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REVIEW-SYMPOSIUM

Avalanche burial pathophysiology – a unique combination of hypoxia, hypercapnia and hypothermia

Giacomo Strapazzon[1,2], Anna Taboni[1], Erik Sveberg Dietrichs[3], Andrew M. Luks[4] and Hermann Brugger[1]

[1]*Institute of Mountain Emergency Medicine, Eurac Research, Bolzano, Italy*
[2]*Department of Medicine – DIMEM, University of Padova, Padova, Italy*
[3]*Institute of Oral Biology, University of Oslo, Oslo, Norway*
[4]*Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of Washington, Seattle, WA, USA*

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Abstract For often unclear reasons, the survival times of critically buried avalanche victims vary widely from minutes to hours. Individuals can survive and sustain organ function if they can breathe under the snow and maintain sufficient delivery of oxygen and efflux of carbon dioxide. We review the physiological responses of humans to critical avalanche burial, a model which shares similarities and differences with apnoea and accidental hypothermia. Within a few minutes of burial, an avalanche victim is exposed to hypoxaemia and hypercapnia, which have important effects on the respiratory and cardiovascular systems and pose a major threat to the central nervous system. As burial time increases, an avalanche victim also develops hypothermia. Despite progressively reduced metabolism, reduced oxygen and increased carbon dioxide tensions may exacerbate the pathophysiological consequences of hypothermia. Hypercapnia seems to be the main cause of cardiovascular instability, which, in turn, is the major reason for reduced cerebral oxygenation despite reductions in cerebral metabolic activity caused by hypothermia. 'Triple H syndrome' refers to the interaction of hypoxia, hypercapnia and hypothermia in a buried avalanche victim. Future studies should investigate how the respiratory gases entrapped in the porous snow structure influence the physiological responses of buried individuals and how haemoconcentration, blood viscosity and cell deformability affect blood flow and oxygen delivery. Attention should also be devoted to identifying strategies to prolong avalanche survival by either mitigating hypoxia and hypercapnia or reducing core temperature so that neuroprotection occurs before the onset of cerebral hypoxia.

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Corresponding author G. Strapazzon: Institute of Mountain Emergency Medicine, Eurac Research, Via Ipazia 2, 39100 Bolzano, Italy. Email: giacomo.strapazzon@eurac.edu

Abstract figure legend Schematic diagram illustrating gas exchange and key physiological responses after critical avalanche burial. The ability to breathe under the snow ensures sufficient oxygen (O_2) delivery to vital organs and elimination of carbon dioxide (CO_2), which is critical for increasing survival time (Strapazzon & Brugger, 2018; Strapazzon et al., 2017). The presence of an air pocket slows the onset of hypoxaemia in relation to the size of the air pocket (Brugger et al., 2003), while decreased density of the surrounding snow has a similar effect because respiratory gases (i.e. O_2 and CO_2) can diffuse through avalanche debris (Brugger et al., 2003; Strapazzon et al., 2017). With a short burial time, an avalanche victim is exposed to hypoxaemia and hypercapnia, which exert effects on the respiratory and cardiovascular systems, and pose a major threat to the central nervous system. Even though minute ventilation increases, alveolar ventilation is reduced in critically buried individuals (inlay A). The snow characteristics influence the speed of gas equilibration between ambient air and the alveoli. Changes in blood gas transport may be seen as hypercapnia causes a rightward shift in the haemoglobin–oxygen dissociation curve (inlay B) (Modified from Woyke et al., 2022, with permission). Such a change may impair uptake of O_2 in the lungs but improves offloading in the peripheral tissues. With a long burial time, an avalanche victim develops hypothermia, which exerts a neuroprotective effect by reducing cerebral metabolism (inlay C), glutamate accumulation, cellular calcium influx and vascular permeability. However, hypoxaemia and hypercapnia usually complicate the pathophysiological status of accidental hypothermia in a critically buried individual. Hypothermia counteracts the Bohr effect and shifts the haemoglobin–oxygen dissociation curve to the left (inlay B) (Modified from Woyke et al., 2022, with permission). Although this reduction in the P_{50} enhances uploading of O_2 in the lungs it may subsequently limit offloading in the peripheral tissues. Hypercapnia is the main cause of cardiovascular instability, which, in turn, is the major trigger for a decrease in cerebral oxygenation because of impaired cerebral blood flow autoregulation. 'Triple H syndrome' refers to the combined effect of hypoxia, hypercapnia and hypothermia (Brugger et al., 2003). Arterial blood, red; air, white; air pocket boarders, grey dotted line; CO_2, black; O_2, red; snow, grey; venous blood, black. Illustration by Eurac Research/Silke De Vivo.

Giacomo Strapazzon is the Head of the Institute of Mountain Emergency Medicine of Eurac Research in Italy. He is a consultant in internal and emergency medicine, and active in applied physiology and in the study of human adaptation to special environments. He has been principal and co-investigator for in-field, clinical and laboratory studies, mainly focusing on cold injuries and hypoxia, which have helped expand the current knowledge on avalanche-accident pathophysiology. He has worked in the development and capacity building of the terraXcube, a facility comprising hypobaric chambers capable of simulating special conditions in a safe, controlled environment.

Introduction

Avalanches are a major natural hazard in snow-covered mountain regions throughout the world and claim the lives of many critically buried winter recreationists (Techel et al., 2016). Survival analyses have shown that the grade of burial ('critical' if the head and chest are buried *vs*. 'partial' if the head and chest remain free) is the main determinant of survival (Falk et al., 1994; Haegeli et al., 2011; Procter et al., 2016). For critically buried victims, short duration of burial, a patent airway and lack of severe injuries increase survival (Boyd et al., 2010), while the ability to breathe under the snow, which ensures sufficient oxygenation of vital organs and elimination of carbon dioxide (CO_2), is critical to increase survival time (Strapazzon & Brugger, 2018; Strapazzon et al., 2017).

Avalanche burial represents a unique model to study the acute interaction between hypoxia, hypercapnia and hypothermia and the human physiological responses to these conditions (see Abstract figure), which share similarities and differences with isolated apnoea or accidental hypothermia. This review focuses on the physiological responses to critical avalanche burial in the hope of stimulating interest in a field of research that has not received sufficient attention. There are three broad sections, each focusing on an important facet of avalanche burial (see Abstract figure). The first section discusses the avalanche survival curves and the insight they provide into the pathophysiological responses following critical burial. The second section provides an overview of the respiratory, cardiovascular and central nervous system responses to progressive hypoxia and hypercapnia following critical avalanche burial. The third section covers the effects of hypothermia combined with the previous two factors. The review concludes by summarizing the state of our knowledge on avalanche burial and proposing questions for future research.

