NEW RESEARCH PAPER

Screening and Risk Stratification Strategy Reduced Decompression Sickness Occurrence in Divers With Patent Foramen Ovale

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ABSTRACT

OBJECTIVES This paper sought to evaluate the occurrence of decompression sickness (DCS) after the application of a patent foramen ovale (PFO) screening and risk stratification strategy.

BACKGROUND PFO is associated with an increased risk of DCS. Recently, transcatheter closure was reported to reduce DCS occurrence in divers with a high-grade shunt. However, to date, there are no data regarding the effectiveness of any PFO screening and risk stratification strategy for divers.

METHODS A total of 829 consecutive divers (35.4 ± 10.0 years, 81.5% men) were screened for PFO by means of transcranial color-coded sonography in the DIVE-PFO (Decompression Illness Prevention in Divers with a Patent Foramen Ovale) registry. Divers with a high-grade PFO were offered either catheter-based PFO closure (the closure group) or advised conservative diving (high grades). Divers with a low-grade shunt were advised conservative diving (low grades), whereas those with no PFO continued unrestricted diving (controls). A telephone follow-up was performed. To study the effect of the screening and risk stratification strategy, DCS occurrence before enrollment and during the follow-up was compared.

RESULTS Follow-up was available for 748 (90%) divers. Seven hundred and 2 divers continued diving and were included in the analysis (mean follow-up 6.5 ± 3.5 years). The DCS incidence decreased significantly in all groups, except the controls. During follow-up, there were no DCS events in the closure group; DCS incidence was similar to the controls in the low-grade group (HR: 3.965; 95% CI: 0.558-28.18; $P = 0.169$) but remained higher in the high-grade group (HR: 26.170; 95% CI: 5.797-118.16; $P < 0.0001$).

CONCLUSIONS The screening and risk stratification strategy using transcranial color-coded sonography was associated with a decrease in DCS occurrence in divers with PFO. Catheter-based PFO closure was associated with a DCS occurrence similar to the controls; the conservative strategy had a similar effect in the low-grade group, but in the high-grade group the DCS incidence remained higher than in all other groups. (J Am Coll Cardiol Img 2021;■:■-■) © 2021 by the American College of Cardiology Foundation.

A patent foramen ovale (PFO) is associated with an increased risk of decompression sickness (DCS) in scuba divers (1). Divers breathe air or other gas mixtures under elevated pressures during the dive, and nitrogen dissolves in all tissues. If the tissues become supersaturated during ascent, bubbles form. This can be observed sonographically in venous blood in most divers after a single properly performed dive (ie, without violation of the decompression regimen) (2,3). In divers with a PFO, these bubbles may embolize into systemic circulation, lodge into peripheral capillaries, and cause ischemic injury (4).

It has been previously demonstrated that a PFO is associated with an increased risk of neurological and cutaneous forms of DCS (5,6). This can range from mild symptoms to severe permanent disability. In previous reports from the DIVE-PFO (Decompression Illness Prevention in Divers with a Patent Foramen Ovale) registry, we have demonstrated that: 1) a high-grade PFO was associated with an increased risk of unprovoked DCS in recreational divers; and 2) catheter-based closure of a high-grade PFO prevented DCS in a long-term follow-up (7,8). In this study, we compared the retrospective data with a prospective follow-up of the whole cohort (ie, divers with no shunt, a low-grade shunt, and a high-grade shunt). We aimed to analyze the effect of the PFO screening and risk stratification strategy on the incidence of DCS.

