Reliability of Plasma D-Dimers for Predicting Severe Neurological Decompression Sickness in Scuba Divers

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Background: A low-grade process of coagulation activation in association with severe neurological decompression sickness (DCS) in divers has been anecdotally observed. We aimed to investigate whether measurement of plasma D-dimers and other hemostatic parameters in injured scuba divers were effective as prognostic biomarkers of neurological DCS, and we compared the diagnostic accuracy of a combination of D-dimers test and initial clinical assessment with either one alone. ***Methods:*** Eligible for the study were 84 recreational divers (69 men, 46 ± 10 yr; 15 women, 44 ± 8 yr) referred for neurological DCS in 2007-2011 and treated with hyperbaric oxygen. Blood tests were collected for D-dimers, fibrinogen, and platelet count with a time interval less than 8 h upon admission. Presentation severity was rated numerically for the acute event with a validated scoring system and clinical outcome was assessed by a follow-up examination at 3 mo. Indices of accuracy for D-dimers test, initial clinical score, and combination were estimated. ***Results:*** Incomplete recovery was reported in 26% of patients with a definite relationship between elevated D-dimers and presence of sequelae after multivariate analysis. We did not find differences for other blood coagulation variables between outcome groups. Combination of positive D-dimers (cut-off value of 0.40 $\mu g \cdot ml^{-1}$) with severe initial presentation attained a higher diagnostic accuracy than either method alone (post-test probabilities = 100%, 86%, and 57%, respectively). ***Conclusion:*** This study suggests that determination of plasma D-dimers, a marker of activation coagulation, improve the prognostication of neurological DCS affecting scuba divers when combined with presenting severity score.

Keywords: D-dimers, biomarkers, diving, decompression sickness.

NEUROLOGICAL decompression sickness (DCS) is a rare disease that may affect scuba divers, leading to potential permanent disability with a prevalence of residual deficits reported of around 30% in the recent literature (9,15,25). Vascular bubble formation is the primary pathologic event in the development of DCS. Besides the classical assumption that gas bubbles lead initially to occlusion of capillary blood flow, other mechanisms have been hypothesized by which bubbles may exert secondary deleterious effects. It has been experimentally demonstrated that decompression-induced gas microemboli may interact with vascular endothelium and blood components (platelet and leukocytes, particularly), resulting in activation of the coagulation cascade, alterations in microcirculation, and hypoxic cell damage similar to pathology seen in ischemia-reperfusion injury.

While extensive studies have demonstrated significant changes in hemostatic parameters during human saturation diving and severe decompression stress procedures in animal models (18,19,24), activation of coagulation is uncertain following the common circumstances of decompression (like recreational diving) with or without DCS occurrence (3,10,13). Anecdotal cases, however, have shown indirect evidence of a low-grade process of disseminated intravascular coagulation in association with severe neurological DCS in divers (3,12), suggesting that biomarkers reflecting activation of coagulation could be of interest for prognostication after a neurological DCS event.

Currently, plasma D-dimers are the best available laboratory marker of activation of coagulation used routinely in the diagnosis of suspected venous thromboembolism with a cut-off value of 0.50 $\mu g \cdot ml^{-1}$ (14). They consist of a specific cross-linked fibrin derivative and they are generated when the endogenous fibrinolytic system (enzyme plasmin) and the thrombin pathway are activated. The intent of this study was, therefore, to determine whether a D-dimers assay at the time of diagnosis of neurological DCS may be helpful in the prediction of incomplete recovery in recreational divers, particularly in combination with the initial clinical assessment. At the same time, we also sought to evaluate the association of other blood coagulation parameters (platelet count, fibrinogen) on clinical outcome.

