Review articles

Effects of CO_2 on the occurrence of decompression sickness: review of the literature

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Abstract
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Introduction: Inhalation of high concentrations of carbon dioxide (CO_2) at atmospheric pressure can be toxic with dose-dependent effects on the cardiorespiratory system or the central nervous system. Exposure to both hyperbaric and hypobaric environments can result in decompression sickness (DCS). The effects of CO_2 on DCS are not well documented with conflicting results. The objective was to review the literature to clarify the effects of CO_2 inhalation on DCS in the context of hypobaric or hyperbaric exposure.

Methods: The systematic review included experimental animal and human studies in hyper- and hypobaric conditions evaluating the effects of CO_2 on bubble formation, denitrogenation or the occurrence of DCS. The search was based on MEDLINE and PubMed articles with no language or date restrictions and also included articles from the underwater and aviation medicine literature.

Results: Out of 43 articles, only 11 articles were retained and classified according to the criteria of hypo- or hyperbaric exposure, taking into account the duration of CO_2 inhalation in relation to exposure and distinguishing experimental work from studies conducted in humans.

Conclusions: Before or during a stay in hypobaric conditions, exposure to high concentrations of CO_2 favors bubble formation and the occurrence of DCS. In hyperbaric conditions, high CO_2 concentrations increase the occurrence of DCS when exposure occurs during the bottom phase at maximum pressure, whereas beneficial effects are observed when exposure occurs during decompression. These opposite effects depending on the timing of exposure could be related to 1) the physical properties of CO_2, a highly diffusible gas that can influence bubble formation, 2) vasomotor effects (vasodilation), and 3) anti-inflammatory effects (kinase-nuclear factor and heme oxygenase-1 pathways). The use of O_2-CO_2 breathing mixtures on the surface after diving may be an avenue worth exploring to prevent DCS.

Introduction

At atmospheric pressure, inhalation of carbon dioxide (CO_2) can quickly become toxic depending on the concentration of inhaled CO_2. In ambient air, the level of CO_2 is about 400 ppm) or 0.04 kPa at atmospheric pressure (101.3 kPa). From 0.2 kPa (2,000 ppm or 0.2% of CO_2 at atmospheric pressure), clinical manifestations may appear with headaches, shortness of breath or tachycardia. At high concentrations (10,000 ppm or 1%), around 1 kPa of CO_2 at atmospheric pressure, consciousness disorders may occur. For these reasons, the European limit value not to be exceeded in occupational medicine is a maximum exposure per day of eight hours at 0.5 kPa at atmospheric pressure (5,000 ppm).[1]

Elevation of blood CO_2 levels endogenously or exogenously defines hypercapnia, which corresponds to an arterial CO_2 pressure ($PaCO_2$) above 6 kPa (45 mmHg). To avoid this situation, the body adapts by increasing its ventilatory response and activating its buffer systems. These physiological adaptations allow the removal of excess CO_2 and thus maintain a stable blood pH.

During hyperbaric exposure, hypercapnia can occur by several mechanisms: either by inhalation of higher CO_2 levels due to equipment failure, or by a disturbance in ventilatory control leading to hypoventilation (induced by increased ventilatory work or physical exercise).[2] It's important to note that some divers, including rebreather divers, appear to develop less sensitivity to CO_2 over time. This tolerance to hypercapnia, fostered by constant hyperoxia during immersion and adaptation to excessive ventilatory work, reduces the ventilatory drive induced by the normal response to increasing CO_2 levels.[3,4]

Hypercapnia appears to be the most frequent biochemical accident involving military rebreathers. A study of 30 years of accidents during rebreather use in the French Navy found that 68% related to gas toxicities, of which 60% were related to hypercapnia.[5] This hypercapnia occurs with rebreathers that use hyperoxic mixes, which protect against the onset of decompression sickness (DCS), but this use can lead to specific inflammatory responses.[6]

