Relationship between migraine and cardiac and pulmonary right-to-left shunts

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ABSTRACT
A relationship between migraine with aura and the presence of right-to-left shunts has been reported in two studies. Right-to-left shunts are also associated with some forms of decompression illness. While conducting research in divers with decompression illness, it was our impression that divers with a large shunt often had a history of migraine with aura in everyday life and after dives. Therefore we routinely asked all divers about migraine symptoms. The medical records of the last 200 individuals referred for investigation of decompression illness were reviewed to determine the association between right-to-left shunts and migraine aura after diving, and migraine in daily life unconnected with diving. Migraine with aura in daily life unconnected with diving occurred significantly more frequently in individuals who had a large shunt which was present at rest (38 of 80; 47.5%) compared with those who had a shunt which was smaller or only seen after a Valsalva manoeuvre (four of 40; 10%) or those with no shunt (11 of 80; 13.8%) (P < 0.001). Hemiplegic migraine occurred in 10 divers, each of whom had a shunt that was present at rest; in eight of these cases the shunt was large. The prevalence of migraine without aura was similar in all groups. Post-dive migraine aura was significantly more frequent in individuals who had a large shunt present at rest (21 of 80; 26.3%) compared with those who had a shunt that was smaller or only seen after a Valsalva manoeuvre (five of 40; 12.5%) or no shunt (one of 80; 1.3%) (P < 0.001). Thus individuals with a large right-to-left shunt have an increased prevalence of migraine with aura in daily life unconnected with diving, and they also have an increased incidence of migraine aura after dives, but only when the dives liberate venous bubbles. These data suggest the possibility that, in some individuals, right-to-left shunts have a role in the aetiology of migraine with aura. The observations suggest that paradoxical gas embolism may precipitate migraine with aura.

INTRODUCTION
Patent foramen ovale (PFO) occur in about one-quarter of the population [1]. Some, but not all, PFO permit right-to-left shunting of blood. Less frequent causes of right-to-left shunts include atrial septal defects and pulmonary arteriovenous malformations. An association has been reported between the presence of right-to-left shunts (detected using transcranial Doppler) and migraine with aura [2,3]. PFO predispose to stroke in young adults as a result of paradoxical thromboembolism [4–8]. These observations may explain the increased incidence of stroke in patients with migraine. Right-to-left shunts are also associated with neurological, cutaneous and cardiorespiratory decompression illness as a result of paradoxical gas embolism [9–14]. Shunts which are large and can be detected at rest were found to be present in 41% of divers that suffered from neurological decompression illness, but occurred in only 4.9% of normal divers who had not had decompression illness [13]. We have performed contrast echocardiography to detect intracardiac shunts in many hundreds of individuals with a history of decompression illness. For some years it was our impression that divers who suffered from...
decompression illness and who were found to have a large shunt commonly reported migraine with aura unconnected with diving, and also commonly reported symptoms characteristic of migraine aura, notably fortification spectra, after diving. In contrast, divers with a history of decompression illness but no shunt did not seem to have an excessive prevalence of migraine symptoms in everyday life or after diving. Therefore for the last 9 years we have recorded a full neurological history in individuals referred to us for investigation of decompression illness, with particular emphasis on migraine symptoms.

**METHODS**

To determine the association between right-to-left shunts and migraine, we reviewed the medical records of the last 200 consecutive individuals (199 divers and one caisson worker) referred for investigation of decompression illness. The study population comprised 137 males (mean age 37.9 years; range 18–60 years) and 63 females (mean age 32.9 years; range 17–55 years). In each case a medical history was taken, including a record of neurological symptoms and migraine. We asked about migraine symptoms both in daily life (unconnected with diving) and after dives. Individuals were categorized as having migraine in daily life if they satisfied the criteria of the International Headache Society [15].

Headache after diving is common. Reasons include carbon dioxide retention, cold stimulation of the face and head, and mild barotrauma of the nasal sinuses. Therefore headache after a dive (including caisson pressure exposure in the caisson worker) was not considered relevant unless it was associated with migraine aura.