METHODS

Subjects

A cohort study of all injured recreational divers admitted for DCS in our hyperbaric facility (Sainte Anne's military hospital, Toulon, France) from October 2007

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through September 2011 was conducted. Data were collected and maintained prospectively in a standardized clinical database, and analyzed retrospectively by two investigators who contributed to this work. The diagnosis of neurological DCS was considered certain when it was associated with the onset of subjective or objective signs evocative of central nervous system involvement (motor weakness, sensory disorders, bladder dysfunction, altered higher function or speech, visual disturbance) that occurred within 6 h following open-sea air diving performed with a minimum depth-time exposure (20 msw for 20 min). Exclusion criteria included: 1) presence of equivocal or ambiguous manifestations not related with DCS after reviewing medical forms; 2) events involving rapid or panic ascent associated with breath-holding, supporting evidence of pulmonary barotraumas with cerebral arterial gas embolism; 3) patients who presented 8 h after onset of symptoms, to allow for reliable and homogenous blood samples analysis in a relatively short time frame after DCS occurrence; and 4) lack of aspirin administration (250-500 mg) before admission (procedure recommended by the French Federation of scuba diving) to avoid potential variability in coagulation activation between divers.

First-aid normobaric oxygen was systematically administered during emergency evacuation. DCS divers were treated initially with hyperbaric oxygen using either 100% oxygen at 2.8 ATA for 150 min (equivalent to U.S. Navy Table 5), or 330 min (equivalent to U.S. Navy Table 6), or a deeper recompression involving breathing 50% oxygen with 50% helium at 4 ATA and 3.4 ATA followed by staged decompression until surfacing at 2.8 and 2.2 ATA with 100% oxygen breathing for a total elapsed time of 7 h (Comex 30 table). The decision of treatment regimen depended on the initial severity and the practice of the physician on duty. It has been previously observed that the choice of recompression procedure was not a determinant factor for treatment outcome (9). Medical treatment consisted of systematic intravenous isotonic fluid administration with methylprednisolone ($1\ mg \cdot kg^{-1}$). Additional hyperbaric oxygen sessions (2.5 ATA for 70-90 min) were given if resolution was incomplete after the initial recompression. The study was approved by the local ethics committee (Sainte Anne's Military Hospital, France). Informed consent was waived because of the retrospective nature of this study.

TABLE I. SEVERITY SCORE OF BOUSSUGES FOR NEUROLOGICAL DCS IN DIVERS.

Manifestation	0	1	2	3	4	5	6
Repetitive dive							
No	X						
Yes			X				
Clinical course before recompression							
Better	X						
Stable				X			
Worse						X	
Objective sensory deficit							
No	X						
Yes					X		
Motor impairment							
No	X						
Paresis					X		
Paraplegia							X
Hemiplegia				X			
Bladder dysfunction							
No	X						
Yes						X	

High severity is defined as a score greater than 7 and low severity as a score less than or equal to 7.

Procedure

Initial severity of neurological DCS was determined by the scoring system of Boussuges and coworkers (4) between the time of presentation and the 6 h that followed to account for the occurrence of delayed symptoms during and after initial recompression. This score is calculated from five weighted clinical variables (**Table I**) and it has been evidenced that cases with scores greater than 7 predict more sequelae than those of cases with a score of 7 or less (9,22).

Clinical outcome was assessed at discharge following all hyperbaric treatment after extensive neurological examination made by a physician of the department. If persistent neurological symptoms were noted, a follow-up examination was repeated at 3 mo by a neurologist in the locality where the patient lives. Incomplete recovery was defined as the presence of residual deficits of varying degrees from case to case, including mild symptoms (e.g., isolated paresthesias, sensory loss with decreased light touch skin or thermal sensation, muscle strain after walking) or severe disability (paresis, urinary or bowel disturbance, ataxia due to sensory spinal myelopathy). The examiners were blinded to the results of biomarkers at the time of injury or at follow-up for 3 mo for patients with persistent neurological symptoms, but not during clinical assessment before discharge. Besides the collection of demographic data and diving parameters, a detailed history was taken from all patients to detect any previous conditions associated with raised D-dimer levels (infection, cancer, renal failure, recent surgery, or thromboembolism diseases).

Hemostatic parameters were measured for each diver at the time of admission to the hyperbaric center. Venous blood samples (8 ml) were collected in two tubes containing citrate or EDTA and then subjected to centrifugation (3500 rpm for 15 min at 4°C) in the following hour. D-dimer assays were quantitatively performed using the immunoturbidimetric technique (Liatest D-di, Diagnostica Stago, Asnières sur Seine, France), while platelet and fibrinogen levels were assessed using standard techniques.