METHODS

PATIENTS AND STUDY DESIGN. A total of 829 consecutive divers (age 35.4 ± 10.0 years, 81.5% males) were screened for a PFO at our center between January 2006 and December 2018 using transcranial color-coded sonography (TCCS). All patients were prospectively included in the DIVE-PFO registry. The screening was offered to all registered Czech diving clubs and was regularly promoted through diving magazines, websites, instructor courses, and diving and hyperbaric medicine meetings. Baseline data (ie, demographic data, diving experience, and DCS history) were collected from all divers at the time of the initial screening examination. Divers with a history of DCS filled out a detailed questionnaire in order to reveal any violation of the rules of safe recreational diving (Supplemental Appendix). The questions included the number and timing of all preceding dives, the maximum depth, the bottom time, and any violation of the regimen advised by a diving computer or table (eg, exceeding the maximum ascent rate or shortening the advised safety stop). The same questions were asked during a telephonic follow-up, which was performed at the end of the study (June 2019). For the patients for whom follow-up was not available, survival was checked in the National Database of Deaths. To ascertain the cause of death for deceased patients who died outside hospitals, interviews or mail communication with the general practitioner or next of kin were performed. The study was approved by the local ethics committee, and all study subjects gave written informed consent to participate in the study.

IMAGING AND RISK STRATIFICATION. TCCS was used for the detection of a right-to-left shunt as described previously (9). The shunt was graded as follows according to the International Consensus Criteria: grade 1, 1 bubbles-10 bubbles; grade 2, >10 bubbles but no curtain (uncountable number of bubbles); and grade 3, curtain (10). TCCS was performed by experienced neurologists (M.S. and A.T.) blinded to the diver's DCS history. Transesophageal echocardiography (TEE) was offered to divers: 1) with a history of DCS; 2) with a grade 3 shunt on TCCS; and 3) in whom TCCS examination was unsuccessful (insufficient bone window). The same grading system was used for TEE examination. If the result of TEE was available, the higher grade of the 2 examinations (TEE or TCCS) was counted. Divers with a grade 3 PFO were offered either catheter-based PFO closure (the closure group) or advised conservative diving (the high-grade group). Divers with grades 1 and 2 shunts were advised conservative diving (the low-grade group), whereas those with no PFO continued unrestricted diving (the control group) (8). The term PFO was used for all right-to-left shunts detected by TCCS because PFO is the most prevalent shunt, and timing of the bubble signals after contrast agent injection is inconsistent in the differentiation between intracardiac and extracardiac shunts (10).

PROCEDURES. The PFO closure procedures were performed in 5 centers between February 2006 and November 2018. The Amplatzer Septal Occluder (AGA Medical Corporation) was used in 10 (18%) divers. In the remaining 46 (82%) cases, the Occlutech Figulla PFO Occluder N (Occlutech GmbH) was used. The procedures were performed as previously described (11). The indication for the procedure was the presence of a grade 3 PFO according to the International Consensus Criteria and either: 1) a history of unprovoked DCS; or 2) in highly individual cases the procedure was performed in divers with no

history of DCS who would not be able to adapt their diving to conservative recommendations (ie, professionals) (8).

There were no major complications. Bleeding at the puncture site with no need for intervention occurred in 2 patients (3.6%).
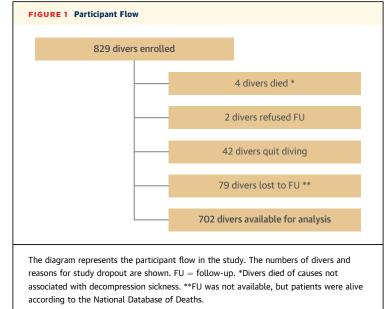
DEFINITIONS. An unprovoked DCS was defined as any DCS symptom that originated <24 hours after a dive or series of dives that complied with all the rules advised to recreational divers, as described previously (7). Briefly, the diver had to perform no-decompression air or nitrox (air enriched with oxygen) dives according to a dive computer or table to a maximum depth of 40 m (7,12).

STATISTICAL ANALYSIS. Normally distributed data are presented as mean ± SD and non-normally distributed data as median with interquartile range. The distribution of data was evaluated by the Shapiro-Wilk normality test. The Student's *t*-test, Mann-Whitney *U* test, Fisher exact test, and chi-square test were used when appropriate.

