

Evidence for Increasing Patency of the Foramen Ovale in Divers

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Using a standardized contrast-enhanced transesophageal echocardiographic technique, a group of divers was reexamined for the presence and size of patent foramen ovale (PFO) 7 years after their initial examinations. Unexpected but significant increases in the prevalence and size of PFO were found, suggesting a possible increasing risk for decompression sickness in these divers over time. ©2005 by Excerpta Medica Inc. (Am J Cardiol 2005;95:912-915)

Patent foramen ovale (PFO) of the heart is associated with the occurrence of certain types of decompression sickness (DCS) after scuba diving,^{1,2} by the paradoxical embolization of venous gas emboli (so-called silent bubbles)³ in the decompression phase after a dive. From dissection studies of human hearts,⁴ the natural history of PFO appears to be associated with gradual closure. It is not considered likely for nonpatent interatrial septa to become patent at a later age. Previous reports confirm our own anecdotal observations of divers who, after uneventful diving careers of many years, suddenly seemed to have become extremely susceptible to DCS, with the co-morbid observation of large PFOs.⁵ The objective of this study was to investigate if the prevalence or size of PFO is subject to change over time in a group of divers.

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A group of divers who had undergone investigation for PFO from 1994 to 1996, using a strictly standardized contrast-enhanced transesophageal echocardiographic (cTEE) technique, gave their informed consent for reevaluation using the same technique 6 to 8 years later. Ethics committee approval was obtained for this follow-up echocardiographic study. The group was not a random population sample but consisted of 40 divers, 16 of whom had experienced DCS previously and 24 who had never had DCS but served at the time as matched controls for the initial study. All divers continued diving, and none had experienced DCS since their first cTEE studies. None of the divers had experienced cardiac or pulmonary disease at present or in the past.

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The presence or absence of patency of the foramen ovale was assessed with a very standardized cTEE technique, as previously described.⁶ In short, a normal saline perfusion drip was placed using a large-bore catheter (18 gauge) in the antecubital vein in the right arm. After local anesthesia of the throat, the subject was turned onto the left side, and the ultrasound probe was introduced. No general anesthesia or sedation was given. The interatrial septum of the heart was visualized with a multiplane ultrasound probe. Usually, the interatrial septum was observed in the plane of the aortic valve or slightly above, at an angle of 45° to 60°. The subject was then asked to perform a "straining" maneuver (i.e., a modified Valsalva strain; the subject was instructed to take a deep breath, block the respiration, and "push down" in the abdomen for ≥10 seconds, counted aloud).⁷ During this maneuver, the heart rate could be observed to slow down, and the interatrial septum could be seen shifting to a more horizontal position. The ultrasound probe, however, was kept immobile. Upon release, the septal image became immediately clear again, and the area of the right and left atria was observed for "false respiratory contrast," as described by Van Camp et al (Figure 1).⁸

Then, this maneuver was repeated, but during counting, agitated saline 10 cm³ was prepared by moving a mixture of saline 9.5 cm³ and 0.5 cm³ of air to and fro in a double-syringe system. The agitated saline was injected upon the count of 8. Upon arrival of contrast in the right atrium, the subject was instructed to release the straining and breathe normally. Contrast passage into the left atrium within 3 cardiac cycles was considered proof of paradoxical embolism through a PFO. The quality of the injection and the efficacy of the straining maneuver were considered adequate if the right atrium was completely filled with contrast, up to against the septum. A test's results were considered negative if, after 3 attempts, no contrast passage was observed. The patency of the foramen ovale was semiquantified according to the degree of paradoxical contrast passage (grade 0: no bubble passage; grade 1: <20 bubbles; grade 2: >20 bubbles).

It was acknowledged that there could be a possibility of "falsely increased" PFO detection because of improvements in imaging technology, the increased experience of the cardiologists, and knowledge of the result of the previous examination. To exclude the enhanced detection of PFO compared with the initial tests, performed several years earlier, the following precautions were taken: (1) the examining cardiologist was blinded to the initial cTEE result; (2) all divers were specifically instructed not to talk about their previous examinations; (3) the contrast-enhancing features of the echocardiographic system were not used

Grade	Initial cTEE Study	Evolution			Final cTEE Study
		Grade	No.	Years/Dives	
0	20 (50%)	0	16	7.24/279	19 (47.5%)
		1	3	7.68/557	
		2	1	7.0/150	
		0	3	7.04/217	
1	9 (22.5%)	1	1	5/450	4 (10%)
		2	5	7.54/218	
		0	0		
		1	0		
2	11 (27.5%)	2	11	7.15/325	17 (42.5%)
Total	40				40

	Age at Final cTEE Study	Interval (yrs)	Dives	No.
PFO grade				
0	43.1 ± 9.6	7.31 ± 0.87	314 ± 210	20
1	46.1 ± 7.2	7.14 ± 0.84	243 ± 114	9
2	43.1 ± 6.7	6.99 ± 0.81	271 ± 184	11
PFO grade change				
No change	43.8 ± 8.3	7.19 ± 0.84	286 ± 184	28
1 to 2	46.8 ± 7.6	7.54 ± .066	218 ± 78	5
1 to 0	41.7 ± 3.5	7.04 ± 0.43	217 ± 126	3
0 to 1 or 2	45.0 ± 11.2	7.60 ± 0.95	455 ± 343	4

(harmonic imaging)⁹; and (4) the sequence of the cTEE examination, as described in the original study protocol, was repeated meticulously, even if during everyday cTEE examinations, the cardiologists might have had other “tricks” to improve the detection of PFO.⁷ Furthermore, all cardiologists were already experienced in the cTEE technique at the time of the first examination.

