A Systematic Review and Meta-Analysis of Decompression Sickness in Altitude Physiological Training

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INTRODUCTION: A review of decompression sickness (DCS) cases associated with the NASA altitude physiological training (APT) program at the Johnson Space Center (JSC) motivated us to place our findings into the larger context of DCS prevalence from other APT centers.

METHODS: We reviewed JSC records from 1999 to 2016 and 14 publications from 1968 to 2004 about DCS prevalence in other APT programs. We performed a meta-analysis of 15 APT profiles (488 cases / 385,116 exposures). We used meta-regression to evaluate the relation between estimated exposures and probability of DCS in a test group, accounting for the heterogeneity between studies.

RESULTS: Our in-house review identified 6 Type I DCS (1 from an inside observer) and 1 Type II DCS. There were 6 cases in 9560 student hypobaric exposures from 3 NASA training flights; a student pooled prevalence rate of 0.44 cases / 1000 exposures compared to 1.44 cases / 1000 from 12 published APT profiles. The overall pooled DCS prevalence rate was 1.16 cases / 1000 exposures. There was substantial heterogeneity in DCS prevalence across studies. Denitrogenation time, exposure pressure, and exposure time were associated with probability of DCS in the meta-regression model.

CONCLUSIONS: While the overall DCS prevalence rate is relatively low, there is marked heterogeneity among profiles. The pooled DCS prevalence rate estimate for the NASA profiles was lower than the overall rate. Variability in APT profile DCS prevalence could be further explained given student level and additional test-level covariates.

KEYWORDS: variability in decompression sickness, hypobaric decompression sickness, hypoxia training, evolved gas, altitude chamber.

Conkin J, Sanders RW, Koslovsky MD, Wear ML, Kozminski AG, Abercromby AFJ. *A systematic review and meta-analysis of decompression sickness in altitude physiological training.* Aerosp Med Hum Perform. 2018; 89(11):941–951.

Aviation organizations need to indoctrinate new aviation personnel to the hazards of the aerospace environment, particularly the recognition and corrective response to hypoxia. Altitude physiological training (APT) is organization-specific and includes classroom instruction as well as practical hypoxia training, usually in a hypobaric chamber. Efficient APT must balance hypobaric hypoxia training time with limited denitrogenation (prebreathe, PB) time. One needs to ascend high enough in an altitude chamber to provide effective hypoxia training for students with a wide range of hypoxia and decompression sickness (DCS) susceptibility, but not so high as to invalidate the PB protection for DCS. APT is a hypobaric exposure with high DCS stress but of short duration, but long enough to recognize hypoxia symptoms and to experience other aspects of the aviators' environment. The limited exposure time and minimal physical activity of the students combined with appropriate PB for the desired hypoxic altitude should result in a safe protocol for most students. However, the literature is replete with descriptions of "odd," "unusual," and "unexpected" cases of DCS from APT.[9,21,32] For example, when training a large number of students the conditions that predispose one to DCS can be manifested.[10,25]

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This manuscript was received for review in April 2018. It was accepted for publication in August 2018.

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DOI: https://doi.org/10.3357/AMHP.5135.2018

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APT at various centers balances the reward of efficient training in hypoxia recognition, equipment familiarization, trapped gas expansion, rapid depressurization (RD), free-fall, and other benefits against the risks of barotitis media (middle ear block), DCS, and other adverse outcomes. It is in this dynamic and varied hypobaric exposure environment that we summarize and analyze results from APT profiles. Our process included: a) documenting recent NASA experience with APT; b) summarizing APT DCS experience from a systematic literature review to put the NASA training experience into context; c) performing a meta-analysis on DCS prevalence across APT profiles from NASA and other training environments; and d) exploring the relations between retrospectively collected test-level exposures on DCS event outcomes, accounting for the heterogeneity between studies. To our knowledge, this is the first effort to quantitatively describe DCS outcome from APT with a meta-analysis.

METHODS

NASA APT Profile Review

We first reviewed NASA APT records from 1999 to 2016 archived at the Johnson Space Center's Sonny Carter Neutral Buoyancy Laboratory. APT is provided to potential research subjects (students) and astronauts that experience or will experience aspects of the aerospace environment. The Type I profile was the initial student exposure, and some students returned after 5 yr for a refresher using the same profile. The Type II profile was the astronaut refresher as they often received their initial training elsewhere as many astronauts have a military aviation background. The Type II refresher for astronauts was discontinued in 2012 for economy of time and resources. All astronauts now receive (if needed) the Type I initial or the Type III refresher. The Type III refresher was instituted in 2012 as an alternative to the astronaut Type II refresher and an alternative to repeating the Type I profile as a refresher for students. Our focus is on students and astronauts participating in regimented, controlled APT profiles. The DCS outcomes from inside medical technicians, also designated as inside observers (IOs), at NASA and from our literature search are documented, but not considered further since IOs are not a controlled group. Our records identified a single case of DCS in 3612 exposures of medical technicians since 1999.

Expressing pressure as feet or meters of altitude above mean sea level is not ideal but is the standard convention used in publications we reference. A conversion from kilometers (km) of altitude to millimeters of mercury (mmHg) is through P_B (mmHg) = $760 \times \{288.15 / [288.15 - 6.5 \times \text{altitude (km)}]\}^{-5.25588}$, based on the U.S. Standard Atmosphere – 1976.[35] We report altitude in meters (m) with pressure as pounds per square inch absolute (psia) in parentheses given that the source publications reported hypobaric exposures in terms of distance above mean sea level, often in unit of feet. The conversion from psi to kilopascal is 1 psi = 6.89 kPa. We standardized on psia as unit of pressure for our analysis since a change in pressure is fundamental to DCS as opposed to a change in distance with ascent to altitude.

