Hypobaric Decompression and White Matter Hyperintensities: An Evaluation of the NATO Standard

William Ottestad; Tor Are Hansen; Jan Ivar Kåsin

INTRODUCTION: In their seminal work, McGuire and colleagues reported an increased incidence of white matter hyperintensities (WMH) in a cohort of U2 pilots and hypobaric chamber personnel. WMH burden was higher in U2 pilots with previous reports of decompression sickness (DCS), and McGuire's reports have raised concerns regarding adverse outcomes in the aftermath of hypobaric exposures. Accordingly, a NATO working group has recently revised its standard recommendations regarding hypobaric exposures, including measures to mitigate the risk of WMH. Mandatory recovery time for up to 72 h between repeated exposures has been suggested on the basis of experimental evidence. However, we argue that the evidence is scarce which supports restricting repeated exposures to mitigate WMH. It is plausible that WMH is correlated with DCS and emphasis should be made on limiting the duration of exposures rather than restricting short and repeated exposures. The profiles in the NATO recommendations are meant to mitigate the risk of DCS. Still, they will potentially expose NATO Air Force and Special Operations personnel to flight profiles that can give rise to DCS incidence above 35%. Awaiting reliable data, we recommend limiting the duration of exposures and allowing for short repeated exposures.

KEYWORDS: HAHO, decompression sickness, white matter hyperintensities, STANAG 7056, airdrop operations.

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The NATO Standard (STANAG 7056) defines the minimum functional requirements for the physiological protection of personnel during high altitude airdrop operations. It describes three potential adverse outcomes during high altitude airdrop operations: hypoxia, decompression sickness (DCS), and potentially white matter hyperintensity (WMH) lesions. In the following, we discuss the revised NATO Standard recommendations for the protection from DCS and WMH lesions.

Hypobaric Decompression Sickness

The NATO standard describes a high risk of incapacitating symptoms of DCS above Flight Level 250 (FL250). This is not always the case since the risk for DCS is dependent on multiple factors, including workload, duration of prebreathe, and time at altitude. The onset of DCS symptoms tends to occur in a delayed fashion (**Fig. 1**) and hypobaric chamber studies have demonstrated that short exposures carry a low risk of clinical DCS even at altitudes up to FL300. Incapacitating symptoms are extremely rare in the context of short exposures following proper prebreathe.[20]

In a given flight profile, the risk for incapacitating or severe symptoms of DCS increases when cumulative DCS incidence exceeds 20%.[4] In controlled chamber studies at FL250, the cumulative DCS incidence increases exponentially at 60 min and reaches approximately 20% at 80 min and 35% at 110 min following a 1-h prebreathe.[18] The risk of severe DCS and incapacitating symptoms are negligible for hypobaric exposures with $<$ 60 min duration (**Fig. 2**).

The NATO recommendation for FL249 is maximum exposure of 110 min following a 30-min prebreathe, potentially exposing personnel to a cumulative DCS incidence $>$ 35% (Fig. 2).[18] By following the NATO recommendations, personnel will be exposed to a high risk of severe DCS with potentially incapacitating symptoms, including neurological symptoms.

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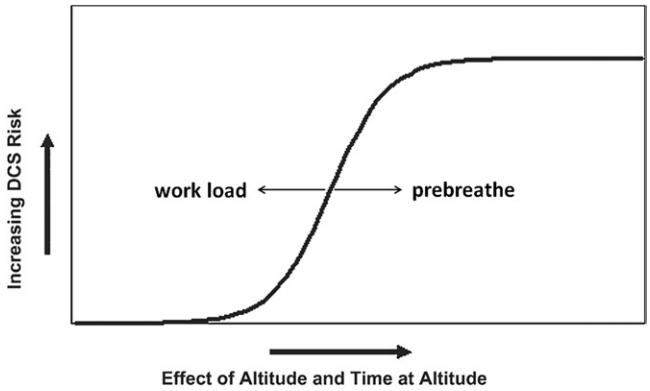

Fig. 1. DCS symptoms showing a sigmoidal relation to the time at altitude. Increasing length of prebreathe right-shifts the curve and increasing workload left-shifts the curve.

Hyperbaric DCS is associated with spinal or cerebral symptoms that can be resistant to treatment.[17] In contrast, hypobaric DCS is a relatively benign disease most often self-limiting and resolving with recompression to ground level. However, timely recognition of symptoms and prompt initiation of treatment is important to assure good outcome.[4] Neurological decompression sickness (NDCS) is rare among the general population of military pilots, and very few cases lead to neurological sequelae.[14,18] In the context of altitude physiological training in a controlled altitude chamber environment, DCS incidence has proven to be insignificant with the proper implementation of prebreathe procedures and limitations on exposure duration.[1] In contrast, among U2 pilots, DCS has been a common and probably underreported condition, and the incidence of severe NDCS has been reported to be high in the U2 pilot population.[6] Until recently, U2 pilots have been exposed to extreme decompression stress due to cabin pressure equivalent to FL300 and missions lasting for up to 9 h.[10]

