Decompression Illness Medically Reported by Hyperbaric Treatment Facilities: Cluster Analysis of 1929 Cases

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Introduction: The term decompression illness (DCI) describes maladies resulting from inadequate decompression, but there is little consensus concerning clinically useful DCI subclasses. Our aim was to explore an objective DCI classification using multivariate statistics to assess naturally associated clusters of DCI manifestations. We also evaluated their mapping onto other DCI classifications and investigated the association with therapeutic outcome. ***Methods:*** We defined the optimal number of clusters using "two-step" cluster analysis and Bayesian information criterion with confirmation by hierarchical clustering with squared Euclidian distances and Ward's method. The data were 1929 DCI cases reported by hyperbaric chambers to the Divers Alert Network (DAN America) from 1999–2003. ***Results:*** Four robust and highly significant clusters of DCI manifestations were demonstrated containing 300, 741, 333, and 555 patients. Each cluster had characteristic manifestations. Cluster 1 was effectively pain only. For Cluster 2, characteristic manifestations included numbness, paresthesia, and decreased skin sensitivity; for Cluster 3, malaise, paralysis, muscular weakness, and bladder-bowel dysfunction; and for Cluster 4, hearing loss, localized skin swelling, tinnitus, skin rash and mottling, confusion, dyspnea/chokes, muscular problems, vision problems, altered consciousness, headache, vertigo, nausea, fatigue, dizziness, and abnormal sensations. ***Discussion:*** Internal reliability was confirmed by arbitrarily dividing the dataset into two parts and repeating the analysis. The clusters mapped poorly onto traditional DCI categories (AGE, Type I DCS, Type II DCS), but more specifically onto the Perceived Severity Index (PSI). All three classification methods (DCI, Cluster, PSI) predicted complete relief of manifestations equally well. We conclude that cluster analysis is an objective method for classifying DCI manifestations independent of clinical judgment.

Keywords: multivariate statistics, decompression sickness, signs and symptoms, diving.

THE TERM "DECOMPRESSION illness" (DCI) has historically been used to refer to any medical disorder, illness, or injury arising as a result of decompression from higher to lower ambient pressure. This includes decompression sickness (DCS) related to gas freed from solution in tissues during decompression and to arterial gas embolism (AGE) caused by penetration of alveolar gas into the circulation. Free gas in tissues and the circulation may affect a variety of organs and functions, often at the same time, resulting in complex presentations from mild to severe and often not specific for the cause of injury or reliable predictors of evolution.

There have been many attempts to classify DCI for facilitating diagnosis and treatment decisions. The classification into AGE, Type I DCS, and Type II DCS (11,14) is most widely used, but the distinction between these categories is not always consistent (10). Type I DCS is most often described as limb or joint pain, skin itch, rash, or localized swelling. Type I DCS does not include neurological manifestations (even subjective symptoms) and is generally considered less severe and of better prognosis than Type II DCS. The later includes neurological, vestibular, and cardiopulmonary manifestations (14). The differential diagnosis of AGE and DCS types was used by the U.S. Navy as a principal guide to treatment modalities. However, attempting differential diagnosis in the field between DCS and AGE has been found difficult and unnecessary since treatment for both AGE and DCS is recompression. Thus, the use of the term "DCI" that encompasses both AGE and DCS is encouraged for clinical purposes (7), although some countries still prefer the differentiation and suggest different treatment protocols for AGE and DCS (12). Other classification systems found in the literature also motivated our search for naturally associated manifestations. These systems included three categories (mild, moderate, and severe) (4), seven categories (limb pain, neurological, vestibular, cardiopulmonary, cutaneous, lymphatic, and constitutional) with different treatment protocols advised for each category (3), and six hierarchical categories (serious neurological, cardiopulmonary, mild neurological, pain, lymphatic or skin, and constitutional or nonspecific) known as the Perceived Severity Index (PSI) (16).

