Prevalence of Patent Foramen Ovale (PFO) and MRI-lesions in mild neurological Decompression Sickness (Type B-DCS/AGE).

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Koch AE, Kirsch H, Reuter M, Warninghoff V, Rieckert H, Deuschl G. Prevalence of Patent Foramen Ovale (PFO) and MRI-lesions in mild neurological Decompression Sickness (Type B-DCS/AGE). Undersea Hyperb Med 2008; 35(3):197-205. Background: Neurological decompression sickness (DCS/AGE) may cover two variants with either severer and probably central nervous (Type A) or milder and sometimes doubtful neurological symptoms (Type B). The pathophysiology of the Type B-DCS/AGE might be different from the Type A-variant. In Type A-DCS/AGE a higher PFO-prevalence (patent foramen ovale) points towards an embolic origin of the Type A-symptomatology. This is not necessarily expected for the Type B-DCS/AGE if the pathophysiology here is micro-embolic or even non-embolic. Methods: 18 patients with Type B-DCS/AGE were tested against matched controls for presence and size of a PFO with echocardiography and transcranial ultrasound with echo-contrast. Prevalence and number of Type A-brain lesions were visualized by cranial MRI as possible sequelae from gas-embolic events. Results: PFO-prevalence in both groups, the patients with Type B-DCS/AGE (5/18) as well as the controls (7/18) was similar to published PFO-prevalences in normals without any difference between patients and controls (p=0.725). Also the number of MRI-lesions (ACFs) was the same for Type B-DCS/AGE cases (15 ACFs in 5 patients) and controls (37 ACFs in 8 divers). Conclusion: Indirect findings suggesting embolic brain injuries are found with similar frequency in patients with Type B-DCS/AGE and normal controls, which is in contrast to data about Type A-DCS/AGE. This is compatible with different pathophysiological mechanisms involved in the Type A- and Type B-DCS/AGE.

INTRODUCTION

The ascent at the end of a dive is a risky phase because of possible decompression hazards. Although modern decompression tables and diving computers help to reduce diving-associated risks to a minimum, decompression illness (DCI) with neurological symptoms is estimated to occur in 2.7 out of 10,000 dives (1). However, in many cases of neurological DCI the clinical presentation does not allow a clear separation into decompression sickness and arterial gas embolism, and therefore the clinical term “DCS/AGE” was proposed before for decompression related incidents with neurological symptoms (2).

In DCS/AGE there is evidence that paradoxical arterial gas embolisms due to right-
to-left shunting through a Patent Foramen Ovale (PFO) may be responsible for severe central nervous and often stroke-like neurological symptoms (1,3-9) after decompression.

A PFO is found in approximately 30% of the normal population (1, 10, 11) and its role as a major risk factor for DCS/AGE has been confirmed by several reports on diving accidents (1, 3,4,6-8,12,13). In addition, there is a still ongoing discussion about the PFO as a possible risk factor for ischemic stroke due to paradoxical embolism of thrombotic material from the venous system (14-17) or migraine with aura (18). In diving, the PFO was estimated to increase the overall risk for a DCS/AGE by a factor of 2.5 (1).

However, neurologists dealing with diving accidents are familiar with a broad spectrum of clinical presentations of patients with DCS/AGE. The symptoms can vary from milder and sometimes even doubtful neurological symptoms (Type B-DCS/AGE) to the mentioned above severer, more stroke-like and sometimes life-threatening conditions (Type A- DCS/AGE).

In the previous published studies about the role of a PFO in diving accidents cases with severe neurological symptoms (Type A) were not separated from those with a milder symptomatology (Type B), but it seems that the majority of the reported cases had suffered from a Type A-DCS/AGE with severer symptoms (1,3,4,6-8,12,13).

Assessment for a PFO in patients presenting exclusively with the milder neurological symptoms of a Type B-DCS/AGE after diving with a relative safe depth-time profile or a hyperbaric exposure has not been reported so far, although this clinical picture is common in professional as well as sports diving. Instead, conclusions and recommendations for risk factors and treatment in DCS/AGE are mostly based on data from cohorts suffering primarily from severer neurological symptoms and cannot necessarily be generalized to the whole variety of clinical presentations.