Survival curves of critically buried avalanche victims

The survival of critically buried avalanche victims is time dependent. In 1994, the first data-based survival analysis, published in *Nature* (Falk et al., 1994), showed significant differences when compared with previous survival functions. Brugger and Falk applied the computer-assisted Turnbull algorithm to data from 422 critically buried victims (1981–1991) to estimate the probability of remaining alive during avalanche burial (Fig. 1) (Turnbull, 1974). Since rescue data indicate each victim's status as dead or alive at the time of extrication, the actual times of death during avalanche burial remain unknown. If a victim is found dead at extrication, it can be assumed that death occurred between the time of burial and the time of extrication (left-censored data); if a victim is found alive it can be assumed that death would have occurred any time after extrication (right-censored data). The algorithm, applied to left- and right-censored data, allowed an accurate estimation of survival probability. In contrast to the previous assumption that 20% of critically buried avalanche victims are dead at the time of burial (Schild, 1975), the calculated avalanche survival function showed a survival probability as high as 93% until 15 min after burial ('survival phase'), followed by a steep drop to about 30% at 35 min ('asphyxia phase'), a plateau in survival until 90 min ('latent phase') and a second drop to 3% at about 90 min. The initial steep decrease in survival gave reason to hypothesize that about two-thirds of avalanche victims die from asphyxia within the first 35 min because survival beyond this point is possible only in the presence of a patent airway and an air pocket (i.e. any space in front of mouth and nose). Asphyxia in a buried victim can result from obstruction of the upper airway because of inhaled avalanche debris or vomitus, compression of the chest by avalanche debris, an ice shield in front of the face (ice-mask), or a combination of hypoxaemia and hypercapnia because of inadequate gas diffusion (Strapazzon & Brugger, 2018).

Since 1994, survival curves have been recalculated using the Turnbull or similar non-parametric methods, as shown in Fig. 1 (Brugger et al., 2001; Haegeli et al., 2011; Procter et al., 2016). In a comparison between Canada and Switzerland from 2011, the overall mortality rates were similar, but the time course of survival curves differed significantly. The earlier drop in survival in the Canadian curve was associated with areas of high

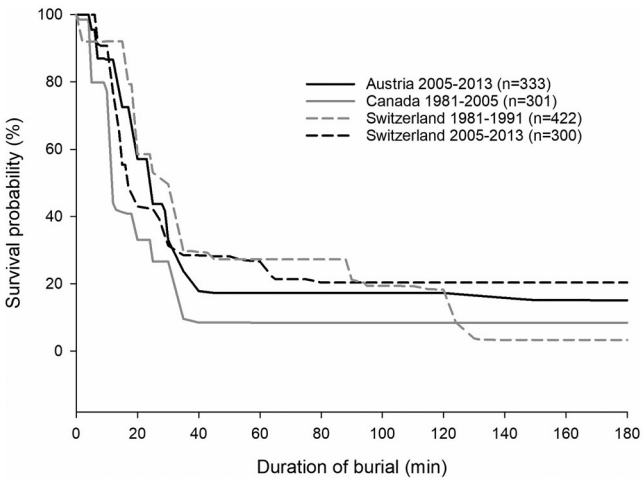

Figure 1. Survival curve for critically buried avalanche victims
Survival curve for critically buried victims in Austria (solid black line: 333 victims between 2005 and 2013), Canada (solid grey line: 301 victims between 1981 and 2005) and Switzerland (dashed grey line: 422 victims between 1981 and 1991; dashed black line: 300 victims between 2005 and 2013). (Modified from Brugger et al., 2001; Falk et al., 1994; Haegeli et al., 2011 and Procter et al., 2016, with permission).

snow densities (maritime climate) and suggested that snow characteristics had a possible influence on the pathophysiological responses and survival of avalanche victims. Avalanche victims buried in such areas are likely to have a higher risk of developing normothermic hypoxic cardiac arrest because of insufficient oxygen supply and excessive CO_2 accumulation (Haegeli et al., 2011). Although no data are available yet, survival curves may change over the coming decades as snow properties are altered with climate change (Strapazzon, Schweizer et al., 2021). A comparative analysis of Swiss and Austrian data from 633 critically buried avalanche victims (2005–2013) showed the importance of the airway patency and the presence of an air pocket for prolonged survival (Procter et al., 2016).

Hypoxia and hypercapnia in avalanche burial

The respiratory system. Avalanche burial has multiple effects on the respiratory system when a victim has an unobstructed airway, the most important of which is progressive development of hypoxaemia and hypercapnia. The extent of these problems is not uniform across snow burials. The presence of an air pocket slows the onset of hypoxaemia in relation to the size of the air pocket (Fig. 2) (Brugger et al., 2003), while reduced density of the surrounding snow has a similar effect because respiratory gases more easily diffuse through avalanche debris (Abstract figure) (Brugger et al., 2003; Strapazzon et al., 2017). Larger air pockets are associated with smaller reductions in oxygen saturation in experimental studies (Brugger et al., 2003; McIntosh et al., 2020; Strapazzon et al., 2017; Wik et al., 2022), while longer burials are tolerated if an air pocket is connected to larger air spaces or to the outside (Pasquier et al., 2023). The density of the snow is positively correlated with the reduction in oxygen partial pressure (PO_2) and increase in carbon dioxide partial pressure (PCO_2) in the air pocket, although some individuals surrounded by low density snow still experience rapid accumulation of CO_2 in the air pocket because of other, still unknown, snow characteristics (Strapazzon et al., 2017).

