The causes of migraine are still unknown, but several triggers of the attacks have been identified so far. It has been hypothesized that the presence of patent foramen ovale (PFO) and of paradoxical cerebral micro-embolism may increase the risk of migraine, in particular migraine with aura. In facts, patients suffering from migraine (with aura and without aura) showed higher prevalence of PFO. Moreover, the trans-catheter closure of cardiac shunts showed a certain effect on the frequency and severity of attacks in patients with migraine. However, when an incomplete closure can be detected by contrast echocardiography, i.e. echocardio-
circulation during the diagnostic procedure is sufficient to induce migraine crises.\textsuperscript{7}

This supports the idea that micro-bubbles entering the brain circulation can trigger a headache, as also shown in rats, in which many cortical stimuli including ischemia can induce cortical spreading depression, the putative electrophysiological event underlying migraine.\textsuperscript{8}

Diving, an activity characterized by high intra-thoracic pressures and frequent Valsalva manoeuvres which are performed to re-equilibrate the pressure in the middle ear, is accompanied by high risk of paradoxical brain micro-embolism and migraine.\textsuperscript{9-12}

It has been shown that divers with PFO suffer from migraine more frequently than divers without PFO. In particular, larger PFO are associated with increased prevalence of migraine with aura, both after diving and in everyday life.\textsuperscript{13}

Contrast trans-thoracic echocardiography is a safe and simple procedure to assess the presence of a foramen ovale pervium. The contrast, an agitated air-saline solution, causes a harmless pulmonary micro-embolism. When a PFO is present, the inoculation of the solution in a peripheral vein may cause an apparently innocuous cerebral micro-embolism.

To establish whether cerebral micro-embolism may initiate migraine crises in PFO carriers we studied 24 divers, using a contrast trans-thoracic echocardiographic technique.

If cerebral micro-embolism represents a trigger for migraine, we should expect that in divers with PFO, rather than in divers without PFO, the inoculation of the contrast may induce migraine attacks during or after the echocardiographic procedure.

**METHODS**

**Study population.** Twenty-four professional male scuba divers participated in this study. The subjects are part of the Emergency firefighter scuba unit of Rome, throughout the Italian region of Lazio, working in safety operations. The enrolment was based on volunteer participation.

All the participants were given a complete description of the study and gave their informed consent to take part. The local ethics committee approved the study.

Women were not included, to avoid an additional variable represented by hormonal therapy or menses, which may conceal the occurrence of migraine.

Divers use compressed air and limited their descent to 50 metres depth (see Table 1).

The subjects were interviewed carefully for their diving and medical history, including medication, alcohol use and smoking habits. No subject had a history of stroke or transient ischemic attack. The blood screening, including hemochrom, glycaemia, liver and kidney functions, protein electrophoresis, blood

| Table 1: General characteristics of a population of divers (n=24) |
|----------------------|----------------------|----------------------|
| Age, years           | 40.1 ± 6.4 (range 29-53) |
| Education, n (%)     | Elementary school 1 (4) |
|                      | Intermediate school 19 (79) |
|                      | High school 2 (8) |
|                      | Degree 2 (8) |
| Body Mass Index      | 26.6 ± 4.2 |
| Hypertension, n (%)  | Never 1 (4) |
| Smoking, n (%)       | <3 cigarette/day 10 (42) |
| Alcohol use, n (%)   | >3 cigarette/day 0 (0) |
| Diabetes, n          | 0 |
| Drugs, n             | 1 (4) one diver assumes furosemide per os (10mg/3 times a week) |
| Coagulation abnormalities, n | 0 |
| High cholesterol, n | 0 |
| Tendon hyper-reflexia | 0 |
| Scuba dives per year (max 50 mt) | 467 ± 441 (range 40-1950) |
| Migraine, n (%)      | 6 (25) |
| MoA                   | 5 (20.8) one crisis/week (n=3), one crisis/month (n=2) |
| MA                    | 1 (4.2) one crisis > three months |
| Tension type headache, n (%) | 9 (37.5) |
| Decompression Sickness, n (%) | 3 (12.5) |

MoA=migraine without aura; MA=migraine with aura; n=number
coagulation, cholesterol and lipoprotein dosage, and the blood pressure at rest were normal. Body-mass index (BMI) was calculated as weight (Kg)/height (m)². All subjects underwent a normal electrocardiogram stress test, performed in a separate session.

An otolaryngologic evaluation, including audiological and vestibular assessment excluded any malfunction of the middle or inner ear. No diver showed any abnormality at the neurological examination.