Therefore, it was the approach of the presented study to compare patients exclusively presenting with symptoms of the mild Type B-DCS/AGE after a relative safe dive or hyperbaric exposure with a control group of divers without any history of DCI. Both groups were investigated with respect to the prevalence of a PFO and the number of lesions on magnetic resonance imaging (MRI) of the brain as possible sequelae of gas embolisms inside the cerebrum.

**METHODS**

180 patients, who had suffered from a DCS/AGE with neurological symptoms and were treated in the hyperbaric chamber of the German Naval Medical Institute in Kiel between 1991 and 2001, were retrospectively classified into the Type A- or the Type B-subgroup of DCS/AGE.

The symptom-based criteria for classification into the Type A-DCS/AGE and the Type B-DCS/AGE were defined in cooperation with experienced neurologists according to typical clinical neurological standards. These criteria were widely concordant to the SANDHOG-criteria used recently for DCS-diagnosis by Grover et al (19).

Criteria of classification into Type A- and Type B-DCS/AGE:

Type A-criteria:
- Paresis, paralysis and/or complete anesthesia of one or more limbs (3 points SANDHOG)
- pathological reflexes (3 points SANDHOG)
- signs of incontinence (3 points SANDHOG)
- severe vertigo (2 points SANDHOG)
• complete loss of consciousness after surfacing
• obvious anisocoria
• nystagmus

Type B-criteria:
• signs of dysaesthesia and paraesthesia/numbness without a clearly defined neurological pattern (1/2 - 2 points SANDHOG)
• subjective muscle weakness (of minor degree)
• blurred vision (1 point SANDHOG)
• nausea / vomiting (1/2 point SANDHOG)
• extreme fatigue and/or headache after surfacing (1/2 point SANDHOG)
• dizziness (doubtful symptom SANDHOG)

41 patients with a Type B-DCS/AGE fulfilled all inclusion criteria for the presented study, which were
[1] “Type B” neurological symptoms
[2] within less than 30 minutes after decompression from a dive/hyperbaric exposure
[3] without decompression related problems, e.g. omitted decompression or emergency ascent, likely to cause severe DCS or barotrauma, and
[4] full recovery from the symptoms after hyperbaric treatment (overview in Table 1, see page 200).

18 of the 41 patients participated in the study (15 males and 3 females, age 37±10.2 years; mean of 888 dives, ranging from 7 to 6,000 dives). Selection was only based on the random process of availability of assessment slots. The control group consisted of 18 healthy divers matched for gender, age and diving experience (age 40.3±12.7 years; mean of 870 dives, ranging from 110 to 5,500 dives), with no history of DCI randomly selected from Navy personnel during routine tests.

All participants had given written informed consent. The study protocol was approved by the Ethical Committee of the University of Kiel, Germany, and had been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Each control subject was examined according to the current German Navy rules, with special screening for neurological abnormalities suggestive for sequelae of previous DCS/AGE. All controls confirmed that they had never had any symptoms of DCI.

All subjects underwent a cranial MRI with T1-weighted SE-images coronally, T2-weighted transverse TSE-images, sagittal T1-weighted TSE images, and transverse FLAIR-technique images (1.5 Tesla Vision, Siemens, Erlangen, Germany). They were then examined and documented by two radiologists independently. The radiologists were also blinded to the results of the PFO-detection testing (11, 20) (bubble test) performed by the PFO-detection team, which was blinded to the MRI results. Venous access was obtained in the right antecubital vein, and the test subjects assumed the left lateral decubitus position. Two bi-directionally pulsed Doppler probes for Transcranial Doppler Ultrasound (TCD) were positioned and fixed with a headset to measure blood flow velocity in both middle-cerebral arteries (MCA) and to detect gas bubbles in these vessels (Multi-Dop X4, DWL, Sipplingen, Germany). Exact time and flow data were stored digitally on a DAT recorder and on hard disk. The echocardiography (Aloka SSD 870 and Aloka PhD 5500) was performed in the four-chamber view from apex and stored on videotape.