The Type I profile included a 30-min PB using either an MBU-5P or MBU-12P oral-nasal mask connected to a CRU 68A/A "flat-panel" demand regulator switched to 100% oxygen (O_2) and then ascent at 1524 m · min^{-1} to 6620 m (5.45 psia). A 15-min maximum hypoxia demonstration ensued where half the students removed masks and breathed air to note hypoxia symptoms. They then donned masks with 100% O_2 and the other half removed masks and breathed air to note hypoxia symptoms. Then they donned masks with 100% O_2. The CRU 68A/A regulators for all students were switched to diluter-demand to provide near-normoxic conditions as descent commenced at 914 m · min^{-1} to 6096 m (6.75 psia). The regulators were then switched back to 100% O_2 and descent continued at 610 m · min^{-1} to 3048 m (10.1 psia), at which time masks were removed to facilitate replacing 100% O_2 in the middle ear with air during the Valsalva maneuver to minimize posttest barotitis media as descent continued to site pressure. Students exited the main chamber, then groups of two students experienced a RD in the smaller transfer chamber (lock). Ascent at 305 m · min^{-1} to 305 m (14.1 psia) was followed by ascent at about 3505 m · min^{-1} to 3353 m (9.72 psia), at which time masks were donned with 100% O_2 and after about 2 min a descent was initiated at 610 m · min^{-1}. The minimum elapsed time for the Type I profile, including the RD, was 75 min from the start of PB. There were 8694 exposures from 1999 to 2016 resulting in 4 cases of DCS in students and 1 case in the medical technician. A female student had cutaneous symptoms, 2 males had left elbow symptoms, and 1 male had neurological symptoms (Type II DCS). The male medical technician had left knee symptoms.

The Type II profile also included a 30-min PB, but then ascent at 1524 m · min^{-1} to 10,668 m (3.46 psia), and immediate descent at 3048 m · min^{-1} to 8534 m (4.78 psia). The peak exposure to 10,668 m was to experience gut gas expansion. A 5-min hypoxia demonstration ensued at 8534 m where all removed masks and breathed air to note hypoxia symptoms. Then masks were donned and switched to diluter-demand to provide near-normoxic conditions as descent commenced at 1524 m · min^{-1} to 6096 m (6.75 psia). The regulators were then switched to 100% O_2 and descent continued at 1524 m · min^{-1} to 3048 m (10.1 psia), at which time masks were removed and everyone breathed air to site pressure. The minimum elapsed time for the Type II profile was 48 min from the start of PB. There were 718 exposures from 1999 to 2011 resulting in 1 case of DCS in a female who had left shoulder symptoms.

The Type III profile included a 29-min PB, ascent at 1524 m · min^{-1} to 2438 m (10.9 psia), after which masks were removed in preparation for a rapid ascent on air at 3048 m · min^{-1} to 7620 m (5.45 psia). Students were hypoxic for 1.7 min during ascent and then for 3.3 min at 7620 m (5 min total) to note hypoxia symptoms, then returned to 100% O_2 for 3 min. Total time from start of rapid ascent to start of descent did not exceed 8 min. Then the regulators were switched to diluter-demand to provide near-normoxic conditions as descent commenced at 1524 m · min^{-1} to 6096 m (6.75 psia). The regulators were then

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switched to 100% O_2 and descent continued at 1524 m · min^{-1} to 3048 m (10.1 psia), at which time masks were removed and everyone breathed air to site pressure. The minimum elapsed time for the Type III profile was 44 min from the start of PB. There were 148 exposures from 2012 to 2016 resulting in 1 case of DCS in a male student who had left arm symptoms.

Literature Review

We searched information sources including PubMed, Defense Technical Information Center, and Google Scholar using combinations of key words such as hypoxia, hypobaric chamber, physiological training, altitude, and hypobaric decompression sickness. We specifically sought publications that contained details about the hypobaric training profile and specific association of DCS outcomes with a hypobaric training profile. Publications that did not have these details were excluded from further consideration. For example, publications that summarized hypoxia training through the use of combined altitude and depleted oxygen or reduced oxygen breathing devices were excluded since DCS risk is eliminated by these methods. Fourteen English language publications from 1968 to 2004 met our selection criteria and were summarized into a table: U.S. Army,[27] Navy,[5,6,20,30] Air Force,[7,8,37,39] Federal Aviation Administration,[36] Canadian Armed Forces,[15] Australian Defense Force,[31] Jordan Armed Forces,[2] and Japan Air Self-Defense Force.[26]

Meta-Analysis

Confidence intervals (CI) for individual study prevalence rates were calculated using the Clopper-Pearson method.[11] We performed a meta-analysis using a random effects model to estimate the pooled DCS prevalence rate and 95% CI, applying a double arcsine transformation.[4] Since the probability of DCS ranges between 0 and 1, a double arcsine transformation preserves interpretation of the CI (i.e., produces CI between 0 and 1) and stabilizes variance estimates, as variance is underestimated at the boundaries.[4] Additionally, we performed subgroup analysis on the pooled prevalence of DCS for NASA versus other studies. Heterogeneity between studies was assessed with I^2 values.[22] I^2 is interpreted as the percentage of total variation across studies that is due to heterogeneity rather than chance and ranges from 0% (no heterogeneity) to 100% (strong heterogeneity). A measure of study heterogeneity is a check that the effects found in the individual studies are similar enough that a combined estimate will be a meaningful description of the set of studies. Publication bias was assessed using funnel plots and the null hypothesis of symmetric funnel plots was tested using the technique from Egger.[18] Note that all results are expressed in # DCS events / 1000 exposures.

