Original articles

The effectiveness of risk mitigation interventions in divers with persistent (patent) foramen ovale

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Abstract
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Introduction: Persistent (patent) foramen ovale (PFO) is a recognized risk for decompression sickness (DCS) in divers, which may be mitigated by conservative diving or by PFO closure. Our study aimed to compare the effectiveness of these two risk mitigation interventions.

Methods: This was a prospective study on divers who tested positive for PFO or an atrial septal defect (ASD) and either decided to continue diving without closure ('conservative group'), or to close their PFO/ASD and continue diving ('closure group'). Divers' characteristics, medical history, history of diving and history of DCS were reported at enrollment and annually after that. The outcome measures were the incidence rate of DCS, frequency and intensity of diving activities, and adverse events of closure.

Results: Divers in both groups dived less and had a lower incidence rate of confirmed DCS than before the intervention. In the closure group ($n = 42$) the incidence rate of confirmed DCS decreased significantly. Divers with a large PFO experienced the greatest reduction in total DCS. In the conservative group ($n = 23$), the post-intervention decrease in confirmed DCS incidence rate was not significant. Of note, not all divers returned to diving after closure. Seven subjects reported mild adverse events associated with closure; one subject reported a serious adverse event.

Conclusions: PFO closure should be considered on an individual basis. In particular, individuals who are healthy, have a significant DCS burden, a large PFO or seek to pursue advanced diving may benefit from closure.

Introduction

Persistent (patent) foramen ovale (PFO), a remnant of foetal interatrial communication which persists after birth in about 30% of people, has been suspected as a risk factor for decompression sickness (DCS) for nearly four decades.[1–3] The role of a PFO as a conduit that enables arterialization of post-dive venous gas emboli (VGE) and occurrence of DCS is feasible in cerebral, spinal, cutaneous and vestibular manifestations of DCS.[4–6]

The prevalence of PFO in divers is probably similar to that in the general population.[7] However, very few divers experience DCS. The risk of DCS in recreational divers in the United States is 3.4 per 10,000 dives and less than 1 per 10,000 dives for neurological DCS.[8] Research suggests that only about 10% of divers experience some form of DCS in their lifetime.[9,10] However, for divers with a PFO the overall risk of DCI doubles, for neurological DCS it increases four-fold, and for divers with a large PFO, it increases six-fold.[11,12]

In order for DCS associated with PFO to occur, at least three conditions need to be met:

- Post-dive venous gas emboli must be present.
- A right-to-left shunt must occur, whether spontaneous or due to a provocation factor such as Valsalva or breathing effort.
- The target tissue must be saturated with inert gas.[13–15]

Although a large PFO is associated with an increased risk of DCS, testing of divers for PFO is only deemed necessary if divers have a history of cerebral, spinal, vestibular or cutaneous DCS, migraine with aura, cryptogenic stroke or a history of PFO or ASD in a first-degree relative.[16,17] The obvious risk mitigation strategy for such divers is to stop diving or to reduce the probability of post-dive venous gas bubbles by diving more conservatively.[18]

Since the trans-catheter closure of PFO was approved for secondary prevention of stroke, interventional cardiologists have begun to offer it to divers as a risk-mitigation strategy

for DCS. The closure of a PFO ablates the major pathway for arterialization of venous bubbles.[19] However, at the time this study was initiated the indications and practice of screening for (and closure of) PFO had not been standardized, and not all interventional cardiologists willing to provide these services had extensive experience with divers or were familiar with diving medicine. Also, divers were not always properly educated about how a PFO affects the risk of DCS and what their options were to mitigate this risk. The present study aimed to establish the effectiveness of conservative diving versus the closure of PFO for risk mitigation of DCS in this environment.

Methods

This study was approved by the Institutional Review Board of the Lakeland Regional Medical Center, Lakeland, Florida. The study combined retrospective data about the period before enrollment and prospective data collected after enrollment in the study.

SUBJECTS

Subjects were eligible for this study if they were adult certified divers diagnosed with PFO regardless of their DCS history, and if they intended to continue diving. Subjects responded to study advertisements in social media or were referred by other divers. All participants were volunteers who provided written informed consent.