The evolution of the cTEE score was evaluated using Analyze-It version 1.68 (Analyze-It Software, Ltd., Leeds, United Kingdom) for Microsoft Excel (Microsoft Corporation, Redmond, Washington), using nonparametric testing of the difference in ranks. The confidence interval around the difference between medians was computed using the Hodges-Lehman method.¹⁰ Demographic data were analyzed with GraphPad Prism version 4.00 (GraphPad Software, Inc., San Diego, California), using 1-way analysis of variance with the Bonferroni multiple-comparisons test.

The initial prevalence of PFO in this group of divers was 50% (20 of 40 divers); 9 divers had grade 1 PFOs and 11 had grade 2 PFOs (Table 1). The mean years of diving between the 2 cTEE examinations was 7.19, and the mean number of dives was 286 (mean 39 dives/year). At the second cTEE examination, of the 9 divers with initial grade 1 PFOs, 5 had increased their permeability to grade 2 PFOs. Three others had apparently closed (evolution to grade 0). Three of the 20 divers with initially no patency (grade 0 PFOs) were found to have grade 1 PFOs at their second cTEE examinations. One had a grade 2 PFO. The difference of cTEE score on an ordinal scale was statistically significant (Wilcoxon signed rank test, $p = 0.0354$). Using a Friedman 1-way analysis of variance by ranks, this difference approached significance ($p =$

0.0833, chi-square approximation with correction for ties). There was no significant difference in years of diving, the number of dives performed, or age in any of the groups (PFO increased, decreased, or no change; all $p > 0.05$ on 1-way analysis of variance with the Bonferroni multiple-comparisons test). There was, however, a trend difference in the number of dives between the 4 divers who initially had no PFOs but were found to have grade 1 (3 divers) or grade 2 (1 diver) PFOs and the others: 455 versus 286 (PFO no change), 217 (grade 1 to grade 0), and 218 dives (grade 1 to grade 2). Because of the small numbers, these differences were not statistically significant ($p > 0.05$; Table 2).

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The diagnosis of PFO in living humans is only possible using indirect techniques. Of the different techniques used, contrast-enhanced transesophageal echocardiography is considered the “gold standard.”^{11,12}

However, even this technique is subject to intra- and interobserver variabilities, because of a number of factors: echocardiographic probe positioning, contrast injection, the site of contrast injection, and the straining maneuver used.¹³ Unless a strictly standardized technique is adhered to, as we did here, comparisons are difficult, even in a longitudinal study.¹⁴

This study showed that over 7 years, the permeability of PFO in a group of sports divers had significantly changed: closure occurred in 7.5% of the divers and increased permeability in 22.5% (half of whom, 10%, had no initial permeability).

The autopsy assessment of 965 heart specimens⁴ has suggested that the prevalence of PFO decreases with age, whereas the mean size of the remaining PFOs increases. This is consistent with the finding in this series: 5 divers increased from grade 1 to grade 2, whereas 3 divers' grade 1 PFOs spontaneously closed. However, in our series, the general prevalence of PFO increased over this period (from 47.5% to 52.5%), because of the appearance of PFOs that were previously not patent.

To our knowledge, this is the first prospective follow-up study to actually document the increase in PFO size in humans, using a standardized and reliable indirect technique. For scuba divers, we consider this an important finding because it may imply that divers could develop increased susceptibility to neurologic DCS over time. A statistical correlation has been shown between large PFOs (grade 2) and ischemic cerebral incidents in diving (cerebral DCS). Outside of the diving context, the same is true for PFO and “unexplained” thrombotic cerebrovascular events.^{15,16} For small PFOs (grade 1), no such correlation has been demonstrated.

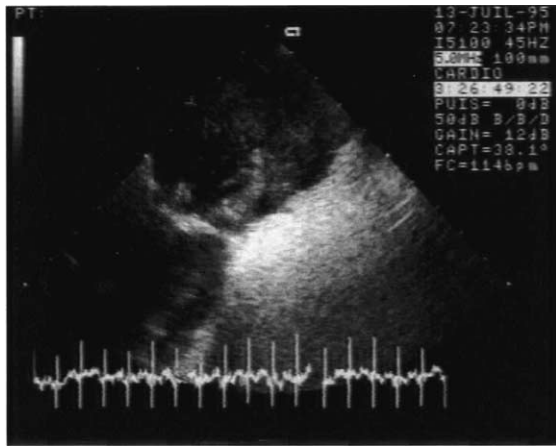


FIGURE 1. Typical image of "false contrast" upon the release of the straining maneuver, without the injection of contrast.