Statistical Analysis

Data were expressed as mean ± SD or median with range for nonparametric variables. The optimal cut-off level for D-dimers that can discriminate between outcome groups was determined using the receiver operating characteristic curve. Comparisons between outcome groups (i.e., DCS divers without sequelae and those

with incomplete recovery) for a given continuous variable were completed using the Mann-Whitney test and the unpaired Student's *t*-test where appropriate, and categorical variables were compared using the Chi-squared test with Yates' correction. Variables yielding *P*-values of less than 0.10 in the univariate analysis were then entered as covariates into a multivariate logistic regression analysis to identify independent risk factors of unfavorable outcome.

The diagnostic value of the initial severity score of Boussuges and the D-dimers test were estimated through the calculation of sensitivity, specificity, and likelihood ratios. To determine the accuracy of the D-dimers method alone or combined with the clinical score, we calculated for each strategy the post-test probability of sequelae (i.e., the risk that a diver will have an incomplete recovery after a positive or negative test) from pre-test probability (i.e., prevalence of sequelae) by using the likelihood ratio nomogram of Fagan (8). Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated when needed, along with *P*-values, for which the level of statistical significance was set as less than 0.05. Statistical analysis was done using Sigmastat 3.0 (Systat Inc., Richmond, CA).

RESULTS

During the study period, 108 consecutive neurological DCS divers were treated. After exclusion of 24 cases on the basis of the predefined criteria, 84 patients (69 men, 46 ± 10 yr, and 15 women, 44 ± 8 yr) were selected and served as the cohort for the present work. Diving parameters with individual and laboratory characteristics of divers with resolution and those with incomplete recovery are presented in **Table II**. At 3 mo, 22 (26%) patients developed sequelae, including 5 (6%) divers with severe disability. The median time from surfacing to blood draw was 2.5 h (1.5–8). Only one injured diver had the underlying condition of elevated D-dimers levels with a history of prostate cancer treated surgically several years before. He was included in the analysis because the results of biomarkers were normal and he was cured without persistent symptoms or relapse after the first hyperbaric oxygen session.

Univariate analysis (Table II) revealed that median D-dimers values were higher in the subgroup of patients with residual deficits ($P = 0.002$), while no changes were observed with other hemostatic parameters. There were significant differences in mean age ($P = 0.007$) and in mean depth dive ($P = 0.002$) between outcome groups, but not in mean total diving time ($P = 0.13$). After adjustment, however, the results showed that D-dimers alone (OR = 4.7; 95% CI, 1.4–15; $P = 0.01$) independently predicted the occurrence of sequelae, unlike age (OR = 1.04; 95% CI, 0.9-1.1; $P = 0.12$) and depth (OR = 1.05; 95% CI, 1-1.1; $P = 0.05$). In an alternative analysis, we noted that the subgroup of patients with severe disability had higher D-dimers values than those with mild sequelae (0.31 vs. 0.88 $\mu g \cdot ml^{-1}$, respectively, $P = 0.049$).

Using receiver operating characteristic curve analysis, the threshold value of D-dimers highly predictive of poor outcome was determined as above 0.40 $\mu g \cdot ml^{-1}$ with corresponding indices of sensitivity and specificity as follows: 54% (95% CI, 34–73) and 85% (95% CI, 74–92), respectively. We calculated that neurological DCS divers with incomplete recovery were 3.8 times (positive likelihood ratio) as likely to have positive D-dimers (95% CI, 1.8–7.7) and 0.5 times (negative likelihood ratio) as likely to have negative D-dimers (95% CI, 0.3–0.8) than those without sequelae. From these findings, the post-test probabilities for positive and negative D-dimers were estimated to be 57% (95% CI, 40–73) and 16% (95% CI, 10–23), respectively. This means that the risk of sequelae for a DCS diver increased from 26 to 57% after testing positive and reduced from 26 to 16% after testing negative.

Our data confirmed the strong association found in our cohort of injured divers between initial presentation according to the severity score and clinical outcome ($P < 0.0001$). The diagnostic accuracy for the clinical scoring method gave the following indices with a cutoff point of 7: sensibility = 86% (95% CI, 66–95), specificity = 95% (95% CI, 86–98%), positive likelihood ratio = 18 (95% CI, 5.8–55), and negative likelihood ratio = 0.14 (95% CI, 0.05–0.4). The post-test probabilities for high and low scores were estimated to be 86% (95% CI, 67–95) and 5% (95% CI, 2–13), respectively.