Baseline measurements of the flow in the MCA and a four-chamber view by TTE (21) were recorded. The subjects were trained to perform a Valsalva maneuver (VM), controlled by the visible decrease in cerebral blood flow velocity of about 20 percent (5).
### A

<table>
<thead>
<tr>
<th>Type B-DCS/AGE</th>
<th>Age / Gender</th>
<th>Body Mass Index</th>
<th>Smoking Pack-Years</th>
<th>No. of Dives</th>
<th>Dive profile of incident [m]</th>
<th>No. of Hyperbaric Treatments</th>
<th>Symptoms</th>
</tr>
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<tr>
<td>1</td>
<td>41/45m</td>
<td>28</td>
<td>0</td>
<td>240</td>
<td>15</td>
<td>pos. 1</td>
<td>Dysesthesia, hyperesthesia</td>
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<tr>
<td>2</td>
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<td>22</td>
<td>9</td>
<td>30</td>
<td>45</td>
<td>0 neg. 2</td>
<td>Dizziness, nausea, paraesthesia</td>
</tr>
<tr>
<td>3</td>
<td>27/f</td>
<td>26</td>
<td>12</td>
<td>14</td>
<td>131 Chamber</td>
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<td>Paresthesia left leg, back pain</td>
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<tr>
<td>4</td>
<td>57/m</td>
<td>28</td>
<td>37</td>
<td>3500</td>
<td>15</td>
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<tr>
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<td>28</td>
<td>10</td>
<td>600</td>
<td>22</td>
<td>20</td>
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</tr>
<tr>
<td>6</td>
<td>36/m</td>
<td>32</td>
<td>16</td>
<td>13</td>
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<td>27</td>
<td>6000</td>
<td>30</td>
<td>55</td>
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</tr>
<tr>
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<td>24/m</td>
<td>24</td>
<td>6</td>
<td>30</td>
<td>45</td>
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<td>59/m</td>
<td>26</td>
<td>39</td>
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<td>50</td>
<td>30 Chamber</td>
<td>10 neg. 1</td>
</tr>
<tr>
<td>10</td>
<td>24/m</td>
<td>27</td>
<td>7</td>
<td>20</td>
<td>35</td>
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<td>Nausea, paraesthesia both lower limbs</td>
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<td>11</td>
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</tr>
<tr>
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<tr>
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<td>21</td>
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### B

<table>
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<th>Control Group</th>
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<th>Body Mass Index</th>
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<th>No. Dives</th>
<th>No. of Hyperbaric Treatments</th>
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<td>pos. 0</td>
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<tr>
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</tr>
<tr>
<td>24</td>
<td>62/m</td>
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<td>250</td>
<td>0</td>
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</tr>
<tr>
<td>25</td>
<td>36/m</td>
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<td>8</td>
<td>780</td>
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<tr>
<td>26</td>
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</tr>
<tr>
<td>27</td>
<td>32/m</td>
<td>29</td>
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<td>400</td>
<td>0</td>
<td>neg. 0</td>
</tr>
<tr>
<td>28</td>
<td>36/m</td>
<td>24</td>
<td>0</td>
<td>300</td>
<td>2</td>
<td>pos. 0</td>
</tr>
<tr>
<td>29</td>
<td>39/m</td>
<td>32</td>
<td>0</td>
<td>550</td>
<td>5</td>
<td>pos. 0</td>
</tr>
<tr>
<td>30</td>
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<td>180</td>
<td>5</td>
<td>neg. 0</td>
</tr>
<tr>
<td>31</td>
<td>20/m</td>
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<td>0</td>
<td>110</td>
<td>0</td>
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</tr>
<tr>
<td>32</td>
<td>32/m</td>
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<td>400</td>
<td>0</td>
<td>neg. 0</td>
</tr>
<tr>
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<tr>
<td>34</td>
<td>52/m</td>
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<td>110</td>
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<td>1 neg. 0</td>
</tr>
<tr>
<td>35</td>
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<td>19</td>
<td>950</td>
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<tr>
<td>36</td>
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<td>480</td>
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</tr>
</tbody>
</table>

### Tab 1, A and B.

Synopsis of the clinical data in the 18 patients with Type B-DCS/AGE and the 18 divers of the control group. All dives with compressed air; chamber-exposures with compressed air, decompression partly with oxygen.

