionally, for standard in-hospital use, the software is programmed in order to minimise false alarms. This means that rapid brief changes in oxygen saturation are suppressed, as in the hospital settings, they are usually caused by motion artefacts, bad connections or poor contact [136,137]. However, these rapid changes in SpO_2 are typical for field breathing experiments in the simulated avalanche snow [12,17,18,26,34,41,43,44] as well as, for instance, in breath-hold divers [75].

Moreover, the popular breathing experiment study endpoints of SpO_2 75% to 88% lie in the interval where the mean error in SaO_2 measured by pulse oximeters is more pronounced [92,94]. Several studies observed the tendency of SpO_2 to underestimate [90,91] or overestimate [97-99] the SaO_2 value. However, to date, no study has examined the bias in adult subjects during field breathing experiments with progressive hypoxia and hypercapnia due to rebreathing, so the tendency of the pulse oximeters in this scenario is unknown. Moreover, Figure 5.8 suggests there is no systematic shift in SpO_2 readings in any of the devices, although this analysis may be affected by the performance of one of the pulse oximeters.

Also, in general, differences in performance among pulse oximeters under hypoxic conditions have already been demonstrated [82,83,88,90,133], but to my best knowledge, not in field experiments with concomitant progressive hypoxemia, hypercapnia and increased work of breathing. A complex assessment of different brands of pulse oximeters from different manufacturers during desaturation is not possible as each study uses different devices, and the pace of introduction of new types exceeds the rate of new studies. We can only say that in some studies, the Masimo devices with the SET technology were found to be superior to some other devices under motion and low perfusion conditions [82,115,138].

During desaturation, the loss of displayed value in our experiment occurred during intervals lasting tens of seconds. Moreover, we have observed the phenomenon of a prolonged display of a stationary value (Fig. 5.6). Compared to that, Trivedi *et al.* [90] reported only a rare and transient loss of displayed value, lasting just a few seconds.

A delay in response to resaturation has also been discussed in the literature. Kawagishi and colleagues [138] speculated that faster response to resaturation following pressure cuff release in Masimo-SET Radical (Masimo Corp, Irvine, CA), compared to Nellcor N-395, N-20PA, and D-25 (Nellcor, Inc, Pleasanton, CA) might be caused by the setting of the algorithm, or an ability of Masimo to detect even a low level of signal. Thus, this technology might be more suitable for hypoperfusion states. During laboratory experiments in lowered ambient temperature [115], the SpO_2 failure rate (proportion of time when the device failed to display SpO_2 value to total test time) was 0% for Masimo Radical, 1.3% Datex-Ohmeda TruSat, and 9.3% for Nellcor N-600. The average recovery time from failure events in the same study with desaturation and motion artefacts was 0.60 ± 1.1 min for volunteer-generated motion.

During outdoor breathing experiments, the volunteers are standardly monitored by vital sign monitors, and additionally, they are continuously assessed by an experienced physician. The physician and supervising investigator make decisions regarding the conduction of the experiment based on the physiological parameters presented to them on the screens of vital sign monitors. For this reason, in this study, all analysed data were obtained from simultaneous video recordings of the pulse oximeters' screens, which are purely values that are accessible to the user of the monitor. Raw data recorded directly from the monitors were not used during the analysis of the performance of pulse oximeters.

Although data for this study were acquired during a breathing trial with a simulated avalanche snow and snow model, the findings are relevant to other clinical situations where rapid changes in oxygen saturation may occur, e.g., in difficult airway management in anaesthesia. In these cases, the physicians also rely on only one physiological parameter, standardly displayed by a single device. Delayed displaying of low SpO_2 values may result in a belated appropriate physician's reaction. On the other hand, repetitive presentation of low values for a prolonged period of time after the acute situation ceased—as was exhibited by the Edan M3B monitor in 41% of the recorded experiments (example on Fig. 5.6)—can lead to unfitting decisions and improper procedures.