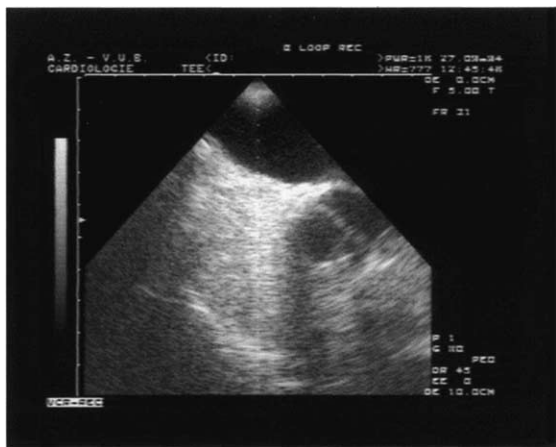


FIGURE 2. Initial cTEE image of a diver (1995), showing grade 0 PFO (no contrast passage).



FIGURE 3. Follow-up cTEE image of the same diver as in Figure 1 (2002), showing grade 2 PFO (>20 bubbles).

The finding that 4 divers presented with PFO, whereas 7 years before, they were "contrast negative," is novel. The suggestion that this is merely a reflection of an increased detection rate due to more powerful equipment, a more optimized examination technique, or more experienced cardiologists was anticipated by deliberately

"downscaling" our detection technique to have the same quality of images as 7 years ago. Moreover, our cardiologists, who were already experienced 7 years ago, used the exact same criteria to score PFO patency and were blinded to the result of the initial tests. Third, as before, the images were evaluated independently by all cardiologists involved. Therefore, we believe that this finding is not an artifact. However, it is possible that the fusion of the interatrial septum was from the onset incomplete in these divers. No contrast passage could be shown during the initial cTEE examination, indicating either complete closure or minimal opening of the interatrial valve (Figure 2). It is acknowledged that only autopsy studies would give a definite diagnosis, but a longitudinal follow-up study is difficult to set up using this detection technique.

If the "initially closed" PFOs would have been "microscopically patent" PFOs, then the total number of subjects with "increased permeability of PFO" would be 9 (22.5%). This would be an important and worrying find, because it would imply that many (more than half) of the divers with grade 1 PFOs would eventually develop grade 2 PFOs (Figure 3). The finding of a PFO prevalence of 65%, with grade 2 PFOs in 38%, in a recent study in which a random sample of very experienced divers was examined¹⁷ seems to confirm this possibility. The relative risk for incurring DCS when diving with a grade 2 PFO has been estimated at 2.5 to 5.7,^{6,18,19} so even if the divers in this study did not have DCS in the 7-year interval, they may be considered "at increased risk" for future diving activities.

Mechanisms for this de novo opening or increasing permeability of PFOs could involve diving-related phenomena, such as variations in right atrial pressures during the end stages of or events immediately after a dive. However, such pressure fluctuations are equally associated with straining-release events, such as can be found in certain types of exercise and activities of daily living, and no specific diving-related hypothesis is suggested at this time.

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Impact of Methadone Treatment on Cardiac Repolarization and Conduction in Opioid Users

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We prospectively assessed the effect of oral methadone on the corrected QT interval (QTc) among 160 patients free of structural heart disease and measured serum methadone concentrations and simultaneous QTc intervals in a subset of 44 participants. Mean \pm SD QTc increased by 12.4 ± 23 ms ($p < 0.001$) at 6 months, by 10.7 ± 30 ms ($p < 0.001$) at 12 months, and the QTc change from baseline to 12 months correlated with the trough ($r = 0.37$, $p = 0.008$) and peak ($r = 0.32$, $p = 0.03$) serum methadone concentrations. ©2005 by Excerpta Medica Inc.

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An increase in methadone-related deaths has recently been reported.^{1,2} Although these deaths are generally caused by overdoses involving multiple substances, reports of Torsade de pointes associated with methadone suggest that its potential impact on cardiac repolarization merits investigation.³ We sought to prospectively define whether an association exists between methadone treatment and QTc prolongation, bradycardia, or QRS widening. We conducted serial electrocardiographic measurements immediately before and after methadone induction. Initially, we observed a small but statistically significant increase in QTc interval after 2 months of treatment.⁴ This relatively short follow-up period precluded an assessment of the duration of this effect or whether such prolongation was associated with the development of arrhythmia. In addition, the relation of QTc prolongation to serum methadone levels has not been described. To address these questions, we assessed the electrocardiographic impact of methadone treatment 6 and 12 months after drug initiation.

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Between December 2001 and January 2003, we recruited consecutive patients admitted to the Division of Substance Abuse of Albert Einstein College of Medicine, Bronx, New York. Criteria for admission were opioid addiction for ≥ 1 year, age > 18 years, and ≥ 1 previous attempt at supervised ambulatory detoxification. Patients were excluded from the study if they self-reported methadone use in the 2 weeks before admission or had been transferred from another methadone program. The institutional review board of the Albert Einstein College of Medicine approved the study.

At baseline (immediately before methadone induction), a complete medical history and laboratory tests were obtained, and standard 12-lead electrocardiogra-