For the meta-regression model, we took a hierarchical approach, as there are $i = 1,\ldots,n_j$ tests (level-1) that are nested with $j=1,\ldots,7$ studies (level-2). We used a generalized linear mixed model[29] to evaluate the relation between exposures, PB time in minutes including time for any ear and sinus check before ascent (PBTM), the peak altitude in psia attained (PKALT), the time in minutes at or above 7620 m (TM ≥ 25K), and the total exposure time in minutes from the start of ascent to the end of any RD event (EXPOTM), and DCS in a test group. The response variable was the presence or absence of any symptom diagnosed as DCS during or after the APT. We imposed a logit link function, $\eta_{ij} = log(\frac{\varphi_{ij}}{1-\varphi_{ij}})$, and a Binomial (m_{ij}, φ_{ij}) sampling model, where m_{ij} is the number of subjects, and φ_{ij} is the probability of DCS in the ith test group in the jth study. Under these assumptions the expected and variance of Y_{ij}, the number of DCS events are:

$$E\left[Y_{ij}\middle|\varphi_{ij}\right] = m_{ij}\varphi_{ij}$$

and

$$\mathrm{Var}\left[Y_{ij}\middle|\varphi_{ij}\right] = m_{ij}\varphi_{ij}\left(1-\varphi_{ij}\right).$$

Next, the log odds of DCS, η_{ij}, is potentially related to covariates $X_{1ij},\ldots,X_{pij}$, through the Level-1 structural model:

$$\eta_{ij} = \beta_{0j} + \beta_{1j}X_{1ij} + \ldots + \beta_{pj}X_{pij},$$

and the Level-2 structural model:

$$\beta_{0j} = \gamma_{00} + u_{0j},$$

$\beta_{pj} = \gamma_{p0}$, for $p>0$, where $u_{0j} \sim N(0,\tau_{00})$ and $\beta_{0j},\ldots,\beta_{pj}$ are the level-1 regression coefficients. Note that in this parameterization, β_{0j} is a random intercept term that accounts for the heterogeneity between studies. Full and reduced models were compared with Akaike Information Criterion (AIC).[1] The final model selected had the smallest AIC. *P*-values for regression coefficient significance were obtained using a parametric bootstrap test with 500 bootstrap samples. All analyses were performed in R®.[28]

We noticed during our literature review that Type I "pain-only" DCS symptoms were predominately distributed in the upper body (wrist, elbow, shoulder). This is contrary to our experience from our research protocols.[13,14] So, in addition to the meta-analysis, we also compared the distribution of Type I DCS symptoms from our combined NASA PB research data to selected APT results using Pearson's χ^2 to evaluate if this was more than coincidence. The selected APT results were from publications[5,6,37] where Type I DCS symptoms were clearly assigned to upper and lower body location.

RESULTS

Table I is a compilation of summary information extracted from 16 sources covering a period from 1959 to 2016. Fourteen are published sources (1968 through 2004) and two are technically not published but the data were documented by secondary sources (Bason et al.,[6] Rice et al.[30]). We could not determine counts of DCS associated with total APT exposures from two sources.[2,26] Table I includes our unpublished findings from

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Table I. DCS Prevalence Rates from Altitude Physiological Training (1959–2016).

STUDENTS						
SOURCE	**POPULATION**	**TIMEFRAME**	**APT PROFILE***	**# CASES/# STUDENTS**	**DCS CASES/1000**	**ADDITIONAL INFORMATION**
Smart[31]	Australia, RAAF	1989–2001	Type A PT	22/6129	3.60	Most students did Type A, B, and C PT in sequence with 24-h rest intervals.
Smart[31]	Australia, RAAF	1989–2001	Type B PT	12/3671	3.20	Most students did Type A, B, and C PT in sequence with 24-h rest intervals.
Smart[31]	Australia, RAAF	1989–2001	Type C PT	6/911	6.60	Most students did Type A, B, and C PT in sequence with 24-h rest intervals.
Valdez[36]	FAA, U.S.	1965–1975	Type A PT	0/3034	0.00	FAA - conservative PT.
Valdez[36]	FAA, U.S.	1965–1975	Type B PT	0/1725	0.00	FAA - conservative PT.
Ohrui[26]	Japan, military	1960–1998	Not Specified		0.50	Counts not available; only Type I DCS observed.
NASA unpublished	NASA JSC	1999–2016	Type I PT	4/8694	0.46	
NASA unpublished	NASA JSC	1999–2016	Type II PT	1/718	1.39	
NASA unpublished	NASA JSC	1999–2016	Type III PT	1/148	6.75	
Watson[37]	USAF	1965–1967	Type I PT	31/37,219	0.83	
Watson[37]	USAF	1965–1967	Type II PT	103/162,285	0.63	
Weien[39]	USAF	1979–1986	Not Specified	348/601,126	0.58	
Baumgartner[8]	USAF	1985–1987	Type I PT	32/25,806	1.24	
Baumgartner[8]	USAF	1985–1987	Type II PT	59/24,171	2.44	
Baumgartner[8]	USAF	1985–1987	Type III PT	15/11,414	1.31	
Baumgartner[8]	USAF	1985–1987	Type V PT	71/53,185	1.33	
Piwinski[27]	U.S. Army	1980–1985	25K PT	7/10,754	0.65	Used "standard" USAF PT.
Piwinski[27]	U.S. Army	1980–1985	35K PT	1/1200	0.83	Used "standard" USAF PT.
Piwinski[27]	U.S. Army	1980–1985	45K PT	0/642	0.00	Used "standard" USAF PT.
Bason[5]	U.S. Navy	1972–1975	Not Specified	22/73,561	0.29	
Furry[20]	U.S. Navy	1959–1968	Not Specified	266/252,564	1.05	
Furry unpublished	U.S. Navy	1976–1977	Not Specified	10/31,645	0.30	See Table IV in Bason,[6] 1991 and Table IV in Rice,[30] 2003.
Bason unpublished	U.S. Navy	1978–1981	Not Specified	39/47,380	0.80	See Table IV in Rice,[30] 2003.
Bason[6]	U.S. Navy	1981–1988	Not Specified	78/111,674	0.70	
Rice[30]	U.S. Navy	1993–2002	Type II PT	67/23,436	2.90	Documents unpublished data from Furry and Bason.
Rice[30]	U.S. Navy	1993–2002	Type IIA PT	13/7575	1.70	Documents unpublished data from Furry and Bason.
Bassett[7]	USAM	1968–1972	Combined Type I, II, III, and Pressure Suit PT	2/9056	0.22	Males
Bassett[7]	USAM	1968–1972	Combined Type I, II, III, and Pressure Suit PT	7/3190	2.19	Females
INSIDE OBSERVERS						
SOURCE	**POPULATION**	**TIMEFRAME**	**APT PROFILE**	**# CASES/# IOs**	**DCS CASES/1000**	**ADDITIONAL INFORMATION**
NASA unpublished	NASA, JSC	1999–2016	Type I, II, III PT	1/3612	0.27	
Weien[39]	USAF	1979–1986	Not Specified	81/139,584	0.58	
Baumgartner[8]	USAF	1985–1987	Type I PT	25/8156	3.06	
Baumgartner[8]	USAF	1985–1987	Type II PT	12/7639	1.57	
Baumgartner[8]	USAF	1985–1987	Type III PT	6/3607	1.66	