Each individual referred to us for investigation of decompression illness underwent transthoracic contrast echocardiography to detect the presence of a right-to-left shunt and for semi-quantitative assessment of shunt size [11]. We always perform contrast echocardiography blind to history and physical findings, to avoid bias in interpretation, as described previously [13]. The heart was imaged (apical four-chamber view) with a Hewlett Packard Sonos echocardiography machine. Bubble contrast was produced by pushing approx. 5 ml of sterile saline (0.9% NaCl), 0.5 ml of the patient’s blood and 0.5 ml of air back and forth between two syringes connected by a three-way tap until there were no visible bubbles. This mixture was injected through a 21 gauge butterfly needle into a left antecubital vein. The first contrast injection was performed with the patient resting and breathing normally. If no shunt was seen with the first contrast injection, up to five subsequent injections were performed with sudden release of Valsalva manoeuvres, as described previously [11]. The size of the shunt was graded according to the maximum number of bubbles seen in the left heart on frame-by-frame analysis: small shunts, fewer than six bubbles; medium shunts, six to 20 bubbles; large shunts, more than 20 bubbles [16]. A pulmonary shunt was indicated by the late appearance of a constant stream of bubbles in the left heart, whereas with an atrial shunt (PFO or atrial septal defect) groups of bubbles were seen earlier. When a pulmonary shunt was suspected, additional tests, including pulse oximetry assessment of orthodeoxia and, in some cases, pulmonary angiography, were performed.

Nine of the divers described in these studies were reported previously in descriptions of percutaneous transvenous techniques for closure of PFO [17,17a,18].

Statistical analysis of categorical variables was with the Chi-square test. Yates’s correction was used for fourfold tables. A value of P < 0.05 was considered to be significant.

The Shropshire Research Ethics Committee confirmed that ethics approval was not required for a review of notes.

**RESULTS**

Of the 200 cases with a history of decompression illness reported in this study, 120 (60%) had a shunt. The shunt was graded as small in 18 cases (9%), medium in six cases (3%) and large in 96 cases (48%) (Table 1). In 80 cases (40%), a large shunt was present at rest. In 14 cases (7%), the shunts (six small, one medium and seven large) were thought to be through pulmonary arteriovenous malformations. In the other 106 cases with shunts (53%), shunting was thought to be across the atrial septum.

**Migraine without aura in daily life**

Migraine without aura that occurred at times unconnected with diving was reported by 18 (9%) of the 200 cases with a history of decompression illness (Table 1). These consisted of seven of 80 (8.8%) with no shunt, two of 18 (11.1%) with a small shunt, three of 16 (18.8%) with a large shunt on Valsalva manoeuvre and six of 80 (7.5%) with a large shunt at rest. There was no significant difference in the prevalence of migraine without aura in daily life between cases grouped according to the presence and size of shunts.

Migraine without aura in daily life was significantly more frequent in women (11 of 63; 17.5%) than in men (seven of 137; 5.1%) (P < 0.02).

**Migraine with aura in daily life**

Migraine with aura (or episodes of migraine aura without headache) that occurred at times unconnected with diving was reported by 53 (26.5%) of the 200 divers (Table 1). In all cases there were fortification spectra, but some had hemimotor and hemisensory symptoms/signs, dysphasia, or memory or cognitive impairment. Those affected
comprised 11 of 80 divers (13.8%) who had no shunt, one of 18 (5.6%) with a small shunt, one of six (16.7%) with a medium shunt and 40 of 96 (41.7%) with a large shunt. Migraine with aura was significantly more frequent in those with a large shunt that was present at rest (38 of 80; 47.5%) than in those with a large shunt that was only seen with release of a Valsalva manoeuvre (two of 16; 12.5%) ($P < 0.05$). The occurrence of migraine with aura unconnected with diving was significantly more frequent in divers who had a large right-to-left shunt that was present at rest (38 of 80; 47.5%) than in the other groups with or without a shunt (15 of 120; 12.5%) ($P < 0.001$). Migraine with aura occurred in four of 14 (28.6%) subjects with pulmonary arteriovenous shunts: one of six (16.7%) with a small shunt and three of seven (42.9%) with a large shunt.