For the contrast medium application (Echovist 300, Schering, Berlin) the subject was instructed to perform the same effective Valsalva maneuver for 10 seconds and then to release it. In the 7th second, 8 ml of contrast agent were injected as a bolus (4, 22). If a PFO was detected with VM, the same procedure was repeated without VM to detect additional spontaneous right-to-left shunting.

### Diagnostic criteria

**MRI:** Hyperintense lesions in MRI were counted as abnormal cerebral findings (ACFs) in the study as published before (23).
The combination of T1, T2 and FLAIR sequences used in this study allowed for a discrimination against liquid-filled (cerebrospinal fluid) normal anatomical structures, e.g. Virchow-Robin spaces.

**PFO detection (Bubble test):** PFO testing was considered positive by TTE when at the time of opacification of the right atrium signals of contrast medium were clearly visualized in the left atrium. PFO testing was positive by TCD when at least five HITS (hyperintense transient signals) were recorded in the flow of the MCA within a time window of 10 seconds after Valsalva release (11). Later signals in TCD and TTE were attributed to pulmonary shunts.

**RESULTS**

No study participant from both, the Type B-DCS/AGE- and the control group, showed any abnormal neurological signs on medical exam. All patients in the Type B-DCS/AGE-group were free of any residual symptoms after a maximum of two hyperbaric chamber treatments (Table 1).

The bubble test revealed a PFO in 5/18 patients from the on-Type A-DCS/AGE-group. Three patients had spontaneous shunting of which one was also seen on TEE. In the control group, 7/18 divers showed a PFO. Three had spontaneous shunting; four showed shunting only during the Valsalva maneuver (Table 2). There is no significant difference between the PFO-prevalence and PFO-grading in Type B-DCS/AGE and controls.

<table>
<thead>
<tr>
<th>No PFO</th>
<th>PFO ≥ 10 signals in TCD</th>
<th>PFO ≥ 20 signals in TCD</th>
<th>PFO with spontaneous shunting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type B-DCS/AGE</td>
<td>13</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Controls</td>
<td>11</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

**Tab. 2.** PFO-prevalence and PFO-grading in the Type B-DCS/AGE-group and the controls. No differences were found between Type B-DCS/AGE and controls.

A total of 15 abnormal cerebral findings (ACFs) was found in five patients with Type B-DCS/AGE: in three cases only one ACF was found in MRI, one patient showed two ACFs, and one patient showed 10 lesions (59 years, male, 1500 dives, headache, PFO-negative, 39 pack-years of smoking).

In the control group 37 ACFs were found in 8 divers; in three cases only one ACF was found in MRI, in one case two ACFs, in two cases five ACFs, in one case 10 (62 years, male, 2500 dives, PFO-positive (10 HITS in TCD), non-smoking), and in one case 12 ACFs (45 years, male, 400 dives, PFO-negative, non-smoking). There is no significant difference between the groups in prevalence ($p=0.489$, Fisher test) or number of ACFs ($p=0.230$, Mann-Whitney-U test; since the ACFs are patently not normally distributed, this test was used for all comparisons involving ACFs).

Of the 18 patients in the Type B-DCS/AGE-group, only two (11 percent) were found to be positive in both, PFO testing and in MRI (at least one ACF by MRI). In the control group, three divers (17 percent) were positive in PFO testing and MRI scanning (Table 3).

<table>
<thead>
<tr>
<th>No PFO</th>
<th>PFO-test positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ACFs in MRI</td>
<td>ACFs in MRI</td>
</tr>
<tr>
<td>Type B-DCS/AGE</td>
<td>10</td>
</tr>
<tr>
<td>Controls</td>
<td>6</td>
</tr>
</tbody>
</table>

**Tab. 3.** Comparison of Type B-DCS/AGE-group vs. controls with respect to the combinations between PFO-negativity / -positivity and abnormal cerebral findings (ACFs) in MRI / no ACFs in MRI. No differences were found between Type B-DCS/AGE and controls.