TABLE II. CHARACTERISTICS OF STUDY SUBJECTS, DIVING INDICES, AND LABORATORY FINDINGS OF 84 DIVERS WITH NEUROLOGICAL DCS.

	Resolution	Sequelae	
	(*N* = 62)	(*N* = 22)	*P*
Sex ratio (M/F)	49 / 13	20 / 2	0.33
Mean age (yr)	44 ± 10	50 ± 9	0.007
Mean depth (msw)	39.8 ± 12	49.3 ± 11	0.002
Mean total diving time (min)	36 ± 12	31 ± 7.5	0.13
Median D-dimers ($\mu l \cdot ml^{-1}$)	0.23 [0.22–0.32]	0.43 [0.22–0.74]	0.002
Mean fibrinogen ($g \cdot L^{-1}$)	3.09 ± 0.5	2.88 ± 0.5	0.11
Mean platelet count	210,364 ± 32,815	215,871 ± 45,151	0.99

Divers meeting the inclusion criteria were treated at Sainte Anne's Military Hospital from October 2007 to September 2011. "Resolution" corresponds to patients without residual symptoms at discharge. "Sequelae" represents injured divers with incomplete recovery at 3 mo post-injury.

Given the differing accuracy of both methods and the less favorable figure for the laboratory test used alone, D-dimers were combined with the clinical scoring system applied at initial presentation with the aim of improving the performance of the diagnostic screening process. For a high severity score (i.e., Boussuges' score > 7), the post-test probabilities for positive and negative D-dimers were estimated to be 100% (95% CI, 68–100) and 73% (95% CI, 62–85), respectively. For a low severity score (i.e., Boussuges' score ≤ 7), the post-test probabilities for positive and negative D-dimers were estimated to be 10% (95% CI, 2–38) and 4% (95% CI, 2–8), respectively. This means that the risk of sequelae for a diver with a severe presentation increased from 86 to 100% after testing positive. Conversely, the risk of sequelae for a diver with mild symptoms reduced only from 5 to 4% after testing negative. **Fig. 1** illustrates the positive and negative post-test probabilities of the combination of D-dimers test and the severity score with either one alone.

DISCUSSION

While there have been a number of clinical scoring systems devised for acute neurological DCS that have proved reliable for the prediction of residual deficits (1,4,6), little biological marker research in humans has been conducted to test their value in diagnosing DCS and assessing prognosis. Numerous studies have documented a variety of hematologic and biochemical changes associated with decompression stress or the occurrence of DCS, but their utility as diagnostic tools has not yet been evidenced (7,17,19). A recent pilot study failed to demonstrate that S100β protein, a promising serum marker of acute neurological injury, may be clinically useful for the diagnosis of DCS in recreational divers (23). Most attention has focused on the measurement of hematocrit, which has been noted to rise in severe cases of neurological DCS (5). However, normal values (i.e., less than 48%) have also been commonly observed in patients with a poor outcome, limiting the prognostic performance of this test in routine clinical use.

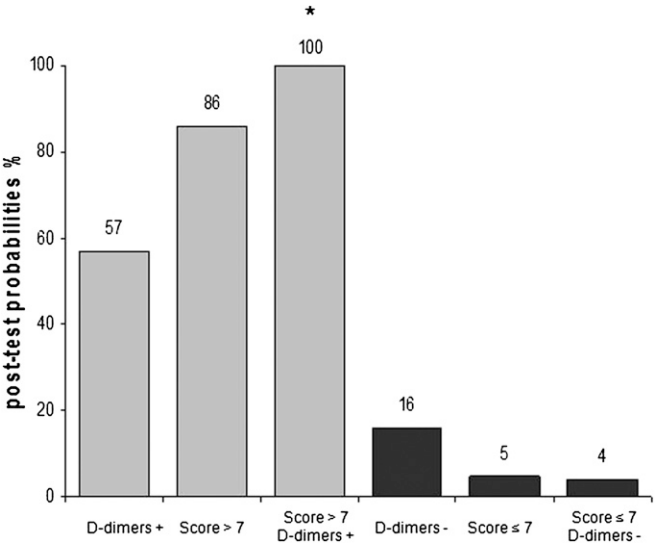

Fig. 1. Histogram comparing the post-test probabilities (PtP) of the D-dimers test, initial severity score, and combination of both. Gray bars and black bars correspond to positive PtP and negative PtP, respectively. * denotes $P < 0.05$ from the D-dimers test alone.

