Comparison of the size of persistent foramen ovale and atrial septal defects in divers with shunt-related decompression illness and in the general population

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Abstract

(Wilmshurst PT, Morrison WL, Walsh KP, Pearson MJ, Nightingale S. Comparison of the size of persistent foramen ovale and atrial septal defects in divers with shunt-related decompression illness and in the general population. *Diving and Hyperbaric Medicine*. 2015 June;45(2):89-93.)

Introduction: Decompression illness (DCI) is associated with a right-to-left shunt, such as persistent foramen ovale (PFO), atrial septal defect (ASD) and pulmonary arteriovenous malformations. About one-quarter of the population have a PFO, but considerably less than one-quarter of divers suffer DCI. Our aim was to determine whether shunt-related DCI occurs mainly or entirely in divers with the largest diameter atrial defects.

Methods: Case control comparison of diameters of atrial defects (PFO and ASD) in 200 consecutive divers who had transcatheter closure of an atrial defect following shunt-related DCI and in an historic group of 263 individuals in whom PFO diameter was measured at post-mortem examination.

Results: In the divers who had experienced DCI, the median atrial defect diameter was 10 mm and the mean (standard deviation) was 9.9 (3.6) mm. Among those in the general population who had a PFO, the median diameter was 5 mm and mean was 4.9 (2.6) mm. The difference between the two groups was highly significant ($P < 0.0001$). Of divers with shunt-related DCI, 101 (50.5%) had an atrial defect 10 mm diameter or larger, but only 1.3% of the general population studied had a PFO that was 10 mm diameter of larger.

Conclusions: The risk of a diver suffering DCI is related to the size of the atrial defect rather than just the presence of a defect.

Key words

Patent foramen ovale (PFO); persistent foramen ovale; right-to-left shunt; decompression illness; venous gas embolism; neurology; migraine

Introduction

About one quarter of adults have a persistent foramen ovale (PFO).[1] The prevalence is greater in individuals with cryptogenic stroke, decompression illness (DCI) and migraine with aura.[2–5] It is postulated that a PFO allows paradoxical thromboembolism in some cases of cryptogenic stroke, paradoxical gas embolism in some cases of DCI and some unidentified migraine-inducing agent to bypass the lungs in some cases of migraine with aura. The higher incidence of stroke and DCI in people with migraine with aura compared with the general population may be because migraine with aura is an indicator of a high prevalence of PFO, particularly large ones.[6–8]

However, there is no absolute concordance between PFO and cryptogenic stroke, DCI or migraine with aura. Therefore, when considering whether a PFO should be closed to prevent recurrence of events such as stroke or DCI, we need to differentiate those PFOs that were causal from those that were coincidental. Only rarely in cases of stroke is there unequivocal evidence of paradoxical embolism, for example, when echocardiography demonstrates a venous thrombus straddling a PFO. There is currently no way of demonstrating in an individual patient whether a PFO has a role in the aetiology of migraine with aura. The situation with DCI is different. Shunt-related DCI usually has characteristic clinical features which distinguish it from DCI caused by pulmonary barotrauma or an unsafe dive profile.[4,9] Analysis of the dive profile allows us not only to rule out an unsafe dive, but also to determine whether the patient's inert gas load at the onset of symptoms was likely to have resulted in venous bubble liberation. Contrast echocardiography then allows us to determine whether there is a right-to-left shunt that would allow significant numbers of these venous bubbles to bypass the lung filter.

Contrast echocardiography provides a semi-quantitative assessment of functional shunt size. A right-to-left shunt graded "*large at rest*" on contrast echocardiography is found 8–10 times more frequently in divers with cutaneous DCI (49.2%) and with neurological DCI (41%) than in controls (4.9%, $P < 0.001$).[10,11] Large shunts demonstrated with a Valsalva manoeuvre and medium shunts at rest are 2–4 times more frequent in divers with DCI than controls, but small shunts are no more frequent in divers with DCI than controls.[10,11] These data suggest that the risk of shunt-related DCI is related to the size of the shunt rather than simply the presence or absence of a PFO.

Shunt size is also likely to be important in the role of PFO in stroke and migraine with aura. Certainly in patients with severe migraine the high prevalence of right-to-left shunts is related to an excess of large shunts and not small

shunts and similarly the prevalence of migraine with aura is related to shunt size on contrast echocardiography.[12–14] It is also intuitively probable that risk of paradoxical thromboembolism is greater with a large shunt than with a small shunt.