White Matter Hyperintensity

WMHs are nonspecific lesions in the central nervous system identified by magnetic resonance imaging (MRI) that develop with increasing frequency during normal aging. The pathogenesis of WMHs remains unclear. The development of WMHs is correlated with underlying cardiovascular disease, as well as a number of other inflammatory and infectious disease etiologies.[7] McGuire et al. have documented an increased WMH burden among U2 pilots compared to a healthy control group of fighter pilots. Lower neurocognitive function in U2 pilots was reported; although statistically significant, the effects are barely measurable in absolute terms.[13] Increased WMH burden has also been reported among athletes with a history of sports-related concussion[15] and, recently, pathological WMH volume was documented in 15% of endurance runners ($N = 110$).[5] In light of these findings, several occupational hazards might contribute to WMH pathogenesis, and U2 pilots might be exposed to several confounding factors, including exposure to many hours of accumulated oxygen breathing. However, it seems plausible that the increased WMH burden is primarily attributed to nonhypoxic hypobaric decompression. Supporting this notion, McGuire et al. also documented an increased volume of WMH in a cohort of U.S. Air Force altitude chamber personnel ($N = 83$).[12] In contrast, this finding could not be reproduced in an MRI study of a population of UK chamber personnel ($N = 20$). However, only nine UK participants were directly comparable to the U.S. Air Force cohort participants regarding the severity of decompression stress.[3]

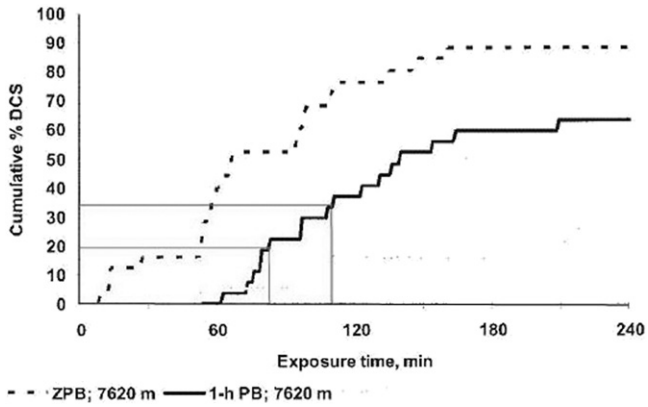

Fig. 2. Comparison of zero-prebreathe exposures with exposures following a 1-h prebreathe at 7620 m (25,000 ft). The figure is modified from the original as presented by Webb and Pilmanis.[18]

To mitigate the risk of WMH lesions, the NATO STANAG group has suggested limiting the frequency of exposures above FL180 and ensuring a minimum recovery time (time between exposures) of 24 h for exposures in FL180–FL249, and 72 for exposures ≥ FL250. These recommendations are founded on expert opinion and a recent study by McGuire et al. reporting increased white matter cerebral blood flow sustained up to 24 h after a chamber decompression to FL250 (white matter cerebral blood flow remained elevated at 72 h vs. baseline; however, it was not statistically significant: $P = 0.6$).[9] Notably, there were no significant changes in white matter integrity in this study. Therefore, this study does not substantiate a relationship between increased cerebral blood flow and risk of WMH development. In our opinion, the data from this single experimental study is insufficient to infer the minimum recovery time between nonhypoxic hypobaric exposures. The experimental setup applied a hypoxic training procedure with decompression to FL250 with breathing of ambient air for 2–4 min, and the subsequent hypoxemia experienced in this profile is short-lived but severe. Consequently, the persistent changes in cerebral blood flow might be partly attributed to the physiological response to severe hypoxia. Additionally, increased cerebral blood flow is not necessarily a pathological response, but could be a normal physiological adaptation to the combined stress of hypobaric decompression and hypoxemia.

The relationship between hypobaric decompression and white matter injury is unclear.[3,8,9] None of the studies regarding WMH in hypobaric exposures have succeeded in establishing a dose-response relationship in terms of cumulative hours of decompression or relation to factors such as exposure frequency, decompression rate, or duration of single exposures. WMH lesions have been reported in U2 pilots after single hypobaric

exposures[6] and have also been found to be absent in individuals exposed to severe decompression stress.[10] This suggests that some individuals are more susceptible to developing WMH while others seem to be protected. Interestingly, McGuire et al. reported that pilots who had experienced NDCS had a significantly higher WMH burden.[10] In light of these findings, we suggest that white matter injury is a part of a continuum from subclinical to clinical NDCS. It is plausible that WMH and DCS are highly correlated, and emphasis should be on avoiding hypobaric exposures that pose a high risk of clinical DCS.