Estimates for long-term event-free survival were made by the Kaplan-Meier method, and differences in survival were assessed by the log-rank and Wilcoxon tests. We used Cox proportional hazards models to compute a HR with a 95% CI. The number of dives was used as a pragmatic measure of time. A *P* value of ≤0.05 was considered to indicate a statistically significant difference. When comparing before and after screening, the robust generalized estimating equation–based approach was used (13). In particular, we used the Huber-White sandwich–type estimator of SEs (amounting to elaboration on an independence working model) and also the robust score test (reflecting lack of within-individual independence) for hypothesis of interest. All reported *P* values were 2-sided. Statistical analyses were performed using GraphPad Prism version 6 (GraphPad Software) and survival library in R (13,14).

RESULTS

A total of 829 divers were screened for the presence of a right-to-left shunt between January 2006 and December 2018 using TCCS. The mean age was 35.4 ± 10.0 years, and 81.5% were men. Follow-up was available in 748 (90%) divers; 702 of them continued diving during follow-up and thus were included in the analysis (**Figure 1**). The mean follow-up was 6.5 ± 3.5 years. The baseline characteristics are summarized in **Table 1**. For the baseline characteristics of the divers who were lost to follow-up or who stopped diving, see Supplemental Table 1.

FIGURE 1 Participant Flow

829 divers enrolled

4 divers died *

2 divers refused FU

42 divers quit diving

79 divers lost to FU **

702 divers available for analysis

The diagram represents the participant flow in the study. The numbers of divers and reasons for study dropout are shown. FU = follow-up. *Divers died of causes not associated with decompression sickness. **FU was not available, but patients were alive according to the National Database of Deaths.

During the follow-up, there were a total of 702 divers: 55 in the closure, 98 in the high-grade, 128 in the low-grade, and 421 in the control groups, respectively. Of the 702 divers, 616 (82%) had prior diving history (at least 1 dive before screening) and were included in the survival analysis of the retrospective data (55 in the closure, 90 in the high-grade, 106 in the low-grade, and 365 in the control groups, respectively). A survival analysis was performed, and Kaplan-Meier curves were created for both the retrospective and prospective data. The number of dives was used as a measure of time. The incidence of DCS was compared between the groups, and the retrospective and prospective data were compared.

The DCS occurrence decreased significantly in all groups, except the controls: closure group HR: 9.876e-10; 95% CI: 6.55e-10 to 1.489e-09; $P < 0.0001$; high-grade group HR: 0.3327; 95% CI: 0.1857-0.5961; $P = 0.0002$; low-grade group HR: 0.1154, 95% CI: 0.0279-0.4771; $P = 0.0029$; controls HR: 0.3653; 95% CI: 0.0711-1.877; $P = 0.228$). During the follow-up, there were no DCS events in the closure group; the DCS incidence was similar to the controls in the low-grade group (HR: 3.965; 95% CI: 0.558-28.18; $P = 0.169$) but remained higher in the high-grade group (HR: 26.170; 95% CI: 5.797-118.16; $P < 0.0001$). For the Kaplan-Meier curves, see **Central Illustration and Figure 2**. **Table 2** summarizes the number of dives, the number of DCS episodes, and the DCS incidence rate for all groups before and during the follow-up. The incidence rate before PFO screening and during follow-up is compared for each group.

