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Investigation of Brain Impairment Using Diffusion-Weighted and Diffusion Tensor Magnetic Resonance Imaging in Experienced Healthy Divers

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Manuscript Preparation E
Literature Search F
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Background: The aim of this study was to understand the changes of decompression illness in healthy divers by comparing diffusion-weighted (DWI) and diffusion tensor MRI findings among healthy professional divers and healthy non-divers with no history of diving.

Material/Methods: A total of 26 people were recruited in this prospective study: 11 experienced divers with no history of neurological decompression disease (cohort) and 15 healthy non-divers (control). In all study subjects, we evaluated apparent diffusion coefficient (ADC) and type of diffusion tensor metric fractional anisotropy (FA) values of different brain locations (e.g., frontal and parieto-occipital white matter, hippocampus, globus pallidus, putamen, internal capsule, thalamus, cerebral peduncle, pons, cerebellum, and corpus callosum).

Results: ADC values of hippocampus were high in divers but low in the control group; FA values of globus pallidus and putamen were lower in divers compared to the control group. DWI depicted possible changes due to hypoxia in different regions of the brain. Statistically significant differences in ADC values were found in hypoxia, particularly in the hippocampus ($p=0.0002$), while FA values in the globus pallidus and putamen were statistically significant ($p=0.015$ and $p=0.031$, respectively). We detected forgetfulness in 6 divers and deterioration in fine-motor skills in 2 divers ($p=0.002$ and $p=0.17$, respectively). All of them were examined using neuro-psychometric tests.

Conclusions: Repeated hyperbaric exposure increases the risk of white matter damage in experienced healthy divers without neurological decompression illness. The hippocampus, globus pallidus, and putamen are the brain areas responsible for memory, learning, navigation, and fine-motor skills and are sensitive to repeated hyperbaric exposure.

MeSH Keywords: Cell Hypoxia • Diffusion Magnetic Resonance Imaging • Stroke

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/911475>



Background

Scuba (self-contained underwater breathing apparatus) diving is a form of underwater diving using a completely independent apparatus. In the United States, there are approximately 9 million certified divers [1]. Divers are repeatedly exposed to high pressure and must inevitably experience decompression stress upon return to the surface. Thus, intense periods of hypobaric decompression stress (known as decompression illness) and cerebral hypoxia promote injuries in different brain regions in healthy high-altitude workers, as well as in scuba divers. A recent meta-analysis reported on prevalence of white matter lesions as the proportion of the total number of participants having any (≥ 1) white matter lesion on magnetic resonance imaging (MRI) brain scan in a well-defined (intervention) cohort of professional divers and in a matched non-diver control group [2]. The incidence of decompression illness (DCI) among recreational scuba divers is estimated to be 1 per 5000–10 000 dives [1].

Severe injuries and death are uncommon in scuba diving accidents; however, the increasing popularity of scuba diving had led to a dramatic increase in the number of diving-related central nervous system complications. Dive-related complications range from nonspecific complaints such as dysesthesia to serious complications such as quadriplegia, encephalopathy, and death [3,4].

DCI is the result of releasing inert gas bubbles (usually nitrogen) into the bloodstream, interstitial fluids, tissues, and organs after rapid reduction of ambient pressure [4–7]. Nitrogen bubbles affect the brain, spinal cord, cranial and peripheral nerves, and the neural vasculature by vascular stenosis or obstruction, mechanical disruption, compression, and activation of inflammatory mechanisms (e.g., cytokines and complement) [4,7]. The cerebral cortex, cerebellum, hippocampus, basal ganglia, and thalamus are usually sensitive to hypoxia and ischemia [8]. The caudate nucleus, putamen, insula, precentral gyrus, inferior frontal, and middle frontal gyri are the regions most sensitive to decreased cerebral blood flow (CBF) and to hypoxia [9].

About 30–40% of cerebral DCIs affect arterial circulation, while 50–60% of spinal cord DCIs involve obstruction of venous drainage, which follows formation of bubbles within the cord parenchyma [10]. In DCI, clinical symptoms depend on origin, location, and size of the lesions. Although conventional neuroimaging modalities are mostly inadequate in the assessment of lesions, various MRI sequences are helpful in identifying lesion pathophysiology [11].

Diffusion-weighted magnetic resonance imaging (DWI) and apparent diffusion coefficient (ADC) provide cell-level information about the movement and functional environment of

water in normal and pathological tissue. DWI is sensitive to changes in the micro-diffusion of water within the intra- and extra-cellular spaces. ADC reflects these changes and provides an important quantitative biophysical parameter [12–14]. A type of diffusion tensor metric, fractional anisotropy (FA), is highly sensitive to microstructural changes, but not very specific to the type of change (e.g., radial or axial) [15].

The hippocampus, globus pallidus, and putamen are the brain areas responsible for memory, learning, navigation, and fine-motor control movements [16,17]. In this study, signal changes due to hypoxia in different brain areas were detected in DWI scans of 11 experienced divers (cohort group) and 15 healthy non-divers (control group). We also compared DWI findings between healthy professional divers and healthy non-divers who had no diving history.