All subjects underwent brain magnetic resonance investigation (Gyroscan NT Intera Philips 1.5 Tesla), and cerebral ischemic lesions were defined as areas of abnormally high signal intensity (hyper-intense lesions) on DP-T2 and FLAIR sequences, according to the article of Vermeer et al. 14

Divers were interviewed about major decompression sickness episodes (DCS). This syndrome, frequently observed in PFO carriers includes a wide spectrum of neurological signs, such as paralyses, paresthesias, vertigo, ataxia, speech disturbances, unconsciousness, cognitive and visual deficits, urinary incontinence, as well as headache.15,16 Guidelines for the diagnosis of migraine, according to the International Classification of Headache Disorders, 2nd edition, were applied in the study group.17

A questionnaire about migraine was completed after the echocardiography, with divers unaware of the results of the cardiologic procedure. Blood pressure measured after the echocardiogram was normal.

The results of the magnetic resonance and echocardiography were given directly to the participants.

**Results**

The general characteristics of the participants are shown in Table 1.

In their medical history, six out of 24 (25%) divers suffered from migraine, one diagnosed as migraine with aura. Among the six migraineurs, one diver showed a small PFO and another diver had a medium-sized PFO. This latter suffered from migraine with aura, which consisted of rare episodes of paresthesia on the left side of the body.

In all subjects, the history of migraine predated the diving career.

The migraineurs reported a crisis once a week (n=3) or once a month (n=3). Nine divers (37.5%) complained of episodic tension headache (one to two crises per month).

The intensity of the migraine crises was generally described as low, and rarely divers reported nausea, photo- or phonophobia. The six migraineurs complained of worsening of the symptoms with physical exertion. Only one diver reported a migraine crisis soon after diving.

Eight PFO were detected in 24 divers (33%). In five subjects, the dimension of PFO was minimal, i.e. visible only during Valsalva. In one diver, PFO was of small entity, and in two, a medium foramen ovale was found. No large foramen ovale was recognized in this study group.

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**Table 2: Characteristics of divers without and with PFO**

<table>
<thead>
<tr>
<th></th>
<th>Divers without PFO (n=16)</th>
<th>Divers with PFO (n=8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>38.9 ± 5.5</td>
<td>44.5 ± 6.9</td>
<td>ns</td>
</tr>
<tr>
<td>Dives, n</td>
<td>447.5 ± 486.3</td>
<td>513.9 ± 359.2</td>
<td>ns</td>
</tr>
<tr>
<td>Bio-mass Index</td>
<td>26.6 ± 4.7</td>
<td>26.4 ± 3.0</td>
<td>ns</td>
</tr>
<tr>
<td>Education level, years</td>
<td>2.3 ± 0.7</td>
<td>1.9 ± 0.4</td>
<td>ns</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177.9 ± 6.1</td>
<td>173.7 ± 4.9</td>
<td>ns</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>82.0 ± 11.6</td>
<td>79.6 ± 10.1</td>
<td>ns</td>
</tr>
<tr>
<td>Cigarettes, n</td>
<td>1.5 ± 2.3</td>
<td>1.9 ± 2.6</td>
<td>ns</td>
</tr>
<tr>
<td>Brain lesions, n</td>
<td>1.3 ± 2.4</td>
<td>10.8 ± 26.5</td>
<td>ns</td>
</tr>
</tbody>
</table>

n=number; ns=not significant

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**Trans-thoracic Echocardiography investigation.** It was performed with an imaging system Acuson Sequoia using a multi-hertz probe and second harmonic function. The images were acquired from apical, para-sternal and sub-costal views. A patent foramen ovale was defined as the occurrence of at least one detected in the left atrium within three cycles after peripheral injection of contrast agent into the ante-cubital vein (agitated saline: 9 ml of saline solution plus 1 cc of air). The test was repeated twice at rest and twice during ten seconds of Valsalva manoeuvre, performed three seconds after the saline injection. The shunt was considered small when less than ten micro-bubbles were detected, medium if more than ten micro-bubbles were seen and large if all the left atrium was opaque after contrast injection. Regarding the classification used in the article of Souteyrand et al, we established the “minimal” grade of PFO as if any micro-bubble was detected only with Valsalva manoeuvre but not at rest.18

**Statistical analysis.** We used the unpaired two-tailed Student’s t-test to compare normally distributed variables (age, BMI, height, weight, number of dives per year, number of cigarettes per day, education level) between the two groups (PFO/no PFO carriers).

The Statistical Package for the Social Sciences (SPSS) for Windows, version 16.0 was used for the analyses.
Twelve out of 24 divers (50%) showed brain spots on MR. Seven divers (29.1%) had multiple cerebral foci (>2). The majority of the foci were detected in the frontal and temporal regions, mostly consisting of spots <5 mm in the deep white matter.

The divers with PFO were similar to the divers without PFO, with respect to the age, BMI, height, weight, dives performed per year, education level, and smoking habits.

