Citation: Horáková, L., Sýkora, K., Sieger, L., Roubík, K. (2019). Breathing Experiments into the Simulated Avalanche Snow: Medical and Technical Issues of the Outdoor Breathing Trials. In World Congress on Medical Physics and Biomedical Engineering 2018 (pp. 711-717). Springer, Singapore. DOI: https://doi.org/10.1007/978-981-10-9035-6_132

Breathing experiments into the simulated avalanche snow: Medical and technical issues of the outdoor breathing trials

Lenka Horáková[1[0000-0003-1510-8412]], Karel Sýkora[2[0000-0003-0212-1247]], Ladislav Sieger [3[0000-0002-6097-7062]] and Karel Roubík[1[0000-0001-5813-6355]]

[1] Czech Technical University in Prague, Faculty of Biomedical Engineering, nám Sítná 3105, 272 01 Kladno, Czech Republic
[2] Charles University in Prague, Faculty of Physical Education and Sport, J. Martího 31, 162 52, Prague 6, Czech Republic
[3] Czech Technical University in Prague, Faculty of Electrical Engineering, Technická 2, 166 27 Prague 6, Czech Republic
horakle5@fbmi.cvut.cz

Abstract. Avalanche burials represent one of the most dangerous risks associated with winter activities in the mountains. Asphyxiation occurs as a consequence of blocked airways; or, due to a severe hypoxia and hypercapnia resulting from rebreathing previously exhaled gas. Recently, outdoor breathing experiments with healthy volunteers were conducted in order to investigate the gas exchange limitations and work of breathing effects on the probability of survival under avalanche snow. Ambient conditions during the experiments differ significantly from the recommended operating conditions of the medical devices. Therefore, special measures need to be applied during the experiments not only to assure proper functioning of the devices used for the monitoring of the breathing subjects, but also ensuring their required precision and accuracy. As the subject starts to suffer from hypoxia and hypercapnia short after beginning of the breathing trial, careful and detailed monitoring and advanced safety precautions must be adopted. Using our experience from real outdoor breathing trials, we aim to recommend both the technical and medical precautions that should be undertaken in future studies.

Keywords: Avalanche victims, snow burial, survival, hypercapnia, hypoxia, work of breathing, technical limits, outdoor experiments.

1 Introduction

Avalanche burials represent one of the most dangerous risks associated with winter activities in the mountains. The survival chances depend on multiple factors: on trauma sustained during the accident, on the length and depth of the snow burial, and the presence of an air pocket [1–3]. The most common cause of death in avalanche victims is suffocation. Up to 90% of the casualties die because of asphyxia, as was analysed in numerous studies [4–6]. This occurs as a consequence of blocked airways, or due to a severe hypoxia and hypercapnia resulting from rebreathing previously exhaled gas. However, the mechanism of gas exchange in a snow buried avalanche victim has not yet been fully elucidated and is a subject of worldwide research activities. Recently, 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.

In these studies, the endpoints and safety limits of the breathing trials are specified using oxygen (O_2) and carbon dioxide (CO_2) concentrations in the inhaled or exhaled gas and peripheral oxygen saturation (SpO_2). The set limits vary among the studies. Brugger et al. [7] used monitoring of end-tidal CO_2 content ($EtCO_2$) to describe the effect of an air pocket of a different size in front of the subject's airways. The endpoint was based on SpO_2 monitoring, which was set at SpO_2 75%. Many studies set their limits on values SpO_2 of less than 85% [8, 9]. In study of Roubík et al [10] much lower pulse oximetry readings were recorded. In some studies, combined limits have been used, based on both SpO_2 and CO_2 concentration. Strappazon et al. [11] used for example SpO_2 limit of 75% with an additional criterion of inspired CO_2 concentration ($FiCO_2$) higher than 8%. An overview of the physiological parameters used for safety monitoring of the subjects during breathing experiments is presented in Table 1.