This study examined a specific situation of short rapidly developing periods of desaturation associated with hypercapnia in an outdoor environment. The intention was not to analyse the particular pulse oximetry devices and find the most suitable one but rather to document their behaviour during short-term rapid desaturation and resaturation. Additionally, as a standard, the ac-

curacy of pulse oximeters is formally tested during desaturation experiments where subjects experience gradual plateaus of hypoxemia with a maximum duration of 10 min [96]—a protocol different from this study. In studies with stepwise protocol, cerebral oxygenation was not critically altered despite periods of desaturation up to SpO_2 of 50%, lasting several minutes [96,119]. A recent study by Strapazzon *et al.* [44] showed that whilst breathing into artificial air pockets in avalanche snow, the peripheral pulse oximetry does not correspond to regional cerebral oximetry, measured by near-infrared spectrometry. The authors of [98] hypothesise that cerebral oxygenation may not be impaired despite a significantly reduced oxygen supply.

The limitations of this study include mainly the lack of randomisation of finger probe placement or, alternatively, simultaneous placement of the same saturation probes in different locations. The pulse oximetry probes were placed on fingers in a standardised manner (Fig. 4.3, Table 4.2). The possible differences among fingers could have affected the displayed values, although the variability between fingers is small [76,85-88]. On the other hand, due to the nature of these experiments, a more complex study protocol with randomisation and cross-over design would be very complicated. In the current study, compared to laboratory experiments, the test site preparation was elaborate, and the subjects needed a significant amount of time to recover from each breathing experiment. This is another particularity of the field breathing experiments—some conventional study designs are very challenging to be employed.

An important limitation of this study is also the lack of a gold standard reference for pulse oximeters, like SaO_2 repetitively measured in arterial blood samples during a steady state of hypoxemia [96]. The nature of this experiment does not favour this type of assessment, although arterial blood sampling [41] and mixed capillary blood [44] gas analyses have already been employed in these experiments. Still, the fast changes in subject oxygenation make this test hard to be evaluated.

Additionally, a restricted number of tested devices and the use of only peripherally placed pulse oximetry probes, known to have delayed detection of desaturation compared to centrally placed probes (earlobe, forehead), limited the study. The difference in the response time between the ear probe and the finger probe can be up to 20 s [90]. However, we studied finger probes as they are the most popular, mainly due to their simple use. Based on the experience from the ICU, it can be speculated that earlobe probes might not stay in place during the subjects' head movements, and they may produce even less reliable data. That should be a subject of further research.

Another limitation was the different response time of each device, although it was set to the minimal available value. Finally, the number of study subjects was only thirteen, which could be considered a small trial. However, some studies of pulse oximetry accuracy under hypoxic con-

ditions had ten or fewer subjects [90,133,139]. Furthermore, only male subjects were included, even though there is a known difference in SpO_2 values between men and women [140].

Further studies are needed to compare devices currently used in clinical practice in hospitals and during field experiments. With the fast development of these monitoring means, testing of the devices in in-hospital and out-of-hospital settings can change the perceived reliability in non-standard situations. Additionally, this study documents that monitoring during short-term changes of peripheral saturation with oxygen has several limitations and clinical assessment by a skilful physician is irreplaceable. Moreover, relying on a single parameter as a study endpoint or a safety limit could not be recommended.

6.3 Perfusion index during field breathing experiments

The main finding is that during hypoxemia and hypercapnia associated with field experiments simulating breathing under avalanche snow, the perfusion index derived from pulse oximetry does not vary significantly from the baseline values. When the breathing experiment is ceased, and the hypoxemia quickly resolves, the *PI* value shoots up. These findings suggest that the subjects of these experiments do not suffer from inadequate perfusion of acral regions. Thus, the values of SpO_2 displayed by the pulse oximeter during the progressive hypoxemia and hypercapnia should not be significantly affected by the low perfusion state. To my knowledge, this is the first analysis of the perfusion index during field experiments in a situation of combined hypoxemia, hypercapnia and increased work of breathing.

Our results suggest (Figures 5.6 and 5.7) that discrepancies among SpO_2 values displayed by different pulse oximeters may be an issue during field breathing experiments. The question is whether these incongruent results could have been caused by poor perfusion of the subjects' fingers, a well-known limitation of this method [76,78]. In the field experiments, the low perfusion state due to low ambient temperature can be an issue; however, during the current study, all effort was made to guarantee maximal thermal comfort. The subjects were lying on an insulated mat, well dressed, with the test hand placed in a glove pre-heated by a warmer and before arriving at the outdoor test site, they were waiting in a close heated hut.