The application of statistical classification techniques to the medical field is relatively recent and infrequently

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applied to DCI classification, although a study using principal component analysis to investigate symptom groups corresponding to traditional DCI classifications (AGE, Type I DCS, and Type II DCS) found poor correlation (8). Cluster analysis is a multivariate statistical procedure that attempts to organize data into naturally occurring groups (1). It is used mainly for empirical grouping of patients by disease manifestations, but occasionally by observed frequencies (9). Previous hierarchical cluster analysis using squared Euclidian distances and Ward's Method for DCI manifestations assigned cases to three clusters, but the sample size was too small for statistical significance (13). The objective of the present study was to investigate the existence of natural groups of DCI manifestations. These were compared to the other classification systems and evaluated for association with therapeutic outcome.

METHODS

DCI data were retrieved from the Diving Injury Database maintained by the Divers Alert Network in America (DAN America) and based on reports provided by participating hyperbaric facilities using a standardized Diving Incident Report Form (17). Up to 200 hyperbaric facilities submitted data, but most cases came from 80 chambers. The form provided manifestation reports and diagnoses by the treating physicians in the categories Type I DCS, Type II DCS, and AGE. Discharge outcomes after therapy were included as complete or incomplete recovery. Cases were retrospectively assigned to one of six hierarchical PSI categories defined as: 1) serious neurological, 2) cardiopulmonary, 3) mild neurological, 4) pain, 5) lymphatic or skin, and 6) constitutional or nonspecific (16). The study was approved by Institutional Review Board of Duke University Medical Center for the use of de-identified data.

There were 1929 de-identified DCI cases from 1999 to 2003, including 1368 male and 561 female divers. The average age was 38 yr with a range of 13 to 73. As listed in **Table I**, 25 manifestations were reported. These may have been caused by decompression and were interpreted as DCI.

Cluster analysis is the generic name for a wide variety of procedures that can be used to create a classification. Clustering techniques may differ from each other in methods used to calculate "distances" or similarity measures between subjects and to distribute the subjects into groups. In this study, we applied the two-step clustering and hierarchical clustering with squared Euclidian distances and Ward's method to classify DCI patients. Analyses were made using the Statistical Package for Social Sciences (SPSS 13.0, SPSS Inc., Chicago, IL).

Two-Step Clustering

The two-step cluster analysis involves pre-cluster and cluster steps and has proved to be effective for very large datasets (5,6). The goal of pre-clustering is to reduce the size of the matrix that contains log-likelihood distances between all possible pairs of cases. Pre-clusters are just clusters of the original cases that are used in place of the raw data in hierarchical clustering. When pre-clustering is complete, all cases in the same pre-cluster are treated as a single entity. The size of the distance matrix is no longer dependent on the number of cases but the number of pre-clusters.

TABLE I. FREQUENCIES AND PERCENTAGES OF SYMPTOMS IN CLUSTERS.