Material and Methods

This prospective study was approved by the Medical Ethics Committee of our hospital (decision number B.30.2.BAV.0.05.05/500). Written informed consent was obtained from all applicants for performing MRIs and for publication of their characteristics and accompanying images.

Inclusion and exclusion criteria

Out of a total of 26 healthy males (2 of the 28 experienced divers were excluded due to loss to follow-up or losing their control MRIs), 11 were experienced divers with no history of past acute neurological DCI and 15 were healthy non-divers, and these 26 individuals were selected as the core sample used for this study. Inclusion criteria for the cohort group were: certified diver, diving time was more than 1000 hours, depth of diving was more than 30 meters, number of dives was more than 500 times, and all divers were selected with no history of past acute neurological DCI, trauma, or chronic diseases such as diabetes mellitus, hypertension, chronic obstructive pulmonary diseases, coronary artery diseases, or thyroid dysfunction. Individuals in the control group were randomly selected from among male volunteers who had normal neurological examination results and who were in same age range as the cohort group.

One of the divers used Trimix (a breathing gas consisting of oxygen, helium, and nitrogen, and is often used in deep scuba diving), 3 divers used Trimix and Nitrox (oxygen-enriched air), and the remaining 7 divers used only Nitrox air sources.

Radiologic assessment

There was a minimum interval between neurological examination and the last dive of 2 days, and not more than 1 week, with an average interval of 4 days. MRI for all participants was performed using a 1.5-T machine (Avanto, Siemens Healthcare). The MRI protocol included the following sequences: T1-weighted images, T2-weighted images and fluid attenuation inversion recovery (FLAIR) images. T1-weighted imaging was performed with TR/TE 350–650/16–19 ms, T2-weighted images with TR/TE 1500–3000/70–90 ms, and FLAIR with TR/TI/TE 4000/1700/60 ms. Axial images were obtained in individuals of both groups. Slice thickness was 5 mm with a 1.0 mm interval between obtained slices. A 256×256 matrix corresponding to a 0.75×0.75 mm pixel size and 4 excitations were used in all examinations. The field of view was 18–30 cm. Obtained MR images were evaluated by 3 experienced neurosurgeons with 25, 2, and 4 years of experience (MHS, AA, and TD, respectively) and 2 radiologists with 15 and 4 years of experience (AA and HS, respectively). Evaluation was by consensus, and when the observers disagreed, they discussed the case until and consensus was reached. Observers were blinded to the history of the individuals. Apparent diffusion coefficient (ADC, mm²/s) and a type of diffusion tensor metric fractional anisotropy (FA) were performed. Diffusion tensor imaging was performed with TE/TR=22/2000 ms; nex=4; FOV=30 cm; slice thickness=1.5 mm; matrix=192×192 reconstructed to 256×256; 31 slices; 3 non-weighted reference images, and 30 diffusion-weighted images (b=1000 s/mm², non-colinear gradient directions). Measurements were done from 15 different sites of the brain with same-sized regions of interest (ROI) area by using an MRI workstation (Leonardo, software version 2.0, Siemens Healthcare) (Figure 1). ADC and FA values of bilateral frontal lobes and parieto-occipital white matter, hippocampi, globus pallidi, putamina, anterior and posterior crura of internal capsule, thalami, cerebral peduncles, pontes, cerebellar white matter, and corpus callosum anterior and posterior portions were evaluated. ADC and FA values were averaged from both sides.

Individual follow-up

As part of the standard neurological examination and follow-up, the individuals were examined neurologically by 3 neurosurgeons (MHS, AA, and TD). The divers' neurological symptoms after diving were recorded. The divers who experiences forgetfulness, impairment in navigation ability, or impaired fine-motor skills were examined by neuro-psychometric tests.

Statistical analysis

The continuous variables presented hereafter are expressed as the mean ± standard deviation values together with the range

between parentheses. Univariate analyses were conducted to examine the association between radiological and histopathological features. Differences among groups were assessed with the Mann-Whitney U test, using the IBM SPSS 19 statistical software (SPSS Inc., Chicago, IL, USA). Significance in the multivariate model was determined using a p value <0.05, and a trend-level effect was assigned to a p=0.05–0.10. All p values were 2-tailed.

Results

The mean age of the divers group was 35.27±7.6 (range 25–51) in divers and 34.93±7.9 (range 25–52) in the control (non-divers) group, and all were male. Mean maximum diving depth was 69.4 meters (14–150 meters) (Table 1). Two divers had additionally performed saturation dives to depths of 210–600 meters. Table 2 shows the number of dives.

ADC values of hippocampi were high in divers but low in non-divers (min=880, max=983; p=0,0002). FA values of globus pallidi (min=290, max=442; p=0,015) and putamina (min=154, max=396; p=0,031) were lower in divers than in non-divers. These findings demonstrated the high sensitivity to hypoxia in the hippocampus, globus pallidus, and putamen [11]. ADC and FA values of both groups are shown in Table 3 and Figures 2 and 3.