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Table I, *Continued.*

INSIDE OBSERVERS						
SOURCE	**POPULATION**	**TIMEFRAME**	**APT PROFILE**	**# CASES/# IOs**	**DCS CASES/1000**	**ADDITIONAL INFORMATION**
Baumgartner[8]	USAF	1985–1987	Type V PT	18/16,810	1.07	
Piwinski[27]	U.S. Army	1980–1985	25K PT	5/1654	3.02	Used "standard" USAF PT.
Piwinski[27]	U.S. Army	1980–1985	35K PT	4/180	22.20	Used "standard" USAF PT.
Piwinski[27]	U.S. Army	1980–1985	45K PT	3/115	26.10	Used "standard" USAF PT.
Bason[5]	U.S. Navy	1972–1975	Not Specified	57/14,959	3.88	
Furry[20]	U.S. Navy	1959–1968	Not Specified	35/60,000	0.60	
Furry unpublished	U.S. Navy	1976–1977	Not Specified	20/6470	3.10	See Table IV in Bason,[6] 1991 and Table IV in Rice,[30] 2003.
Bason unpublished	U.S. Navy	1978–1981	Not Specified	48/10,020	4.80	See Table IV in Rice,[30] 2003.
Bason[6]	U.S. Navy	1981–1988	Not Specified	62/25,022	2.50	
Rice[30]	U.S. Navy	1993–2002	Type II + PB	7/4658	1.50	Documents unpublished data from Furry and Bason.
Rice[30]	U.S. Navy	1993–2002	Type IIA PT	4/1248	3.20	Documents unpublished data from Furry and Bason.
COMBINED						
SOURCE	**POPULATION**	**TIMEFRAME**	**APT PROFILE**	**# CASES/# EXPOSURES**	**DCS CASES/1000**	**ADDITIONAL INFORMATION**
Crowell[15]	Canada, military	1977–1981	Combined Type I, II, III, IV PT	69/19,573	3.52	All Profiles Combined; Assume students but IO may be included.
Al-Wedyan[2]	Jordan, military	1986–1994	Not Specified; Alt chamber at 3000 ft.		0.00	Total population; Small sample, counts not available.
NASA unpublished	NASA JSC	1999–2016	Type I, II, III PT	7/13,172	0.53	All Profiles Combined; Combined students and IOs.
Bassett[7]	USAF	1968–1972	Combined Type I, II, III, and Pressure Suit PT	42/337,971	1.20	All Profiles Combined.
Weien[39]	USAF	1979–1986	Not Specified	429/740,710	0.58	Combined students and IOs.
Baumgartner[8]	USAF	1985–1987	Type I PT	57/33,962	1.67	Combined students and IOs.
Baumgartner[8]	USAF	1985–1987	Type II PT	71/31,810	2.23	Combined students and IOs.
Baumgartner[8]	USAF	1985–1987	Type III PT	21/15,021	1.40	Combined students and IOs.
Baumgartner[8]	USAF	1985–1987	Type V PT	89/69,995	1.27	Combined students and IOs.
Bassett[7]	USAF & USAM	1968–1972	Combined Type I, II, III, and Pressure Suit PT	51/350,217	1.40	All Profiles Combined.
Furry[20]	U.S. Navy	1959–1968	Not Specified	301/312,564	0.96	Combined students and IOs.
Furry unpublished	U.S. Navy	1976–1977	Not Specified	30/38,115	0.78	Combined students and IOs.
Bason unpublished	U.S. Navy	1978–1981	Not Specified	87/57,400	1.50	Combined students and IOs.
Bason[6]	U.S. Navy	1981–1988	Not Specified	140/136,696	1.00	
Rice[30]	U.S. Navy	1993–2002	Type IIA PT	17/8823	1.90	Combined students and IOs; Documents unpublished data from Furry and Bason.
Bassett[7]	USAM	1968–1972	Combined Type I, II, III, and Pressure Suit PT	9/12,246	0.73	All Profiles Combined.

* Same profile designation across sources does not mean same profile.

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1999 through 2016 for the NASA Type I, II, and III APT profiles.