Migraine associated with hemimotor or hemisensory effects in addition to fortification spectra occurred in 10 divers. Each had a shunt that was present at rest: one had a small pulmonary arteriovenous malformation, one had a medium atrial shunt and eight had large atrial shunts. Migraine with hemimotor or hemisensory effects was significantly more frequent in divers with a large shunt present at rest (eight of 80; 10%) than in all other groups combined (two of 120; 1.7%) ($P < 0.05$).

Migraine with aura in daily life occurred in 22 of the 63 women (34.9%) and 31 of the 137 men (22.6%). This difference was not significant ($P < 0.1$).

There were no significant differences in the mean age of cases when grouped according to symptom classification (no migraine, migraine with aura and migraine without aura) or by sex.

### Migraine aura associated with diving

A total of 27 divers described migraine auras with or without headache after surfacing from a dive. Post-dive migraine auras occurred in 13 of the 63 women (20.6%) and 14 of the 137 men (10.2%). The difference was not significant ($P < 0.1$). Migraine auras were never present immediately at the end of a dive, but started after a latent interval of between 10 min and 4 h (median 30–60 min). The aura, which consisted of fortification spectra in all affected cases and hemimotor or hemisensory effects in nine cases, was associated with headache on some or all occasions in 11 divers, and was never associated with headache in 16 divers. With regard to frequency, 21 divers reported migraine aura after diving on between one and four occasions, and five divers reported migraine aura after diving on five to eight occasions. One man estimated that he had had his usual migraine with aura after diving on between 20 and 30 occasions. He had fortification spectra leading to scotoma and then developed unilateral pulsating headaches (usually right-sided) associated with unilateral (usually left-sided) paraesthesia and weakness. The arm was affected more than the leg, and the face was only occasionally affected. There was also usually expressive dysphasia and sometimes amnesia of events during the episode. He also had hemiplegic migraine after contrast echocardiography.

Only one diver who experienced post-dive migraine aura had no shunt. He had a history of migraine when
under emotional stress and described a migraine aura (fortification spectra) associated with headache on a single occasion after an emotionally stressful dive. That dive was of short duration and only to 7 m depth. The depth–time profile was unlikely to cause venous bubble liberation. The other 26 divers with post-dive migraine aura with or without headache reported that symptoms never occurred after shallow dives, but only after deeper dives. Analysis of the depth–time profiles showed that these dives could be associated with liberation of venous bubbles, as they were less conservative than the limits of the Defence and Civil Institute of Environmental Medicine (Canada) Sport Diving Table, which is based on empirical assessment of venous bubble nucleation using Doppler ultrasound.

One woman with a small pulmonary shunt and a history of migraine with hemisensory effects related to her menstrual cycle had identical migraine attacks on eight occasions after dives. We were unable to demonstrate significant variation in the size of the pulmonary shunt during her menstrual cycle.

Migraine auras after diving also occurred in one diver with a medium shunt present at rest, three divers with large shunts seen with a Valsalva manoeuvre and 21 divers with a large shunt present at rest. Post-dive migraine auras were significantly more frequent in divers with a large shunt present at rest (21 of 80; 26.3%) than in the other groups combined (six of 120; 5%) (P < 0.001). Seven of the divers with large shunts present at rest and one with a medium shunt present at rest had hemimotor or hemisensory effects with migraine.

Of the 27 divers who had migraine aura after diving, 22 also had migraine at other times, but five divers had never experienced migraine symptoms unrelated to diving. Each of the five had a large atrial shunt; this was detected with a Valsalva manoeuvre in two subjects and was present at rest in three subjects.