Functional shunt size assessed by contrast echocardiography is governed by variable factors, such as inter-atrial pressure gradient and atrial blood-flow patterns, and constant factors, such as the dimensions of the foramen ovale. Of these factors governing shunt size, the PFO diameter should be easiest to measure reproducibly. We compared the anatomical diameter of PFO and atrial septal defects (ASD) in 200 consecutive divers who had balloon-size measurement at the time of transcatheter closure of atrial shunts after shunt-related DCI with PFO sizes reported in a large population study.[1]

Methods

INVESTIGATION OF DIVERS

The divers had attended our clinic for investigation of divers who have suffered DCI. Investigations included chest X-ray and dynamic spirometry in all and high resolution computer tomogram scans of the chest in some when there was rapid onset of neurological symptoms but chest X-ray and lung function tests were normal to exclude lung disease capable of causing pulmonary barotrauma. Contrast echocardiography was done to determine the presence and functional size of any right-to-left shunt. The heart was imaged (apical, four-chamber view) with a Hewlett Packard Sonos machine. Bubble contrast was produced by pushing 6–8 ml sterile saline (0.9% NaCl), 0.5–1 ml of the patient's blood and 0.5–1 ml air back and forth between two syringes connected by a three-way tap until there were no visible bubbles. This mixture was then injected through a 21-gauge butterfly needle into a left antecubital vein with the arm slightly elevated to ensure rapid contrast arrival in the right atrium. 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 Valsalva manoeuvres, with the operator causing sudden release of the manoeuvre, as described previously.[15] Shunts were 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 and large shunts – more than 20 bubbles.[2]

Divers with clinical features of one or more episodes of shunt-related DCI, using criteria described previously,[9] are counselled on three possible ways to reduce their risk of DCI in the future – namely to stop diving, to modify their diving to prevent venous bubble formation or to have transcatheter closure of their atrial shunt. Patients are advised to go home and think about the options carefully. The decision on which option to choose is left entirely to the patients.

CLOSURE OF ATRIAL DEFECTS

In a series of 207 consecutive divers who decided to have transcatheter closure of their inter-atrial defect following shunt-related DCI, a 25 mm Amplatzer™ PFO device (AGA Medical Corporation, Minnesota, USA) was inserted in seven without measuring the PFO diameter. It is generally believed that insertion of this device does not require balloon sizing of a PFO. Between 11 December 1996 and 22 November 2007 the remaining 200 divers had balloon sizing of the atrial defect at the time of the procedure to aid selection of an appropriate diameter Amplatzer Septal Occluder™ (AGA Medical Corporation, Minnesota, USA). For the purposes of this report, the consecutive series was terminated at 207 to provide a large and convenient sample size of 200 divers who had undergone balloon sizing to compare with the historic control group. Since then more than 100 further divers seen at our centre after they suffered DCI have had closure of a PFO or an ASD.

COMPARISON OF DEFECT SIZE IN DIVERS AND A GENERAL POPULATION

We compared retrospectively the diameter of the atrial defect in the 200 divers who had a closure procedure with the PFO diameter data reported in 263 (27.3%) people who had a PFO in a series of 965 post-mortem examinations in the general population using a Student's *t*-test.[1] Diameters are expressed as mean (standard deviation) and median. Permission to incorporate in our paper the post-mortem data from the earlier report was granted by the authors and Mayo Clinic Proceedings, which published that paper.[1] In their study, the PFO diameters were measured post mortem in formalin-fixed hearts using calibrated probes.

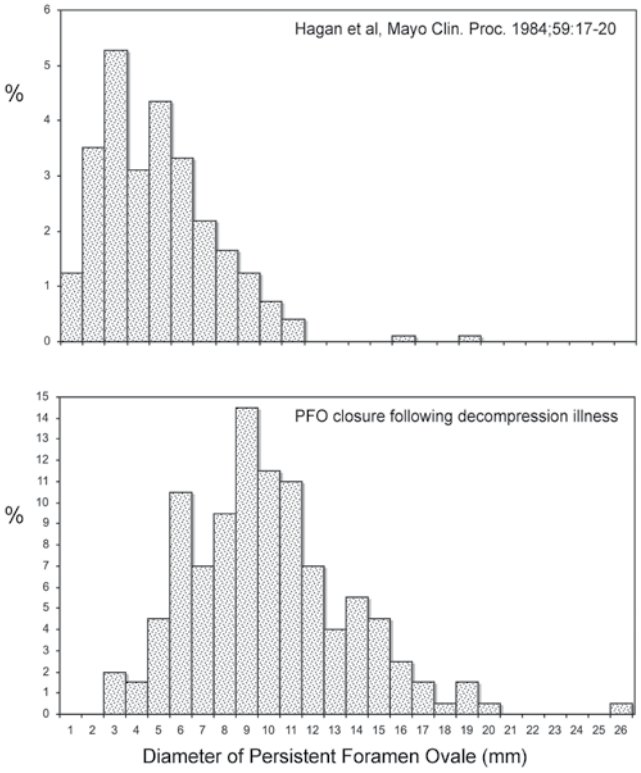
In the divers, PFO diameter was measured using an Amplatzer™ sizing balloon (AGA Medical Corporation, Minnesota, USA), which has calibration markers. The balloon was inserted across the atrial defect over a wire. It was inflated gently at low pressure until a waist was seen in the balloon and there was cessation of colour flow across the atrial septum using transoesophageal echocardiography. The diameter of the waist was measured using quantitative X-ray fluoroscopy in a view orthogonal to both the long axis of the balloon and to the plane of the interatrial septum.