Hypoxaemia and hypercapnia have further downstream effects on other aspects of respiratory system function. Within seconds of onset, both factors cause an increase in minute ventilation (Haldane & Priestley, 1905; Weil et al., 1970). A strong compensatory ventilatory response was demonstrated in several studies with human subjects breathing into simulated avalanche debris in mock burials, as evidenced by rapid increases in respiratory rates, tidal volumes, minute ventilation and end-tidal CO_2 in parallel with a decreased fraction of inspired O_2 (F_IO_2) and increased fraction of inspired CO_2 (F_ICO_2) (Brugger et al., 2003; Grissom et al., 2000, 2004; Strapazzon et al., 2017, 2023; Wik et al., 2022). There is a synergistic effect of hypoxia and hypercapnia on these ventilatory responses. Hypoxaemia augments the hypercapnic ventilatory response and hypercapnia augments the hypoxic ventilatory response (Lloyd et al., 1958; Weil et al., 1970). The ventilatory response and sense of dyspnoea with hypercapnia are greater than that seen with hypoxaemia alone. This may contribute to significant dyspnoea in buried victims experiencing rapid accumulation of CO_2. Increases in minute ventilation can be attenuated in buried individuals receiving supplemental air in an air pocket (Wik et al., 2022) or by using an artificial air-pocket device that diverts exhaled CO_2 away from the face (Fig. 3) (Grissom et al., 2000; Strapazzon et al., 2023).

Hypoxia and hypercapnia cause vasoconstriction in the pulmonary circulation (Sylvester et al., 2012; Viswanathan et al., 1976), although the response to hyper-

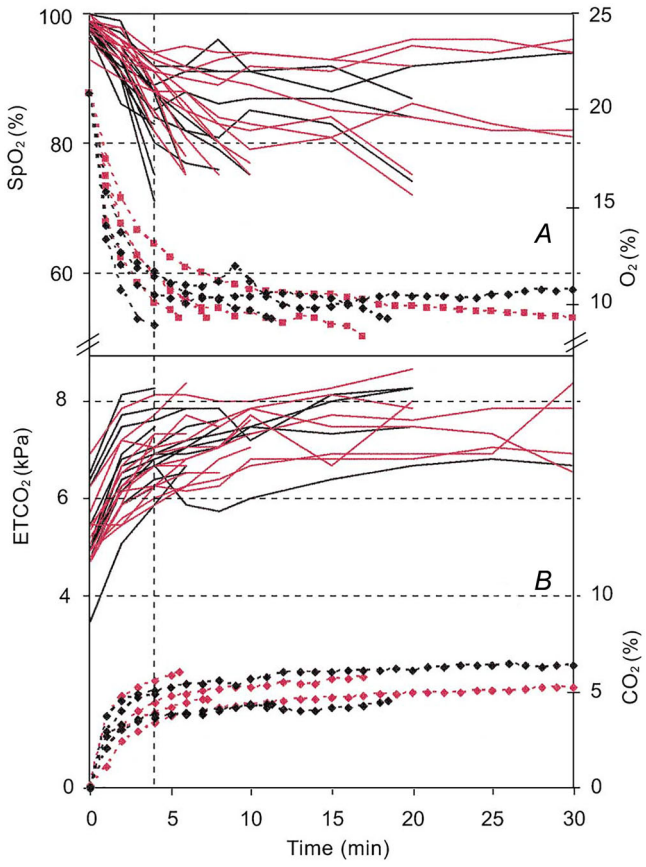

Figure 2. Physiological responses of humans breathing in simulated avalanche debris
Curves demonstrating changes in respiratory parameters and respiratory gases over time in humans breathing into an artificial air pocket; peripheral oxygen saturation (SpO_2), end-tidal carbon dioxide ($ETCO_2$) and percentage of air-pocket oxygen (O_2) and carbon dioxide (CO_2). Colours indicate air-pocket volume: black 1 L; red 2 L. (Modified from Brugger et al., 2003, with permission).