Table 1. Physiological parameters used for safety monitoring of the tested subjects during breathing experiments

Parameter	Meaning	Nomal/physio logical values	Comments
FiO_2	Fraction of oxygen in inspired gas	20.9476 %	dry air
EtO_2	End tidal fraction of oxygen in expired gas	16%	value after a single breath expiration when inhaling FiO_2 of 21% and negligible $FiCO_2$
$FiCO_2$	Fraction of carbon dioxide in inspired gas	0.0314%	dry air
$EtCO_2$	End tidal fraction of carbon dioxide in expired gas	4 %	value after a single breath expiration when inhaling FiO_2 of 21% and negligible $FiCO_2$
SpO_2	Peripheral haemoglobin oxygen saturation	94-98%	
PaO_2	Arterial partial pressure of oxygen	10-13 kPa (75-100 mm Hg)	can be obtained only via arterial blood analysis
$PaCO_2$	Arterial partial pressure of carbon dioxide	4.7-6.0 kPa (35-45 mmHg)	can be obtained only via arterial blood analysis

For monitoring of the subjects throughout these experiments, medical vital sign monitors are commonly used. Nevertheless, these monitors are designed mainly for the use in critical care units, and a direct use in the field can cause errors and misinterpretation of data. Furthermore, when they are taken into the outdoor environment, unquestioning operation in such experiments may pose the participants of the study into threat.

The aim of this study is to analyse possible peculiarities, risks and limitations of the use of medical devices in outdoor breathing experiments simulating avalanche snow burial and to help in designing of future experiments in order to avoid erroneous results and their misinterpretation.

2 Outdoor breathing experiments and their technical management

2.1 The environmental condition effects on correctness of the methodology

As the breathing experiments to the snow are usually conducted in the mountain areas, the effect of high altitude should be considered. The most important parameter is a reduced ambient pressure that may be significantly lower than the atmospheric pressure measured at the sea level. This situation may have serious consequences for both safety of the participants and for evaluation of the experiment results.

Medical devices usually allow the user to select several forms of result presentations and units for one particular measure. For example, composition of respiratory gases (FiO_2, EtO_2, $FiCO_2$ and $EtCO_2$) may be expressed as a fraction of the corresponding gas in the gas mixture (i.e., expressed in %), or, as a partial pressure of the corresponding gas in the mixture (expressed in kPa or mm Hg). Furthermore, the partial pressure may be expressed by the monitor under several conditions denoted as B.T.P.S. (body temperature, ambient pressure and saturated with water vapour), A.T.P.D. (ambient temperature and pressure, dry) or recalculated to standard conditions at standard temperature of 0 °C and standard pressure of 101.325 kPa (760 mm Hg), denoted as S.T.P.D. (standard temperature and pressure, dry). S.T.P.D. 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 B.T.P.S. describe the real physiological state of the organism optimally. The detailed description of standardized conditions of measurement is presented in Table 2.

Table 2. The detailed description of standardized conditions of measurement.

Abbreviation	Meaning	Values	Comments
B.T.P.S.	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 mm Hg) at 37°C*	Gas under conditions in the human body, i.e. heated to body temperature and saturated with water vapours at this temperature.
A.T.P.D.	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.
S.T.P.D.	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.

** variations in the range of 35 to 39°C are of a little importance*

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 1 000 m and only 6.4 kPa at 2 000 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 1 000 m and even 10% at 2 000 m.

For snow-based experiments, in addition to the density of snow, its temperature is also important. Changes in weather 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 continuously (e.g., for the whole week of experiments) by a data-logger at reasonable (e.g. five-minute) time intervals. According to the international standard ISO 2533:1975/Add.2:1997 [12], 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 record of temperature development over four days is presented in Fig. 1. The graph documents that the snow temperature variability significantly decreases with the increasing depth of snow.