The summary counts are shown for students, IOs, and the totals. There appear to be minimal overlaps in reporting results by two investigators from the same institution. Overlap seems evident in the U.S. Air Force data reported by Weien and Baumgartner[39] from 1979 to 1986 and data reported by Baumgartner and Weien[8] from 1985 to 1987. We accept that there may be minimal double counts in our table. There are also gaps of time where APT data from the U.S. Navy and Air Force were not published, so gaps exist where data were collected but were not available for analysis. There are no historical records for the number of students that repeated APT or participated in a refresher course. We focus on student outcomes but summarize outcomes for IOs, as this was the focus of several investigations. IOs often had a higher prevalence of DCS attributed to physical activity at altitude. In total, there were 1328 cases of DCS diagnosed in students in 1,870,511 exposures from a variety of APT profiles; a grand total prevalence rate of 0.71 cases / 1000 exposures. There were 388 cases of DCS diagnosed in IOs in 303,734 exposures from a variety of APT profiles; a grand total rate of 1.27 cases / 1000 exposures. IOs are always more physically active than students during the training. Students had a DCS rate that ranged from 0 to 6.6 cases / 1000 exposures compared to 0.6 to 4.8 cases / 1000 exposures for IOs. The overall rate for students was 0.71 cases / 1000 exposures compared to 1.27 / 1000 for IOs. Also of note is a 10-fold increase in DCS prevalence for female students compared to male counterparts reported by Bassett[7] for a small sample, which reduced to a 2.3-fold increase reported in a larger sample by Baumgartner and Weien.[8] Additional information about gender and DCS is available from several sources.[12,23,35]

Table II is a subset of student information from Table I where details about 15 APT profiles were published. There was no duplication of data in this subset. Note that the same designation for the APT profile for different centers in Tables I and II does not necessarily mean the same profile. The details in Table II allow for a level of analysis not possible with just the aggregate of count data in Table I. The data from Crowell[15] were not parsed among the four APT profiles, so simple, unweighted means of the explanatory variables are used in the analysis. The data from Smart et al.[31] are unique in that most students were sequentially exposed to Type A, B, and C profiles separated by 24 h of rest. We include only the data for the Type A profile in the analysis to eliminate any bias from sequential exposures. The 15 profiles contributed 488 cases of DCS in 385,116 exposures.

Meta-Analysis Results

Overall the pooled prevalence of DCS across 15 studies was 1.16 / 1000 exposures (95% CI = 0.66 - 1.76), see **Fig. 1**. For the 3 NASA subgroups, the pooled DCS prevalence was 0.44 / 1000 (95% CI = 0.00 - 3.53) exposures compared to the other 12 at 1.44 (95% CI = 0.90 - 2.10). We found highly significant ($P < 0.01$, $I^2 = 93\%$) and strong heterogeneity across studies. However, the heterogeneity across NASA studies was nonsignificant ($P = 0.10$, $I^2 = 56\%$). There was no evidence of publication bias in the funnel plot, see **Fig. 2**, and we failed to reject the null hypothesis that the funnel plot was symmetric at the 0.05 α-level with P-value = 0.15.

The far-right column of Table II shows the predicted probability of DCS (P[DCS]) expressed as cases / 1000 exposures $\pm$ the 95% CI from the meta-regression. P(DCS) is based on regression intercepts for each study (β_{0j}) and 3 of the 4 test-level covariates: PBTM, PKALT, and EXPOTM. Time spent at or above 7620 m (TM $\geq$ 25K) did not provide significant information to the regression. The NASA Type III protocol was a potential outlier in the meta-regression model as 1 DCS event was observed in only 148 students. However, there was no evidence of over-dispersion in the fitted model when this protocol was removed and its exclusion had marginal effects on the regression coefficients. **Fig. 3** is a plot of data from Table II; the predicted DCS prevalence rate in 15 samples from the meta-regression model versus the observed rate. Overall, the model fit the data well as the plot follows the identity line, with the exception of a small-sample profile that observed only 1 case of DCS. To investigate the model's sensitivity to this outlier, we reran the model without the outlier and observed relatively small effects on parameter estimates.

The results of the meta-regression are presented in **Table III**. Here a single regression intercept (β_0) applies to all 15 studies. We observed a negative relation between DCS and PBTM and PKALT and a positive relation between DCS and EXPOTM. The exponent of the regression coefficients estimated in the meta-regression model are interpreted as odds ratios. We would expect for a 1-min increase in PBTM and 1-psia increase in PKALT about a 3% [$1\text{-}\exp^{(-0.032)}$)] and 24% decrease in the odds of DCS for the typical study ($u_{0j} = 0$), holding all else constant. We would expect for a 15-min increase in PBTM a 38% [$1\text{-}\exp^{(-0.032 \times 15)}$)] decrease in the odds of DCS for the typical study ($u_{0j} = 0$), holding all else constant. Additionally, we would expect for a 1-min increase in EXPOTM a 2.5% increase in the odds of DCS for the typical study ($u_{0j} = 0$), holding all else constant.

Table IV shows the number of upper and lower body Type I symptoms from APT and the number from a large sample of NASA PB research results. Upper body locations for symptoms include finger, hand, wrist, forearm, arm, elbow, and shoulder. Lower body locations include toe, foot, heel, ankle, shin, leg, calve, knee, thigh, and hip. The upper and lower body prevalence ratios in columns 4 and 5 summarize the difference in Type I symptom distributions between APT and 30 yr of NASA PB research experience. For example, the upper body prevalence ratio for the Watson[37] and NASA data[13,14] is 6.90, computed as [47 / (47 + 13)] / [22 / (22 + 172)]. We used Pearson's χ^2 to evaluate if APT had a greater prevalence of upper body symptoms relative to the NASA PB research data. We compared in a 2 $\times$ 2 matrix the combined Bason et al.[5,6] 136 upper body counts and 87 lower body counts with the NASA 22 upper body counts and 172 lower body counts. We combined the Bason data to approximately match the sample size of the NASA data. The computed χ^2 was 108.6 with a P-value < 0.01. It appears

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Table II. Subset of APT Profiles and Computed P(DCS).