The subjects provided anthropometric data, PFO testing data, a medical and diving history before the intervention*, and an annual report* about their diving activities and related outcomes after that.

Divers were classified as 'conservative' if after diagnosis with a PFO they decided to continue diving without undergoing closure, or 'closure' if they decided to get their PFO closed. In the conservative group, the intervention was the diagnosis of PFO and the post-intervention period began with that diagnosis. In the closure group, the intervention was the closure of PFO and the post-intervention period began with the closure. Subjects who dived with a diagnosed PFO before they underwent closure were included in both the conservative and the closure group. For the subjects in the conservative group, the pre-intervention period included history up to the diagnosis and the post-intervention period was from the diagnosis until closure. For the subjects in the closure group, the pre-intervention period included history up to the closure and the post-intervention period was from the closure until the end of the study.

Subjects were further classified based on their reported diving practice as recreational or technical divers. For this study, divers who performed more than 40% of their air dives at depths greater than 30 metres, used mixed gas (other than enriched air nitrox), closed circuit rebreather (CCR) or engaged in cave diving, were classified as technical divers.

The PFO was classified as 'large' if the reported diameter was 5 mm or larger, if bubble contrast used in diagnosis arterialized spontaneously, or if a cardiologist qualified it 'large' without an explicit report of PFO diameter. Divers with an ASD were also classified in the 'large' group because of the continuous patency of that lesion.

OUTCOMES

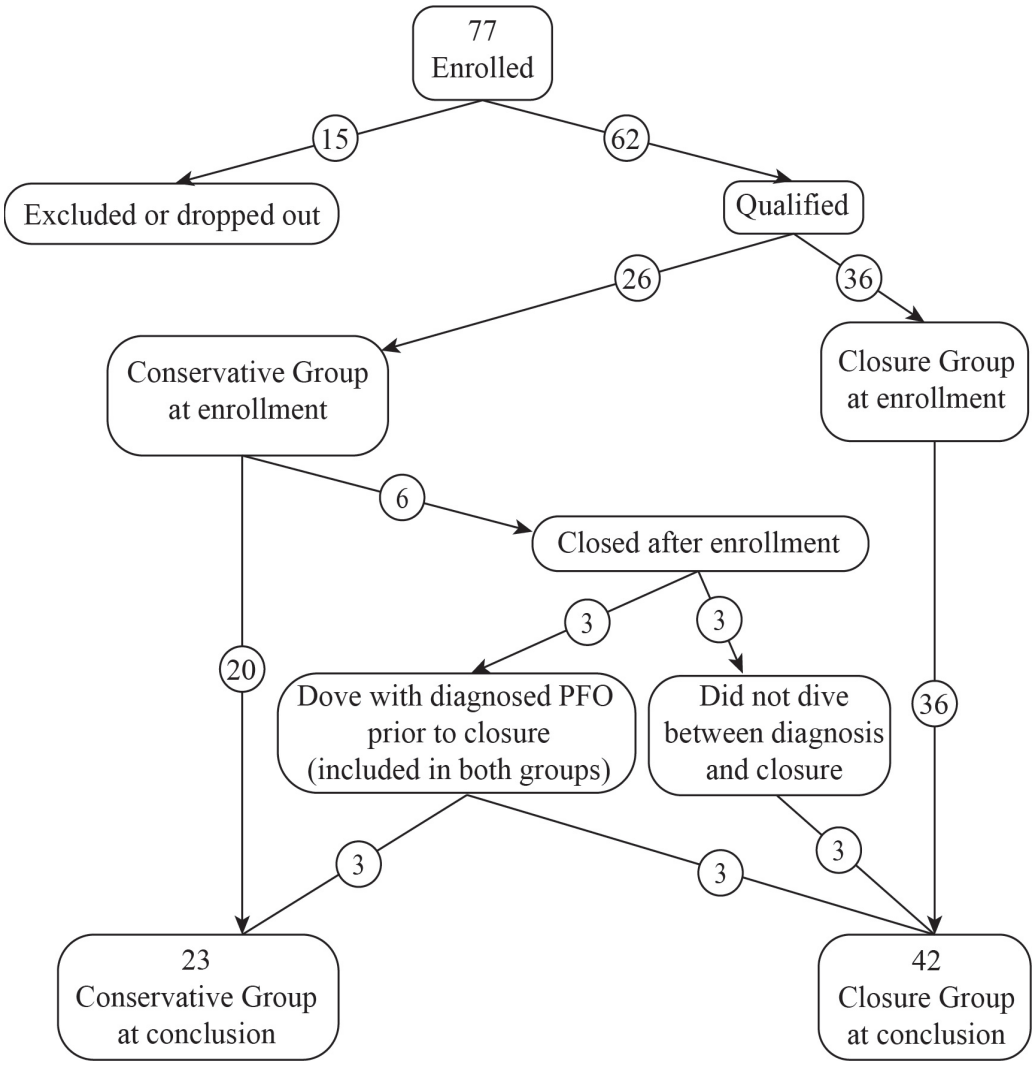
The main outcome of interest was DCS. The primary outcome was 'confirmed DCS', defined as cases diagnosed by a medical professional and treated in a recompression chamber. The secondary outcome was 'possible DCS' which was based on solicited subjective reports of the presence of symptoms usually associated with DCS and explicitly listed in the list of reportable symptoms. Examples of reportable symptoms were instances of vertigo, joint pain, skin itching and rash, post-dive skin mottling, breast swelling, muscular weakness, or use of in-water recompression or surface oxygen to alleviate symptoms. Isolated instances of a headache, fatigue or nausea were not considered possible DCS. Other outcomes were return to diving, frequency and intensity of diving after the intervention and possible adverse events related to the closure.