All information reported in this paper was obtained as part of normal patient care. In particular, we routinely measure PFO diameter as part of the closure procedure. Therefore, no additional research consent was obtained for this retrospective data analysis.

Results

The patients in this report were in a consecutive series of 636 divers who attended our clinic for investigation of divers with DCI. Of these, 370 (58.2%) had features of

Figure 1
Histograms showing the distribution of diameters of persistent foramen ovale (PFO) in the general population[1] (with permission) (upper panel) and the distribution of the diameters of PFO and atrial septal defects in divers with shunt-related DCI (lower panel)



shunt-related DCI and had a significant right-to-left shunt (large or medium shunt at rest or large shunt with a Valsalva manoeuvre). The remaining 266 (41.8%) were diagnosed as having DCI as a result of an unsafe dive profile or arterial gas embolism secondary to pulmonary barotrauma as a result of an uncontrolled ascent or lung disease. Of the 266, 185 (69.5%) had no shunt. The remaining 81 (30.5%) had a shunt, which in 80 was a small atrial or small pulmonary shunt. In one there was a large shunt at rest, but the onset of neurological symptoms was during ascent from a dive to 15 metres' depth and a CT scan of her chest showed pulmonary bullae.

Of the 370 who had shunt-related DCI, 346 (93.5%) were considered to have an atrial shunt and 24 (6.5%) had features of a pulmonary shunt. One of those with a significant pulmonary shunt returned to diving after coil occlusion of a single large pulmonary arteriovenous malformation. Two-hundred-and-seven (59.9%) of the 346 with an atrial shunt (or 32.5% of divers attending the clinic) chose to have transcatheter closure of their atrial defect, but in seven cases the diameter of the defect was not measured.

In the 200 divers (140 men and 60 women) who had balloon sizing of their atrial defect, 11 (5.5%) had a secundum ASD and 189 (94.5%) had a PFO. On one or more occasions, 150 of the 200 divers (75%) had suffered neurological, 12 (6%) cardiorespiratory and 99 (49.5%) cutaneous DCI. Some divers had more than one manifestation of DCI at a time. Others had different manifestations on separate occasions. On one or more occasion, 63 divers (31.5%) had post-dive migraine with aura or aura without headache. According to the criteria of the International Classification of Headache, 15 divers (7.5%) had migraine without aura and 104 (52%) had migraine with aura unconnected with diving.[16] Three divers had a cryptogenic stroke, confirmed on computerised tomography brain scans at ages 18, 37 and 58 years. Their strokes were unrelated to diving and none of the three had migraine.

Figure 1 shows the distributions of diameters of atrial defects (PFO or secundum ASD) in the divers with DCI and the distribution of PFO diameters in the general population. The overall prevalence of PFO in the general population was 27.3%. Of those in the general population with a PFO, the median PFO diameter was 5 mm and mean was 4.9 (SD 2.6) mm. In the divers who had suffered shunt-related DCI the median atrial defect diameter was 10 mm and the mean was 9.9 (SD 3.6) mm. The difference between the two populations is highly significant ($P < 0.0001$). Of divers with shunt-related DCI, 101 (50.5%) had an atrial defect that was10 mm diameter or larger, but only 1.3% of the general population had a PFO that was 10 mm diameter or larger.