Symptoms of acute DCI (e.g., alteration of mentation or confusion, weakness, stool disturbance, fatigue, diplopia or visual loss, neurological disorders, and forgetfulness) were not observed in any divers or non-divers. We detected forgetfulness in 6 divers and deterioration in fine-motor skills in 2 divers (p=0.002 and p=0.17, respectively). All of them were examined using neuro-psychometric tests. The difference in ADC and FA results among divers who had symptoms (i.e., forgetfulness and deterioration in fine-motor skills) and divers who were symptomless was not statistically significant (p>0.05). ADC and FA values of both groups are shown in Table 4.

Discussion

The causal relationship between white matter lesions and hypobaric exposure is unclear. No relationship has yet been demonstrated between presence of these lesions detected using diffusion MRI and total hypobaric (dose) (numbers of exposures or total hours of exposure), but it is possible that periods of more intense hypobaric exposure are important [2,18,19]. Professional divers may experience DCI, which is a condition that commonly appears after surfacing from a dive, usually within a few hours. Vann et al. extensively described the symptoms and findings that may associated with DCI as well as

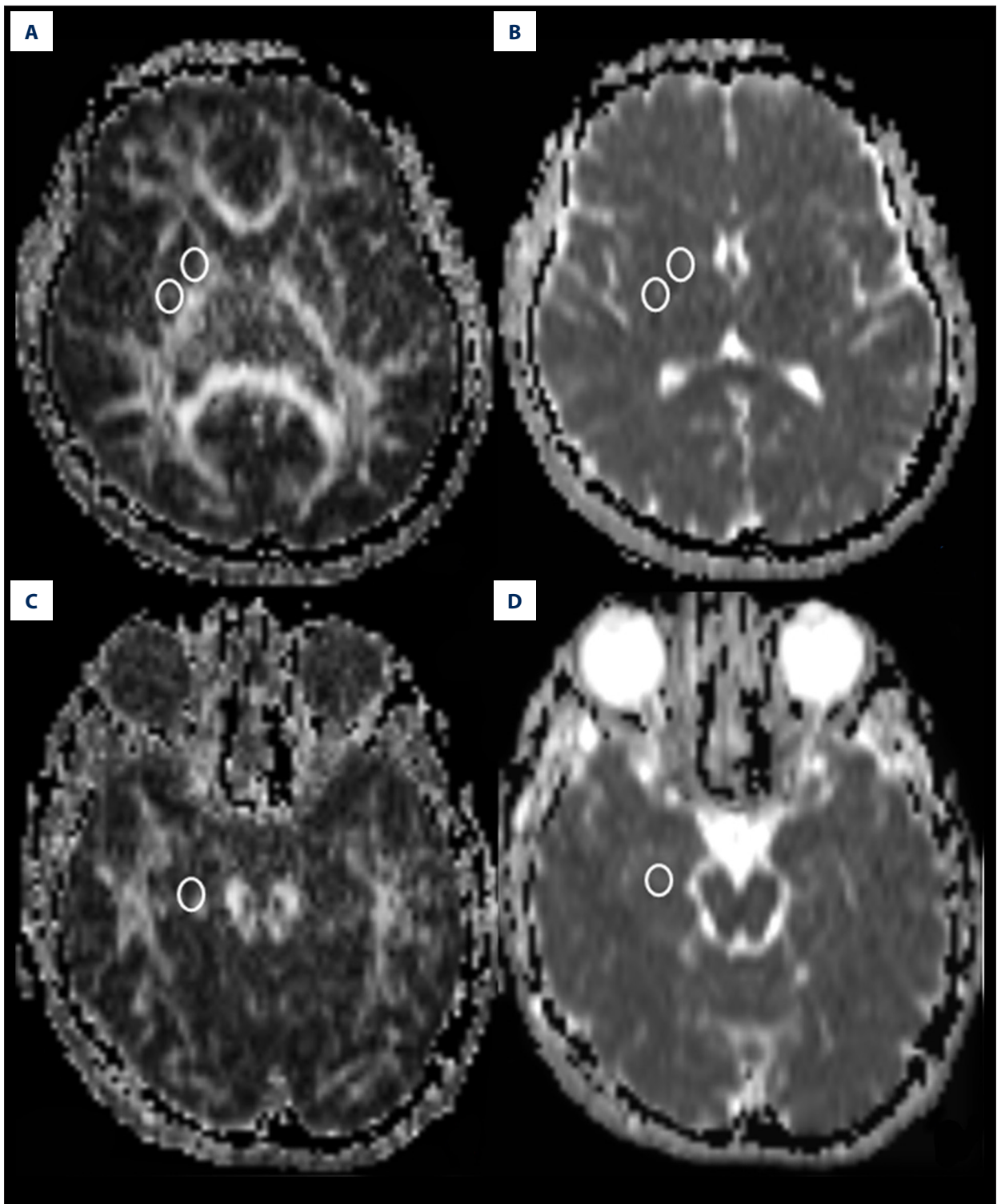


Figure 1. Regions of interest (ROIs) from globus pallidus and putamen are seen on FA (A) and corresponding ADC (B) maps. The ROI placed on the corpus part of the hippocampus are shown on FA (C) and corresponding ADC (D) maps. Note that ROIs all have same size.