Figure 5.12 shows no systematic relationship between the proportion of incongruent SpO_2 segments from the total experimental time and the perfusion index (data of all subjects presented in Supplementary table S2 in Appendix A). It can be seen that 0% congruent segments were observed in subjects with the whole range of *PI* values. The attempted general linear regression model for elucidation of the relationship between the perfusion index and the proportion of the SpO_2 congruent segments yielded statistically insignificant results, suggesting minimal explanatory power of the model. The analysis suggests that the incongruence of the SpO_2 values dis-

played by the five different pulse oximeters could not be explained only by the finger low perfusion monitored by the perfusion index.

To date, the threshold *PI* value indicating a low perfusion state has not been defined. In an attempt to evaluate finger perfusion using the *PI*, the cutoff value suggesting a low perfusion state for critically ill adult patients was proposed at a *PI* of 1.4 [103]. Hummler *et al.* [116] recommended verifying the SpO_2 value with arterial blood gas analysis in situations when *PI* drops below 0.5.

During our study, the baseline *PI* in the subjects reached values of 1.54 ± 1.01. This result corresponds to values measured in several studies [103-105,107]. Some studies reported higher mean baseline *PI*, over 2.0 [106], or even nearly 5.0 [108]. Reasons for slightly lower *PI* in our study could have been the stress from the experiment and moderately impeded peripheral perfusion due to the cold environment, despite maximal effort to guarantee a thermal comfort. When Shah *et al.* [115] studied perfusion index under low ambient temperature and desaturation conditions, the resulting mean *PI* was 0.95 (0.63 at the first quartile)—a value lower than in our study.

The association between decreased *PI* and increased SpO_2-SaO_2 bias has been documented in two studies. Hummler *et al.* [116] observed the bias exceeding the declared 3% limit when the perfusion index was below 0.5 in septic rabbits. On the other hand, Louie *et al.* [83] identified significantly higher bias in case $PI < 2.0$, compared to $PI \geq 2.0$ during laboratory desaturation study. The SpO_2-SaO_2 bias in our study has not been evaluated because of the lack of arterial blood gas analysis.

As discussed above, the accuracy of pulse oximetry is crucial, especially during the breathing phase, when rapid changes of SpO_2 occur, predominantly in case the peripheral saturation of blood serves as a study endpoint [17,18,34,43]. On the other hand, advancing hypoxemia and hypercapnia (as can be seen in Figure 5.9) may potentially affect the vascular tonus and, thus, the perfusion of the monitored site. The changes in vascular activity are complex, with several synergic and antagonistic processes.

In this study, the perfusion index in some subjects tended to decrease between the stabilisation and the breathing phases (as seen in Figure 5.10, Suppl. table S2). However, these changes were not statistically significant. The drop in perfusion index could have been caused by prolonged exposure to the cold environment despite all efforts to protect the subjects. The effect of hypoxemia and hypercapnia on the perfusion index is uncertain. In studies, hypoxia increased blood flow into the forearm due to concomitant vasodilation [113,130]. Yet Abramson *et al.* [113] observed that this increased forearm blood flow is associated with vasoconstriction in the hand,

which might be an oxygen-sparing mechanism. On the other hand, hypercapnia is a potent vasodilator and promotes increased blood flow through the brachial artery by 10–30% [132]. We can speculate that the vasodilatory and vasoconstrictive effects are in a delicate balance during the breathing phase, and the perfusion of the fingers is preserved. A completely different situation is in the recovery phase: the hypoxia resolves swiftly when the subjects stop re-breathing the exhaled gas, but the elimination of the accumulated carbon dioxide is prolonged and hence its effect on the vascular tone. The unmasked vasodilation due to hypercapnia is represented by the perfusion index of double or triple values compared to the baseline.

The presented results can have implications in clinical practice as well. Not only during the outdoor experiments but also in pre-hospital care and operation theatres, the cold environment can raise questions regarding the perfusion of the peripheral tissues and, hence, the accuracy of the pulse oximetry. The perfusion index can help us assess the perfusion of the fingers where the pulse oximeter probe is placed. Although we are unable to set a distinctive threshold *PI* value for low perfusion state (mainly due to the significant inter-individual variability, as seen in Fig. 5.10), the perfusion index can serve as a trend marker.