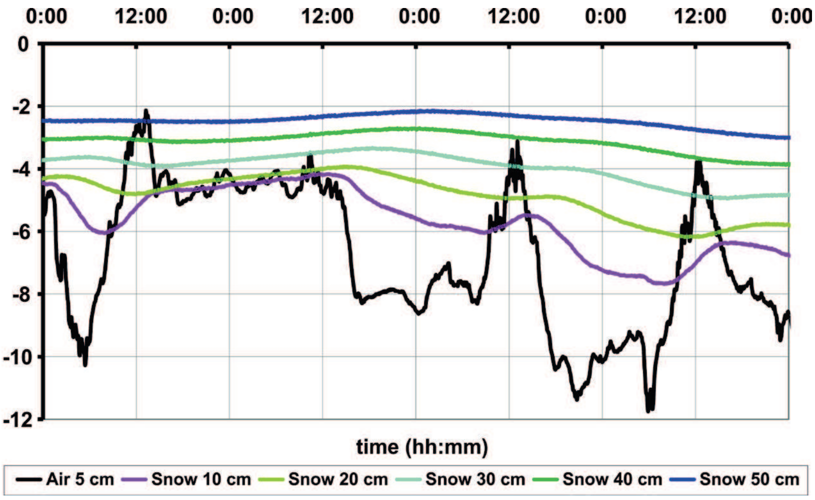

Fig. 1. Variation of air temperature during a four day experiment measured 5 cm above the snow surface (the black line) and its effect on temperature of snow measured at different depths of 10, 20, 30, 40 and 50 cm below the surface.

In general, the measuring technique is influenced by sudden temperature fluctuations, especially at lower temperatures. For this reason, a thermal comfort for the devices is pivotal. In a shelter, all the devices should be individually thermo-insulated and heated.

A deleterious source of measurement errors is the leakage in a circuit that may occur at any time during the measurement (leakage of the nasal clip, mask, experimental set in the snow, etc.). Nitrous oxide (N_2O) can be used as the tracing gas during the experiments. The anaesthesia monitors are capable of detecting N_2O even at very low concentrations, which are lower than the values affecting the subject's cognition. N_2O may be administered to the space in the vicinity of the breathing subject with a respiratory circuit. The absence of N_2O in the respiratory circuit carries the information about its tightness [10].

2.2 Performance of medical devices during outdoor breathing experiments

Vital sign monitors are often used for both assuring safety of the subjects and for measuring parameters that may serve as study endpoints or providing data suitable for subsequent analysis and evaluation. If a non-standard breathing circuit is used (e.g. two arms equipped with one-way valves), a significant distortion of the gas concentration curves may occur compared to a standard configuration. This deformity may represent a problem for the breath detection algorithm present in the monitor that may affect evaluation of parameters derived from the measured concentration curves. The monitors are designed for monitoring of critically ill patients; therefore, their measuring capability covers a wide range of each parameter well exceeding normal physiological limits. Nevertheless, during extreme breathing experiments, the physiological parameters exhibit very rapid changes and their values may temporarily fall outside the measuring range of vital sign monitors.

In their experiments, Roubík et al. [10] discovered that values of end-tidal CO_2 concentrations ($EtCO_2$) displayed on the screen of Datex-Ohmeda S/5 anaesthesia monitor often did not correspond with the CO_2 concentration curve displayed on the same screen of the monitor. After analysis of other parameters, the same disproportion was documented for all the parameters evaluated from the CO_2 and O_2 concentration curves, i.e. $EtCO_2$, $FiCO_2$, EtO_2 and FiO_2 values. An example documenting the observed error is presented in Fig. 2.