Subjects were determined to have returned to diving in one year if they had reported doing any dives in the year following the intervention. Frequency and intensity of diving after the intervention were classified as either: 'diving less', if they reported fewer dives per year (less than 70% of pre-intervention dives per year), or switched from technical to recreational diving; or 'diving same or more', if they reported the same or more dives per year (greater than or equal to 70% of pre-intervention dives per year), or switched from recreational to technical diving. Individuals who stopped diving were included in the 'diving less' group.

The group incidence rate of DCS before and after the intervention was calculated per 10,000 dives, based on the sums of reported dives and of DCS cases. These calculations were completed for both confirmed DCS and possible DCS. These calculations were also performed while stratifying groups based on PFO size. Individuals who stopped diving were excluded from these calculations. Changes in confirmed DCS and possible DCS were considered on an individual basis before and after the intervention.

*** Footnote:**
The baseline survey and annual dive symptom report forms are available on request from the authors at pdenoble@dan.org

Figure 1
Enrollment and group allocation pathway



Reported adverse events of closure were classified as mild, such as minor bleeding, bruising, temporary palpitations or atrial fibrillation. Adverse events were classified as severe if they required surgical intervention, caused a serious threat to life, or resulted in permanent consequences.

STATISTICAL ANALYSIS

The difference in the incidence rate of DCS before and after intervention in each group was tested by calculating the risk ratio. The difference in the proportion of subjects in each group who dived the same or more was tested by calculating the odds ratio.

Continuous characteristics of subjects in the two groups were compared using the Mann-Whitney rank sum test. Discrete characteristics of subjects in the two groups were tested by calculating odds ratios.

Results

CHARACTERISTICS OF DIVERS BEFORE INTERVENTION

In the period from 2011 to 2017, 77 subjects enrolled in this study. During this time, 15 subjects were excluded for the following reasons: three subjects reported a PFO but its presence could not be confirmed during repeated testing after enrollment, five subjects were lost to follow up, and seven subjects asked to be removed from the study. The total number of remaining subjects was 62. Fifty-two subjects were treated in 38 different medical centres. Four subjects did not report the name of the centre they were treated in but provided sufficient detail about the findings. Eleven divers were diagnosed with a PFO without a history of previous DCS. Four of these were diagnosed while undergoing tests for non-DCS related medical issues and