In addition, hypercapnia has been shown to potentiate the narcotic effects of nitrogen.[7] Symptoms of narcosis, including loss of consciousness, may be increased by exercise in hypercapnia.[8] Hypercapnia has also been shown to potentiate the neurological toxicity of oxygen, with observations of hyperoxic convulsive seizures occurring in combat swimmers using closed-circuit oxygen equipment. Most of these dives were long and sustained. At the end of the dive, the soda-lime cartridge filtered CO_2 less efficiently, resulting in higher inspired CO_2 levels.[5,9,10] The potentiation of oxygen toxicity effects is thought to be mediated in part by the vasodilatory action of CO_2 on cerebral arteries.[11]

Scuba diving also exposes divers to the risk of decompression sickness (DCS) if the removal of supersaturated inert gases from blood or body tissues during decompression is not performed properly. Increased CO_2 levels in the air or breathing mixture during underwater and hyperbaric exposure could also contribute to this type of accident. In fact, CO_2 may play a role in bubble formation and growth.[12,13] This hypothesis was raised during an investigation following a series of neurological diving accidents in 2020 at the French Army Diving Training Centre. Eight subjects developed neurological symptoms consistent with DCS after a training dive.[14]

Given the exceptional nature of this unprecedented group of accidents, both in terms of incidence and clinical presentation, an investigation was carried out to identify the contributing factors. In particular, all changes related to the 'COVID-19' context implemented in the organisation of this course were analysed in detail, as well as the environmental or individual causes[15] that could be at the origin of the onset of neurological clinical symptoms. The retention of CO_2 and the inhalation of part of it, linked to the sanitary conditions (wearing of a protective mask), was a possible explanation, based on the hypothesis of the activation of gaseous nuclei by CO_2 before diving.[13]

It appears that the increased risk of DCS is rather poorly documented and seems to be related only to the situation of CO_2 exposure during bottom time.[16] On the other hand, different or even opposite effects are observed when CO_2 exposure occurs during the decompression phase.[17] In view of these divergent results, we felt it was important to review all published studies on the subject, concerning both hyperbaric and hypobaric exposures, based on experimental data or studies conducted in humans.

The aim of this study is to clarify the effect of CO_2 inhalation on the occurrence of decompression sickness as a function of the duration and concentration of inhaled CO_2 relative to hypobaric or hyperbaric exposure. We define low concentrations of inhaled CO_2 as a $PiCO_2$ of less than 1 kPa (equivalent to 1% of inhaled CO_2 at surface pressure) and high concentrations as a $PiCO_2$ of 1 kPa or more.

Methods

INCLUSION CRITERIA

This study focuses on available clinical or experimental data based on CO_2-enriched mixtures and does not address hypercapnia issues related to endogenous production.

We considered all experimental animal studies or descriptive human studies performed under hyper- or hypobaric conditions that evaluated the effect of CO_2 on bubble formation, denitrogenation, or the occurrence of DCS. The MEDLINE and PubMed search engines were used with the following keywords: carbon dioxide, nitrogen, decompression sickness, decompression illness, bubble, denitrogenation, diving. We did not limit the bibliographic search by publication date or language.

We have also included documents from specialist books on underwater and hyperbaric medicine and aeronautical medicine, as well as archival documents from specialist websites.

Results

SELECTION OF ARTICLES

Forty-three articles were identified based on the inclusion criteria, of which 31 were from MEDLINE or PubMed and 12 from other sources. Thirty-two articles were excluded. The decision on the retention of articles was taken by consensus of a number of authors on the basis of criteria of relevance to the topic. A total of 11 articles were included in the review (Figure 1).