Table 1. Number of divers according to the depth of dives.

Depth of diving (meters)	Divers	Mean age (min-max)	%
14-80	9	38 (25-51)	81.8
81-150	2	30 (27-33)	18.2

Table 2. Stratification according to number of diving.

Number of dives	Divers	Mean age (min-max)	%
500-700	2	30 (25-35)	18.2
700-900	4	33 (29-37)	36.4
>1000	5	39 (27-51)	45.4

Table 3. Comparison of ADC and FA values among experienced divers and healthy non-divers.

		Professional divers (n=11)					Non-divers (n=15)					Mann-Whitney	
		Mean	St. Dev	Median	Min	Max	Mean	St. Dev	Median	Min	Max	z	p
	Age	35.2	7.6	33.0	27.0	51	34.9	7.9	32.0	25.0	51.0	-0.156	0.876
1	Frontal WM ADC	753.9	39.4	741.0	706.0	821.0	776.8	46.7	771.0	715.0	867.0	-1.298	0.194
	Frontal WM FA	388.0	48.4	390.0	321.0	479.0	414.0	81.1	409.0	274.0	540.0	-0.779	0.436
2	Parieto-occipital WM ADC#	781.6	61.1	767.0	712.0	904.0	812.3	40.6	815.0	740.0	880.0	-1.739	0.082
	Parieto-occipital WM FA	468.8	98.8	449.0	319.0	591.0	446.8	70.6	439.0	338.0	566.0	-0.649	0.516
3	Hippocampus ADC*	922.0	37.6	917.0	880.0	983.0	833.0	45.4	831.0	755.0	907.0	-3.686	0.0002
	Hippocampus FA	259.2	66.3	237.0	172.0	408.0	267.5	52.6	266.0	176.0	375.0	-0.649	0.516
4	Globus pallidus ADC#	807.3	53.6	810.0	710.0	878.0	767.7	57.9	767.0	668.0	866.0	-1.713	0.087
	Globus pallidus FA*	345.4	46.7	339.0	290.0	442.0	418.8	82.5	384.0	308.0	530.0	-2.440	0.015
5	Putamen ADC	707.4	46.1	688.0	634.0	772.0	721.8	53.0	723.0	610.0	789.0	-0.831	0.406
	Putamen FA*	223.4	71.9	195.0	154.0	396.0	268.1	53.8	274.0	164.0	340.0	-2.155	0.031
6	Caudate Nucleus ADC	711.4	48.0	701.0	648.0	786.0	724.1	38.1	727.0	642.0	772.0	-0.857	0.391
	Caudate Nucleus FA	218.4	24.7	220.0	188.0	247.0	235.1	44.8	237.0	166.0	326.0	-1.013	0.311
7	Hypothalamus ADC	756.7	47.6	769.0	638.0	810.0	782.2	64.1	774.0	699.0	888.0	-0.701	0.483
	Hypothalamus FA	401.9	36.5	406.0	346.0	449.0	417.9	73.3	398.0	333.0	589.0	-0.182	0.856

Table 3 continued. Comparison of ADC and FA values among experienced divers and healthy non-divers.