TABLE 1 Baseline Data

	A	B	C	D	A vs B vs C vs D
	Controls (n = 421)	Closure Group (n = 55)	High Grades (n = 98)	Low Grades (n = 128)	P Value
Follow-up (y)	6.5 ± 3.4	7.1 ± 3.9	6.5 ± 3.2	6.3 ± 4.0	0.750
Age (y)					
Start of follow-up	35.2 ± 9.8	40.3 ± 7.8	37.3 ± 9.8	33.3 ± 9.8	<0.001
End of follow-up	41.7 ± 10.4	47.4 ± 8.0	43.8 ± 10.0	39.7 ± 10.7	<0.001
Male	358 (85)	44 (78)	78 (80)	94 (73)	0.024
Dives, total at the end of follow-up	232,679	63,586	48,069	52,121	
Mean ± SD	553 ± 1,020	1,156 ± 1,656	491 ± 667	407 ± 768	<0.001
New dives during follow-up	124,521	30,689	25,328	28,254	<0.001
Mean ± SD	296 ± 696	558 ± 757	258 ± 407	221 ± 506	
BMI (kg/m^2)					
Start of follow-up	26.0 ± 3.4	27.7 ± 3.6	26.2 ± 3.6	24.9 ± 3.6	<0.001
End of follow-up	26.5 ± 3.5	27.9 ± 4.0	26.6 ± 3.7	25.5 ± 3.7	0.002
Smoking					
Start of follow-up	65 (15)	8 (15)	13 (13)	21 (16)	0.927
End of follow-up	56 (13)	9 (16)	10 (10)	19 (15)	0.679

Values are mean ± SD, n (%), or n.
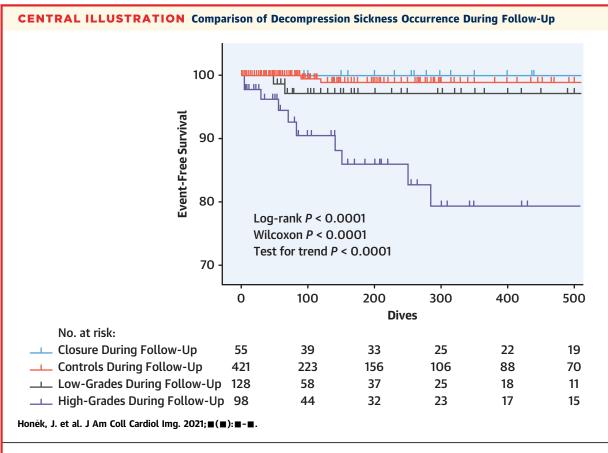
BMI = body mass index; DCS = decompression sickness.

DISCUSSION

Our results provide the first evidence that a PFO screening and risk stratification strategy might lower DCS occurrence in a large cohort of divers. The main findings of this study may be summarized as follows: 1) after the application of the risk stratification strategy, the DCS occurrence decreased significantly in all groups, except the controls; 2) PFO closure was associated with DCS occurrence similar to the controls; and 3) the conservative strategy had a similar effect in low grades, but in high grades the DCS incidence remained higher than in all other groups.

UNPROVOKED DCS. DCS is caused by nitrogen bubbles that form in supersaturated tissues during a diver's ascent (15). These bubbles cause symptoms by local tissue damage, embolization into pulmonary circulation, or systemic arterial embolization (4). To prevent DCS, divers routinely use specialized dive computers or tables that are based on mathematical models calculating nitrogen kinetics (1). Unprovoked DCS is defined as symptoms originating after a dive or a series of dives that comply with the rules of recreational diving, including the adherence to the decompression model (7,12).

It has been speculated that paradoxical embolization through a PFO might be the reason why some divers develop clinical symptoms after a properly performed dive (16). In our previous study, we demonstrated that a high-grade PFO was a major risk factor for unprovoked DCS in 489 scuba divers (7). In this study, 7% of the divers experienced an unprovoked DCS after recreational diving. The frequency of PFO was 97.2% in divers with a history of unprovoked DCS and 35.5% in controls. In a multivariate analysis, PFO grade 3 was a major risk factor for unprovoked DCS; there was a slight protective effect of increasing age, and no difference was found in sex, body mass index, or the total number of dives. On the other hand, in other studies that did not specifically focus on recreational diving, age, body mass index, and repetitive diving were identified as risk factors of DCS (2,17,18). By contrast, in a small case-controlled study of divers with recurrent DCS, a right-to-left shunt and a lack of changes in the way of diving after a prior DCS were found to be the only predictors of neurological DCS recurrence (5). In the present study, DCS occurrence was higher only in the high-grade group compared with divers with no PFO. In divers after catheter-based PFO closure and in divers with a low-grade shunt managed conservatively, the DCS occurrence was similar to controls.