The present study showed that elevated D-dimers levels on admission were independently associated with the persistence of residual symptoms 3 mo after the initial insult, with a discriminant threshold value equal to 0.40 $\mu g \cdot ml^{-1}$. There also seems to exist a quantitative dose-response relationship between D-dimers levels and severity of DCS, as demonstrated by the higher median level of D-dimers in the subset of divers with the poorer outcome. Previous clinical investigations with a small sample of DCS divers have yielded mixed results regarding the influence of D-dimers in the course of neurological DCS. In a prospective work, Boussuges and coworkers did not find statistical differences in median D-dimers values between 25 injured divers and 15 controls with only 3 DCS patients presenting plasma levels > 0.5 $\mu g \cdot ml^{-1}$ (3). Of these, only one diver was found to be suffering from neurological sequelae, supporting the idea that the D-dimers test was not a good indicator of severity. Conversely, another study with 18 divers treated for various forms of DCS have reported findings that suggest activation of coagulation with increased fibrin degradation products only among individuals with neurological impairment (12).

We found no change in platelet count and fibrinogen values between subjects that were cured and those with residual symptoms. This result is not in accordance with prior animal experiments (16,20,24) that noted a correlation between the degree of platelet loss and the severity of DCS. In clinical studies, it is well documented that decompression lowers platelet count, and increases platelet activation and fibrinogen turnover (2,18,21), but the impact of the severity of DCS injury on these hematologic changes has never been confirmed in man. The lack of alterations of these two parameters in this series of neurological DCS may be related to the great difference in the magnitude of decompression stress and dive profiles between animals and human studies, as already suggested by Goad et al. (10).

Our findings demonstrated that the D-dimers test did not have a good diagnostic performance when used alone. Actually, this biomarker was most helpful to the clinician for suspecting an incomplete recovery when the values were positive in association with a clinical scoring system revealing a severe presentation. Conversely, D-dimers levels below the threshold value combined with a low severity score did not improve the efficiency of the Boussuges score used alone, with a negligible risk of developing sequelae when the initial symptoms were mild.

In this study, the prevalence of divers with incomplete recovery is consistent with the existing literature, with apparent detection of similar risk factors, i.e., advanced age and maximum depth > 40 msw (1) after completing univariate analysis. The nonsignificant association but trend toward a deleterious effect of these determinants on outcome after adjustment might be due to the relatively small sample size of divers. The difference of aging

between outcome groups could represent a limitation of our study if we consider that D-dimers levels increase linearly with age (11). However, the average D-dimers levels between patients within the age strata of 40-49 yr and those of 50-59 yr has been evidenced as quite similar in a clinical investigation of 671 healthy individuals (14), limiting the likelihood that this discrepancy may have influenced the results. Actually, the potential association between these two cofactors of DCS severity (i.e., aging and depth) with an increased prevalence of positive D-dimers may be explained by their ability to promote conditions that increase the formation of intravascular bubbles during decompression. The high bubble load would facilitate the interactions between blood components and the endothelium, hence favoring a prothrombotic state with hypercoagulability and increased fibrinolysis.

Although the usefulness of the D-dimers test alone is limited by its low sensitivity, our results offer evidence that elevated plasma D-dimers levels during the acute phase of neurological DCS can act as an additional predictor of the likelihood of incomplete recovery when combined with a high initial clinical severity score. Further prospective work is needed to introduce this biomarker as a weighted variable in existing scoring systems for prognostication. The influence of anticoagulation therapy on clinical outcome when D-dimers are elevated remains questionable.