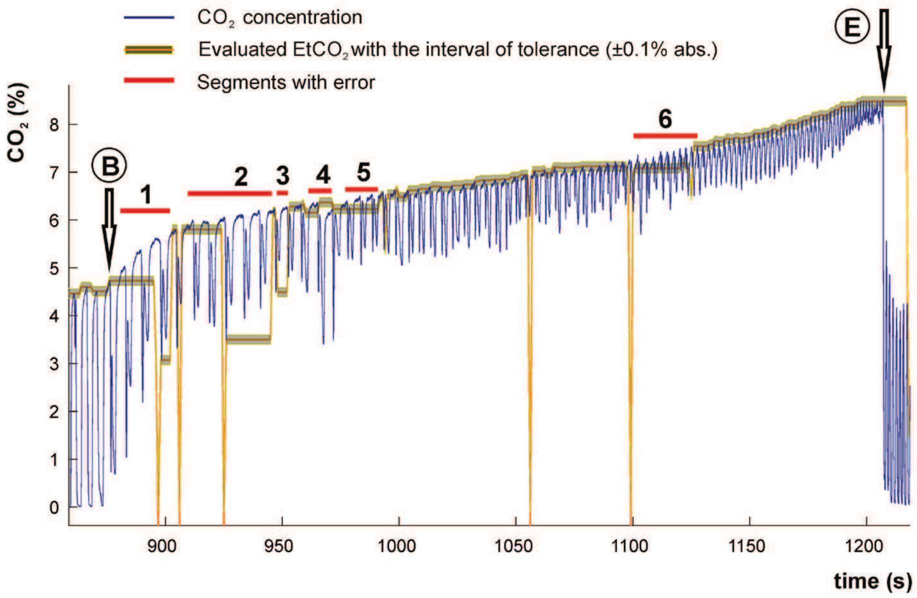

Fig. 2. Example of a curve of measured CO_2 concentration (blue line) and the values of $EtCO_2$ (yellow line) evaluated by the monitor. Segments where $EtCO_2$ does not correspond to the CO_2 concentration curve are marked with red horizontal lines. B—beginning of breathing trial in the snow after the initial stabilization period; E—end of the breathing trial. Reprinted from [13] under CC BY license.

In order to explain this disproportion, Roubík and Filip [13] conducted a detailed analysis and several additional laboratory experiments. The results show that the error of $EtCO_2$ and EtO_2 occurred in 39% and in 30% of the total experimental time of breathing into snow, with and without an air pocket respectively (range from 13% to 93% of time). The breathing experiments with simulated avalanche snow, conducted in order to find the cause of the error determined that the error occurs immediately after a significant increase of CO_2 in the breathing circuit as a consequence of expired gas rebreathing and is independent of other breathing parameters. The study confirmed that a newer model of the monitor (Carescape B650) is prone to this error as well. The last experiment conducted with a standard anaesthesia machine confirmed, that the error occurs even in a standard clinical setup, in the presence of rebreathing simulated by removing soda lime from the CO_2 absorber.

During the same outdoor breathing experiments [10], tidal volumes of majority of participants during the most pronounced hypercapnia state went beyond the maximum value of tidal volume that the monitor is able to record. As a consequence, the flow rate signal was distorted and the correct tidal volume could not be calculated. To prevent this situation, a modified flow sensor might be used, but due to the sensor non-linearity, the recalculation cannot by accomplished by a simple correction with a constant. Actual tidal volumes should be calculated directly from the flow rate curves after their non-linear correction using an experimentally acquired calibration curve.

Inaccessibility of the correct flow signal and thus correct tidal volumes make impossible to calculate the Work of Breathing (WoB) that is typically expressed in J, J/breath or J/min. As a surrogate of WoB, another measure may be used for evaluation of breathing effort of the subject: Pressure-Time Product (PTP) expressed typically in Pa.s or Pa.s/min. According to physiological studies, PTP is even more reliable in assessment of energy cost of breathing because it is a good indicator of the metabolic work of breathing [14]. Field et al. [15] documented that oxygen consumption of the respiratory muscles is only weakly correlated with the mechanical WoB (the product of $\Delta P \cdot \Delta V$), whereas it is well reflected by the PTP. PTP takes into account the isometric phase of muscle contraction [16] and represents a good indicator of energy expenditure [17].