The presence of PFO was not associated with higher prevalence of migraine, DCS or brain lesions (Table 2).

No diver suffered from any headache crisis soon after or in the 24 hours following the echocardiographic exam. Only one diver reported nausea, without migraine, starting after the echocardiography. The following day, he suffered from flu-like symptoms. This diver did not usually have migraine.

**DISCUSSION**

Several elements, such as physical exertion, stress, intense lights, noises, odours or a variety of foods are capable of provoking an attack of migraine, although the relationship between these triggers and the crises is not always obvious.1,19

Diving, an activity associated with several conditions which promote the haematic formation of air micro-bubbles, can favour the passage of micro-emboli to the brain circulation through a right-to-left shunt.9,11,13

In divers, cerebral embolism caused by nitrogen bubbles entering the brain circulation leads to decompression sickness, a neurological disease often including headache.13,15,16

Divers suffer commonly from migraine and show a high prevalence of PFO.15,20 Wilmshurst et al described 37 patients who improved the severity and the frequency of migraine attacks after PFO trans-catheter closure. Two of them developed migraine during the contrast echocardiogram performed six weeks and six months after the closure procedure.13

Therefore, we decided to investigate whether direct cerebral micro-embolism, provoked during contrast echocardiography, represents a trigger for migraine in a group of professional divers, who are usually exposed to increased environmental pressures and perform the Valsalva manoeuvre routinely.

Migraine, characterized by infrequent and weak crises, was found in 25% of divers studied. Although there are no case-control studies investigating the prevalence of migraine in divers with respect to a normal population, the particular stressful conditions such as, for instance, increased environmental pressures, immersions in cold water, the rocking of the boat, intense solar brightness, and physical exertion, that divers have to deal with, may account for the common diagnosis of migraine in these subjects.15

The patent foramen ovale was evident in 33% of our study group, resembling the prevalence in the Caucasian population,21 but no large foramen was detected.

We did not induce any migraine crisis in the divers with PFO when we injected the contrast solution and in the 24 hours following the cardiologic protocol. One subject, who had a medium PFO, developed nausea, without migraine, after the echocardiography, and the following day he was suffering from flu. This diver did not usually complain of migraine.

Subjects with migraine with aura may experience a migraine attack during contrast echocardiography, performed after the surgical closure of PFO, even if the residual communication is minimal.13 Whilst other data in the literature support the hypothesis that brain micro-embolism can be linked to migraine,2,3 the contrast protocol that we used to assess the presence of PFO did not trigger any migraine crisis in our divers. This result can be explained by hypothesizing that small brain micro-embolization is not sufficient to induce migraine crises or it can trigger migraine only if a previous sensitization has been produced, as in carriers of large PFO who have experienced migraine with aura for many years.5,7,13

If we embrace the current hypothesis proposed by several authors4,11-13,20 that the PFO size increases the risk of paradoxical brain embolism, i.e. only larger PFO are at high risk, we are not surprised by the absence of significant differences in the prevalence of migraine, cerebral lesions and decompression sickness episodes between our group of divers with PFO and our group of divers without PFO. Major DCS episodes requiring an hyper-baric treatment occurred in only three subjects (segmental paresis in two subjects and dysarthria in one), who did not show patency of foramen ovale. Moreover, the striking difference in the number of brain lesions between non-carriers and carriers of PFO, as evident in Table 2, was due to one diver who had a medium PFO and 76 lesions. When he was excluded from the statistical analysis, the amount of brain lesions was similar in the groups (divers without PFO vs divers with PFO: 1.3 ± 2.4 vs 1.5 ± 3.7  P= ns).

Furthermore, migraineurs did not show an increased prevalence of PFO, brain lesions or DCS in our study population.

The major concern about our study is the small sample size, which makes our results exploratory, but not definitive. A more definitive research should study a broader population, which includes subjects with larger PFO, although the use of contrast in these subjects may not be completely devoid of risks.13 Moreover, although contrast echocardiogram showed good accuracy in detecting the presence of right-to-left shunts, contrast trans-cranial Doppler would be more appropriate in assessing the actual amount of micro-bubbles reaching the brain circulation.18

Although bubbles have been clearly identified in the left cardiac circulation of PFO carriers during echocardiography, it is not possible to assess the real amount of brain emboli during diving.

In conclusion, our preliminary findings support the hypothesis that cerebral micro-embolism is not a reliable mechanism capable of provoking migraine crises when a minimal-to-medium patent foramen ovale is present. It would be interesting to test our protocol in several cases of larger PFO when massive cerebral micro-embolism is supposed.

**ACKNOWLEDGEMENTS**

The authors thank Roberto Proietti who contributed to the organization of the divers schedules and the subjects who voluntarily participated in this study.
REFERENCES