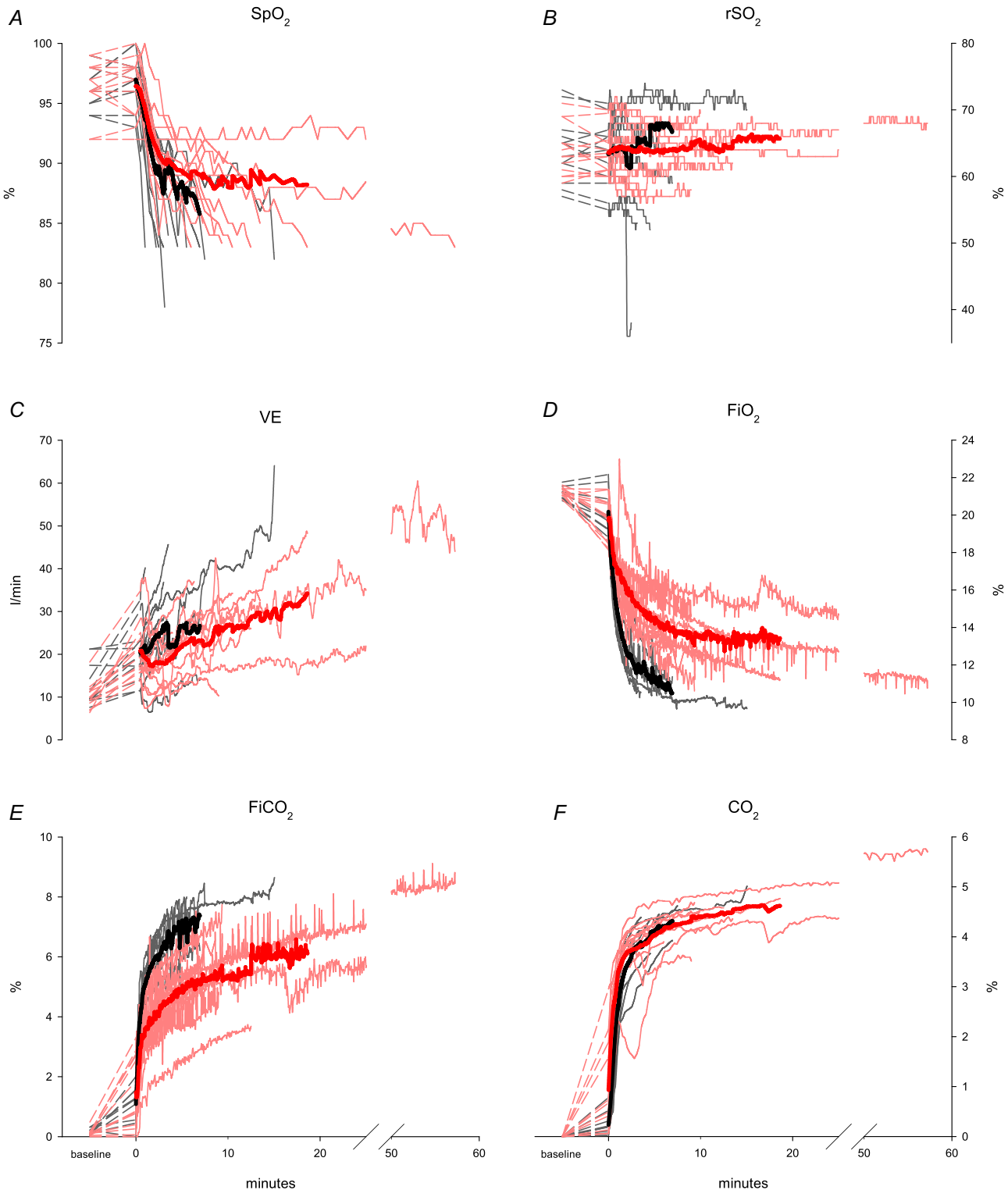

Figure 3. Physiological responses of critically buried humans breathing in simulated avalanche debris
Curves demonstrating changes in respiratory parameters and respiratory gases over time in critically buried humans in simulated avalanche debris; peripheral oxygen saturation (SpO_2), cerebral oxygen saturation (rSO_2), minute ventilation (VE), fraction of inspired oxygen (F_IO_2) and carbon dioxide (F_ICO_2), carbon dioxide (CO_2) concentration measured at the end of the exhalation tube. The 2 thicker lines represent the mean values. Colors indicate respiration into an air pocket (black) or with an artificial air-pocket device (red). (Modified from Strapazzon et al., 2023, with permission).

capnia is weaker than the response to alveolar hypoxia (Kregenow & Swenson, 2002). Increased pulmonary vascular resistance with increased pulmonary artery pressure may occur with potential adverse effects on right-heart function. Finally, changes in blood-gas transport may also be seen, as hypercapnia causes a rightward shift in the haemoglobin–oxygen dissociation curve such that for any PO_2 there is a lower oxygen saturation (Abstract figure). This may impair uploading of oxygen in the lungs and improves offloading in the peripheral tissues (Woyke et al., 2022). In acute asphyxia, when lung oxygen uptake may not be possible, a rightward shift may possibly improve O_2 delivery at the tissue level. The effects of such changes on avalanche burial survival and other outcomes have not been examined. Hypoxia increases the binding of CO_2 to haemoglobin, facilitating CO_2 transport from the periphery to the lungs. Whether this actually increases CO_2 elimination is a function of the extent of CO_2 rebreathing, which is affected by the presence and size of air pocket and whether the buried victim has an artificial air-pocket device.

In addition to the effects of hypoxaemia and hypercapnia, avalanche burial has other potential effects on the respiratory system. Compression of the chest by surrounding snow may limit diaphragm and chest excursion and reduce tidal volume. This will increase the dead space fraction and worsen hypercapnia if the buried subject cannot increase minute ventilation sufficiently. Breathing through snow also increases resistance to airflow and the work of breathing, particularly in the absence of an air pocket. Further, it increases oxygen consumption and carbon dioxide production which, in turn, aggravates hypoxaemia and hypercapnia (Roubík et al., 2015). Excessive reductions in airway pressure to maintain airflow in the face of very high resistance may also contribute to the development of non-cardiogenic pulmonary oedema (Glisenti et al., 2016; Sumann et al., 2012).

The cardiovascular system. Chemoreceptor activation by hypoxaemia and hypercapnia increases parasympathetic and sympathetic activity (Fitzgerald & Lahiri, 1986). The net effect of this is arterial and venous vasoconstriction, and, if there are no constraints on increasing ventilation, tachycardia (Marshall, 1994). The observed vasoconstriction increases peripheral resistance, venous return and systemic blood pressure (Abboud & Thames, 1983; Eyzaguirre et al., 1983; Fitzgerald & Lahiri, 1986). Although hypercapnia alone reduces cardiac output and peripheral resistance (Rothe et al., 1990), the combination of hypoxia, acidosis and hypercapnia increases the hypertensive response. Studies in humans, in which chest compression was absent and ventilation increased freely, have consistently shown that breathing into avalanche debris evokes a hypertensive response (Brugger et al., 2003; Strapazzon et al., 2017; Strapazzon, Gatterer et al., 2021; Wik et al., 2022). This explains the observed increase in heart rate, as hyperventilation is known to oppose chemoreflex-induced bradycardia (Abboud & Thames, 1983). Under snow, however, the body can be confined in positions that impede chest and abdomen excursion, hindering ventilation and altering the cardiovascular function. This must be taken into account when interpreting experimental results and accounting for burial depth, which independently increases the likelihood of mortality as shown by analysis of survival curves (Procter et al., 2016).

The vascular responses to hypoxia and hypercapnia play a role in thermoregulation, which can affect the body's insulating capacity. It is known that hypoxia and hypercapnia can accelerate the core temperature cooling rate by increasing convective heat loss and delaying onset of shivering (Johnston, Elias et al., 1996; Johnston, White et al., 1996). Studies have shown that with burial under snow debris in lightweight clothing, the cooling rate was greater in hypercapnia than in normocapnia because of increased respiratory heat loss by hyperventilation (Grissom et al., 2004, 2008). There might be an additional component of cutaneous conductive heat loss from vasodilatation, but the extent of this component remains unclear.

Prevention of hypercapnia (Grissom et al., 2000; McIntosh et al., 2020) or constant provision of fresh air (Wik et al., 2022) dampens the tachycardic response and delays the need for extrication during snow burial (Radwin et al., 2001). This led to the idea that avoiding or delaying the onset of hypoxia and hypercapnia might prolong survival (Grissom et al., 2000; McIntosh et al., 2020; Strapazzon et al., 2023; Wik et al., 2022). When anaesthetized pigs were buried under the snow, they showed higher cardiac output and heart rate and a longer time to asystole after 30 min of burial time when breathing ambient air compared with breathing in high-density snow (Fig. 4) (Paal et al., 2013).