PFO SCREENING AND RISK STRATIFICATION. Although the issue of PFO in divers has been studied for nearly 4 decades, it is noteworthy that a consensus among experts on practical issues such as PFO screening recommendations and risk stratification has not yet been reached (19). Routine PFO screening in divers is currently not recommended (19-21). Some authors have recommended testing for the presence of PFO in divers with recurrent or severe neurological DCS (22,23). However, to date, there are no prospective data evaluating any PFO screening strategy. The most important practical

CENTRAL ILLUSTRATION Comparison of Decompression Sickness Occurrence During Follow-Up

No. at risk:						
Closure During Follow-Up	55	39	33	25	22	19
Controls During Follow-Up	421	223	156	106	88	70
Low-Grades During Follow-Up	128	58	37	25	18	11
High-Grades During Follow-Up	98	44	32	23	17	15

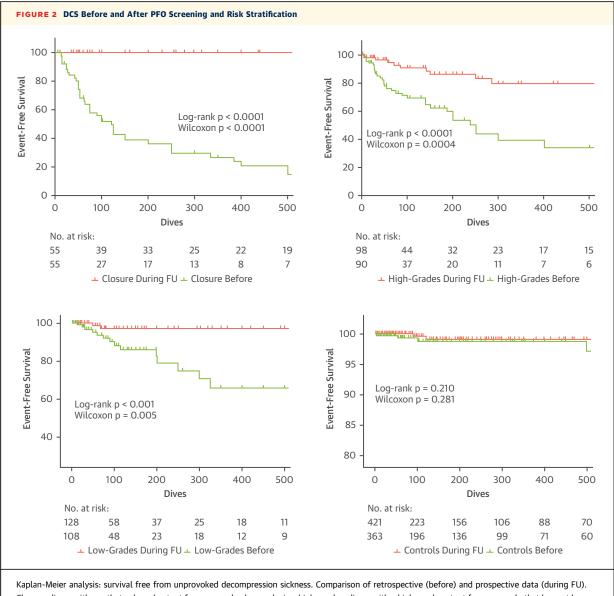Honĕk, J. et al. J Am Coll Cardiol Img. 2021;■(■):■–■.

Kaplan-Meier analysis: survival free from unprovoked decompression sickness. Comparison of prospective data (during FU) between study groups. Closure, divers with a catheter-based patent foramen ovale closure device; high-grades, divers with a high-grade patent foramen ovale that has not been occluded; low-grades, divers with a low-grade patent foramen ovale; controls, divers with no patent foramen ovale. The number of dives is used as a measure of time. FU = follow-up.

questions discussed are how to risk stratify the divers with a PFO and what preventive measures should be recommended. Theoretically, there are 3 ways to reduce the risk of DCS: cessation of diving, a conservative approach to diving, and PFO closure. So far, however, there has been a lack of clinical studies that could support our clinical decisions.

In the DIVE-PFO registry, we screened all recreational and professional divers by means of TCCS. It has been demonstrated previously that the risk of DCS parallels the shunt grade (24). We have applied the International Consensus Criteria for PFO grading (10). A choice of catheter-based PFO closure or conservative diving was offered only to divers with a grade 3 shunt (high grade), whereas divers with grades 1 and 2 shunts (low grade) were advised to conservative diving. This strategy led to a decrease in DCS occurrence in all groups.