	Professional divers (n=11)					Non-divers (n=15)					Mann-Whitney		
	Mean	St. Dev	Median	Min	Max	Mean	St. Dev	Median	Min	Max	z	p	
Age	35.2	7.6	33.0	27.0	51	34.9	7.9	32.0	25.0	51.0	-0.156	0.876	
8	Internal Capsule Anterior Crus ADC	721.9	54.0	712.0	638.0	805.0	742.7	52.6	744.0	659.0	810.0	-1.245	0.213
	Internal Capsule Anterior Crus FA	536.6	81.4	574.0	385.0	681.0	538.8	101.0	515.0	350.0	703.0	-0.078	0.938
9	Internal Capsule Posterior Crus ADC	729.0	48.7	725.0	645.0	792.0	710.5	65.8	711.0	592.0	824.0	-0.779	0.436
	Internal Capsule Posterior Crus FA	702.0	44.0	700.0	606.0	767.0	720.0	82.0	691.0	608.0	880.0	-0.025	0.979
10	Thalamus ADC	732.5	39.2	731.0	679.0	787.0	760.4	68.8	770.0	675.0	885.0	-0.960	0.337
	Thalamus FA	353.1	52.9	332.0	302.0	437.0	378.6	48.5	396.0	257.0	429.0	-1.064	0.287
11	Cerebral peduncle ADC	724.5	28.9	718.0	681.0	763.0	738.9	58.2	762.0	632.0	818.0	-1.169	0.243
	Cerebral peduncle FA	722.8	56.0	733.0	630.0	791.0	702.4	71.0	713.0	547.0	802.0	-0.675	0.500
12	Pons ADC#	711.8	55.6	688.0	624.0	789.0	756.2	53.3	746.0	686.0	867.0	-1.817	0.069
	Pons FA	525.1	80.5	529.0	404.0	632.0	492.8	89.7	484.0	331.0	678.0	-0.909	0.364
13	Cerebellar WM ADC	669.5	50.0	662.0	608.0	781.0	684.2	43.4	679.0	624.0	778.0	-0.779	0.436
	Cerebellar WM FA	537.8	95.6	587.0	366.0	632.0	502.1	108.7	528.0	353.0	651.0	-0.858	0.392
14	Corpus Callosum anterior ADC	779.0	40.7	771.0	723.0	837.0	776.6	59.1	783.0	669.0	868.0	-0.182	0.856
	Corpus Callosum anterior FA	725.4	57.2	747.0	613.0	816.0	745.8	80.1	763.0	600.0	861.0	-0.987	0.324
15	Corpus Callosum Posterior ADC	712.5	70.9	696.0	602.0	841.0	747.9	83.5	758.0	562.0	886.0	-1.220	0.223
	Corpus Callosum Posterior FA	809.9	70.4	804.0	641.0	917.0	827.0	67.1	835.0	638.0	971.0	-0.753	0.451

* Statistically significant values (p<0.05); # trend-level effect values. WM – white matter; St. Dev – standard deviation; Min – minimum; Max – maximum; ADC – apparent diffusion coefficient; FA – a type of diffusion tensor metric fractional anisotropy.

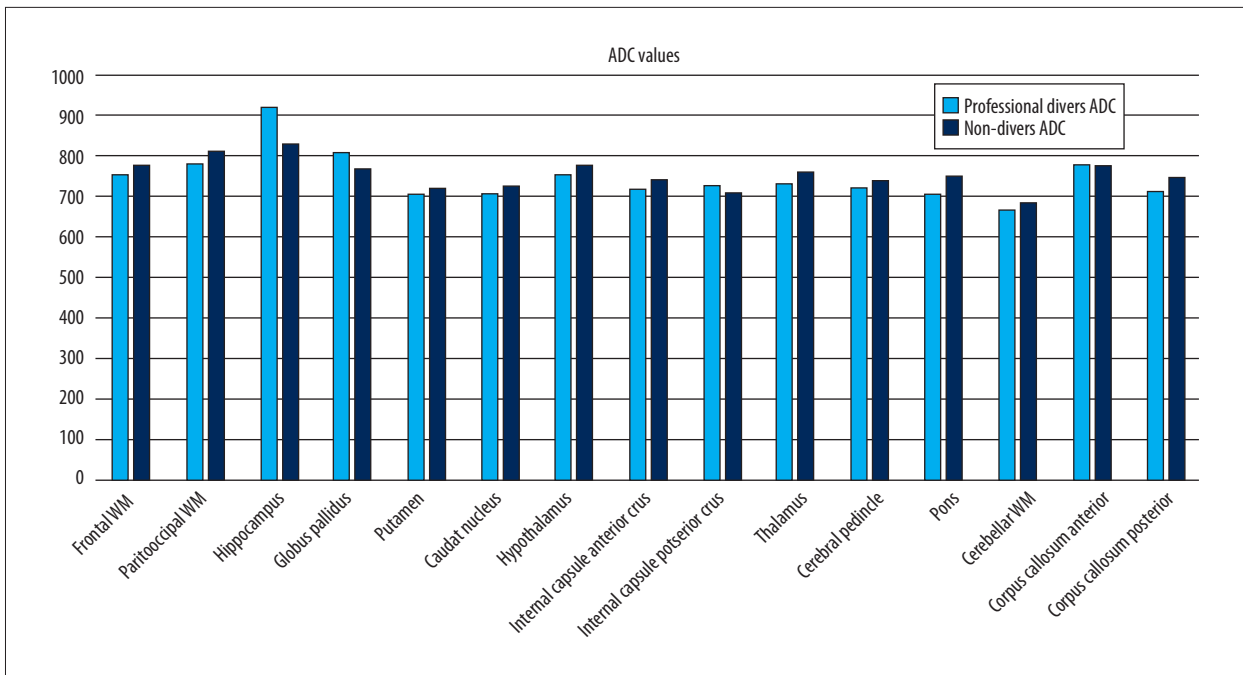


Figure 2. Comparison between ADC values of professional drivers and non-divers.