The central nervous system. Oxygen is vital for the central nervous system as oxidative phosphorylation is the major mechanism for ATP generation (Turetz & Crystal, 2007). As the central nervous system has negligible oxygen stores (Brown & Ransom, 2007; Gjedde, 2002), effective regulation of the cerebral blood flow (CBF) is crucial for continued supply of oxygen and other nutrients (Willie et al., 2014). CBF regulation is complex with important influences from arterial blood gases (Kety & Schmidt, 1948a; Willie et al., 2014) and cerebral perfusion pressure (Morris et al., 1953), as well as localized neurovascular and neurogenic regulation (Harper et al., 1972; Kety & Schmidt, 1948b). In particular, the cerebral vasculature

is highly sensitive to alterations in the partial pressure of arterial carbon dioxide (P_aCO_2) (Ogoh, 2019), such that under normothermic, normoxic conditions, every 1 mmHg change in P_aCO_2 yields a ∼3% change in CBF in the same direction (Markwalder et al., 1984; Ringelstein et al., 1992).

Within just a few minutes, avalanche victims may experience a marked increase in F_ICO_2, leading to an increase in P_aCO_2. A study of human subjects breathing in simulated avalanche debris showed that cerebral oxygenation could increase in response to increased F_ICO_2 (Strapazzon, Gatterer et al., 2021). Despite a lack of studies investigating CBF in an experimental model of avalanche burial, we expect that such changes are related to increased CBF. The extent of the benefit is likely related to the extent of hypercapnia and individual vasomotor reactivity. In the same study, human subjects experienced decreased cerebral oxygenation when breathing in high-density snow, which led to termination of the test (Strapazzon, Gatterer et al., 2021). In addition to differences in density of the snow, the presence of an air pocket, its size as well as its connection to the outside, determine the extent and the rate of change in cerebral oxygenation (Strapazzon et al., 2017; Wik et al., 2022). Another study in human subjects breathing in avalanche debris showed that an air supply of 2 L/min prevented a decrease in cerebral oxygenation (Wik et al., 2022).

In the face of reduced blood supply, ATP utilization continues despite reduced synthesis, leading to acidosis and disruption of neuronal ionic homeostasis. Both in humans and animals, acidosis worsens outcomes from ischaemia (Moskowitz et al., 2010) and cerebral hypoxia, which could reduce the chance of successful resuscitation with intact neurological function (Cohen et al., 2016).

Breath-holding as a model to understand avalanche burial. Cardiorespiratory responses to voluntary apnoea have been extensively investigated and can be useful for understanding the physiological responses to hypoxia and hypercapnia in the healthy lung. Changes in

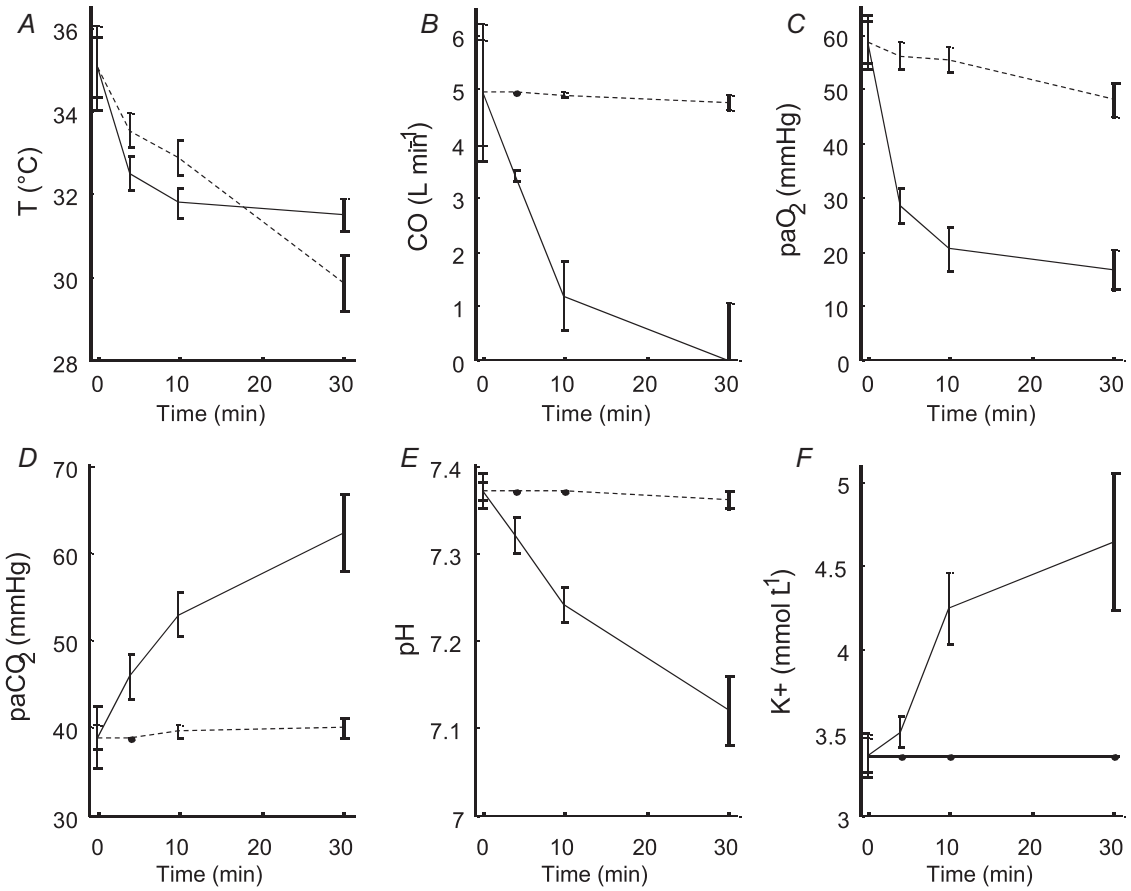

Figure 4. Porcine physiological responses to breathing in simulated avalanche debris
Curves demostrating changes in physiological parameters and laboratory data in critically buried pigs in simulated avalanche debris; pulmonary artery temperature (T), cardiac output (CO), arterial oxygen partial pressure (PaO_2), arterial carbon dioxide partial pressure ($PaCO_2$), arterial pH, and serum potassium (K^+). Changes are showns as mean and standard error. Solid line indicates respiration into an air pocket, while dashed line into ambient air (Modified from Paal et al., 2013, with permission).

blood gases during avalanche burial are sustained by a combination of rebreathing and alveolar hypoventilation. The few studies that have investigated the expired gas composition during avalanche burial have shown that the time course of changes in end-tidal CO_2 follows a capacitor-like exponential increase (Brugger et al., 2003; Strapazzon et al., 2017, 2023; Wik et al., 2022) similar to that described for voluntary apnoea (Lanphier & Rahn, 1963; Hong et al., 1971; Lin, 1988). It is difficult to collect data partly because of technical issues, such as the need to seal the air pocket, the freezing of the gas line during simulated burials, and snow characteristics that can influence the speed of gas equilibration (Abstract figure). To date, the alveolar gas composition during avalanche burial can only be inferred based on the models developed for breath holding (Taboni et al., 2020) and rebreathing in a non-sealed volume (Conway, 1976).