SOURCE[ref] PROFILE*	POPULATION	DCS	EXPO	CASE/1000	PBTM (min)	PKALT (psia)	TM ≥ 25K (min)	EXPOTM (min)	P(DCS)** CASE/1000 ± 95% CI
Crowell[15]	Canada								
I					35.0	2.36	22.0	38.0	
II					5.0	5.45	20.4	43.0	
III					35.0	2.36	53.9	77.4	
IV					35.0	4.36	21.6	45.4	
Crowell I, II, III, IV mean	Canada	69	19,573	3.52	27.5	3.63	29.5	51.0	3.50 ± 1.17–10.4
Valdez[36]	FAA, U.S.								
A		0	3034	0	5.0	4.57	10.4	42.2	0.27 ± 0.09–0.83
B		0	1725	0	8.5	5.45	10.0	28.5	0.13 ± 0.04–0.41
NASA	NASA JSC								
I		4	8694	0.46	30.0	5.45	15.0	45.0	0.65 ± 0.20–2.0
II		1	718	1.39	30.0	3.46	8.5	18.0	0.56 ± 0.17–1.8
III		1	148	6.75	30.0	5.45	6.3	14.0	0.29 ± 0.07–1.1
Watson[37]	USAF								
I		31	37,219	0.83	23.0	3.46	24.5	51.0	0.71 ± 0.23–2.1
II		103	162,285	0.63	23.0	2.35	18.5	36.0	0.66 ± 0.21–2.0
Baumgartner[8]	USAF								
I		32	25,806	1.24	30.0	3.46	15.0	60.0	1.46 ± 0.46–4.6
II		59	24,171	2.44	30.0	2.35	10.8	64.0	2.20 ± 0.63–7.6
III		15	11,414	1.31	30.0	3.46	7.9	53.1	1.22 ± 0.40–3.7
V		71	53,239	1.33	30.0	3.46	7.7	57.0	1.35 ± 0.43–4.2
Rice[30]	U.S. Navy								
II		67	23,436	2.90	0	5.45	4.0	17.6	2.81 ± 0.86–9.1
IIA		13	7575	1.70	38.0	3.46	6.2	25.6	1.77 ± 0.55–5.7
Smart[31] A	Australia	22	6129	3.58	30.0	5.45	6.8	16.0	3.40 ± 0.91–12.5

* Same profile designation across sources does not mean same profile.

** P(DCS) based on regression intercept for each study (β_{0j}).

Abbreviations: PBTM (min) = prebreathe time; PKALT (psia) = peak altitude; TM ≥ 25K (min) = time above 25,000 ft altitude (7620 m, 5.45 psia); EXPOTM (min) = total exposure time; P(DCS) = probability of DCS event.

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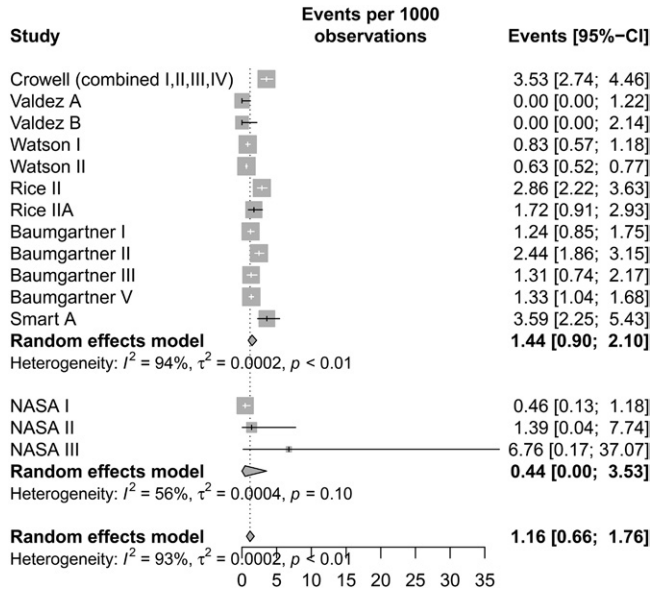

Fig. 1. Forrest plot for the individual and pooled DCS prevalence in terms of # DCS / 1000 exposures. Pooled prevalences are then grouped by NASA or other profiles.

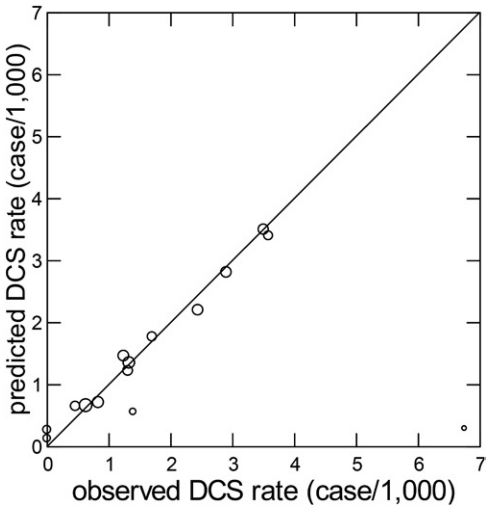

Fig. 3. The observed DCS prevalence rate in 15 samples compared to the predicted rate from the meta-regression. The size of each circle is proportional to group size. All but 1 small-sample outlier (far lower right) fall near the identity line. The regression evaluated 488 cases of DCS in students during APT involving 385,116 exposures.

from both the data in Table IV and our χ^2 test that there is evidence for a different distribution of Type I DCS between APT and research protocols that included extensive denitrogenation before long exposures at reduced pressures.

DISCUSSION

We performed a comprehensive review and meta-analysis across APT profiles. This study found a pooled DCS prevalence rate of 1.16 / 1000 exposures (95% CI = 0.66 - 1.76). The pooled-DCS rate from the 3 NASA profiles was 0.44 / 1000 (95% CI = 0.00 - 3.53) exposures compared to 1.44 / 1000 (95% CI = 0.90 - 2.10) exposures for the 12 other profiles. While there is strong heterogeneity across all of the studies in this meta-analysis, there was no statistically significant heterogeneity across NASA studies. The strong heterogeneity across profiles may be due to the wide variability in human response to short-duration but high DCS stress due to no or minimum denitrogenation as well as unmeasured test-level covariates.