Table 1
Characteristics of divers in conservative and closure groups before intervention; CI – confidence interval; PFO – persistent foramen ovale; SD – standard deviation

Characteristics	**Conservative** (n = 23)	**Closure** (n = 42)	***P*-value**
Age [median (95% CI)]	52 (43–55)	45.5 (40–50)	NS
Male/female ratio	12/11	22/20	NS
Height, cm [mean (SD)]	175 (8)	173 (10)	NS
Weight, kg [mean (SD)]	81 (14.5)	83 (18)	NS
Body mass index, $kg \cdot m^{-2}$ [mean (SD)]	26.3 (3.8)	27.4 (4.7)	NS
Years diving at enrollment [median (95% CI)]	7.0 (6–12)	8.5 (6–11.6)	NS
Total dives at enrollment (n) [median (95% CI)]	213 (129–461)	231 (142–363)	NS
Number of dives per year [median (95% CI)]	41 (22–49)	33 (24–49)	NS
Number of technical divers	8	17	NS
Number of subjects with large PFO	8/18	26/34	< 0.05
DCS prior to intervention			
Possible [median (range)]	0.0 (0–6)	2.0 (0–60)	< 0.05
Confirmed [median (range)]	1.0 (0–1)	1.0 (0–2)	NS

Table 2
Diver practice in conservative and closure groups after intervention; bottom two rows refer to comparisons with diving prior to the intervention; no differences between groups were significant; CI = confidence interval

Outcome	**Conservative**	**Closure**
Years diving [median (95% CI)]	5 (3–8)	6 (5–7)
Dives per year [median (95% CI)]	16 (12–19)	20 (15–29)
Dived less (n)	16/23	23/42
Dived the same or more (n)	7/23	19/42

seven asked for testing to comply with the requirements of their technical diving associations or because of personal concerns. Initially, 36 subjects were classified as closure, and 26 subjects were classified as conservative. During the follow-up period, six of the subjects from the conservative group underwent closure and were subsequently reclassified into the closure group. Three of those subjects executed dives between diagnosis and closure and they were included in both groups as described in the methods. As a result, the study yielded 42 subjects in the closure group and 23 in the conservative group. The classification algorithm is shown in Figure 1 and the characteristics of divers in each group are shown in Table 1.

Age, years diving, the total number of dives, and the number of DCS instances were not distributed normally. Divers in both groups were similar in body characteristics and dive history, although the number of reported possible DCS cases was significantly greater in the closure group while

Table 3
Incidence rate of confirmed and possible DCS per 10,000 dives in the conservative and closure groups before and after the intervention; values in brackets are 95% confidence intervals

Group	DCS	Before	After	Relative risk	*P*-value
Conservative	Confirmed	12.8 (6–23)	6.2 (0.3–23)	0.49 (0.05–2.24)	NS
	Possible	31.3 (21–46)	131.2 (95–177)	4.2 (2.5–7.1)	< 0.0001
Closure	Confirmed	13.1 (9–19)	2.7 (0.3–10)	0.21 (0.02–0.83)	< 0.05
	Possible	144.5 (129–162)	42.1 (29–60)	0.3 (0.2–0.4)	< 0.0001

Table 4
Number of subjects in the conservative and closure groups reporting episodes of DCS before and after the intervention

Group	DCS	Before	After
Conservative	Confirmed	12	2
	Possible	10	11
Closure	Confirmed	24	2
	Possible	30	10

the number of confirmed DCS cases was similar. Divers in the closure group appeared younger than those in the conservative group, but the difference was not significant.

The median follow-up period after the intervention was five years (95% confidence interval (CI) 3–8) for the conservative group and six years (95% CI 5–7) for the closure group. These were not significantly different. In about half of the subjects (22 closure subjects, ten conservative subjects) intervention occurred years before enrollment in the study. Within one year, 85% of subjects in the conservative group and 90% of subjects in the closure group returned to diving (NS). Details of their diving practices are shown in Table 2.