		Cluster 1	Cluster 2	Cluster 3	Cluster 4		
Manifestation	**Total**	**Freq. (%)**	**Freq. (%)**	**Freq. (%)**	**Freq. (%)**	**Chi-square**	***P*-value**
Numbness	1003	0 (0)	690 (69)	201 (20)	112 (11)	1061.36	< 0.0001
Pain	935	300 (32)	337 (36)	137 (15)	161 (17)	412.91	< 0.0001
Paresthesia	740	0 (0)	555 (75)	161 (22)	24 (3)	891.03	< 0.0001
Malaise	306	0 (0)	0 (0)	301 (98)	5 (2)	1675.16	< 0.0001
Muscular Weakness	258	2 (1)	0 (0)	256 (99)	0 (0)	1400.93	< 0.0001
Sensitive Skin	248	0 (0)	140 (56)	79 (32)	29 (12)	132.31	< 0.0001
Fatigue	195	0 (0)	40 (21)	37 (19)	118 (61)	128.17	< 0.0001
Dizziness	168	0 (0)	35 (21)	35 (21)	98 (58)	100.68	< 0.0001
Headache	157	0 (0)	28 (18)	25 (16)	104 (66)	129	< 0.0001
Confusion	142	0 (0)	22 (15)	42 (30)	78 (55)	94.72	< 0.0001
Paralysis	123	0 (0)	7 (6)	113 (92)	3 (2)	512.33	< 0.0001
Skin rash & mottling	122	0 (0)	18 (15)	21 (17)	83 (68)	109.01	< 0.0001
Nausea	96	0 (0)	22 (23)	13 (14)	61 (64)	65.29	< 0.0001
Dyspnea/chokes	92	0 (0)	10 (11)	32 (35)	50 (54)	73.25	< 0.0001
Incoordination	60	0 (0)	15 (25)	23 (38)	22 (37)	29.8	< 0.0001
Vision problems	53	0 (0)	10 (19)	16 (30)	27 (51)	28.48	< 0.0001
Muscular problems	52	0 (0)	12 (23)	13 (25)	27 (52)	23.39	< 0.0001
Vertigo	47	0 (0)	7 (15)	10 (21)	30 (64)	35.46	< 0.0001
Altered consciousness	43	0 (0)	2 (5)	12 (28)	29 (67)	45.64	< 0.0001
Abnormal sensations	37	0 (0)	7 (19)	11 (30)	19 (51)	19.68	0.0002
Bladder/bowel trouble	36	0 (0)	1 (3)	35 (97)	0 (0)	164.25	< 0.0001
Local skin swelling	22	0 (0)	4 (18)	1 (5)	17 (77)	26.11	< 0.0001
Hearing loss	16	0 (0)	0 (0)	2 (13)	14 (88)	28.26	< 0.0001
Cardiovascular signs	4	0 (0)	1 (25)	2 (50)	1 (25)	3.32	0.3450
Tinnitus	4	0 (0)	1 (25)	0 (0)	3 (75)	4.48	0.2140

In the first step of the analysis, the observations were pre-clustered using log-likelihood distances, creating a modified Cluster Feature Tree (19). The resulting subclusters were further grouped in the second step by comparing their distances. The distance D(j,s) between two clusters j and s is defined as the decrease in log-likelihood due to merging of the clusters:

$$D(j,s) = \xi_j + \xi_s - \xi_{\langle j,s \rangle} \qquad \text{Eq. 1}$$

where:

$$\xi_j = -N_j \sum_{k=1}^{K} \hat{E}_{j,k} \quad \text{and} \quad \hat{E}_{j,k} = -\sum_{l=1}^{L_k} \frac{N_{jkl}}{N_j} \log \frac{N_{jkl}}{N_j}$$

K is the total number of variables used, L_k is the number of levels for the kth variable, N_j is the number of observations in cluster j, N_{jkl} is the number of observations in cluster j whose kth categorical variable takes the lth level and (j,s) represents the cluster formed by merging cluster j and s.

The Bayesian Information Criterion (BIC) developed by Bacher et al. (2) suggests a two-phase estimator in order to determine the optimal number of clusters. For J clusters, we have:

$$\mathrm{BIC}(J) = -2\sum_{j=1}^{J} \xi_j + m_J \log(N) \qquad \text{Eq. 2}$$

where: $m_J = J\sum_{k=1}^{K}(L_k - 1)$ and N is the total number of observations. In the first step, BICs for each number of clusters within a specified range are calculated to find an initial estimate for the number of clusters. The second step refines the initial estimate by finding the greatest change in distance between the two closest clusters in each clustering stage. The optimum number of clusters yields the relatively low BIC value and relatively high distance ratio.

Hierarchical Clustering with Ward's Method

An agglomerative hierarchical cluster analysis with squared Euclidian distances and Ward's method (18) was also applied to the DCI data in order to compare the results with two-step clustering. In this method, a proximity matrix is built in order to list the distances between all the cases. The squared Euclidian distance between two n dimensional variables p and q were calculated as follows:

$$r^2 = \sum_{i=1}^{n} \left(p_i - q_i\right)^2 \qquad \text{Eq. 3}$$

With binary variables $(p_i - q_i) = 0$ when $p_i = q_i$, and $(p_i - q_i) = 1$ when $p_i \neq q_i$.