The results also demonstrate that the effect of hypercapnia can be observed on the perfusion index; however, the effect of hypoxemia is uncertain. Clinically, similar dynamic changes of the perfusion index might be observed, for example, in patients suffering from respiratory failure with hypoxemia and hypercapnia. However, the data from these patients are not available, and it is a matter of further research.

This study has several limitations. Firstly, the statistical comparison was difficult as the duration of each breathing phase differed significantly among the subjects. Secondly, all breathing experiments into different materials were analysed together. However, the assessment of the effect of the different snow model materials was not the aim of this study. Finally, the number of study subjects was small and only young fit male volunteers were recruited, although sex differences in *PI* have been reported and female baseline *PI* tends to be below 2.0 [82]. The lack of female participants in these studies, or an imbalance between men and women in the study group [83,88,133,141], can be a weak point in this research. Further research in more groups of subjects is needed.

For the analysis, a possible confounding factor could have been mild systemic hypothermia, despite all measures included in the protocol in order to prevent heat loss of the subjects (warm clothing, waiting in the heated hut before the experiment, insulated mat, warmed winter gloves). The slow decrease in *PI* during the stabilisation period prior to the main breathing phase was likely due to mild hypothermia and decreased cardiac output of the resting subjects. In a study by Keramidas *et al.* [142], in mild hypothermic conditions, the hypoxemia in a reaction to local

cold stimulus was not proved to potentiate the finger vasoconstriction; however, the lower oxygen blood content affected the perception of coldness by the subjects. In the same study under thermo-neutral conditions, the hypoxia also did not potentiate the already occurring vasoconstriction caused by a local cold stimulus.

6.4 Specifics of medical equipment use in field breathing experiments

Monitoring devices originally designed for anaesthesia or ICU may provide inaccurate or misleading data during field breathing experiments even though they are used according to the operating conditions listed in the manual. A straight use in the outdoor environment, and unquestioning operation in such studies may pose the study participants into threat.

On the other hand, the summary of environmental parameters of the devices used in the recent studies on breathing into simulated avalanche snow (Table 2.3) revealed that the ambient temperature, humidity, and pressure limits of the ICU and anaesthesia monitors do not differ much from the parameters of the monitors used in emergency medicine. These "emergency monitors" are designed also for transport in a helicopter and for monitoring in outdoor environment [68-70]. Unfortunately, the ambient temperature value is not accessible in the raw data of any of the monitors used in this study; only ambient pressure is recorded, although both these parameters are used by the monitor for calculations, e.g., for ventilatory parameters. The medical device's ambient temperature should be logged externally in future experiments.

Although the vital sign monitors are constantly improving, the users—in clinical environment, or during field experiments—should bear in mind their limitations. For instance, pulse oximeters have recently obtained an improved algorithm for resistance to motion artefacts and low perfusion states. Both these situations interfere with the original model of SpO_2 measurement and can mimic desaturation [82]. Our current study does not directly support the findings about the superiority of the Masimo Radical-7 with the SET technology (described in [65,84]). However, our aim was not to compare the devices in order to find the best one, and the study lacks a gold standard like SaO_2 measurements.

Not only the choice of the appropriate monitored physiological parameters but also the particular monitoring device can be crucial for the course of the experiment. This study demonstrated that the choice of a specific pulse oximeter can shorten the experiment by up to one-quarter of its length (Fig. 5.6). In the past, Roubík and Filip [8] showed the discrepancy between the trend data and displayed waveform in capnography during simulated avalanche breathing experiments. Also, Wik *et al.* [41] experienced a limitation in the monitoring device. They placed a gas monitor Dräger, X-AM 5600 (Dräger, Vienna, Austria) into the air pocket. However, this monitor is able to measure the maximal CO_2 concentration at only 5%; higher concentrations

are indicated as “over the range”. The use of this measuring instrument caused a loss of potentially valuable experimental data when the limiting CO_2 concentration had been exceeded.