Discussion

A criticism of this study is that the PFO diameters in the two groups (divers and controls) were measured using different techniques, but there is currently no other ethically justifiable method of measuring PFO diameter in normal controls. In this analysis we wished to compare PFO and ASD diameters obtained during closure procedures in divers who had had shunt-mediated DCI with the only available information we have on PFO diameter in normal hearts – namely the post-mortem data from Hagen et al.[1] There are no data for the general population comparable to ours in divers. Given the large magnitude of the differences in PFO diameters between the groups, any small difference caused by differences in measurement techniques would not have significantly affected the conclusions. The post-mortem study showed that the PFO rates in males and females were not different (26.8% and 27.6% respectively overall), and did not differ in each of the 10 decade subgroups. Neither did PFO size differ between males and females.

The seven divers who did not have balloon sizing of their defects did not differ clinically from the 200 that did have balloon sizing and their contrast echocardiogram appearances were comparable to those who had balloon sizing. Their PFOs were considered to be similar to those who had balloon sizing, so omission of their defect diameters is unlikely to have had a significant effect on the findings in this study.

Many of the divers with a significant shunt and who had no closure procedure have returned to diving using breathing gases and dive profiles that are unlikely to liberate venous bubbles on decompression. The decision to undergo closure was not influenced by whether the shunt was graded on contrast echocardiography as large or medium at rest or large with a Valsalva manoeuvre, so PFO diameter results of those who underwent closure are likely to be representative of all 346 divers who had shunt-related DCI with an atrial shunt.

It has already been shown, using contrast echocardiography, that a right-to-left shunt is found in a significantly greater proportion of divers with cutaneous DCI (77%) and with neurological DCI (58%) than in controls (27.6%, $P < 0.001$).[10,11] It has been concluded that a PFO increases the risk of DCI by a factor of approximately 2.5.[17] However, this risk assessment does not take into account the fact that the excess of shunts in affected divers is comprised of large shunts. Our data suggest that the risk of DCI is greatest in divers with the largest right-to-left shunts, as determined by PFO diameter. Comparably sized PFOs are found in a very small proportion of the general population. When considering pathogenesis of paradoxical embolism through a septal defect, it should be remembered that the risk is probably related to defect area rather than diameter. A doubling of a diameter will increase the area four-fold and may have a similar exponential effect on risk.

These observations may provide insight into the relationship of migraine with aura and DCI.[7] Contrast echocardiography in 432 patients with severe migraine with aura in the MIST (Migraine Intervention with STARFlex Technology) Trial, showed that 260 (60.2%) had a right-to-left shunt.[12] The large number of right-to-left shunts compared with population studies was the result of an excess of large shunts, which were usually across a large PFO. There was no excess of small shunts. In keeping with other studies showing a strong association between migraine with aura and large right-to-left shunts, 52% of our divers had migraine with aura, a rate approximately 12–15 times higher than in the general population.[12-14,18] As in other studies, there was no increase in prevalence of migraine without aura. These data support the evidence that the link between DCI and migraine with aura is shunt size, which is a reflection of PFO diameter.[13,14]

These observations may also provide insight into the relationship of stroke and DCI. Three divers in the study (1.5%) had a history of cryptogenic stroke at relatively young ages. It is difficult to draw conclusions from observations in just a few individuals, but this is a high rate of premature stroke. We have previously reported another man who had a cryptogenic stroke when straining at stool at age 23 and who subsequently had two episodes of shunt-related DCI.[19] These anecdotal observations suggest that if a PFO is large enough to permit paradoxical gas embolism then in some cases it may be large enough to also permit paradoxical thromboembolism.

Others have reported, using transoesophageal echocardiography, that the magnitude of the right-to-left shunt across a PFO, shunting at rest and opening dimension of a PFO are all greater in patients who have had an ischaemic arterial event considered to be the result of paradoxical embolism than in patients with an ischaemic event without features of paradoxical embolism or in patients without an ischaemic event.[20–22] Because the excess right-to-left shunts in patients with migraine with aura are mainly large PFOs and to a lesser extent pulmonary arteriovenous shunts,[12] these data support the hypothesis that the increased incidence of stroke in patients with migraine compared with the general population is because patients with migraine have a high prevalence of large atrial shunts and hence an increased risk of paradoxical embolism.[8]

Conclusions

The risk of a diver suffering shunt-related DCI is related to the size of the right-to-left shunt. When shunting is across an atrial defect, the dimensions of the defect are important rather than just the presence of the defect.

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Acknowledgements

We are grateful to the Mayo Foundation for Medical Education and Research and to the authors for permission to reproduce data from Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc*. 1984;59:17-20.

Contributions

PTW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in clinical care of patients, conception of the study and writing the paper.

Conflict of interest

KPW has acted as a proctor for AGA Medical. No other author has any conflicts of interest.

Funding: none

Submitted: 30 March 2015
Accepted: 01 May 2015

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