A proper care should be devoted to the optimum setting of the individual pieces of equipment. Each vital sign monitor for example allows selection of data averaging and display refreshment time, usually referred to as 'response', i.e. how fast the SpO_2 value follows the measurement. Concerning SpO_2, several modes of the value presentation may be selected from beat-to-beat presentation to averaging results for 20 seconds, which is the default setting for Datex S/5 monitors. The long averaging is preferred at intensive care unit (ICU) setup, where stable readings are convenient as the patient physiological parameters do not change rapidly. During extreme breathing experiments, averaging with such a long time base may cause a significant delay in reaction to the current state of the volunteer that may represent a threat to the volunteer's health.

3 Medical aspects of extreme outdoor experiments

While conducting outdoor clinical trials, it is essential to minimise any medical risks posed on the subjects of the experiment. This can be primarily ensured by meticulous selection of participants. Most of the studies are designed for healthy volunteers, scoring ASA 1 according to the American Society of Anaesthesiologists, without any known cardio-respiratory disease and non-smokers. One study had 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 has been manifested [8]. In case of any emergencies, a presence of a skilled physician is crucial conjointly with advanced vital sign monitoring, as mentioned above.

Fortunately, only minimal medical issues have been reported 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. The protocol design and end point parameters should help to prevent any deleterious effects of these states. The value limits for each trial are conventionally approved by an ethical committee based on the emergency medicine criteria and they might not reflect brief changes in healthy volunteers' physiology.

3.1 Hypoxia and hypercapnia

The main medical risks are associated with the consequences of hypoxia and hypercapnia. The end-tidal O_2 (EtO_2 in %) and end-tidal CO_2 ($EtCO_2$ in %) in some of the trials reached values that would be considered as critical in ICU setting. Extreme alveolar gas partial pressures were documented in other sports and outdoor experiments.

For instance, a similar situation in terms of short lasting profound changes in arterial partial pressures of gases as in an avalanche victim can be seen in breath-hold divers: a combination of hypoxia and hypercapnia together with a concomitant acidosis due to cumulation of blood and tissue CO_2. For example, Willie et al. [18] measured the end-apnoea end-tidal partial pressure of oxygen (pO_2) and carbon dioxide (pCO_2) during a static dry apnoea reaching 37±14 mmHg and 45±7 mmHg respectively. SpO_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 sportsmen is the hypobaric hypoxia, typical for the high altitude where the hypoxemia is in general accompanied by respiratory alkalosis and hypocapnia due to a compensatory hyperventilation. The lowest values of arterial partial pressure of O_2 (PaO_2) recorded during a simulated high altitude ascent to 8 848 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 arterialized capillary blood was 67.9% in 8 000 metres above sea level [19]. In the course of an experiment conducted on Mt. Everest in Himalaya, there were arterial blood samples obtained at the altitude of 8 400 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 6 400 m [20].

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

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

After their experiments, Roubík et al. [10] conducted a short interview with each of the volunteers to evaluate their subjective perception of the changes in their consciousness. From the answers it was clear that the subjective sensation of the arterial gas changes differed a lot. The sentience of losing control of 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 seconds when his $EtCO_2$ reached 8.4%. Another one was describing a worsening dyspnoea which suddenly started to improve and he had experienced a sensation of relief. He was also disconnected at this point and reached a maximum $EtCO_2$ of 10.2%; compare to another subject, who at the level of CO_2 of 9.5% did not have any problems with dizziness, changes in mental state or headache.

From the above mentioned reasons, it is clear that one isolated value of any parameter is not sufficient itself for overall assessment of the participant's physiology during a breathing experiment. Inter-individual differences are considerable. When defining endpoints for safety and ethical reason, not only one isolated physiological limit should be considered.

3.2 Hypothermia

Although only 1-2% avalanche victims die on account of hypothermia [4], the changes in core temperature of outdoor breathing experiment participants may occur. Despite a careful heat protection, a temperature drop happens. Grissom et al had one subject who requested an experiment termination because he was cold and shivering [8]. Another subject in Radwin's snow burial trial had to be removed from the snow, as his core body temperature dropped after 73 minutes below 35 °C [9].

3.3 Arrhythmias

As a side effect of both hypoxia and hypercapnia, different types of arrhythmias have been reported. In one study, participants were studied for haemodynamic changes at end-tidal CO_2 of 7 kPa and an increase in QT dispersion has been showed [21]. 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 [8].