The mean number of ACFs in all PFO-positives was $1.58±3.03$, not significantly different from the PFO-negatives ($1.38±3.17$).
ACFs; p=0.625). The same results were found in the patients-group alone (PFO-positives 0.4±0.55 ACFs; PFO-negatives 1.00±2.77 ACFs; p=0.661) as well as in the controls (PFO-positives 2.43±3.82 ACFs; PFO-negatives 1.82±3.68 ACFs; p=0.842). We found a significant correlation between age and the number of ACFs in the entire group of examined divers (Spearman rho=0.49; p=0.002) as well as in the Type B-DCS/AGE-group (rho=0.52; p=0.026) and the control-group (rho=0.43; p=0.074). The number of dives was also significantly correlated with the MRI findings (rho=0.39; p=0.019), since it increased with age in our group. Smoking habits were not correlated with the MRI-findings (all data in Table 1).

**DISCUSSION**

Our patients, who had shown exclusively the mild neurological symptoms of a Type B-DCS/AGE within 30 minutes after decompression from a dive or hyperbaric exposure did neither present with an elevated number of hyperintensities in MRI in comparison to the matched control group of healthy divers, nor with an elevated prevalence of PFO-positivity. Thus, both results are compatible with the hypothesis that in contrast to the more severe Type A-DCS/AGE (1,3,4,6-8,12,13) PFO-positivity is not a risk factor for the Type B-variant of DCS/AGE.

In the current literature there is still a lack of informations regarding possible differences in the pathophysiologies of decompression related incidents with milder neurological complaints (Type B-DCS/AGE) versus the much better investigated Type A-DCS/AGE. Wilmshurst & Bryson (24) had defined ‘indeterminate DCS’ but had too few cases to address the significance of PFO. Cantais (13) noted a lack of correlation between PFO and ‘osteomyoarticular’ (non-neurological) DCS but did not address mild neurological DCS. Torti (9) had defined ‘minor DCI signs’ but did not analyze them. Germonpré (4), finally, did not observe a relationship between spinal DCS and PFO. He alluded to some mild cases in his series, but detailed information was not presented.

The objection might be raised here that our study was underpowered to detect a relation between PFO-positivity and occurrence of Type B-DCS/AGE due to the limited number of cases. If we assume as an alternative hypothesis that the prevalence of PFO in Type B-DCS/AGE patients is really as high as in patients presenting with severer Type A-symptoms, i.e. around 60% according to the available literature, as opposed to a value of about 30% in the general population, then the two-sided Fisher test with n=18 patients/controls per group has a power of only about 36% to discover this difference as significant. Note, however, that in our study we have a p-value, which is comfortably away from the significance limit of 0.05 and that, moreover, the PFO-prevalence in our group of Type B-DCS/AGE even lies below that of the control group. Such an outcome is very unlikely under the alternative hypothesis. In fact, if we assume our patients to be randomly drawn from a group with 60% PFO-prevalence and the controls randomly drawn from a group with 30% PFO-prevalence (4,6,8,10,11,13,25), then all outcomes with an odds ratio at least as extreme as ours have a probability of less than 1% altogether of occurring. Thus, this particular alternative hypothesis can be rejected.

All patients in our study had fulfilled the criteria of showing exclusively signs of a Type B-symptomatology within 30 minutes after surfacing from a regular dive/hyperbaric exposure, and all had shown a full recovery from the symptoms after a maximum of two HBO-treatments. We could also have included the question if there was evidence for unsafe diving,
for example emergency ascents. However, there is at least one study demonstrating that even under the conditions of diving safely such severe Type A-DCS/AGE can occur (9). In this particular group, however, the frequency of PFOs was significantly higher. Thus, even when diving safely according to the established rules the formation of bubbles and secondary arterialization via right-to-left shunting cannot be entirely excluded. A weakness of our study is that we do not have a group of divers with Type A-DCS/AGE included into the design of this study. However, the proposed separation of DCS/AGE into the Type A- and the Type B-variant is based on such simple clinical criteria that the findings of our study could validly be distinguished from earlier publications about Type A-DCS/AGE (4,8).