Figure 1
PRISMA flow diagram to show study selection

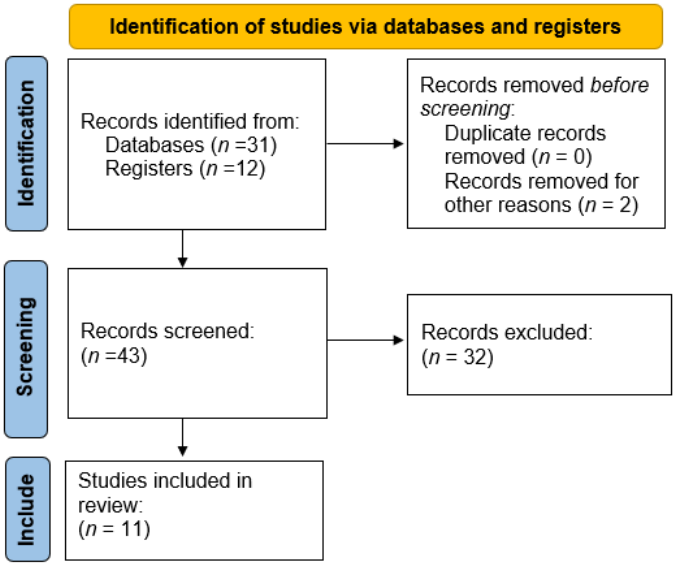

Table 1
Classification of CO_2 studies according to exposure and type of study

Type of exposure	Effects studied	Author's name & year	Type of study
Hypobaric	Effects of elevated CO_2 prior to exposure	Harris et al. 1945	Animal
		Andicochea et al. 2019	Human
	Effects of CO_2 elevation before and during exposure	Hill et al. 1994	Animal
		Katuntsev et al. 1994	Human
Hyperbaric	Effects of elevated CO_2 prior to exposure	Seddon, 1997	Animal
	Effects of elevated CO_2 during exposure	Mano et al. 1978	Human
	Effects of elevated CO_2 during decompression	Margaria et al. 1950	Human
		Bell et al. 1986	Human
		Gennser et al. 2014	Animal
	Effects of elevated CO_2 during exposure and just before decompression	Gennser et al. 2008	Animal
		Huang et al. 2018	Animal

The 11 articles selected were classified according to the criteria of hypo or hyperbaric exposure, taking into account the timing of CO_2 inhalation in relation to exposure and distinguishing between experimental work and studies carried out in humans (Table 1).

STUDIES DURING HYPOBARIC EXPOSURE

Effects of inhaling high concentrations of CO_2 prior to hypobaric exposure in animals

In 1944, Harris et al. conducted several animal model studies by exposing frogs to rapid depressurisation (2–10 minutes) to simulated altitudes of 10,000–70,000 ft for 30 minutes.[18] On return to atmospheric pressure, the number of bubbles formed was analysed by a venous sampling method. These experiments determined the levels of depressurisation and muscle stimulation in the frogs necessary to observe bubble formation.

The animals were then subjected to very high levels of CO_2 inhalation ranging from 25 to 70 kPa for 1.5 hours and up to 4 hours prior to depressurisation.

The authors demonstrated the concept of CO_2 as a facilitator of bubble formation. It greatly increased the ease with which bubbles can be initiated and may be responsible for their rapid growth in the early stages of development.

Effects of inhaling high concentrations of CO_2 before and during hypobaric exposure in animals

Hill et al. conducted an animal study in 1994, in which seven goats were repeatedly exposed to hypobaric exposure at equivalent altitudes of 5,000–33,000 ft for 30 min.[19] The rate of depressurisation was 19 kPa·min^{-1}. The protocol involved inhalation of O_2–CO_2 mixtures before and during the hypobaric exposure. Before the exposure, the mixtures breathed for 15 min contained 0 to 6.1 kPa of CO_2. Throughout the exposure, the mixtures breathed contained 0 to 4 kPa CO_2.

The risk of decompression events was assessed by measuring precordial circulating bubbles during hypobaric exposure.

When CO_2 levels were increased before and during hypobaric exposure, no significant changes in the number of circulating bubbles were observed. According to the authors, this negative result may be related to insufficient numbers or too short periods of CO_2 exposure before depressurisation.

Effects of inhaling high concentrations of CO_2 before and during hypobaric exposure in humans

Katuntsev et al. conducted a study to evaluate the effect of CO_2 on the occurrence of DCS during hypobaric exposures simulating extravehicular activity protocols.[20]

They exposed 46 healthy male volunteers to simulated altitudes of 21,325 to 26,574 ft for up to six hours. During the hypobaric exposure, the subjects performed a calibrated intermittent exercise. The subjects breathed a 97% O_2–3% CO_2 mixture for two hours prior to depressurisation. Inhalation of this mixture was maintained during the hypobaric exposure. A total of 106 experimental exposures were performed while breathing 3% O_2–CO_2 versus 101 control exposures breathing pure O_2. The subjects who inhaled the CO_2-enriched mixture showed a decrease in mean blood pH values from 7.40 to 7.37 and an increase in $PaCO_2$ from 5.26 to 5.82 kPa.