Recently, the monitoring of cerebral oxygenation using NIRS monitors has been introduced to the experimental protocols of field breathing experiments [41,43,44]. Also, this non-invasive optical method has significant limitations [143]. For field experiments, the most relevant limitations might be the unknown effect of extracranial tissues on NIRS signal—including the skin blood flow changes due to, for instance, cold environment—no clear reference values defined, ambient light and movement artefacts, and the lack of standardisation for signal processing, or data analysis [143,144]. In the study by Wik *et al.* [41], it was stated that it was the first time that saturation cerebral tissue oxygenation ($SctO_2$) had been used, compared to cerebral oxygen saturation (ScO_2) used in previous studies by Strapazzon *et al.* [43,44]. However, the use of NIRS with multiple different wavelengths and optode arrangements is problematic to be seen as a new method, although some upgrades of the optodes can improve the distinction between cerebral and extracranial tissue oxygenations [120]. As this method lacks an international standard similar to that for pulse oximetry [96] and the validation methods differ [120], the comparison of NIRS values between monitors is controversial [143,144].

6.5 Clinical application of the results

Although the presented study was conducted on subjects during outdoor breathing experiments in simulated avalanche snow, the results and conclusions may be applicable to clinical practice in anaesthesia, intensive care, and emergency medicine.

Fast changes in oxygenation can occur, for instance, during difficult airway management and intubation failure, not only in anaesthesia but also in critical care or emergency medicine settings. The behaviour of the pulse oximeters can directly affect patient management. Delayed display of desaturation or even resaturation can lead to improper treatment.

I myself have had a patient who desaturated during induction to anaesthesia due to a difficult airway situation. The monitor displayed the lowest measured SpO_2 value for a prolonged period of time even though, clinically, the ventilation and oxygenation had already been restored. After a couple of minutes, the displayed SpO_2 suddenly jumped to 100%. This case report is going to be published.

The changes in *PI* during hypoxia and hypercapnia are also potentially relevant to anaesthesia and other medical fields where this parameter is in use. As *PI* is used for pain assessment during anaesthesia, the simultaneous effect of hypercapnia, for instance, during pneumoperitoneum insufflation with carbon dioxide, can be potentially important. However, the parameter has not

been examined under these circumstances, and further studies are needed. The combination of hypoxemia and hypercapnia can be seen in hypoventilating patients, for instance, following general anaesthesia or with other reasons for combined respiratory failure. Also, in these cases, the effects on *PI* should be investigated.

6.6 Recommendations for future experiments

Based on the conclusions from the study and literature review, some recommendations for future studies can be listed.

Vital sign monitors used for the safety of the subjects and for recording study data should be operated with the awareness of their limitations under these conditions. Using a single physiological parameter as a study endpoint, if the parameter is monitored by a single medical device, may affect the duration of the study, and it seems to be an unreliable method. More parameters, together with a clinical assessment by an experienced physician, appear to be a safer procedure. Devices with adjustable and short response times should be preferred as they can more reliably record and display rapidly changing physiological parameters of the study subjects. The study protocol should include measurement of baseline values of the parameters (potentially valuable for *PI* and ScO_2, but other parameters like heart rate, blood pressure, or SpO_2 may also be of a value).

All monitors should be properly secured from environmental conditions. The manufacturers' recommendations regarding environmental condition limits should be followed. We should also bear in mind that these limits differ from device to device, and some monitors for critical care use can have a similar working temperature and other parameters as emergency medicine monitors designed for monitoring patients in out-of-hospital settings. The environmental conditions of the medical devices—like ambient temperature and pressure—should be monitored by an external gauge, and the thermal comfort of the devices should be secured throughout the experiments. A heated shelter for medical devices close to the subject may be an option.

Pulse oximetry is probably not an ideal single study endpoint in these studies, but it can be used as one of the monitored parameters for the safety of the subjects. Attention should be paid to the settings of the device, especially choosing the shortest possible response time, in order to recognise profound hypoxemia without a delay caused by the averaging. All precautions should be taken to eliminate the already known limitations relevant to field experiments, like hypoperfusion due to low ambient temperature, motion artefacts, or improper probe position. Centrally placed probes might probably have a better response to desaturation changes, but there is no data on their use in these experiments. Cerebral oxygenation measurement using the NIRS method should be considered for the study protocol. The data suggest that ScO_2 is preserved despi-

te considerable desaturation recorded via a finger pulse oximetry probe. The use of pulse oximeters with the SET technology might be beneficial in case of motion artefacts and low perfusion states, but their superiority in field experiments has not been convincingly demonstrated.