In 10 divers fortification spectra (with or without headache) occurred after a dive, but additional non-migraine symptoms (neurological in four, cutaneous in one and both neurological and cutaneous in five) caused them to seek treatment for decompression illness. In 17 other divers there were episodes after dives that were entirely characteristic of their usual migraine, so these individuals did not seek recompression at those times. However, on a subsequent dive they all had classical symptoms of decompression illness and were referred for investigation. The diver who had post-dive migraine and had no shunt was referred because of a history of joint decompression illness. The 26 divers who had post-dive migraine auras and had a shunt were diagnosed as suffering neurological or cutaneous decompression illness, or both. For example, the man with a large atrial shunt at rest who had recurrent episodes of hemiplegic migraine unconnected with diving had between 20 and 30 identical episodes of hemiplegic migraine starting 10–60 min after dives, but he only sought medical advice when he developed cutaneous decompression illness.

**Transient global amnesia**

One woman with a large atrial shunt present at rest and who experienced migraine with aura (fortification spectra, hemiplegia and disturbed mentation) both in everyday life and after diving gave a history suggestive of transient global amnesia unconnected with diving. Another woman who had a large shunt present at rest and migraine with aura in everyday life, but not after dives, described an episode of transient global amnesia after a dive that had a depth–time profile likely to liberate venous bubbles. She had no history of transient global amnesia unconnected with diving.

**DISCUSSION**

Migraine has a number of causes. These data from a group of individuals with a history of decompression illness, and hence a high prevalence of large right-to-left shunts, provide evidence that migraine with aura is more frequent in individuals who have shunts. This relationship has been investigated by two other groups using trancranial Doppler. Del Sette and colleagues [2] showed that right-to-left shunts were present in 41% of patients with migraine with aura, compared with 16% of controls (P < 0.005) and 35% of patients younger than 50 years of age with focal cerebral ischaemia. Anzola and colleagues [3] obtained similar results which showed that right-to-left shunts were present in 48% of individuals with migraine with aura, compared with 20% of controls and 23% of patients with migraine without aura. Our data support those observations, and show that there is also a relationship between shunt size and prevalence of migraine with aura, but not of migraine without aura. The prevalence of migraine with aura was similar in those with no shunt, those with a small or medium shunt and those with a large shunt detected with a Valsalva manoeuvre. However, the prevalence was significantly higher in those with a large shunt present at rest. Such large shunts are present in only 4.9% of the general population [13]. These data suggest that the presence of a large shunt increases the predisposition of an individual to migraine with aura, without being necessary for or a guarantee that an individual will suffer migraine with aura. A shunt does not appear to affect susceptibility to migraine without aura.

Amateur diving organizations estimate that approximately one-third of divers in the U.K. are female. Women comprised 31.5% of the cases we investigated following decompression illness. This is compatible with a similar susceptibility of men and women to decompression illness, provided that diving histories (exposure to risk)
are similar. There is no convincing evidence of an increased prevalence of PFO in women [1]. However, our data are consistent with the general finding that migraine affects women more frequently than men. Therefore additional or alternative mechanisms must be responsible for the higher prevalence of migraine in women.

Pulmonary arteriovenous fistulas are more common in women than in men. The size of pulmonary shunts can vary according to circulating levels of female hormones [19–21]. Although this could provide an interesting mechanism to explain variations in migraine symptoms during the menstrual cycle and pregnancy, we were unable to demonstrate significant menstruation-related variation in pulmonary shunting in the woman with a small pulmonary arteriovenous shunt and frequent episodes of catamenial hemiplegic migraine.