CONSERVATIVE DIVE PROFILES. Conservative dive profiles (CDPs) are measures that should lead to lower

bubble production and a reduction in the incidence of clinically overt DCS. This may be achieved by limiting exposure to higher nitrogen partial pressures or by allowing for more gradual tissue desaturation. To reduce nitrogen exposure, various CDP recommendations limit the maximum depth, dive time, or number of dives per day or recommend the use of oxygen-enriched gas mixtures (5,25). To slow down tissue desaturation, a slower ascent rate and longer safety stops are recommended (25). In our pilot study in a hyperbaric chamber, we demonstrated the effect of a slower ascent rate on the occurrence of venous and arterial bubbles in divers with a PFO (26). In the present study, we observed a reduction in the incidence of DCS after CDP recommendations in divers with a PFO compared with retrospective data. However, the DCS occurrence was similar to controls only in the low-grade group; in divers with a high-grade shunt, it remained significantly higher. Besides CDP, there is also experimental evidence that

FIGURE 2 DCS Before and After PFO Screening and Risk Stratification

Kaplan-Meier analysis: survival free from unprovoked decompression sickness. Comparison of retrospective (before) and prospective data (during FU). Closure, divers with a catheter-based patent foramen ovale closure device; high-grades, divers with a high-grade patent foramen ovale that has not been occluded; low-grades, divers with a low-grade patent foramen ovale; controls, divers with no patent foramen ovale. The number of dives is used as a measure of time. FU = follow-up.

preconditioning methods, such as predive heat exposure, oxygen administration, hydration, or exercise, might decrease the occurrence of venous bubbles (27-31). None of these measures have been tested in divers with a PFO.

PFO CLOSURE. Several authors suggested that a catheter-based PFO closure in divers might eliminate the arterialization of bubbles and prevent unprovoked DCS (32-34). We have previously reported from the DIVE-PFO registry that catheter-based PFO closure was more effective in DCS prevention than CDP in divers with a high-grade PFO (8).

To date, there are no other prospective studies that would assess the clinical benefit of PFO closure in divers. However, some small retrospective studies are available (35-37). Koopsen et al (35) retrospectively reviewed records of 62 divers referred for TEE after DCS. A PFO or an atrial septal defect (ASD) was found in 35 (56%) of the divers, and a closure procedure was performed in 21. Of the 14 divers with a PFO/ASD and no closure, only 7 continued diving. In a telephonic follow-up (mean = 6.8 years), no case of DCS was found in either the divers with PFO/ASD closure or the divers with no closure. In another study, Henzel

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TABLE 2 DCS Occurrence DCS Occurrence

Group	Divers A		Dives B	Divers With Unprovoked DCS C	Total of Unprovoked DCS Episodes D	Incidence Rate, n/1,000 dives D/B	P Value
Controls	363	Prior	108,158	5 (1.4)	12	0.11	0.259
	421	During	124,521	2 (0.5)	2	0.02	
	421	Total	232,679	7 (1.7)	14	0.06	—
Low grades	108	Prior	23,883	14 (13.0)	42	1.76	**0.0005**
	128	During	28,254	2 (1.5)	8	0.28	
	128	Total	52,137	16 (12.5)	50	0.96	—
Closure	55	Prior	32,897	39 (70.9)	136	4.13	**<0.0001**
	55	During	30,689	0 (0.0)	0	0.00	
	55	Total	63,586	39 (70.9)	136	2.14	—
High grades	90	Prior	22,741	33 (36.7)	119	5.23	**<0.0001**
	98	During	25,328	11 (11.2)	19	0.75	
	98	Total	48,069	44 (44.9)	138	2.87	—
All groups	616	Prior	187,679	91 (14.8)	309	1.65	**<0.0001**
	702	During	208,792	15 (2.1)	29	0.14	
	702	Total	396,471	106 (15.1)	338	0.85	—

Values are n or n (%), unless otherwise indicated. Comparison of incidence rate of decompression sickness including repeated episodes before patent foramen ovale screening (prior) and during follow-up (during). **Bold** values notes statistically significant differences.