If the chosen pulse oximeter calculates the perfusion index, we can use this parameter to assess the finger perfusion and, thus, the reliability of the pulse oximetry. However, the threshold *PI* value, which is insufficient for reliable SpO_2 monitoring, has not been defined, and perhaps a baseline indoor measurement of *PI* prior to the main experiment might be helpful. There is a possible effect of hypoxia, hypercapnia, increased work of breathing, or an unknown combination of these states on the *PI,* which should be considered when this parameter is evaluated.

Also, $EtCO_2$ does not seem to be an acceptable single study endpoint, and its monitoring has notable limitations. During the experiment, not only the numerical value should be displayed to the supervising physician, but also the waveform, as there are considerable differences between these two. Raw data analysis is strongly recommended. It is imperative to verify the measuring limits of each gauge utilised in the experiment to prevent data loss when variables exceed the designated range.

Not only monitoring of hypoxia and hypercapnia but also their potential medical risks should be fully appreciated. An experienced physician equipped for resuscitation should be an essential member of the experimental team. The assessment of cognitive functions of the subject during hypoxemia and hypercapnia—for instance, by simple mathematical operations—is an important safety measure due to inter-individual susceptibility to hypoxemia, hypercapnia and their combination.

In case a specially designed breathing apparatus or any other way of separation of the air pocket gas and ambient gas is in use, detection of possible air leaks should be adopted. The use of nitrous oxide for this purpose might be a promising technique, but validation of this method has not been done yet.

6.7 Future work

Some aspects of field breathing experiments have not been covered by this thesis and can become a motivation for future work. Mainly the system for air leak detection via nitrous oxide requires improvement in dosing and validation of the whole technique.

7. Conclusions

During field breathing experiments, the use of monitoring medical equipment has notable limitations. The devices are used in conditions substantially different from anaesthesia and intensive care unit settings. Safety limits of physiological parameters must be interpreted in these experiments considering the limiting conditions; otherwise, the data may be falsely interpreted, and the safety of the subjects may be endangered. Along with technical issues, medical precautions must be applied during the breathing experiments. The physiological parameters of the subjects get quickly out of the normal range, which increases the risk of complications.

In the study, the peripheral oxygen saturation (SpO_2) readings displayed by the five pulse oximeter devices during short periods of rapid onset hypoxemia and hypercapnia were significantly different. They varied in the time of desaturation onset, in the lowest measured SpO_2 value, and in the duration of the recovery phase, when the subject was already breathing ambient air and the oxygen saturation was returning to pre-experimental values. The results suggest that peripheral oxygen saturation might not be a reliable parameter as a study endpoint or, more importantly, as a safety limit in field experiments. The choice of a particular pulse oximeter device can significantly affect the duration of the breathing experiment.

The perfusion index (*PI*) derived from pulse oximetry does not decrease significantly during hypoxemia and hypercapnia, which are associated with field experiments simulating breathing under avalanche snow, compared to baseline *PI* values. When the experimental breathing is ceased and the hypoxemia resolves, the perfusion index tends to double or triple its values. This surge of *PI* in the recovery phase is likely due to the effect of carbon dioxide on the vascular tonus. The average baseline *PI* in this study is within the range or just slightly lower compared to values observed in other clinical situations. These findings suggest that the subjects of these experiments do not suffer from insufficient perfusion of acral regions, so a low perfusion state should not be a source of the inaccuracy of pulse oximetry.

The irreplaceable role of clinical assessment by a skilled physician should be considered. More parameters and continuous clinical assessment should be included in the design of future studies.

8. Contribution to biomedical engineering

Simulated avalanche snow breathing experiments are crucial data sources for constantly developing guidelines for the resuscitation of avalanche burial victims. During these clinical trials, various medical equipment is used for the safety of the subjects and for recording the experimental data. However, this equipment operates in non-standard ambient conditions, and the changes in physiological parameters of the study volunteers are rapid, and the patterns of these changes are uncommon for the population of critically ill patients. These rapid changes in vital signs can create potential errors, which can pose a threat to the safety of the subjects and also it can devaluate the results of the trial.