The incidence of joint pain DCS was significantly higher in the CO_2-exposed group before and during depressurisation than in the control group, with 67.9% DCS versus 32.7%, respectively.

Effects of inhaling low concentrations of CO_2 prior to hypobaric exposure in humans

In 2019, Andicochea reported cognitive symptoms suggestive of altitude DCS in six US Army aviators.[21] This involved exposure to high altitudes of 30,000–41,000 feet with a rapid depressurisation protocol. Of the nine pilots who underwent this procedure, six experienced cognitive dysfunction including difficulty concentrating, a feeling of psychic slowing down, and paraesthesias in the limbs. Four of the six symptomatic pilots received hyperbaric chamber treatment. The six symptomatic pilots had been exposed several hours before the flight to a slightly elevated level of CO_2 (900 ppm on average, i.e., 0.09 kPa) in their briefing room which was poorly ventilated. The three other pilots who were briefed in another room with better ventilation (560 ppm on average, i.e., 0.056 kPa) and who followed the same protocol did not show any symptoms.

According to the authors, chronic intoxication with 1,000 ppm CO_2 prior to a rapid ascent could have an effect on the occurrence of high-altitude DCS.

STUDIES DURING HYPERBARIC EXPOSURES

Effects of inhaling high concentrations of CO_2 prior to hyperbaric exposure in animals

Seddon conducted a series of experiments to determine the relationship between the pressure at which a goat can become saturated and the maximum depth from which it can then safely escape from a simulated submarine.[22] One of the aims of the study was to assess the effect of prior exposure to a CO_2-enriched environment and its impact on the incidence of decompression sickness and bubble formation. He compared several groups of animals exposed to a high inspired pressure of CO_2 (2.5 kPa) for 23 hours before being subjected to a very rapid compression-decompression protocol simulating an escape procedure at equivalent depths of 240 to 270 metres (787 to 886 ft). In the group maintained at atmospheric pressure and then subjected to an escape procedure at 270 m, none of the 20 animals showed any signs of DCS. The bubble scores of the animals exposed to CO_2 were slightly higher than those of the animals maintained in air, but the difference was not significant.

Seddon's results do not support the hypothesis of increased bubble formation and DCS following normobaric exposure to a CO_2-enriched environment prior to an aggressive escape procedure dive.

Effects of inhaling high concentrations of CO_2 during hyperbaric exposure in humans

The study carried out by Mano and d'Arrigo in 1978 was a retrospective descriptive study of 84 tunnel boring machines involved in the construction of the Tokyo Bay Subway which lasted five months.[16] The authors noted that DCS was only observed at pressures above 273.5 kPa (2.7 atmospheres absolute) and working times of 5.5 to 6 hours maximum.

At the start of the project, the working chambers were not ventilated. For ambient pressures between 304 and 324 kPa, the ambient CO_2 level was between 1.8 and 2.3% ($PiCO_2$ max = 7.36 kPa). Out of 2,430 exposures carried out under these conditions, there were 74 cases of joint pain DCS (90% involving the knee), i.e., an incidence of 3.05%.

Table 2
Number of joint pain decompression sickness (DCS) cases as a function of CO_2 exposure based on data from Mano and d'Arrigo (1978)[16]; Max – maximum; $PiCO_2$ – inspired pressure of CO_2

Pressures (kPa)	Ventilation	Ambient CO_2 (%)	Max $PiCO_2$ (kPa)	Exposures (*n*)	DCS (*n* %)
300–320	No	1.8–2.3	7.36	2,430	74 (3.05%)
320–340	Yes	0.3–0.8	2.70	3,951	38 (0.96%)

At the end of the work, the rooms were ventilated, the ambient CO_2 level was between 0.3 and 0.9% at an ambient pressure of between 324 and 344.5 kPa ($PiCO_2$ max = 3 kPa). Out of 3,951 exposures, 38 DCS were reported, i.e., an incidence of 0.96% of DCS (Table 2).