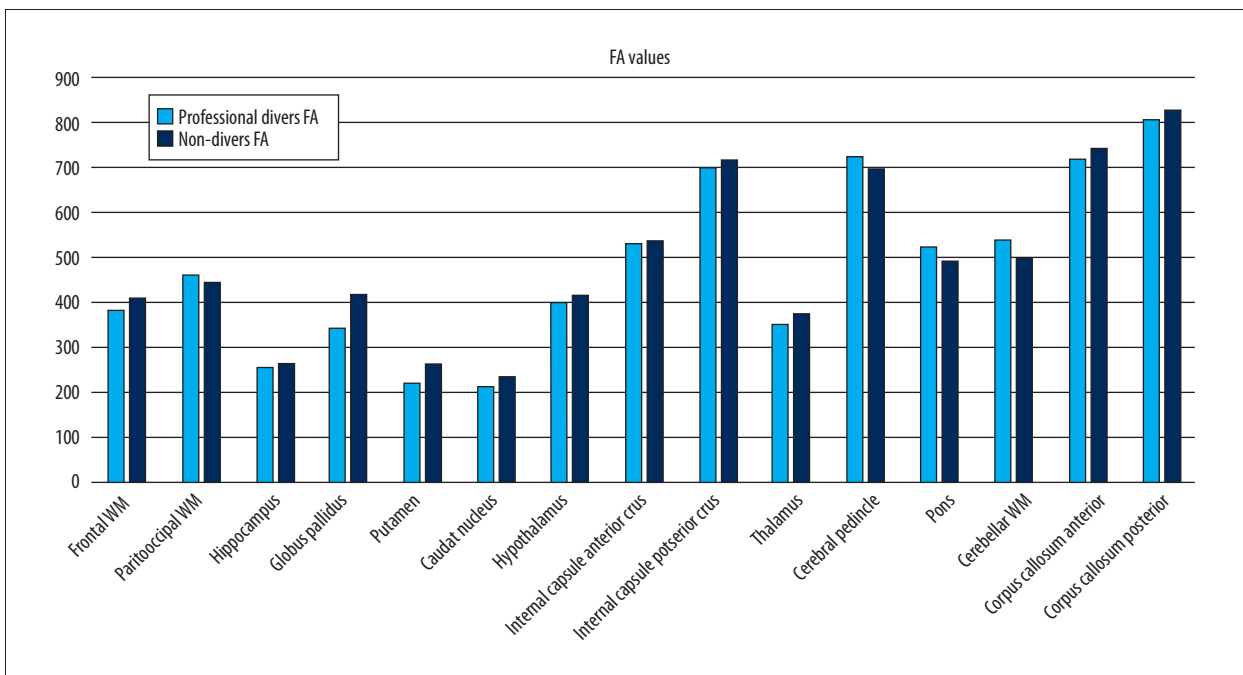


Figure 3. Comparison between FA values of professional drivers and non-divers.

discussing the diagnosis and treatment of DCI [19]. DCI is a complex condition resulting from changed barometric pressure, and includes high-altitude-related events, as well as DCI associated with sudden decrease in pressures during underwater diving [18]. Similarly, healthy experienced divers exposed to frequent hyperbaria also exhibit increased prevalence of such lesions in white matter, even without a past history of acute

neurological DCI. In our study, diving time was more than 1000 hours, depth of diving was more than 30 meters, and the number of dives was more than 500.

Although several relevant case-control studies have been published over the last 15 years, the available reports are inconclusive. Neuropsychological deficit in divers may be related to

Table 4. Comparison of ADC and FA values among divers who had symptoms (forgetfulness and deterioration in fine-motor skills) and divers who were symptomless.

	Professional Divers with forgetfulness and deterioration in fine-motor skills (n=8)					Symptomless Professional Divers (n=3)					Mann-Whitney		
	Mean	St. Dev	Median	Min	Max	Mean	St. Dev	Median	Min	Max	z	P	
1	Hippocampus ADC	925.0	34.2	937.0	904.0	983.0	914.0	42.8	900.0	880.0	962.0	-0.782	0.462
	Hippocampus FA	257.7	62.1	239.0	172.0	379.0	263.3	125.7	201.0	181.0	408.0	-0.632	0.532
2	Globus pallidus ADC#	818.3	56.2	820.0	738.0	878.0	778.1	77.2	762.3	710.0	862.0	-1.746	0.081
	Globus pallidus FA	349.0	48.2	342.0	290.0	442.0	335.7	57.8	309.0	296.0	402.0	-1.328	0.172
3	Putamen ADC	704.0	48.3	698.0	682.0	772.0	716.7	70.9	753.0	635.0	762.0	-0.831	0.406
	Putamen FA	219.3	70.1	193.0	154.0	396.0	234.3	99.0	188.0	167.0	348.0	-1.013	0.311

Trend-level effect values. St. Dev – standard deviation; Min – minimum; Max – maximum; ADC – apparent diffusion coefficient; FA – a type of diffusion tensor metric fractional anisotropy.

a form of subclinical decompression sickness akin to multi-infarct dementia [2,18,19]. This is consistent with the finding that professional high-altitude workers also exhibit increased white matter lesions/changes and supports the proposition that development of white matter injury may be related to intensity of dysbaric exposure (decompression stress). Results of a recently published meta-analysis suggest that repeated hyperbaric exposure increases the prevalence of white matter lesions in experienced divers [2].