During breath holding, cardiac output decreases while peripheral vascular resistance and systemic arterial pressure increase (Costalat et al., 2013, 2015; Fagoni et al., 2015, 2017; Lemaître et al., 2008; Perini et al., 2008, 2010; Sivieri et al., 2015; Taboni et al., 2018), reducing oxygen uptake in the lungs and limiting oxygen utilization in the peripheral tissues (Andersson et al., 2004; Andersson & Evaggelidis, 2009; Lindholm et al., 2002). Similar responses were observed in anaesthetized pigs buried in snow (Paal et al., 2013; Strapazzon, Putzer et al., 2021), while a hypertensive response was observed in human subjects (Brugger et al., 2003; Strapazzon et al., 2017; Strapazzon, Gatterer et al., 2021; Wik et al., 2022). This hypertensive response is associated with hypoxia, hypercapnia and the excessive work of breathing caused by increased airway resistance.

Other physiological responses to hypoxia and hypercapnia were observed during breath holding that could point the way to further investigation of the pathophysiology of avalanche burial. For example, hypercapnia reduces the cerebral metabolic rate of O_2 (Xu et al., 2011), a brain protective mechanism observed during prolonged breath holding (Bain et al., 2016, 2017).

Hypothermia in avalanche burial

The respiratory system. With the onset of hypothermia and a decrease in core temperatures to 32−35°C, respiratory rate and minute ventilation increase (Paal et al., 2018). With further reductions below 32°C, however, minute ventilation decreases. The effects of reducing ventilation on the severity of hypoxaemia and hypercapnia varies depending on core temperature and changes in metabolism. With reductions in core temperature below 36°C, metabolism initially increases because of the shivering response, increasing oxygen consumption and CO_2 production. As a result, for any given degree of hypoventilation, arterial partial pressure of O_2 (P_aO_2) falls and P_aCO_2 rises at a faster rate than in the normothermic state. These changes are exacerbated if there are constraints on the mechanical ability to increase or maintain ventilation, such as compression of the chest by avalanche debris. Once the core temperature falls to 30−32°C, shivering ceases and metabolism decreases, decreasing oxygen consumption and CO_2 production. P_aO_2 still falls and P_aCO_2 still rises because of ongoing reductions in respiratory rate and tidal volume that occur as core temperature decreases. Reduction in metabolism may slow the rates of change in these parameters, which has been shown experimentally in anaesthetized pigs breathing into simulated avalanche debris (Fig. 4) (Paal et al., 2013). Another factor in the development of hypoxaemia with hypothermia is alteration of ventilation–perfusion matching. Hypothermia may blunt the pulmonary vascular response to hypoxia, making it difficult to mitigate the effects of impaired ventilation–perfusion matching on gas exchange (Benumof & Wahrenbrock, 1977; Haavik-Nilsen & Hauge, 1968). An increase in pulmonary vascular resistance (PVR) was observed in a porcine model in which pigs were cooled to 28°C (Strapazzon, Putzer et al., 2021). This is in line with previous animal models (Debaty et al., 2016; Kuhn & Turner, 1959), but the mechanism for this observed change is not clear. Some authors argue that increased PVR during hypothermia may be related to alterations in the blood rather than changes in the vessel wall (Kuhn & Turner, 1959). It may relate to factors such as increased blood viscosity, direct effects of temperature on pulmonary vascular smooth muscle or changes in sympathetic tone. Further increases in PVR, as well as increases in mean pulmonary artery pressure, were seen when the hypothermic pigs breathed a hypoxic and hypercapnic mixture with a reduction in ventilation (Fig. 5) (Strapazzon, Putzer et al., 2021).

While blood oxygen tensions are reduced by the factors described above, hypothermia may counteract some of the effects of hypercapnia on blood oxygen transport, as reductions in temperature below 37°C counteract the Bohr effect and shift the haemoglobin–oxygen dissociation curve to the left (Woyke et al., 2022) (Abstract figure). This reduction in the P_{50} enhances uploading of oxygen in the lungs but may limit offloading in the peripheral tissues (Woyke et al., 2022). The ultimate position of the haemoglobin–oxygen dissociation curve will depend, however, on the relative severity of hypothermia and hypercapnia. Because the magnitude of the latter is a function of changes in metabolism and ventilation, which can vary significantly between individuals, it is difficult to know the ultimate position of the P_{50} in any given buried victim.