The authors highlighted the increased risk of DCS as a function of CO_2 levels in the hyperbaric environment.

Effects of inhaling high concentrations of CO_2 during decompression in humans

In 1950, Margaria and Sendroy exposed four male volunteer divers to a hyperbaric environment at 203 kPa for four hours before decompressing to atmospheric pressure within one minute.[17] Immediately upon returning to the surface, the divers breathed either 100% O_2, O_2 with 3% CO_2 or O_2 with 5% CO_2 in a chamber at 25°C, while seated at rest. Exhaled gas samples were collected in a Douglas bag every 10 to 15 minutes to determine their composition using the Van Slyke and Sendroy method. This method, described by Van Slyke in 1927, consists of measuring the proportion of oxygen and carbon dioxide contained in a gas using a manometric method. The amount of N_2 eliminated (denitrogenation curve) up to two hours after the dive was extrapolated from these measurements.

The results showed a significant increase of 20% in exhaled N_2 when breathing O_2 with 5% CO_2 compared to breathing pure O_2. No clinical symptoms were reported. The pH remained stable with an increase in ventilation in the subjects exposed to the O_2/CO_2 mixture.

The authors expressed interest in breathing a 5% CO_2 95% O_2 mixture at atmospheric pressure after a hyperbaric exposure, to increase the elimination of nitrogen and thereby reduce the occurrence of DCS.

However, in a relevant animal study, Gennser et al. investigated the ability of gases breathed after surfacing to reduce the initial bubble load.[23] Animals breathing oxygen, carbogen (5% CO_2, 95% O_2), or air were compared. Thirty-two goats were subjected to a dry simulated submarine escape profile to and from 240 meters (2.5 MPa). On surfacing, they breathed air (control), oxygen or carbogen for 30 minutes. Bubbles were assessed by audio Doppler, using the Kisman Masurel (KM) scale. There was no significant difference between groups in the median peak KM grade. On the other hand, oxygen showed significantly faster bubble resolution than carbogen and air. It follows that this study did not confirm the value of carbogen breathing during post-surfacing decompression in order to reduce bubbles.

The Bell et al. study, published in 1986, was a prospective study of 65 healthy volunteer divers during a saturation dive.[24] Divers were exposed to either 172 or 182 kPa ambient pressure for 48 hours before being decompressed to atmospheric pressure at a rate of 0.5 $m \cdot min^{-1}$. During decompression, one group of 30 divers breathed nitrox (40% O_2), while the other group of 35 divers breathed nitrox (38% O_2) with 2% CO_2. At the end of the dive, the effect of decompression was assessed by repeated measurement of precordial circulating bubbles, assessed at rest and after movement, during the six hours following hyperbaric exposure, also noting the possible occurrence of DCS within 24 hours.

The study showed no difference in the incidence of DCS between the two groups. None of the 20 subjects exposed to 172 kPa showed any symptoms. However, there were two cases of DCS in both groups exposed to 182 kPa. The main finding of the study concerns the number of circulating bubbles which was lower in the O_2-CO_2-N_2 breathing group with a significant reduction of 55% of the bubble levels (following movement) for divers diving at 172 kPa and 30% (after movement) for those diving at 182 kPa.

The authors expressed a real interest in breathing a CO_2-enriched mixture during decompression in order to reduce the formation of circulating bubbles and thus the risk of DCS.

Effects of inhaling high concentrations of CO_2 before and during decompression in animals

Gennser et al. performed two experiments on goats to determine the influence of breathing gases on the number of circulating bubbles after a submarine simulated escape.[25] In the experiment of interest, goats breathed either 100% O_2, 97.5% (n = 12), O_2-CO_2 2.5% (Carbogen) (n = 8) or air (n = 10) for 15 min after a six hour period at 100 kPa (~10 metres of seawater). Next, an evacuation profile from a submarine at a depth of 240 m was simulated (compression in 24 s followed by decompression at 2.75 $m \cdot sec^{-1}$). Finally, circulating bubbles were measured in each group for 6 h. The number of DCS cases was recorded for each group. The

results showed that circulating bubbles decreased (in number and duration) only in the group pre-exposed to 100% O_2. Only one case of CNS DCS occurred, in the carbogen group. Two animals (also in the carbogen group) suffered from oxygen convulsions. Three fatal events due to pulmonary barotrauma were observed in the 100% O_2 and air groups.