In acute DCI, behavioral changes, memory disturbances, intellectual impairment, depression, and long-term neuropsychiatric conditions can be seen. The symptoms may occur as a result of repeated focal ischemia due to intravascular gas bubbles and mural hyalinosis of the small blood vessels [20,21]. The bubbles first form at capillary and venule levels [22,23]. Reduction in blood flow in cerebral tissue and neuropsychological performance were both associated with a history of frequent diving (≥100 dives/year), environmental factors such as diving in cold water, and depth of diving (≥130 feet; approximately 39.6 meters) [19]. DCI occurs as a result of the rapid decrease in ambient pressure that occurs after dissolved gas forms bubbles in tissues and venous blood [23]. The increase of erythrocyte concentration and aggregation, changes in blood viscosity, decreases oxygen transport, changes in local platelet concentrations in the bubble zone, and especially alternation in local concentrations of vasoactive amines and prostaglandins, have significant roles in the pathophysiology of DCI [24].

Hypoxia can open intrapulmonary anastomoses, thus allowing venous bubbles to pass into arterial circulation. This filtration depends on the bubble size. Microemboli or tiny bubbles that

pass entrapment to brain tissue do not cause injuries such as infarction. Normal cerebral circulation starts with the highly oxygenated arterial blood flowing through the gray matter of the brain, where much of the oxygen is used. Decreased oxygenated blood then flows to the long draining veins that carry blood to the white matter of the brain. As a result, small decreases in oxygen content can impair the blood-brain barrier and cause axonal injury [18]. Bubbles that travel through cardiac chambers and do not cause any symptoms are called as silent bubbles. These bubbles can be diagnosed using ultrasound and can cause subclinical lesions [19].

Histological studies showed definitive evidence of subtle changes with no extensive areas of necrosis, including grossly dilated empty vessels in the white matter, small areas of focal necrosis in the gray matter, and diffusely distributed areas of vacuolation of the myelin around small blood vessels [25–27]. Gempp et al. [28] recently reported that that gas microbubbles generated by decompression can impair endothelial function and cause capillary leakage after inner-ear DCI in divers.

The mechanisms of the transient reduction in vascular function caused by repeated hyperbaric exposure, as in diving, are largely unknown [26]. An *in vivo* study by Eftedal et al. [26] concluded that simulated diving can cause cellular responses to oxidative stress related to breathing gas at high partial pressure of oxygen. They suggested that people with a history of vasculopathy associated with high plasma plasminogen activator inhibitor 1 (PAI-1) levels may be predisposed to developing DCI when PAI-1 is further elevated after repeated hyperbaric exposure, as in diving. Mazur et al. [27] showed in their animal experiments that vascular dysfunction after diving is

dependent on the type of blood vessel. They found that vascular dysfunction is triggered by DCI rather than by repeated hyperbaric exposure, such as the diving accident itself.

Neuroimaging studies are helpful in further clarifying the diagnosis of diseases such as DCI. MRI is the best choice of imaging modalities to find pathological changes of DCI, but not all pathological findings seen in MRI should be treated. About 30–50% of hyperintense lesions (e.g., ischemia, edema, and swelling) of the brain and spinal cord can be demonstrated using MRI. These lesions do not enhance with contrast in post-contrast images [3,4,21,29].

All neuroimaging studies have reported the low sensitivity of MRI for detecting CNS injuries/impairments in patients with DCI [21]. This is related to the delay between the diving and performed imaging studies, because urgent hyperbaric recompression treatment is the priority. Furthermore, most of the authors used a 1.5 Tesla system, which has a low sensitivity compared with the 3 Tesla system. Few previously published MRI studies of DCI have used DWI, ADC maps, and DTI/FA. The use of these MRI sequences can increase MRI sensitivity and even provide additional information on the pathophysiology of brain injuries in professional divers. We used these MRI sequences to accurately assess the impairment, even if it was silent, in professional divers. ADC and FA could provide deeper insight into the relevant pathophysiological processes.

Comparing MRI findings of in various brain regions between professional divers and normal non-diving individuals was the basis of our study. In the present study, 15 brain regions (Table 1) were assessed by ADC and FA. In the divers, there were no signs of acute cerebral DCI. Forgetfulness (detected in 6 divers) was statistically significant in both groups ($p=0.002$), while deterioration in fine-motor skills, which was detected in 2 divers was not statistically significant ($p=0.17$). Although hyperintense lesions detected in hippocampal regions and focal white matter changes of our divers group had been showed in several previous studies, such as Rinck et al. [30], Todnem et al. [31], Hutzelmann et al. [20], and Reul et al. [32], the statistically significant results we obtained agree with the results of Reul et al. [32].