In case of the experiments conducted by Roubík et al. [10] one of the volunteers had to be excluded due to frequent bigeminal ventricular extrasystoles. The medical literature suggests that frequent premature ventricular complexes (PVCs) can evolve into malignant ventricular arrhythmias, ventricular tachycardia or even ventricular fibrillation [22]. These changes in electric cardiac activity have been found to increase a risk of a sudden cardiac death not only in patients with structural heart disease [23], but also among young health athletes with concealed cardiopathy [24]. As these rhythms rank among the shockable ones, availability of emergency equipment and drugs as per Advanced Life Support (ALS) guidelines should be mandatory, including the Automated External Defibrillator (AED) [25].

3.4 Hygiene during experiments

The availability and affordability of plastic single-use kits for the health care made the expensive and labour-extensive decontamination of reusable equipment falling out of favour. On the other hand, this applies mainly to hospital setting.

In case that an outdoor breathing trial includes any sort of breathing circuits, the antimicrobial filters should be used to prevent a cross contamination of the equipment. The Heat and Moisture Exchangers (HME), used mainly in anaesthesia and critical care settings, are not convenient. Firstly, humidification is not necessary in snow breathing experiments as the natural moisture of this substance provides some humidity. In addition, the artificial moisture and heat conserved by the filter would change the microclimate in the designed air pocket. A significant heat exchange between the filter and the snow would occur. In a real avalanche burial, the breath causes thawing of the snow in a close proximity to the victim's airway and hence changing the properties of the air pocket. Despite its disadvantages, the sterilisation of breathing circuits appears to be a better solution.

4 Conclusion

During outdoor breathing experiments, the intensive care monitors and devices are used in conditions substantially different from a standard ICU. Safety limits of physiological parameters must be interpreted considering these conditions; otherwise the intended safety ranges may be falsely interpreted and safety of the subjects may be impaired. The measuring principle used in these devices is essential to consider when evaluating and interpreting the measured data. Along with technical issues, medical precautions must be applied during the breathing experiments. The physiological parameters of the subjects get quickly out of normal range which increases a risk of complications.

Compliance with ethical requirements

The authors declare that they have no conflict of interest.

Acknowledgement

The study was supported by Czech Technical University in Prague grant No. SGS17/203/OHK4/3T/17.