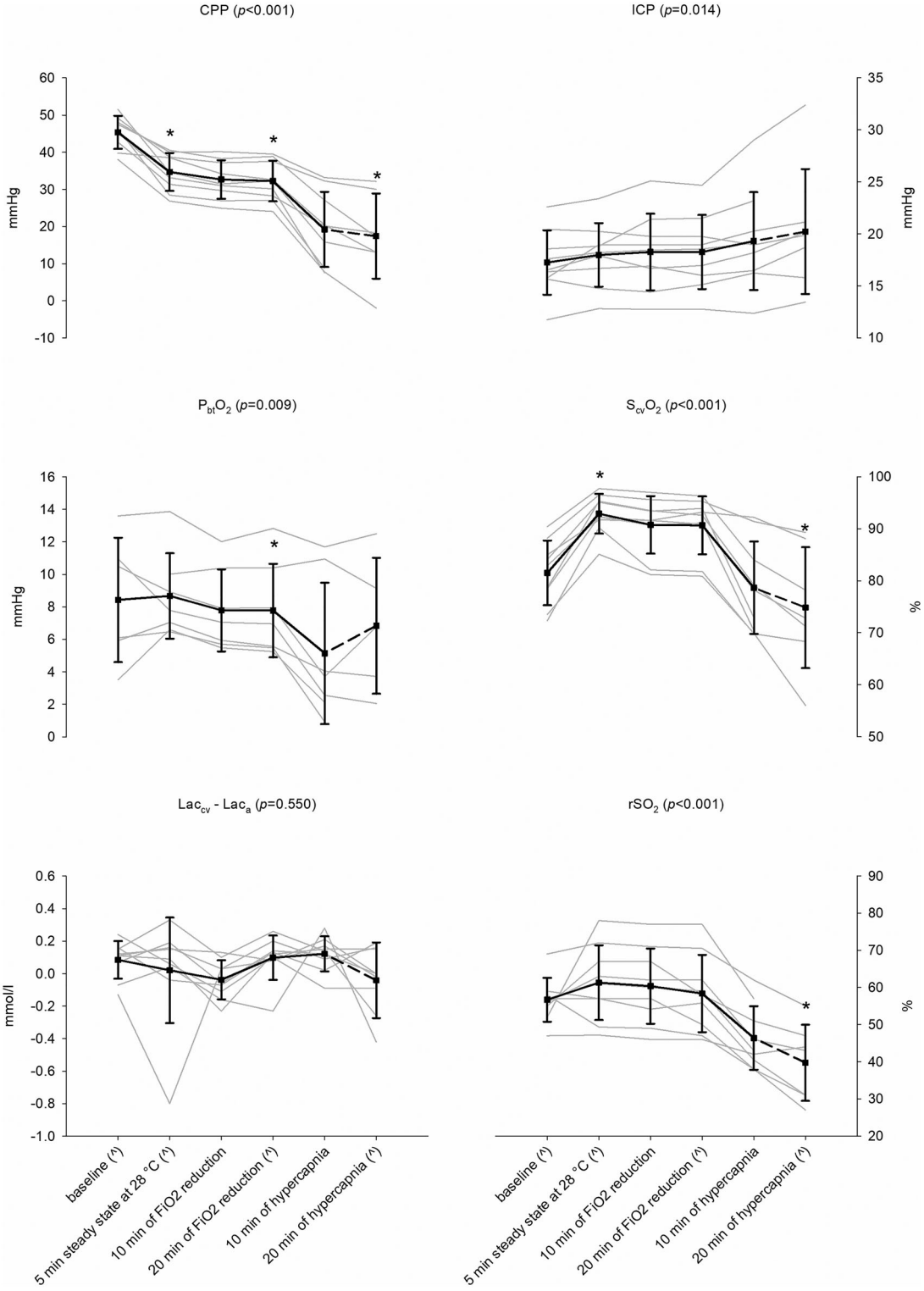

Figure 5. Porcine physiological responses to hypothermia, hypoxia, and hypercapnia
Curves demostrating changes in brain oxygenation and other parameters in anesthetized pigs cooled to 28°C, after reduction of the fraction of inspiratory oxygen to 17% and after induction of hypercapnia; cerebral perfusion pressure (CPP), intracranial pressure (ICP), brain tissue oxygen tension ($PbtO_2$), arterial oxygen saturation (SaO_2), cerebral venous oxygen saturation ($ScvO_2$), arterial and cerebral venous lactate (Lac_a and Lac_{cv}) and regional cerebral oxygen saturation (rSO_2). P values in parentheses are for repeated-measures ANOVA. *Significant difference ($P < 0.05$) from the previous time point is denoted with ^ (indicates baseline or phase end) (Modified from Strapazzon et al., 2021, with permission).

The cardiovascular system. During avalanche burial, changes in blood gases appear before changes in body temperature (Grissom et al., 2000), while hypoxia and hypercapnia accelerate heat loss (Grissom et al., 2004, 2008; Johnston, Elias et al., 1996; Johnston, White et al., 1996). Because of safety concerns, human studies on avalanche burial are limited to non-hypothermic core temperatures above 35°C. With cooling to 32°C, there is activation of the sympathetic nervous system, causing peripheral vasoconstriction with increased heart rate and increased blood pressure (Paal et al., 2018; Pozos et al., 1996). These effects were seen in a study of healthy individuals buried under simulated avalanche debris that reported decreased skin temperatures and increased heart rates (Grissom et al., 2000). With development of moderate hypothermia, bradycardia and myocardial depression occur, leading to decreased cardiac output and hypotension (Paal et al., 2018). A study of pigs cooled to a core temperature of 28°C without changes in blood gases found reduced cardiac output, mean arterial pressure and heart rate (Strapazzon, Putzer et al., 2021). In a case report describing an almost 5 h avalanche burial of a victim wearing a cardiac monitor, heart rate increased transiently in the first few minutes before decreasing for the remainder of the burial (Bracco et al., 2024). Hypothermic bradycardia is caused by decreased spontaneous activity of pacemaker cells in the heart that decreases linearly with heart temperature (Paal et al., 2018) and does not appear to be vagally mediated (Black et al., 1976). The underlying decrease in myocardial cell channel activity (Pozos et al., 1996) increases the risk of atrial and ventricular dysrhythmias. Below 30−32°C, the heart becomes sensitive to mechanical stimulation. This is of particular importance during avalanche rescue, because ventricular fibrillation can be triggered by cardiopulmonary resuscitation or extrication manoeuvres (Pasquier et al., 2023; Strapazzon et al., 2012).

Two studies using anaesthetized pigs investigated the combined effects of hypoxia, hypercapnia and hypothermia. The first study (Paal et al., 2013) showed that pigs breathing through an air pocket in simulated avalanche debris with high-density snow rapidly developed hypoxia and hypercapnia with a mixed respiratory (i.e. hypercapnia-induced) and metabolic (i.e. lactic) acidosis (Fig. 4). Acidotic pigs showed lower cardiac output and a lower rate of cooling than pigs with adequate gas exchange. In the second study (Strapazzon, Putzer et al., 2021), intubated paralysed pigs were ventilated normally while being cooled to a core temperature of 28°C. They were then ventilated with a mild hypoxic gas mixture sufficient to cause hypoxaemia, before being hypoventilated (Fig. 5). The hypothermic, hypoxic and hypercapnic pigs showed lower mean arterial pressure, heart rate and cardiac output with unchanged systemic vascular resistance when compared with the hypothermic, normoxic and normocapnic pigs. Cardiac failure most likely results from the reduction in cardiac output caused by hypothermia as well as from hypoxia and hypercapnia resulting from the reduced F_IO_2 and increased F_ICO_2. Decreased cardiac output during cooling is reversible after rewarming, in contrast to hypoxic injury which is not reversible if hypoxia precedes the onset of hypothermia.