Rinck et al. [30] found that 34% of their professional divers versus 42% of their non-divers had lacunar defects. Todnem et al. [31] showed that high signal changes were detected in 19% of the divers (37 divers) versus 41% of their control group (49 control individuals). Hutzelmann et al. [20] demonstrated that 37.3% of divers group and 47.9% of non-divers group had focal white matter changes. Reul et al. [32] found more brain lesions in divers than in control individuals. In the same study, the authors concluded that diving may cause long-term changes in the brain. A recent study reported a significant increase in lesion

volume and number of white matter hyperintensities on MRI of U-2 pilots with occupational exposure to hypobarica [33].

Lesions such as micro-hemorrhage and edema in the spinal cord and brain white matter appear as hyperintense on T2-weighted imaging of cerebral and spinal DCI cases. However, normal T2-weighted MRI scans do not mean that the patients are normal. Investigation of patient complaints has to include sequences of MRIs such as DWI and FA. Many DCI patients complain of significant neurologic deficits that require further investigation to clarify the relevant pathology. DWI is an advanced MRI technique which can quantify the direction and magnitude of water diffusion indices, including fractional anisotropy (FA) and mean diffusion (MD) to detect tissue microstructural abnormalities. FA can identify abnormalities in myelination and axonal integrity in the brain and spinal cord. On the contrary, MD is very sensitive to cytotoxic or vasogenic edema and vascular changes that may occur following strokes [15,21,34–39]. To investigate complaints in our divers group, we achieved neuro-psychometric tests.

Moen et al. [40] studied cerebral diffusion and perfusion deficits associated with DCI in 91 professional divers and 45 control individuals. They used individual parametric images of ADC, CBF, cerebral blood volume (CBV), and mean transit time (MTT) on the basis of diffusion- and perfusion-weighted imaging. They demonstrated that ADC values were significantly higher in the divers than in the control group and found significant differences in gross white matter of brain regions, particularly in the frontal lobe. Differences were also found in the parietal lobe and temporal lobe regions, including the hippocampus. In the cerebellum, higher ADC values were found in the anterior lobes but not in the posterior part. Similarly, Matsuo et al. [41] reported 2 cases with neurologic DCI in which DWI signal intensity was only slightly high, but the areas with FLAIR and T2 hyperintensity showed high ADC values.

DWI is useful imaging technique to evaluate several pathological processes such as multiple sclerosis, traumatic brain injury, and ischemia. DWI can detect both of demyelination processes and axons loss. Such disorders may cause reduction of FA [15,35].

Hutchinson et al. [42] studied the usefulness of DWI for assessment of spinal DCI-related tissue damage. They measured FA and MD in spinal cord white and gray matter regions of samples taken from sheep following hyperbaric exposure to 60–132 feet of seawater (fsw) and 0–180 minutes of oxygen pre-breathing treatment before rapid decompression. They reported that decompression from more than 60 fsw resulted in reduced FA which was associated with cell death and disruption of tissue microstructure in spinal cord white matter tracts. Furthermore, reduced MD in spinal cord gray matter regions, regardless of dive depth, was demonstrated in animals exposed

to prolonged oxygen pre-breathing prior to decompression. Our results showed the same, but in professional divers. We found lower FA values of globus pallidus and putamen (compatible with repeated hypoxia-induced white-matter tract degradation) in divers compared to our control individuals.

DWI and ADC provide functional information about the behavior of water molecules in tissue and ADC reflects changes quantitatively [12–14]. In our study, ADC values of the hippocampus were found to be higher in divers and lower in control individuals. Increased ADC values were due to repeated hypoxia-induced cell damage, resulting in increased extracellular space fluid. Increased extracellular space fluid can show as being high on ADC maps, and if it is high enough, it can be seen as hyperintense on T2-weighted MRI [12–14,21]. Moen et al. [40] demonstrated higher ADC values in the cerebellum, hippocampus, and frontal and temporal white matter. In our results, ADC values in the pons, parieto-occipital white matter, and globus pallidus showed trend-level effects from DCI ($p=0.069$, $p=0.082$, and $p=0.087$, respectively), which may be due to our small sample sizes.

The present study has some limitations that must be considered. Although this was a prospective study, the sample size was relatively small (11 experienced divers compared with 15

normal individuals). The sample does not represent a wide geographical area, as all the subjects were from Istanbul and surrounding areas. The results represent a single-institute experience, and other institutes may show different results. Further prospective randomized studies with larger samples and homogeneity (in age, diving depth, diving time, and type of gases and equipment used) between cohort and control groups are required to improve the representativeness of the results.

Conclusions

Repeated hyperbaric exposure increases the risk of white matter damage in experienced healthy divers without neurological decompression illness. This is consistent with previously published reports. The hippocampus, globus pallidus, and putamen are the areas of the brain responsible for memory, learning, navigation, and fine-motor skills, and are sensitive to repeated hyperbaric exposure. Further prospective studies with larger sample sizes are necessary to investigate these findings systematically.

Conflicts of interest

None.

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