These observations cannot explain all cases of migraine with aura, but they help us to draw an analogy with decompression illness to postulate mechanisms that may be involved in the aetiology of migraine. Neurological decompression illness can occur in divers with no right-to-left shunt, but it is more frequent in those with a shunt. Small amounts of bubbles liberated during many innocuous dives are filtered in the alveolar capillary bed. A right-to-left shunt allows bubbles to bypass this filter, and the bubbles may then embolize neurological tissues. Divers with the largest shunts are at greatest risk [13]. Divers with large shunts do not suffer decompression illness after every dive, because the depth–time profiles of many dives do not cause venous bubble formation. In addition, after other dives that do cause bubble formation, the nitrogen load in neurological tissues may be inadequate to amplify bubbles if they are embolized. However, divers with no shunt can suffer from decompression illness if the dive profile is sufficiently provocative that a high bubble load overpowers the filtering capacity of the lungs. (Neurological decompression illness can also result from arterial gas embolism as a result of pulmonary barotrauma and autochthonous bubble formation, but these mechanisms have no relevance to consideration of the pathophysiology of migraine.)

Similarly, the lungs could act as a filter for substances in the venous circulation that can trigger an attack of migraine with aura if they reach the brain in sufficient concentrations. Migraine with aura would occur in individuals that have large amounts of these trigger substances in the venous blood, so that the filtering capacity of the lungs is overwhelmed. Migraine with aura would also occur in individuals with a lower amount of the trigger substance in the venous circulation if a shunt permitted the lung filter to be bypassed. Potential trigger substances include vasoactive chemicals and microemboli. The auras that occurred after dives, including those in some divers with no history of migraine, could have been the result of paradoxical gas embolism. In all cases except the one in a diver with no shunt, the dive could have liberated bubbles. In these cases the start of the aura was around the time when there would have been peak venous bubble liberation. It may be relevant that the diver who most frequently experienced post-dive migraine with aura also had migraine with aura after contrast echocardiography. However, we cannot ascribe with certainty these auras to bubbles alone. Bubbles create a surface for coagulation and platelet activation, possibly leading to the liberation of vasoactive substances, which could also trigger migraine with aura.

Two divers experienced transient global amnesia. In one case this occurrence was unconnected with diving, and the other subject had an episode after a dive with a depth–time profile likely to liberate nitrogen bubbles. Each of these women had a large right-to-left shunt present at rest and experienced migraine with aura in everyday life. Transient global amnesia is rare. There is a reported annual incidence of 10 per 100000 of the population [22]. The presence of two divers with a history of this condition in the subgroup of 38 individuals who both had a large right-to-left shunt which was present at rest and experienced migraine with aura may be explicable. There is an association between transient global amnesia and migraine [23–25]. There is also an increased prevalence of right-to-left shunts, detected using transcranial Doppler, in patients with transient global amnesia [26]. The observation that, in one diver with a large shunt, a dive with a depth–time profile likely to liberate venous bubbles caused transient global amnesia rather than migraine aura suggests that migraine with aura and transient global amnesia may have mechanisms in common.

An important conclusion from these data is that individuals with a history of migraine with aura may be at increased risk of decompression illness. This is not a new finding. In 1944, Engel and colleagues [27] reported that, during 1361 experimental subatmospheric decompressions in 155 subjects, there was a subgroup of 17 subjects who experienced 46 episodes of ‘a syndrome characterized by the occurrence of scintillating scotomas and rarely of other neurological signs and usually followed by headache’. Individuals with this syndrome all suffered decompression illness, and they more frequently had a history of migraine unrelated to decompression than those who did not have this syndrome (P < 0.0001). Although the links we report in divers between decompression illness, migraine and right-to-left shunts were not recognized at that time, it seems likely that Engel and colleagues [27] were reporting the clinical equivalent of this during subatmospheric decompression. It would be interesting to know whether their subjects also had a right-to-left shunt. These observations and ours demonstrate that, following decompression, there may be diagnostic difficulty in distinguishing, and an
overlap, between migraine with aura and neurological decompression illness.
Thus these observations suggest that individuals with a history of migraine with aura should be screened for the presence of a right-to-left shunt before they dive or are exposed to subatmospheric decompression.

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REFERENCES


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