Ward's method is an agglomerative procedure, which began with a cluster number equal to the number of cases. For each cluster, the means of all variables, then the squared Euclidian distances between cluster means, were calculated and clusters with means closest to each other were merged. This procedure can be run until all cases are merged in the same group if the number of clusters is not specified. In our study, the optimal number of clusters was determined by two-step clustering to be four. The internal reliability of the method was tested by dividing the dataset into two arbitrary groups and repeating the procedure for each group.

RESULTS

Numbness and pain were the most frequent manifestations and tinnitus and cardiovascular problems were least common (Table I). The two-step clustering method yielded an optimum number of four clusters with a BIC value of 18.021 and a distance ratio of 1.58. The manifestation frequencies within each cluster are shown in Table I. There were 300, 741, 333, and 555 patients in Clusters 1, 2, 3, and 4, respectively. The distribution of each manifestation as a percentage of the total occurrence also appears in Table I in parentheses next to the frequencies. The Chi-square scores and *P*-values were highly significant except for cardiovascular signs and tinnitus, which were rare. Hierarchical clustering with Ward's Method and squared Euclidian distances yielded similar results as two-step clustering: 309, 575, 325, and 720 patients in Clusters 1, 2, 3, and 4, respectively. The correlation between the results of the two methods was 0.97, showing that hierarchical clustering with Ward's method confirmed the results of two-step clustering.

Two-step clustering was the method of choice as it provided a built-in procedure, the BIC, to determine the optimum number of clusters. Ward's method was applied for confirmation. Although there were slight differences in the number of patients in each cluster, the two methods yielded practically the same results and the following discussion was based on the two-step results.

To test the internal reliability of the clusters, we divided the dataset in two parts and applied the two-step clustering separately to each part. The first part consisted of cases 1-966 and the second part of cases 967-1929. The correlation between parts was 0.97. The correlations between the parts and the entire dataset were 0.98 and 0.99, respectively, indicating high internal reliability.

Manifestations characteristic of each cluster were revealed by inspection of the manifestation percentages in Table I. Cluster 1 was characterized by the near total absence of pain, although pain was often present in other clusters. For Clusters 2-4, we defined characteristic manifestations as having more than 50% of their total occurrence in a given cluster. Characteristic manifestations were removed from the other clusters to emphasize their natural hierarchy. These are listed in **Table II**.

All the Cluster 1 patients, 46% of Cluster 2, 41% of Cluster 3, and 29% of the Cluster 4 patients had pain. Only two Cluster 1 patients had a manifestation in addition to pain and that was muscular weakness. Thus, Cluster 1 might be described as "pain only." (Hierarchical

TABLE II. CHARACTERISTIC SIGNS AND SYMPTOMS OF THE CLUSTERS.

Cluster 1	Cluster 2	Cluster 3	Cluster 4
Pain only (99%)	Numbness (42%), Paresthesia (34%), Decreased Skin Sensitivity (9%)	Malaise (30%), Muscular Weakness (30%), Paralysis (11%), Bladder-bowel problems (4%)	Fatigue (15%), Headache (13%), Dizziness (13%), Skin rash and mottling (11%), Confusion (10%), Nausea (8%), Dyspnea/Chokes (7%), Vertigo (4%), Altered consciousness (4%), Muscular problems (4%), Vision problems (4%), Abnormal sensations (2%), Localized skin swelling (2%), Hearing loss (2%), Tinnitus (0.4%)

clustering with Ward's method was less specific and included several Cluster 1 cases with vertigo, altered consciousness, confusion, and vision problems.)

The principal manifestations of Cluster 2 were paresthesia (75%), numbness (69%), and decreased skin sensitivity (56%). In Cluster 3, muscular weakness (99%) was the most common manifestation followed by malaise (98%), bladder–bowel problems (97%), and paralysis (92%). Many of the principal manifestations of Cluster 4 were uncommon: hearing loss (88%), local skin swelling (77%), tinnitus (75%), skin rash/mottling (68%), altered consciousness (67%), headache (66%), nausea (64%), vertigo (64%), fatigue (61%), dizziness (58%), confusion (55%), dyspnea/chokes (54%), muscular problems (52%), vision problems (51%), and abnormal sensations (51%).