Fifty-two subjects had adequate information to classify the size of their PFO. Thirty-three were classified as large; including 11 divers in whom the diagnosis was that of an ASD. A significantly greater number of subjects in the closure group (26 of 34) had a large PFO compared to the conservative diving group (8 of 18) (OR = 3.7, 95% CI 1–13.5, $P < 0.05$).

Before the intervention, the group incidence rate of confirmed DCS per 10,000 dives was similar in both groups while the incidence rate of possible DCS was greater in the closure group (Table 3). However, the incidence rate of confirmed DCS before intervention (12.8 and 13.1 per 10,000 dives) in both groups was greater than in the general recreational diving population.

In three cases, subjects originally decided to dive conservatively, but after executing dives decided to opt for closure. One diver experienced two episodes of possible DCS while diving conservatively, which lead them to pursue closure. A second did not originally pursue closure because their insurance would not cover it but after experiencing two episodes of possible DCS and one of confirmed DCS, elected for closure. The third did not experience any DCS while diving conservatively but wished to pursue more aggressive diving and elected for closure.

OUTCOMES

The number of subjects who experienced confirmed DCS decreased in both groups (see Table 4). The number of subjects experiencing possible DCS decreased in the closure group and remained the same in the conservative group.

The incidence rate of confirmed DCS after the intervention was reduced in the closure group to 2.7 and in the conservative group to 6.2 (Table 3). In the closure group, this was a nearly five-fold reduction in comparison to the pre-intervention value, which was statistically significant, and a two-fold reduction in the conservative group which was not statistically significant.

The median dives per year after intervention decreased in comparison to the pre-intervention period (conservative: from 33 to 20; closure: from 41 to 16). Four subjects stopped diving. Seven subjects in the conservative group and 19 subjects in the closure group maintained or increased their diving in comparison to pre-intervention levels (Table 2), which was not significantly different.

The incidence rate of reported possible DCS (Table 3) increased significantly in the conservative group (RR = 4.2, 95% CI 2.5–7.1; $P < 0.0001$) and decreased significantly in the closure group (RR = 0.3, 95% CI 0.2–0.4; $P < 0.0001$).

Table 5
Incidence rate of possible DCS per 10,000 dives before and after the intervention stratified by size of the atrial defect; values in brackets are 95% confidence intervals except where indicated

Group *(n)*	PFO *(n)*	Before	After	Relative risk	*P*-value
Conservative (17)	Large (7)	45 (16–99)	445 (296–643)	9.7 (4.0–23)	< 0.0001
	Small (10)	30 (17–49)	131 (72–221)	4.4 (2.1–8.9)	< 0.05
Closure (34)	Large (26)	219 (194–247)	48 (31–70)	0.2 (0.1–0.3)	< 0.0001
	Small (8)	38 (25–55)	31 (9–79)	0.8 (0.3–2.3)	NS

LARGE VS SMALL PFO

Of the subjects with available PFO size information, 18 had small, and 33 had large PFOs. Of the 18 subjects with a small PFO, ten were in the conservative group, and eight were in the closure group. Of the 33 subjects with a large PFO, seven were in the conservative group, and 26 were in the closure group. There were only four cases of confirmed DCS, and we could not calculate the incidence rate of stratified data.

The incidence rate of possible DCS stratified by the group and by PFO size is shown in Table 5. Divers with a small PFO in the conservative group had a greater incidence rate of possible DCS after the intervention, while divers with a small PFO in the closure group experienced no significant change in possible DCS incidence rate after the intervention. Divers with a large PFO in the conservative group had a greater incidence rate of possible DCS after the intervention, while divers with a large PFO in the closure group had a decreased incidence rate of possible DCS after the intervention.

ADVERSE EVENTS ASSOCIATED WITH CLOSURE

Adverse events associated with PFO/ASD closure occurred in eight out of the 42 subjects who went for closure. These included post-surgical bleeding, transient atrial fibrillation, migraines with aura, dysrhythmia, heart palpitations, premature atrial and ventricular contractions, supraventricular tachycardia and an allergic reaction to a muscle relaxant used in surgery.