Repeated Exposures

At a specific altitude, the duration of exposure is the dominant risk factor for DCS. However, DCS symptoms occur with a variable lag time, which makes brief exposures relatively safe. Along the temporal course, frequency of DCS symptoms rises exponentially. In FL250, this latent period is approximately 30–45 min depending on the duration of prebreathe and workload during decompression.[14,18] A study of repeated exposures to FL250 comparing a single 2-h continuous exposure with four serial 30-min exposures (1-h ground intervals) showed that repeated exposures carried significantly less accumulated DCS risk.[16] These results are supported by a physiological rationale as well; degassing in the tissues does not occur instantaneously and, in tissues with high solubility for nitrogen (e.g., the brain), the formation of in-situ bubbles increases slowly over time. This may explain the lag time of DCS symptoms following decompression. In contrast, the formation of venous gas bubbles is more abrupt; however, venous gas embolism and clinical NDCS is poorly correlated.[19]

Norwegian Protocol

In 2012 the Norwegian Defense Medical Services Institute of Aviation Medicine implemented a new protocol for high altitude airdrop missions emphasizing restriction of long exposures but allowing for short and repeated exposures. The NATO STANAG group has reached an opposite conclusion and allows longer accumulated time at altitude and imposes restrictions on repeated exposures. The maximum duration of a single exposure is 110 min up to FL249 compared to 45 min (FL250) in the Norwegian protocol. The Norwegian protocol aims to keep the DCS incidence $<$ 5% in FL250 to avoid severe symptoms (**Table I**). The estimation of DCS incidence is based on data from several controlled chamber studies.[1,4,16,18,19]

Discussion

In general, observational studies must be interpreted carefully and the external validity of the discussed studies by McGuire's group might be limited. In our opinion, these data do not automatically justify changes in operational practice outside the U2 pilot environment. However, we would like to acknowledge that McGuires' studies[8–13] are of high quality and raise serious concerns regarding decompression stress and risk of adverse outcomes.

Based on the increased incidence of WMH in U2 pilots with a history of NDCS, it is plausible that WMH burden is correlated with decompression stress, and increased incidence of WMH among healthy scuba divers supports this notion.[2] In line with this, we believe that primary focus should be to limit the duration of single exposures that pose a high risk for DCS, and not impose further restrictions on short and repeated exposures that carry a low risk for DCS. The experimental evidence reported by McGuire et al.[12] is insufficient to infer the minimum recovery time between nonhypoxic hypobaric exposures that could potentially yield protection from the development of WMH. The 72-h mandatory recovery time suggested by the NATO working group will represent a significant obstacle for special operation personnel who rely heavily on repeated exposures during high altitude parachute training and airdrop missions. Implementing the new NATO recommendations will decrease training efficiency and potentially increase other operational risks.

Since 2012 we have recorded approximately 5000 exposures at $\geq$ FL200 among personnel in the Norwegian Special Operations Commandos with only one reported incident of mild DCS after a breach in the prebreathe procedure (limb symptoms after 20 min exposure at FL250). The majority of these exposures have been repeated exposures with up to three exposures a day at FL200–250. Troubled by the reports from McGuire et al.,[8–13] we are now planning an MRI study to investigate WMH burden in personnel exposed to a high number of short but repeated exposures during military parachute training.

In conclusion, there is no robust evidence to support a 24–72 h mandatory recovery time between repeated exposures to high altitude of short duration to mitigate WMH. It is plausible that WMH is a part of a continuum from subclinical to clinical NDCS. The NATO Standard profiles, which are meant to mitigate the risk of DCS, will potentially expose NATO Air Force and Special Operations personnel to a DCS incidence above

Table I. Prebreathe and Exposure Duration at Different Altitudes.

FL	PREBREATHE EXPOSURES PER 24 h	TIME (min) PER SINGLE EXPOSURE	MAX ACCUMULATED TIME (min) AT ALTITUDE PER 24 h	PREBREATHE (min)	DCS RISK
≤180	unlimited	unlimited	unlimited	No	1%
≤200	unlimited	240	240	No	<5%
≤250	3	45	110	30	<5%
≤300	3	30	60	60	<10%
≤350	1	15	15	75	<10%

The Norwegian recommendations aim to keep cumulative DCS incidence below 10% to avoid severe cases of DCS. Pressure altitudes are given in flight level (FL). Duration is defined as the time between the start of decompression and the end of recompression. Decompression starts when cabin altitude reaches FL160 and recompression is completed when cabin altitude reaches FL100. Prebreathe must be completed prior to reaching FL160 and must be continuous. A 1-h ground level interval is required between each exposure. Prebreathe is not required between FL180 and FL 200, but 100% oxygen is required at all times above FL100.

35%, which we believe is unacceptable. We therefore conclude that the restrictions suggested in the NATO Standard to mitigate WMH do not provide a safe operational envelope. We recommend limiting the duration of exposures and allowing for repeated exposures of short duration while awaiting reliable data.

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