DISCUSSION

We successfully demonstrated statistical methods for investigating natural clusters of signs and symptoms within DCI cases. Two different methods confirmed the existence of four clusters. Table II revealed a hierarchical ordering of clusters similar to PSI (16), from less to more severe cases. In general, the severity of the principal manifestations increased from Cluster 1 through Cluster 4 under the assumptions that: 1) pain only (Cluster 1) was least severe; 2) numbness, paresthesia, and skin sensitivity represented local neurological or mild spinal involvement (Cluster 2); 3) muscular weakness, bladder-bowel dysfunction, and paralysis represented serious spinal involvement (Cluster 3); and 4) hearing loss, tinnitus, altered consciousness, vertigo, confusion, dyspnea/chokes, and vision trouble represented cerebral or cardiopulmonary problems and might require urgent and aggressive intervention (Cluster 4). Balance and gait abnormalities might also be expected in Cluster 3, but cases with these signs did not appear in or were omitted from the data. Cluster 1 was similar to PSI 4, Cluster 2 to PSI 3, Cluster 3 to PSI 1, and Cluster 4 to PSI 2.

While the distribution of principal manifestations was reasonably coherent, many of the same manifestations appeared in Clusters 2-4. Notable exceptions were Cluster 1 with the near absence of any manifestation but pain, the absence of paralysis and bladder-bowel problems in Cluster 2, and bladder-bowel problems almost exclusively in Cluster 3. Cluster 4 contained some of the more serious manifestations that were relatively rare. For specific manifestations like bladder-bowel problems, paralysis, altered consciousness, and confusion, "misclassification" may indicate lesser specificity than assumed, data structure and sample size, or vague diagnostic criteria. Vision problems, which may include subjectively reported symptoms, and hearing loss, which can be caused by ear barotrauma and DCI, appear scattered between Clusters 2 to 4.

The four clusters were mapped onto the three traditional DCI categories and the six PSI categories to investigate the correspondence between classifications. For DCI, 74.4% of Cluster 1 cases were in DCS I while 85% of Cluster 2 cases were from DCS II, 80.5% of Cluster 3 cases were from DCS II, and 64.1% of Cluster 4 cases were from DCS II. AGE cases were absent from Cluster 1 and found most often in Clusters 3 (11%) and 4 (9.3%). For PSI, 88.3% of Cluster 1 cases were from PSI 4, 81.7% of Cluster 3 cases were from PSI 3, and 86.4% of Cluster 3 were from PSI 1. Cluster 4 included 34.6% of cases from PSI 3, 30.7% from PSI 1, and 20.6% from PSI 4. The DCS I cases corresponded reasonably well to Cluster 1, but the DCS II cases were distributed among three clusters and AGE cases were split between two clusters. The natural manifestation groupings defined by clustering corresponded more closely to PSI than to DCI.

Differences in the percentage of complete relief from manifestations after therapy among the three classification systems were difficult to resolve. The three DCI groups ranged from 72–81% complete relief, the six PSI groups ranged from 71–86%, and the four clusters ranged from 68–75%. However, each case had a unique treatment regimen and patient demography that may have influenced therapeutic outcome, so these comparisons may be of limited value. Moreover, individual components of clusters may respond more or less completely to therapy. Understanding these influences appears possible through survival analysis (15), but will require information on the timing of manifestation resolution that was not available in the cases we analyzed. We conclude that cluster analysis is an objective method that leads to a hierarchical distribution of DCI manifestations that is independent of (yet consistent with) clinical judgment. Further, cluster analysis, in combination with survival analysis, may be beneficial for investigating the evolution of DCI manifestations and for selecting optimal DCI therapies for individual manifestations.

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