The idea of adding CO_2 to O_2 was that the vasodilatory effect of CO_2 would speed up the elimination of nitrogen, particularly in the CNS. However, this study does not confirm the value of adding carbogen prior to decompression to reduce bubbles and limit the occurrence of DCS. In addition, the vasodilatory effect favours the onset of oxygen-induced convulsions.

In 2018, Huang et al. published an abstract of an animal study investigating the effect of inhaling high levels of CO_2 before the start of decompression on the occurrence of DCS.[26] To do this, the authors exposed rats to 608 kPa for one or two hours with rapid decompression in five min to induce DCS. The rats were divided into three groups and breathed a mixture of 3% CO_2 and 97% air for either 10 min, 30 min or 60 min before the start of decompression. The authors then analysed the histological lung lesions induced by post-decompression bubble formation. The number of animals per group is not given.

They showed that rats that breathed the gas mixture for 10 min just before the onset of decompression had a lower DCS mortality with less decompression-induced lung damage compared to rats that breathed the CO_2-enriched gas mixtures for 30 min or 60 min of hyperbaric exposure.

The authors suggested that a short period of hypercapnia, just before decompression, would have a specific anti-inflammatory effect and thus protect against inflammatory lung lesions associated with decompression sickness. The protective effect of CO_2 would be related to an effect that is independent of the known effects on bubble and nitrogen elimination, but which was not studied in this study.

A summary of these studies is provided in Table 3.

Discussion

HYPOBARIC CONDITIONS

Studies in hypobaric conditions have shown that CO_2 has a predominantly detrimental effect on the risk of DCS at high altitude. This is particularly the case when CO_2 is inhaled prior to depressurisation.

This analysis of articles confirms that the occurrence of hypercapnia prior to depressurisation is a factor that favours the increase in the formation and volume of circulating bubbles and de facto, the risk of the occurrence of a DCS.[27]

On the other hand, there are no mechanisms associated with a change in pH due to CO_2. In fact, in an organism without underlying pathology, $PaCO_2$ is compensated by hyperventilation and activation of the body's buffer systems to maintain a stable pH. Katuntsev found no pH disturbance despite high inhaled CO_2 concentrations.[20]

HYPERBARIC CONDITIONS

CO_2 breathed during time spent at the bottom may have a detrimental effect, as suggested by Mano's observational study, which found an increased incidence of DCS when tunnels were poorly ventilated.[16]

In contrast, several studies in healthy volunteers support a beneficial effect when exposure to elevated CO_2 occurs during decompression.

Margaria et al. were interested in the possible potentiating effect of CO_2 on denitrogenation.[17] This study is the only one to have measured the elimination of nitrogen in humans after breathing an over-oxygenated mixture enriched with CO_2 following hyperbaric exposure. In this study, the measurement of circulating bubbles was not performed and only the measurement of respiratory N_2 elimination was considered. The approach is particularly interesting as it shows a possible beneficial effect of CO_2 when exposure takes place during decompression. The addition of CO_2 to oxygen appeared to be more effective than inhalation of 100% O_2, which could be of practical interest in optimising denitrogenation procedures and thus safety in diving currently based on the use of 100% O_2. Indeed, pre- or post-dive oxygen inhalation is known to have a beneficial effect on nitrogen elimination and protection against DCS events during diving[28,29] and is increasingly used in recreational and professional diving to improve denitrogenation in the context of deep or repetitive dives.

Bell's study also goes in this direction, although the results did not show a reduction in the incidence of DCS, they did note a reduction in circulating bubbles when divers breathed CO_2-enriched air during decompression.[23] However, Gennser's animal study[23] did not confirm the value of carbogen breathing after surfacing following a simulated submarine escape in order to reduce bubble formation and DCS.