This study may help to recognise and address some of these equipment issues and try to prevent them in subsequent trials. The improved protocols of breathing trials in simulated avalanche snow may provide reliable data for the development of newer versions of resuscitation guidelines. Moreover, the conclusions from the study may also be useful for similar clinical situations where medical equipment is facing its technical, environmental or monitoring limits (e.g. in prehospital care, in difficult airway emergency situations in anaesthesia, or in similar field clinical trials).

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Appendix A – Supplementary tables

Supplementary table S1.The congruent and incongruent segments in analysis of five different pulse oximeters in all subjects (numbered 1–13) in all three breathing experiments (S–snow, PD–dry perlite, PW–moisturised perlite).

Subject–experimental phase	Total length of recorded data (s)	Number of congruent segments	Total duration of congruent segments (s)	Total duration of incongruent segments (s)	Congruent segments of SpO_2 (%)
1–S	620	0	0	620	0
1–PD	490	0	0	490	0
1–PW	490	0	0	490	0
2–S	380	0	0	380	0
2–PD	420	0	0	420	0
2–PW	370	4	290	80	78.38
3–S	470	1	210	260	44.68
3–PD	470	0	0	470	0
3–PW	390	1	160	230	41.03
4–S	230	0	0	230	0
4–PD	540	0	0	540	0
4–PW	460	3	160	300	34.78
5–S	540	3	120	420	22.22
5–PD	560	3	150	410	26.79
5–PW	480	0	0	480	0
6–S	400	0	0	400	0
6–PD	390	2	170	220	43.59
6–PW	450	0	0	450	0
7–S	360	4	210	150	58.33
7–PD	350	3	190	160	54.29
7–PW	450	1	70	380	15.56
8–S	430	3	150	280	34.88
8–PD	300	4	140	160	46.67
8–PW	260	2	130	130	50.00
9–S	540	1	100	440	18.52
9–PD	420	2	90	330	21.43
9–PW	550	1	30	520	5.45

10–S	450	3	140	310	31.11
10–PD	510	1	70	440	13.73
10–PW	460	2	120	340	26.09
11–S	250	4	110	140	44.00
11–PD	260	3	140	120	53.85
11–PW	380	2	220	160	57.89
12–S	360	4	110	250	30.56
12–PD	430	1	140	290	32.56
12–PW	300	2	260	40	86.67
13–S	340	3	250	90	73.53
13–PD	390	2	290	100	74.36
13–PW	420	2	290	130	69.05
Mean	419.49		115.64	303.85	30.51
SD	92.42		94.00	152.81	26.35

Supplementary table S2.The mean perfusion index (*PI*) in stabilisation, breathing and recovery phases in all subjects (numbered 1–13) and the ration of congruent segments of SpO_2 in all three breathing phases into all avalanche snow model materials (S–snow, PD–dry perlite, PW–moisturised perlite).

Subject–experimental phase	mean *PI* in stabilisation phase	mean *PI* in breathing phase	mean *PI* in recovery phase	Congruent segments of SpO_2 (%)
1–S	0.85	0.78	1.53	0
1–PD	0.74	0.67	2.52	0
1–PW	0.44	0.41	0.80	0
2–S	1.12	2.24	6.81	0
2–PD	1.22	1.11	6.60	0
2–PW	1.39	1.36	6.48	78.38
3–S	5.64	3.09	9.00	44.68
3–PD	4.82	2.14	7.26	0
3–PW	2.88	1.78	7.30	41.03
4–S	1.55	1.14	4.23	0
4–PD	0.78	0.64	1.44	0
4–PW	2.6	1.34	7.73	34.78
5–S	0.39	0.26	0.56	22.22
5–PD	1.02	0.96	2.77	26.79
5–PW	excluded	excluded	excluded	0
6–S	excluded	excluded	excluded	0
6–PD	1.93	1.31	4.82	43.59
6–PW	1.98	1.58	5.91	0
7–S	2.00	1.67	3.30	58.33
7–PD	1.36	0.87	5.48	54.29
7–PW	0.75	0.74	1.80	15.56
8–S	excluded	excluded	excluded	34.88
8–PD	excluded	excluded	excluded	46.67
8–PW	excluded	excluded	excluded	50.00
9-S	1.33	1.06	4.65	18.52
9–PD	1.01	1.02	3.61	21.43
9–PW	excluded	excluded	excluded	5.45
10-S	1.53	1.27	1.00	31.11
10–PD	1.25	1.19	4.48	13.73
10–PW	1.06	1.20	1.51	26.09