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REFERENCES

1. Blatteau JE, Gempp E, Simon O, Coulange M, Delafosse B, et al. Prognostic factors of spinal cord decompression sickness in recreational diving: retrospective and multicentric analysis of 279 cases. Neurocrit Care 2011; 15:120–7.
2. Bosco G, Yang ZJ, Savini F, Nubile G, Data PG, et al. Environmental stress on diving-induced platelet activation. Undersea Hyperb Med 2001; 28:207–11.
3. Boussuges A, Succo E, Juhan-Vague I, Sainty JM. Activation of coagulation in decompression illness. Aviat Space Environ Med 1998; 69:129–32.
4. Boussuges A, Thirion X, Blanc P, Molenat F, Sainty JM. Neurologic decompression illness: a gravity score. Undersea Hyperb Med 1996; 23:151–5.
5. Boussuges A, Blanc P, Molenat F, Bergmann E, Sainty JM. Haemoconcentration in neurological decompression illness. Int J Sports Med 1996; 17:351–5.
6. Dick APK, Massey EW. Neurologic presentation of decompression sickness and air embolism in sport divers. Neurology 1985; 35:667–71.
7. Ersson A, Walles M, Ohlsson K, Hekholm A. Chronic hyperbaric exposure actives proinflammatory mediators in humans. J Appl Physiol 2002; 92:2375–80.
8. Fagan TJ. Nomogram for Bayes theorem. N Engl J Med 1975; 293:257.
9. Gempp E, Blatteau JE. Risk factors and treatment outcome in scuba divers with spinal cord decompression sickness. J Crit Care 2010; 25:236–42.
10. Goad RF, Neuman TS, Linaweaver PG. Hematologic changes in man during decompression: relations to overt decompression sickness and bubbles scores. Aviat Space Environ Med 1976; 47:863–7.
11. Hager K, Platt D. Fibrin degradation product concentrations (D-dimers) in the course of ageing. Gerontology 1995; 41: 159–65.
12. Hart GB. Screening test for decompression sickness. Aviat Space Environ Med 1976; 47:993–4.
13. Eckenhoff RG, Hughes JS. Hematologic and hemostatic changes with repetitive air diving. Aviat Space Environ Med 1984; 55:592–7.
14. Kelly J, Rudd A, Lewis RR, Hunt BJ. Plasma D-dimers in the diagnosis of venous thromboembolism. Arch Intern Med 2002; 162:747–56.
15. Klingmann C, Gonnermann A, Dreyhaupt J, Vent J, Praetorius M, Plinkert PK. Decompression illness reported in a survey of 429 recreational divers. Aviat Space Environ Med 2008; 79:123–8.
16. Lee HC, Lin TC, Maa HC. Change of coagulation factor and its correlation with decompression sickness. [Abstract]. Undersea Hyperb Med 1998; 25(Suppl.):40.
17. Nyquist P, Ball R, Sheridan MJ. Complement levels before and after dives with a high risk of DCS. Undersea Hyperb Med 2007; 34:191–7.
18. Olszański R, Radziwon P, Piszcz J, Jarzemowski J, Gosk P, et al. Activation of platelet and fibrinolysis induced by saturated air dives. Aviat Space Environ Med 2010; 81:585–8.
19. Philp RB. A review of blood changes associated with compression-decompression: relationship to decompression sickness. Undersea Biomed Res 1974; 1:117–50.
20. Philp RB, Schacham P, Godwey CW. Involvement of platelet and microthrombi in experimental decompression sickness: similarities with disseminated intravascular coagulation. Aerosp Med 1971; 42:494–502.
21. Philp RB, Freeman D, Francey I, Ackles KN. Changes in platelet function and other blood parameters following a shallow open-sea saturation dive. Aerosp Med 1974; 45:72–6.
22. Pitkin AD, Benton PJ, Broome JR. Outcome after treatment of neurological decompression illness is predicted by a published clinical scoring system. Aviat Space Environ Med 1999; 70: 517–21.
23. Poff DJ, Wong R, Bulsara M. Acute decompression illness and serum S100beta levels: a prospective observational pilot study. Undersea Hyperb Med 2007; 34:359–67.
24. Pontier JM, Vallee N, Bourdon L. Bubble-induced platelet aggregation in a rat model of decompression sickness. J Appl Physiol 2009; 107:1825–9.
25. Vann R, Freiberger JJ, Caruso JL, Denoble P, Pollock NW, et al. DAN report on decompression illness, diving fatalities and project dive exploration. Durham, NC: Divers Alert Network; 2005:63-5.