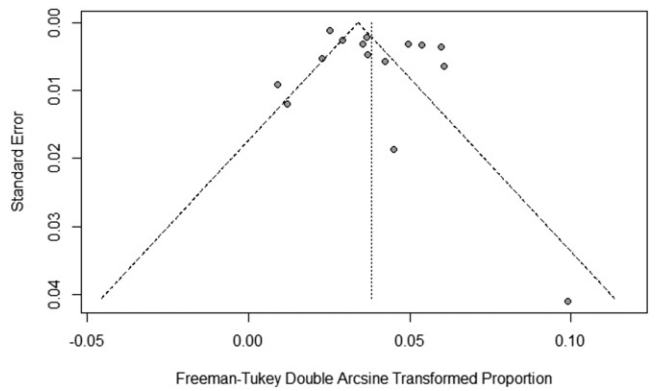

Fig. 2. Funnel plot of APT profile prevalence rate standard error versus point estimate, using a double arcsine transformation for proportions. Fifteen results from seven publications are included on the figure.

Each training organization tailors the APT program to suit their needs. Early APT had no PB requirement except what was provided by the 5- to 10-min ear and sinus check while breathing 100% O_2. Most now provide a minimum of 30 min, with or without the ear and sinus check. Those that included an ear and sinus check ascended to 1524 m (12.2 psia) or 2134 m (11.3 psia) before the training flight, some provided a RD at the conclusion of the hypoxia training, on the order of 12,000 m · min^{-1}. All students experienced some degree of hypobaric hypoxia at 5486 m (7.34 psia), 6096 m (6.75 psia), 8534 m (4.78 psia), 9144 m (4.36 psia), or 10,668 m (3.46 psia), but mostly at 7620 m (5.45 psia). A few profiles ascended briefly to 13,106 m (2.35 psia) or 13,716 m (2.14 psia) for students to experience positive pressure O_2 breathing. Some APT profiles included a rapid descent (free-fall) between 3048 and 5486 m · min^{-1} and then initiated the hypoxia training. Ascent rates, excluding RD, varied between 914 and 1524 m · min^{-1}. Descent rates, excluding free-fall, varied from 610 to 1524 m · min^{-1}, slower at the conclusion of training to minimize barotitis media. It was not stated in any publication if students switched from 100% O_2 to air during recompression past 3048 m (10.1 psia) at the conclusion of training to minimize delayed barotitis media due to O_2 reabsorption in the middle ear, but this seems to be a common practice based on conversation with our medical technicians. Time at altitude varied depending on the hypoxia altitude and the number of students needing time to experience hypoxia. All students were physically inactive (minimal lower-body movement) during the training, with the exception of writing tasks to document symptoms. Finally, symptom(s) onset times ranged from minutes into the hypobaric exposure to days after the exposure.

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Table III. Regression Parameter Estimates from Meta-Regression.

PARAMETER	ODDS RATIO	EFFECT	STD. ERROR	*P* - VALUE
β_0, Intercept*	—	−5.819	0.890	<0.001
β_1, prebreathe time PBTM (min)	0.968	−0.032	0.011	0.004
β_2, peak altitude PKALT (psia)	0.760	−0.274	0.117	0.038
β_3, total exposure time EXPOTM (min)	1.025	0.025	0.012	0.042

* Regression intercept for all studies.

We accept that bubbles are the initial tissue insult and that the resulting multitude of signs and symptoms are the results of both the initial mechanical insult and the cascade of subsequent biochemical insults in response to tissue damage, for example, tissue response to hypoxemia from embolic agents. Permissible ascent limits for divers and aviators are dictated by inert gas supersaturation and stabilized micronuclei. Heterogeneous and not homogeneous nucleation physics is the current approach to understand gas phase separation in living systems.[38] Stabilized micronuclei are irrelevant to venous gas emboli (VGE) and DCS outcomes if no supersaturation exists, while even minimal supersaturation may be sufficient to produce VGE and DCS if many large micronuclei are available to transform and grow into bubbles. A variety of mechanisms to account for a stable distribution of micronuclei sizes have been proposed: crevice models,[34] caveolae structures, and even the presence of microparticles in the blood.[33] Perhaps those few with DCS from APT have a propensity for large stabilized micronuclei that quickly transform into bubbles during the short interval of nitrogen (N_2) supersaturation. Denitrogenation time before ascent must counter the hypoxia training time at altitude so as to minimize the risk of DCS. Except for rare cases of DCS, a working balance is achieved and each training center decides if their training is "safe enough." How safe depends on many factors, such as the organizations' sensitivity to DCS incidents in training activities and the ability to provide quick and effective treatment for symptoms, among others.

Eatock et al.[16,17] is the only investigator identified in our systematic review to measure for VGE during APT. He detected VGE in the pulmonary artery using a 1983 Doppler ultrasound bubble detector. So VGE do have the time to form and travel with venous blood to the lungs during even short, high altitude exposure after minimal PB, analogous to the instant appearance of bubbles when a carbonated beverage is opened. However, the spectrum of signs and symptoms and symptom onset time from within minutes to days of APT is evidence for multiple pathophysiological pathways following an initial insult from evolved gas. For example, a hypoxia-induced increase in shunt fraction (venous admixture) in a few students could be a mechanism to transport bubbles from the venous blood into the arterial blood without invoking a patent foramen ovale.[24] Alterations in portions of the large endothelial vascular surface area as a tissue response to hypoxemia from embolic agents or from mechanical damage by bubbles could be the cause of some symptoms. The response to evolved gas must be multifactorial as no single pathophysiology describes the range of signs and symptoms, nor the few cases of DCS seen in APT. It has been 70 yr since the conclusion of World War II, and extensive APT and research into DCS occurred during and following this period. And yet a definitive pathophysiological understanding of pulmonary DCS (chokes) is still elusive.[3,19] The rare occurrence of chokes during APT suggests to us that the insult must be local, within the lung, and not necessarily a response by the lung to a large embolic load from the venous blood. The time allowed for APT seems too short to allow for the latter mechanism.