It might further be argued that our results should not be compared with these published data from severe DCS/AGE-cases with a Type A-neurologic symptomatology (4,8) because of differences in the techniques used for PFO-detection.

Transthoracic echocardiography (TTE), which had been used by Wilmshurst is known to provide only a reduced sensitivity compared to the alternative methods, the transesophageal echocardiography (TEE) used by Germonpré and our combination of transcranial Doppler-Ultrasound (TCD) and TTE (20, 26-28). In addition, it has been shown recently that Echovist 300® is superior to agitated saline in detecting TEE-proven right-to-left shunts (29-31).

Thus, due to the combination of TCD, TTE and Echovist 300® in our study we can confidently assume that we not have underestimated the occurrence of a PFO in our patient group and therefore our findings can be compared with data from literature.

MRI-imaging was also used in our study to detect possible morphologic sequelae of DCS/AGE-related pathology. Although it is generally accepted that severe sequelae of diving are usually associated with hyperintensities (23, 32-36) we did not find differences between our Type B-DCS/AGE patients and the controls. Only individual age was positively correlated to the number of ACFs in MRI like published before (37), and other possible risk factors, e.g. smoking habits and hypertension, did not play a role in our study. It could have been argued that our control group were also divers, but we know from our earlier work that even professional divers with thousands of diving hours do not exhibit abnormalities of the brain-MRI if diving safely (23). This does not exclude that more sophisticated MRI-methodology of the brain and additional MRI of the spinal cord may uncover abnormalities in Type B-DCS/AGE in the future as shown before in more severe Type A-DCS/AGE (38,39), since the anatomic localization of lesions in mild neurological symptoms is still unknown and might include not only the brain, but also the spinal cord, dorsal root or the peripheral nerve. More research is awaited in this field. At the present state of our knowledge, however, it seems justified to conclude that abnormalities of the brain-MRI are not a feature of the Type B-DCS/AGE but can be a feature of the Type A-variant.

Thus, the negative findings in the combination of PFO-diagnostic and MRI-imaging of the brain compared to our control group support the hypothesis that in our group of Type B-DCS/AGE major embolic events inside the cerebrum were not the cause for the presented clinical symptomatology.

However, exercise-dependent (40) pulmonary shunting of small-sized nitrogen bubbles could be considered as another possible pathomechanism in Type B-DCS/AGE. Such minor embolic events might cause an only mild Type B-symptomatology and might remain without visible lesions in cerebral MRI. Our PFO-testing with transcranial ultrasound
bubble detection during the Valsalva maneuver did not uncover significant pulmonary shunting, but was performed under resting conditions as common. Thus, we cannot finally exclude solely exercise-dependent pulmonary shunting in our divers.

From a clinical point of view we must finally consider that in some cases of Type B-neurological symptoms after a dive or hyperbaric exposure other medical causes like an acute psychiatric disorder, might have imitated a Type B-DCS/AGE. Since in all patients the clinical diagnosis was based only on the initial symptomatology after surfacing, a not diving-related cause for the Type B-neurologic symptoms cannot be excluded in some cases on the basis of the paraclinical test results alone. This issue has also recently been discussed by Grover (19). However, we did not find clinical evidence for a conversion disorder in our patients despite careful clinical assessment.

In conclusion, the negative results of our controlled study support the hypothesis that in Type B-DCS/AGE with milder neurological complaints right-to-left shunting of nitrogen bubbles via a PFO with subsequent gas embolisms in the cerebrum is unlikely to be the cause of the presented symptomatology. This is in contrast to findings in Type A-DCS/AGE with severe neurological symptoms and suggests that in Type B-DCS/AGE a PFO is unlikely to have been involved in the pathophysiology of the diver’s illness.

More research is necessary to elucidate the pathophysiology of the Type B-DCS/AGE, and also other than solely decompression-related reasons must be taken into account.

REFERENCES

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