References

1. Falk, M., Brugger, H. and Adler-Kastner, L., 1994. Avalanche survival chances. Nature, 368(6466), p.21.

2. Brugger H, Falk M, Adler-Kastner L., 2003. Der Lawinennotfall. Eine aktuelle Übersicht. Wiener Klinische Wochenschrift 9(8), pp. 691-701.
3. Stalsberg, H., Albretsen, C., Gilbert, M., Kearney, M., Moestue, E., Nordrum, I., Rostrup, M. and Ørbo, A., 1989. Mechanism of death in avalanche victims. Virchows Archiv A, 414(5), pp.415-422.
4. Hohlrieder, M., Brugger, H., Schubert, H.M., Pavlic, M., Ellerton, J. and Mair, P., 2007. Pattern and severity of injury in avalanche victims. High altitude medicine & biology, 8(1), pp.56-61.
5. Logan N, Atkins D., 1996. The snowy torrents: Avalanche accidents in the United States 1980-1986. Colorado geological survey pp. 240-243.
6. Grossman M.D., Saffle, J.R., Thomas F., Tremper B., 1989. Avalanche trauma. Trauma 29, pp. 1705-1709.
7. Brugger, H., Sumann, G., Meister, R., Adler-Kastner, L., Mair, P., Gunga, H.C., Schobersberger, W. and Falk, M., 2003. Hypoxia and hypercapnia during respiration into an artificial air pocket in snow: implications for avalanche survival. Resuscitation, 58(1), pp.81-88.
8. Grissom, C.K., Radwin, M.I., Harmston, C.H., Hirshberg, E.L. and Crowley, T.J., 2000. Respiration during snow burial using an artificial air pocket. Jama, 283(17), pp.2266-2271.
9. Radwin, M.I., Grissom, C.K., Scholand, M.B. and Harmston, C.H., 2001. Normal oxygenation and ventilation during snow burial by the exclusion of exhaled carbon dioxide. Wilderness & environmental medicine, 12(4), pp.256-262.
10. Roubík, K., Sieger, L. and Sykora, K., 2015. Work of breathing into snow in the presence versus absence of an artificial air pocket affects hypoxia and hypercapnia of a victim covered with avalanche snow: a randomized double blind crossover study. PloS one, 10(12), p.e0144332.
11. Strapazzon, G., Paal, P., Schweizer, J., Falk, M., Reuter, B., Schenk, K., Gatterer, H., Grasegger, K., Dal Cappello, T., Malacrida, S. and Riess, L., 2017. Effects of snow properties on humans breathing into an artificial air pocket–an experimental field study. Scientific reports, 7(1), p.17675.
12. ISO 2533:1975/Add 2:1997. Standard Atmosphere ADDENDUM 2: Extension to - 5000 m and standard atmosphere as a function of altitude in fe. Swiss, 1997. 123 p.
13. Roubík, K. and Filip, J., 2017. Reliability and source of errors in end-tidal gas concentration evaluation algorithms during avalanche snow and rebreathing experiments. Lékař a technika-Clinician and Technology, 47(3), pp.73-80.
14. Bellani, G., Patroniti, N., Weismann, D., Galbiati, L., Curto, F., Foti, G. and Pesenti, A., 2007. Measurement of pressure–time product during spontaneous assisted breathing by rapid interrupter technique. Anesthesiology: The Journal of the American Society of Anesthesiologists, 106(3), pp.484-490.
15. Field, S., Sanci, S. and Grassino, A., 1984. Respiratory muscle oxygen consumption estimated by the diaphragm pressure-time index. Journal of Applied Physiology, 57(1), pp.44-51.
16. Sassoon, C.S.H. and Mahutte, C.K., 1998. Work of breathing during mechanical ventilation. Lung biology in health and disease, 118, pp.261-310.
17. Collett, P.W., Perry, C. and Engel, L.A., 1985. Pressure-time product, flow, and oxygen cost of resistive breathing in humans. Journal of Applied Physiology, 58(4), pp.1263-1272.
18. Willie, C.K., Ainslie, P.N., Drvis, I., MacLeod, D.B., Bain, A.R., Madden, D., Maslov, P.Z. and Dujic, Z., 2015. Regulation of brain blood flow and oxygen delivery in elite breath-hold divers. Journal of Cerebral Blood Flow & Metabolism, 35(1), pp.66-73.

19. Richalet, J.P., 2010. Operation Everest III: COMEX'97. High altitude medicine & biology, 11(2), pp.121-132.
20. Grocott, M.P., Martin, D.S., Wilson, M.H., Mitchell, K., Dhillon, S., Mythen, M.G., Montgomery, H.E. and Levett, D.Z., 2010. Caudwell xtreme Everest expedition. High altitude medicine & biology, 11(2), pp.133-137.
21. Kiely, D.G., Cargill, R.I. and Lipworth, B.J., 1996. Effects of hypercapnia on hemodynamic, inotropic, lusitropic, and electrophysiologic indices in humans. Chest, 109(5), pp.1215-1221.
22. Carrim ZI, Khan AA. Mean frequency of premature ventricular complexes as predictor of malignant ventricular arrhythmias. Mt Sinai J Med 2005, 72, pp. 374-380.
23. Lerma, C. and Glass, L., 2016. Predicting the risk of sudden cardiac death. The Journal of physiology, 594(9), pp.2445-2458.
24. Corrado, D. and Zorzi, A., 2017. Sudden death in athletes. International journal of cardiology, 237, pp.67-70.
25. Resuscitation Council UK. Advanced Life Support, Sixth Edition, 2011.