The central nervous system. The neuroprotective effect of hypothermia has traditionally been ascribed to a reduction in cerebral metabolism (Dietrichs & Dietrichs, 2015; Paal et al., 2018) by 5% for each °C decrease in cerebral temperature (Laptook et al., 1995). This neuroprotective effect, which may be more pronounced in humans (Kawamura et al., 2000), is greater than that expected from reduced metabolism alone (Dietrichs & Dietrichs, 2015) and explains why it is possible to survive prolonged hypoxia without neurological sequelae (Wanscher et al., 2012). Development of ischaemic brain injury through pathophysiological mechanisms such as glutamate-accumulation and cellular calcium influx, are also reduced by hypothermia (Dietrichs & Dietrichs, 2015; Wu & Grotta, 2013; Yenari & Han, 2012). These effects increase neuroprotection along with a possible reduction in vascular permeability of cerebrovascular membranes (Krantis, 1983).

CBF autoregulation also provides neuroprotection, although, as shown in studies of patients (Joshi et al., 2010) and experimental porcine models (Ehrlich et al., 2002; Gaasch et al., 2020), this autoregulation is already impaired by the time buried victims have moderate hypothermia. With impaired autoregulation, energy delivery to the brain becomes dependent on changes in mean arterial blood pressure. Isolated cooling to 32°C is associated with reduced mean arterial blood pressure and reduced CBF, but because both cerebral O_2 delivery and O_2 consumption are reduced, the O_2 extraction rate is not affected (Mohyuddin et al., 2021).

Only one study has specifically investigated the effects of hypothermia, hypoxia and hypercapnia on the brain during avalanche burial. This study showed that hypothermia cannot compensate for the observed mismatch between energy demand and blood flow (Fig. 5) (Strapazzon, Putzer et al., 2021). There was no clinically relevant reduction in brain tissue PO_2 or cerebral venous oxygen saturation during induction of hypothermia to 28°C followed by induction of moderate hypoxaemia. With induction of moderate hypercapnia, however, mean arterial pressure and cerebral perfusion pressure were reduced, resulting in cerebral hypoxia. Reduced cerebral tissue oxygenation in critically buried, but breathing avalanche victims who develop hypothermia is most likely caused by simultaneous reduction in cerebral perfusion pressure and arterial oxygen saturation. The

neuroprotective effect of hypothermia initiated after a hypoxic insult is questionable, both for survival and functional outcome (Fernando et al., 2021; Strapazzon & Brugger, 2018).

Outcomes of critically buried avalanche victims compared with patients with accidental hypothermia alone. Epidemiological investigations of accidental hypothermia commonly involve diverse groups of victims and types of exposure, including individuals of varying health status and victims who have encountered cold ambient temperatures, drowning or avalanche burial (Baumgartner et al., 2008; Herity et al., 1991; Matsuyama et al., 2018; Taylor et al., 1994; Zhang et al., 2019). In contrast to hypothermia victims in urban areas who are often older and have multiple underlying health issues, most avalanche victims are young and healthy. This suggests that hypothermic avalanche victims might have more favourable outcomes than older victims of hypothermia without avalanche burial. However, the survival rate for avalanche victims with out-of-hospital cardiac arrest who undergo extracorporeal rewarming is about 12% (Boué et al., 2014; Hilmo et al., 2014; Mair et al., 2014). This is significantly lower than survival rates for victims with hypothermic cardiac arrest who have not been buried in avalanches, which range from 23 to 100% (Pasquier et al., 2019; Ruttmann et al., 2007, 2017; Wanscher et al., 2012). Hypothermic patients exposed to a cold environment (57% survival) and immersed in cold water (60%) (cases where breathing was possible) have higher survival rates than submersed victims (drowning with the head underwater) (19%) and avalanche burial (12%) (Pasquier et al., 2018). This suggests that hypoxia and hypercapnia are the primary factors behind the considerably lower survival rate among hypothermic avalanche victims and post-submersion patients compared with those experiencing hypothermic cardiac arrest from other causes. Survival appears to hinge on whether hypothermia precedes hypoxia. If hypoxia precedes hypothermia, hypothermia has little or no neuroprotective effect.

Where should the research go?

The survival times of completely buried victims vary from minutes to hours. An individual can survive and sustain organ function if they can breathe under the snow and maintain sufficient oxygen delivery of oxygen and efflux of carbon dioxide. The combination of hypoxaemia and hypercapnia negatively affects the respiratory and cardiovascular systems and poses a major threat to the central nervous system. When there is a long burial time, an avalanche victim becomes hypothermic, but the effects on the body are rarely determined by the effects of hypothermia alone. Despite progressive reductions in metabolism, hypoxia and hypercapnia develop and exert effects across multiple systems. 'Triple H syndrome', which refers to the combined effect of hypoxia, hypercapnia and hypothermia (Brugger et al., 2003), emphasizes the interaction of the three factors. Hypercapnia is likely to be the main cause of cardiovascular instability, which causes decreased cerebral oxygenation despite severe hypothermia. Hypoxia, hypercapnia and hypothermia all increase haemoconcentration, blood viscosity and decrease cell deformability (Deuster et al., 1989; Rostomily et al., 2020; Wallner et al., 2020). These factors, in turn, can affect blood flow and oxygen delivery but no research has been done to evaluate how they affect outcomes in critically buried avalanche victims, especially in lengthy burials.

How snow characteristics and air-pocket size influence gas exchange and affect survival is not well understood either. Few data are available on how gases circulate in the porous structure of snow and how the complex multiphase structure (interstitial air, aerosol particles, ice–air interfaces and ice crystals) is modified when a critically buried victim breathes while buried under avalanche debris. Specific studies on the cardiorespiratory and cerebral physiological responses of victims, as well as the ultimate regulation of CBF and oxygen delivery are lacking. They would be helpful to understand why some individuals have good neurological outcomes and others do not. Future studies should consider how the respiratory gases entrapped in the porous structure of snow influence the physiological responses of victims buried in avalanches and should investigate strategies to prolong avalanche survival by mitigating hypoxia and hypercapnia or reducing core temperature so that hypothermic neuroprotection occurs before cerebral hypoxia.

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Additional information

Competing interests

The authors declare that they have neither competing interests nor conflicts of interest.

Author contributions

G.S. conceived and designed the review. G.S., A.T., E.S.D., A.M.L. and H.B. drafted the first version. G.S., A.T., E.S.D.,

A.M.L. and H.B. revised it critically and prepared the final version together. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Thus, all persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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