HYPOTHESES ON THE RELEVANT EFFECTS OF INHALED CO_2

Physical effects on gas phases

CO_2 is a fat-soluble, highly diffusible gas that may affect the bubble phenomenon via an increase in the growth of gas nuclei and bubbles when the concentration of dissolved CO_2 increases.[12,13,27,30] Gennser et al. speculated that CO_2 inhalation under pressure would promote bubble formation due to the high diffusibility of CO_2.[25]

Table 3
Summary of the different effects of CO_2 as a function of pressure conditions, CO_2 exposure phase and CO_2 levels; DCS – decompression sickness

Exposure	Author, year	CO_2 inhalation phase	CO_2 %	Type of study	Conclusion
Hypobaric	Harris, 1945	Before and during depressurisation	25–70% (25–70 kPa)	Animal	**Deleterious effect:** Increase bubble formation
	Hill, 1944	Before and during depressurisation	3.5–46% (3.5–4.6 kPa)	Animal *n* = 7	**Not significant**
	Katuntsev, 1994	Before depressurisation	3% (3 kPa)	Male *n* = 46	**Deleterious effect**: Increase in DCS occurrence
	Andicochea, 2019	Before depressurisation	~0.1% (0.1 kPa)	Male *n* = 9	
Hyperbaric	Seddon, 1997	Before hyperbaric exposure	2.5% (2.5 kPa)	Animal *n* = 20	**Not significant** on DCS occurence. Slight increase in circulating bubbles
	Mano, 1978	During the hyperbaric exposure	See Table 2	Male See Table 2	**Deleterious effect**: Increase in DCS occurrence
	Margaria, 1950	After surfacing	5% (5 kPa)	Male *n* = 4	**Beneficial effect:** Accelerated denitrogenation
	Gennser, 2014	After surfacing	5% (5 kPa)	Animal *n* = 32	**Not significant** compared to air or oxygen for reducing circulating bubbles. Faster resolution with O_2
	Bell, 1986	During decompression (from saturation dive)	2% (3.6 kPa at 182 kPa)	Male *n* = 65	**Beneficial effect:** Reduction of circulating bubbles compared to air
	Gennser, 2008	(15 min) Before decompression	2.5% (5 kPa at 200 kPa)	Animal *n* = 30	**Not significant** compared to air for reducing circulating bubbles. O_2 more effective in reducing bubbles. **Deleterious effect:** Promotes oxygen convulsions
	Huang, 2018	During (and 10 min before) decompression	3% (18 kPa)	Animal	**Beneficial effect:** Improvement of lung damage induced by bubble formation

Vasomotor effects

In 1990, Bailliart measured changes in carotid artery flow in healthy subjects exposed to 5% CO_2.[31] They found a 30% increase in primary carotid artery flow due to an acceleration of the circulatory flow. Vascular reactivity during CO_2 inhalation has also been studied at the cerebral level by magnetic resonance imaging in healthy volunteers breathing a gas containing 5% CO_2, 21% O_2 and 74% N_2.[32] The study showed rapid cerebral vasodilation during CO_2 inhalation with rapid normalisation at the end of exposure.

Lambertsen et al. in 1955 observed that adding 2% to CO_2 to inhaled oxygen significantly shortened the time to onset of hyperoxic convulsions.[33] In his experiment, where he had humans breathing oxygen at 355 kPa, the PCO_2 at the onset of convulsions was low at 3.06 kPa (23 mmHg). The most likely hypothesis is that the vasodilatory effect of CO_2 outweighs the vasoconstrictive effect of oxygen.

In an attempt to improve decompression Gennser et al. tried to counteract the vasoconstrictive effect of oxygen with the vasodilatory effect of CO_2 by adding CO_2 to oxygen. As previously mentioned, this had no beneficial effect on decompression and hyperoxic crises occurred.[25]

In the context of hyperbaric exposure, the vasodilatory effect of CO_2 appears to have an unfavourable effect on the risk of DCS occurrence by increasing the inert gas load on the tissues during bottom time. Nevertheless, the effects of CO_2 combined with oxygen in the form of carbogen may be of interest in preventing DCS under certain conditions, and may be an avenue for improving surface decompression. It is important to continue research into the administration of carbogen on the surface, as studies are few and contradictory.[17,23]