Discussion

Our study included self-enrolled subjects with widely varied personal diving histories. Before the intervention, some subjects frequently suffered post-dive symptoms such as skin mottling but did nothing about them for a long time, whilst others underwent preventive testing and even closure without experiencing any DCS. Furthermore, the indications for testing, the testing procedures and the description of findings in our sample varied widely and were not always in line with current recommendations, which were published after the start of our study.[16,17]

As reported in the only other study of this type,[20] we found that confirmed DCS was reduced after intervention in the closure group. In the conservative group, the incidence rate after intervention decreased by nearly 50%, but this was not statistically significant as reported by other studies.[18] Interestingly, the incidence rate of possible DCS in the conservative group increased after the intervention, on account of five individuals who reported more cases of skin itch and rash (not mottling) and received first-aid oxygen more often. They may have become more vigilant and anxious after having been diagnosed with PFO, leading them to report subjective symptoms and seek assistance more readily. On the other hand, this also may have been owing to regression to the mean.

When stratified by size, it appeared that individuals with large PFOs would reduce their possible DCS from closure, while those with small PFOs would not. However, individuals with small PFOs started with a lower incidence rate in the first place, and their DCS may not have been related to a PFO at all.

On average, divers in both groups reported fewer dives per year after intervention. In the conservative group, most subjects reported shallower dives and used more nitrox. In the closure group, some subjects who previously had frequent post-dive symptoms reported being able to continue to diving as before or even more aggressively without any problems. Some divers who underwent closure started diving more conservatively, used nitrox more frequently and dove shallower.

In the closure group, one subject suffered a severe vestibular DCS hit resulting in hearing loss before closure and did not continue diving after the procedure. Another subject stopped diving for undisclosed reasons. In the conservative group, one subject stopped diving because he had not been able plan a dive trip, and another stopped for undisclosed reasons.

One diver in the closure group experienced a serious adverse event and seven experienced minor adverse events. The incidence rate of adverse events was more than reported in clinical trials of closure for stroke.[21]

In a prospective, single-centre study including non-PFO divers, divers with PFO and divers with closed PFO, the incidence rate of treated DCS (what corresponds to 'confirmed' DCS in our study) was reduced in both PFO groups in the post-intervention period.[20] However, the total burden of subjectively reported DCS increased in the PFO group after intervention while in the no-PFO and the closed-PFO groups the incidence rates decreased, as in our study. In both studies, the increase in reported post-dive symptoms in divers with an unclosed PFO may have been due to the subject's increased vigilance after being diagnosed.[20]

Another prospective study evaluated the incidence rates of DCS in divers with PFO who received instructions on how to dive conservatively.[18] Both the divers with PFO and with closed PFO benefited from these instructions, and either did not suffer DCS, or their DCS incidence rate was reduced to the overall incidence rate in recreational divers.

The weaknesses of our study include small sample size, bias due to self-enrollment, subjective reporting of DCS burden, differences in clinical practices and deficiencies in the available medical documentation. The sample size was smaller than we originally planned and the study is underpowered for some outcome measures. An extension of the study was not a practical solution due to slow enrollment.

Self-enrollment potentially introduces a selection bias. The sample may not have been representative of all divers who had been diagnosed with PFO and who had undergone closure. It is possible that participants were in better health, had a lesser burden of previous DCS, had a stronger motivation to continue diving and, in general, had better outcomes of the intervention. However, the sample was not homogenous and included both success and failure stories. The study started before the consensus recommendations on investigation and management of PFO in diving were published,[16,17] and instead of imposing stringent selection criteria the study explored implicit criteria for testing and closure in real life. These varied widely. Personal motivations of divers seemed to have been the influencing factor on decisions for undergoing testing and for the election of closure or conservative diving. Despite this, the closure of PFO appeared to be effective in the reduction of DCS burden for most but not for all subjects, and some subjects fared worse either due to adverse events of closure or they stopped diving due to undisclosed causes. If the current consensus criteria had been applied, the success rate could have been higher.

Conclusion

While we could not establish the risk-benefit ratios or relative risk ratios for the two interventions with confidence, we have identified subsets of subjects that could benefit from closure. These are healthy divers with a significant DCS burden and a large PFO who seek to pursue advanced diving.

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