There is a brief hypoxia component to all APT profiles that is absent from the NASA PB research profiles,[13,14] and all profiles included upper body activity. A reason for the difference in upper and lower-body distributions of Type I symptoms may be linked to the brief hypoxia experienced during APT, but a mechanism is elusive. The NASA research protocols (not the NASA APT profiles) provide lengthy PB and long exposure time to reduced pressure where subjects exercise the upper body, as is done in a space suit, and yet Type I DCS symptoms are primarily from the lower body. In the APT protocols the minimal PB would leave the upper body supersaturated with N_2 such that evolved gas might appear earlier in the upper body than the lower body. This might account for the prevalence of symptoms from the upper body in APT. Since this was a serendipitous observation, caution is warranted about our conclusion. Future reports about DCS in APT should always document the anatomical location of symptoms.

In our meta-regression model, we identified three test-level covariates that were associated with DCS. We found that an increase in exposure pressure, decrease in total exposure time, and a longer PB are expected to decrease DCS prevalence. With a 15-min increase in PB time, we would expect a reduction in the odds of DCS by about 38% [$1 - \exp^{(-0.032 \times 15)}$] for the typical test profile, holding all else constant. The estimated prevalence rate for the NASA Type I APT profile using the observed covariate values was 0.65 / 1000 exposures (see Table II). With an increase in PB time from 30 to 45 min our meta-regression results in Table III suggest that the prevalence rate would reduce to 0.40 / 1000 exposures. However, it is important to note that our model was built for explanation and is not validated for prediction. The results of this meta-analysis could be used to help design studies investigating the relation between exposure pressure,

Table IV. Upper vs. Lower Body Prevalence Ratio for Type I DCS in APT and NASA Research.

SOURCE[ref]	UPPER BODY PREVALENCE RATE	LOWER BODY PREVALENCE RATE	APT / NASA UPPER BODY	APT / NASA LOWER BODY
NASA[13,14] (1983–2016)	0.113 (22/194)	0.887 (172/194)	—	—
Watson[37] (1968)	0.783 (47/60)	0.217 (13/60)	6.90	0.24
Bason[5] (1976)	0.543 (50/92)	0.457 (42/92)	4.76	0.51
Bason[6] (1991)	0.656 (86/131)	0.344 (45/131)	5.79	0.38

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total exposure time, and PB time and the risk of DCS during APT.

We quantitatively evaluated the as-described nominal training profiles. The as-executed actual profiles likely varied from class-to-class based on alterations due to student symptoms. For example, a student with an ear block during final descent would extend the depressurization time for all the students, and we did not have this level of detail for each student. Publications never clearly state whether students breathed air during recompression past 3048 m; we assumed 100% O_2 unless the publication stated otherwise. The publications did not state the ambient pressure at the location of the altitude training chamber, with the exception of al-Wedyna et al.[2] The altitude of their chamber was 914 m (13.1 psia). The data we used came from different training centers at different times. DCS was diagnosed by different physicians. It is not reasonable to assume that a standard methodology was applied to diagnose DCS across different training centers, using different physicians, and across 50 yr of APT. Another unreasonable assumption is that there was no bias in students to report symptoms. Students at particular centers and at particular times in history were likely biased. IOs were likely biased not to report symptoms, so the accumulated data for IOs likely under-represents their true prevalence. Additionally, the total counts of DCS included both Type I DCS and Type II DCS as the source publication did not always differentiate the counts as to DCS classification. Multiple symptoms in a student were necessarily counted as one case of DCS. Evaluating total symptoms was not possible since multiple symptoms per student were rarely documented in the literature. Finally, it is important to note that with only three observed NASA studies, it may be statistically difficult to detect heterogeneity across the studies. Indeed the observed prevalence rates for the 3 NASA studies were 0.46 (Type I), 1.39 (Type II), and 6.76 (Type III) per 1000 observations. However, for the Type III study, only 148 observations have actually been collected. Thus, its relatively large prevalence rate may be the attributed to instability in its estimate due to sample size and extrapolating the results from 148 to 1000 observations. While this study had limited access to strictly profile level factors from historical records, future investigations would benefit from studying individual, as well as profile, level factors due to the known heterogeneity in individuals' DCS responses to hypobaric exposures. Better record keeping for APT and a willingness to publish and share records with student-level details would significantly advance our understanding of DCS.

CONCLUSIONS

1. Pooled DCS prevalence rate in the 3 NASA APT profiles was 0.44 cases / 1000 exposures (0.0–3.5, 95% CI) compared to 1.44 cases / 1000 exposures (0.9–2.1) in 12 other pooled profiles. The large uncertainties for these estimates invalidate any claim of a true difference in prevalence rates; the NASA prevalence rate does not fall within the CI for the literature samples.
2. There is little heterogeneity among the NASA profiles but there was heterogeneity across all profiles. DCS variability between APT profiles could potentially be explained further given student-level covariates and additional test-level covariates.
3. From the meta-regression, longer denitrogenation time, greater exposure pressure, and shorter exposure time were associated with a decrease in the risk of DCS.
4. There was about a fivefold increase in prevalence for upper body Type I symptoms for APT as described in the literature compared to 30 yr of NASA PB research results.

ACKNOWLEDGMENTS

We thank Randell Woodard for technical support in compiling the APT records from 1999 to 2016. This work was made possible through the Human Health and Performance Contract (NNJ15HK11B) between the National Aeronautics and Space Administration and KBRwyle. Funding for this research was provided by the NASA Human Research Program. Conclusions are those of the authors and are not necessarily endorsed by the National Aeronautics and Space Administration.

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