Acid-basic effects and anti-inflammatory properties

Acid-base balance is maintained by the combined action of ventilation and the buffering effect of bicarbonates.[34] The body adapts to elevated concentrations of inhaled CO_2 by hyperventilating.[35,36] Exposure to higher concentrations of CO_2 (> 5%) will exceed the regulatory capacity of the organism, leading to disruption of acid-base balance, respiratory acidosis and blood hypercapnia. The severity of these effects depends on the duration of exposure, the CO_2 level and the basal state of the exposed subject.[37,38]

In addition to the effects described above, inhalation of high concentrations of CO_2 appears to activate anti-inflammatory processes. The work of Huang et al. in the DCS animal model suggests an anti-inflammatory effect with amelioration of lung damage when exposure to 3% of inspired CO_2 occurs immediately before and during the decompression phase.[26] The work of this same team has also explored these anti-inflammatory and anti-apoptotic effects in other models of acute lung injury, which would be mediated by hypercapnic acidosis with activation of heme oxygenase-1 anti-oxidant enzyme (HO-1) and inhibition of nuclear factor (NF)-κB signaling.[39,40] This work must be set against that of Katuntsev,[20] who found no variation in pH despite high concentrations of inhaled CO_2.

Therapeutic effects

The therapeutic properties of CO_2 are already being used in the form of an inhaled carbogen. This gas, usually composed of 95% oxygen and 5% CO_2, has long been used to treat sudden deafness.[41] Carbogen induces vasodilation and increased blood flow compared to pure oxygen alone. Measurements of PO_2 and PCO_2 carried out, mainly in the retina of animals under normobaric conditions, show an improvement in O_2 diffusion during carbogen breathing. CO_2 promotes the release of O_2 by haemoglobin (Bohr effect) which contributes to a better tissue oxygen delivery.[42]

In addition, CO_2-induced vasodilation in carbogen may also contribute to better O_2 utilisation and delivery through increased blood flow compared to pure oxygen.[43–45]

In 2009, a Cochrane review was conducted on 189 patients to assess the efficacy of different vasodilators in the treatment of sensorineural hearing loss.[41] Twenty-six patients received Carbogen. The only side effect reported was a feeling of heaviness in the head in five patients, which resolved spontaneously when the treatment was stopped.

These effects of CO_2 combined with oxygen in the form of carbogen may be of interest in the prevention of decompression sickness, in certain post-surfacing conditions. In fact, the vasodilatation and hyperventilation induced by CO_2 could favour denitrogenation with a better elimination of N_2 by the respiratory route. The anti-inflammatory effects could also contribute to a better tolerance of the bubble phenomenon during decompression. However, as previously mentioned, cerebral vasodilation can promote the onset of cerebral oxygen toxicity, which makes it dangerous to use during submersion.

Conclusions

In conclusion, we note that all the studies conducted in the context of hypobaric exposure suggest a detrimental effect of CO_2 on bubble formation and the occurrence of DCS.

In the context of hyperbaric exposures, the effects appear to be related to the duration of exposure, with adverse effects observed when the CO_2 exposure occurs before or during the bottom time, whereas beneficial effects are observed when the exposure occurs after decompression. Overall, there are very few studies on this topic, and human studies are rare and old. The studies presented do not answer the initial question of whether a low dose of CO_2 before diving can increase the

risk of DCS. Only the study on American aviators suggests this, but under hypobaric conditions.[21]

It should be noted that the effect of CO_2, particularly at low doses prior to hyperbaric exposure, has not been reported in the literature.

Given the lack of data on this point, we believe it is important to experimentally investigate the effects of chronic CO_2 exposure prior to hyperbaric exposure.

Furthermore, most studies inferring a possible beneficial effect of CO_2 in the decompression phase are observational and small. Further experimental work is required to confirm this effect and its mechanism(s).

The effect of carbogen inhalation (95% O_2 and 5% CO_2) after decompression could be studied with an aim of optimising decompression procedures. This could help to improve surface decompression procedures in specific contexts such as saturation diving evacuation procedures, submarine rescue or technical deep diving with rebreathers.

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