11–S	excluded	excluded	excluded	44.00
11–PD	excluded	excluded	excluded	53.85
11–PW	2.69	2.44	4.84	57.89
12–S	excluded	excluded	excluded	30.56
12–PD	0.58	0.50	1.13	32.56
12–PW	0.85	0.78	1.53	86.67
13–S	0.87	1.25	2.16	73.53
13-PD	excluded	excluded	excluded	74.36
13–PW	1.30	1.29	2.39	69.05

Appendix B – Author's publications on the topic

A. Journal articles

1. Horakova, L., & Roubik, K. (2022). Pulse Oximeter Performance during Rapid Desaturation. Sensors, 22(11), 4236.

2. Roubik, K., Sykora, K., Sieger, L., Ort, V., Horakova, L., & Walzel, S. (2022). Perlite is a suitable model material for experiments investigating breathing in high density snow. Scientific reports, 12(1), 1-12.

3. Roubik, K., Walzel, S., Horakova, L., Refalo, A., Sykora, K., Ort, V., & Sieger, L. (2020). Materials Suitable to simulate snow during breathing experiments for avalanche survival research. Lékař a technika-Clinician and Technology, 50(1), 32-39.

B. Conference proceedings

4. Horakova, L., Kudrna, P., & Roubik, K. (2021). Dynamic changes of perfusion index during hypoxemia and hypercapnia in outdoor experiments. In: 2021 International Conference on e-Health and Bioengineering (EHB). IEEE, 1-6.

   Awarded: **2nd prize Young Researcher Award** – conference EHB 2021

5. Horakova L., & Roubik, K. (2019). Performance of Different Pulse Oximeters Can Affect the Duration of Field Breathing Experiments. In 2019 E-Health and Bioengineering Conference (EHB) (pp. 1-4). IEEE.

   Awarded: **3rd prize Young Researcher Award** – conference EHB 2019

6. Horakova L., Sykora K., Sieger L., Roubik K. (2018) Monitoring of subjects during avalanche breathing experiments - possible errors. ISSW 2018 Proceedings.

7. Horakova L., Sykora K., Sieger L., Roubik K. (2018) Breathing Experiments into the Simulated Avalanche Snow: Medical and Technical Issues of the Outdoor Breathing Trials. In: Lhotska L., Sukupova L., Lacković I., Ibbott G. (eds) World Congress on Medical Physics and Biomedical Engineering 2018. IFMBE Proceedings, vol 68/1. Springer, Singapore.

Appendix C – Awards for publications

GRIGORE T. POPA UNIVERSITY OF MEDICINE AND PHARMACY IASI

FACULTY OF MEDICAL BIOENGINEERING

The Scientific Committee of the IEEE International E-HEALTH AND BIOENGINEERING

has the pleasure to offer

YOUNG RESEARCHER THIRD PRIZE

To

LENKA HORAKOVA

For their paper

Performance of different pulse oximeters can affect the duration of field breathing experiments

Authors

Lenka Horakova and Karel Roubik

General Chair of EHB 2019

Prof. HARITON COSTIN

Dean, Faculty of Medical Bioengineering

Prof. ANCA GALACTION

e-HB SRBM IEEE Advancing Technology for Humanity IEEE Romania Section IEEE EMB ROMANIAN SECTION ICS IAȘI - ROMANIA ASB

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The Scientific Committee of the IEEE International E-HEALTH AND BIOENGINEERING

has the pleasure to offer

YOUNG RESEARCHER SECOND PRIZE

To

Lenka Horakova, Petr Kudrna and Karel Roubik

For their paper

Dynamic Changes of Perfusion Index During Hypoxemia and Hypercapnia in Outdoor Experiments

General Chair of EHB 2021

Prof. Hariton COSTIN

Dean, Faculty of Medical Bioengineering

Prof. Anca Galaction