DCS = decompression sickness.

et al [36] followed by telephone 11 consecutive divers in whom a device PFO closure was performed. During the mean follow-up of 91 months after PFO closure, no DCS episodes were observed even though the divers returned to unrestricted deep diving. Anderson et al [37] followed 65 divers who volunteered for participation in the study and tested positive for a PFO/ASD in at least 38 different centers. Forty-two divers underwent a catheter-based closure, and 23 continued diving without closure. They compared retrospective data with a prospective follow-up. In the closure group, the occurrence of confirmed DCS decreased significantly compared with preclosure, but this reduction was not significant in the conservative group. Still, the primary end point (confirmed DCS) was not different between the 2 groups (only 2 cases occurred in each group during the follow-up).

The present study, with its follow-up of 702 divers who performed more than 200,000 dives, is the largest available to date. In addition, the uniform screening method by TCCS and prospective inclusion in the registry are, so far, unique in this field. In the present study, there were no DCS events in the closure group during follow-up. This is consistent with the results of numerous retrospective studies that strongly suggest that PFO is the clinically relevant route of paradoxical embolization in divers [6,22,24,34,38]. It has been suggested that the transpulmonary passage of nitrogen bubbles might also play an important role in the occurrence of postdive arterial gas emboli [39]. On the other hand, in a previous experimental study, we had not observed any arterial bubbles in divers after PFO closure even after provocative dive exposures in a hyperbaric chamber [40].

We must bear in mind that PFO closure is an invasive procedure with potential major complications, even though the occurrence is generally low (<1%) [41]. In addition, a recent retrospective study of 59 divers after catheter-based PFO closure reported recurrent DCS in 4 divers. In 3 of them, a residual shunt was subsequently found; the fourth patient had aggravating factors for his recurrent DCS [42]. Therefore, we believe that the decision for the intervention should be very carefully considered and performed in highly experienced centers. The apparent risk reduction strategy is the cessation of diving, but in our experience this suggestion is rarely accepted. In this study, only 5% of the divers reportedly quit diving. We believe that catheter-based PFO closure may be an effective and safe preventive measure for divers who are unable to adopt to strict conservative recommendations (ie, professionals) or who wish to continue frequent or technical diving (ie, deep diving, diving with gas mixtures, etc.)

STUDY LIMITATIONS. This registry study with prospective patient enrollment is subject to inherent limitations, including selection bias. Therefore, the prevalence of PFO and the incidence of unprovoked DCS might not be generalizable to the overall population of recreational divers. However, the incidence

rate of DCS in the whole cohort was comparable with previous reports (43,44). Although this study is, to our knowledge, the largest available, the number of end points is still low. The self-reporting of end points is another limitation of the study because the majority of cases were not examined by a specialist at the time of the DCS event.

CONCLUSIONS

The screening and risk stratification strategy using TCCS was associated with a decrease in DCS occurrence in divers with PFO. Similar DCS rates were observed in the closure and low-grade groups; in the high-grade group, the occurrence decreased but remained higher compared with the controls. We suggest that this strategy may be an effective tool in DCS prevention in divers with PFO. However, for divers with a high-grade shunt managed conservatively, stricter recommendations may be considered.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Screening and risk stratification for PFO was associated with a decrease in DCS occurrence in divers.

COMPETENCY IN PATIENT CARE: Divers should be made aware that PFO is associated with an increased risk of unprovoked DCS. This condition can be ultrasonographically detected, and the risk of DCS can be mitigated by subsequent preventive measures (ie, catheter-based PFO closure or conservative approach to diving).

TRANSLATIONAL OUTLOOK 1: A prospective randomized clinical trial would be beneficial to confirm the results of this study.

TRANSLATIONAL OUTLOOK 2: The incidence of a high-grade PFO was high in this study, and divers benefited from catheter-based PFO closure more than the conservative approach. Therefore, stricter recommendations for divers with a high-grade PFO should be considered.

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APPENDIX For a supplemental appendix and tables, please see the online version of this paper.