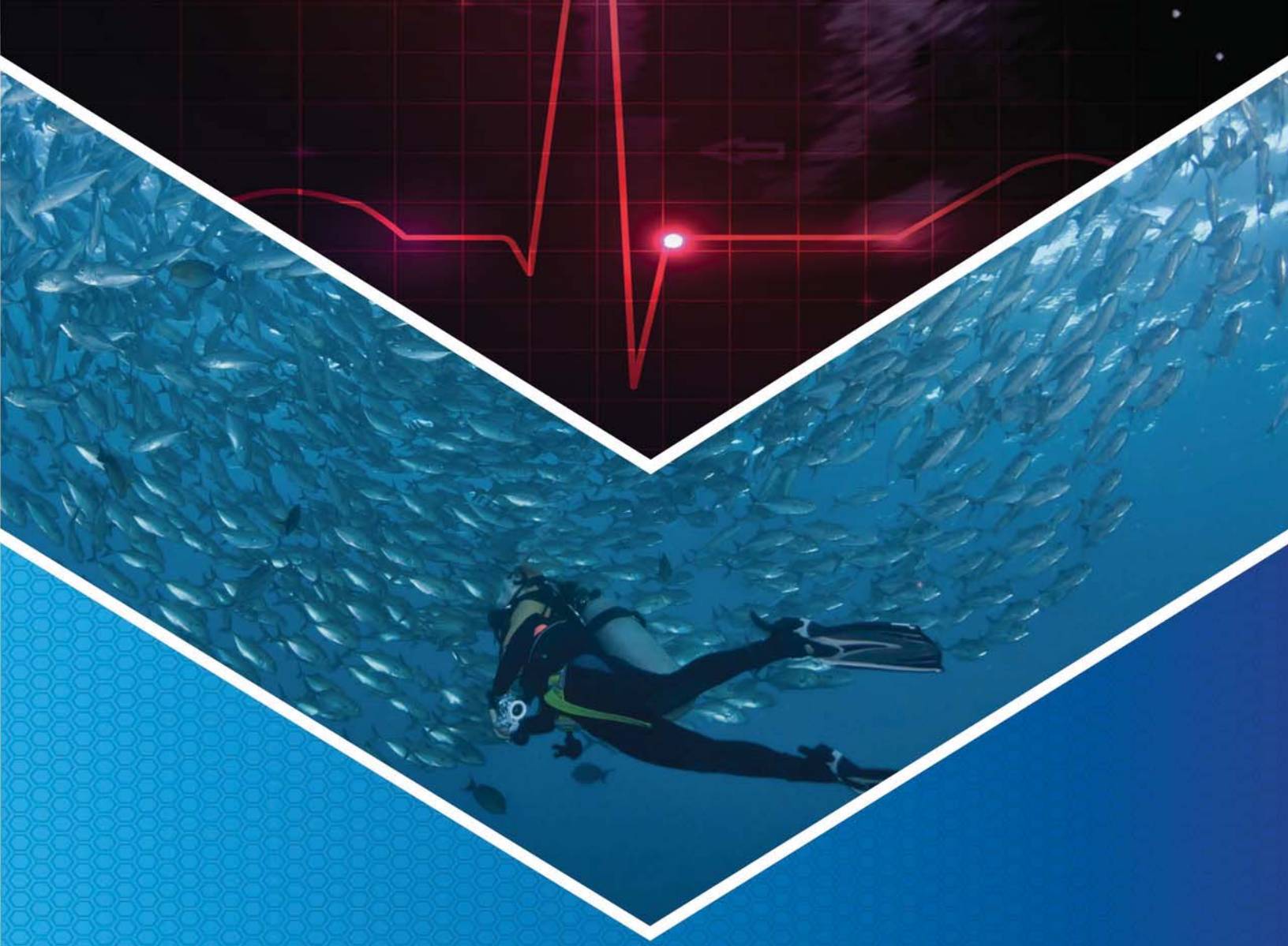

Patent Foramen Ovale and Fitness to Dive Consensus

WORKSHOP PROCEEDINGS

June 17, 2015
Montreal, Canada

SPONSORED BY:

DAN DIVERS ALERT NETWORK

UNDERSEA & HYPERBARIC MEDICAL SOCIETY

UHMS Pre-Course sponsored by Divers Alert Network

Patent Foramen Ovale and Fitness to Dive Consensus

Workshop Proceedings

June 17, 2015

Montreal, Canada

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Denoble PJ, Holm JR, eds. Patent Foramen Ovale and Fitness to Dive Consensus Workshop Proceedings. Durham, NC, Divers Alert Network, 2015, 160 pp.

This symposium and the publication of this document were sponsored by Divers Alert Network.

Opinions and data presented at the symposium and in these proceedings are those of the contributors and do not necessarily reflect those of Divers Alert Network.

Layout by Jeanette Moore, cover design by Rick Melvin.

ISBN 978-1-941027-71-4

These are edited transcripts of the presentations given at the PFO and Fitness to Dive Consensus Workshop, a pre-course to the UHMS Annual meeting in Montreal, Canada, on June 17, 2015.

Alfred A. Bove, MD, PhD, MACC, FUHM

Dr. Bove is the former Chief of Cardiology at Temple University Medical Center and Emeritus Professor of Medicine at Temple University Medical School. He was president of the American College of Cardiology in 2009 and served on their Board of Trustees for 11 years. Dr. Bove was an established Investigator of the American Heart Association, and has published over 300 original research papers on coronary disease, valvular heart disease, cardiac hypertrophy, exercise medicine and physiology, coronary prevention, environmental medicine, and computers in medicine. He has authored texts on coronary disease, exercise medicine and diving medicine. He has conducted research in basic cardiac physiology, coronary disease, exercise physiology, environmental medicine and computer information systems in medicine. His current research involves population-based management of heart failure and cardiovascular risk factors using an Internet communication system. Dr. Bove maintains an active clinical practice in Cardiology, Sports Medicine and Diving Medicine.

Peter T. Wilmshurst, MB ChB

Dr. Wilmshurst is a physician, cardiologist and diver. He is currently a consultant cardiologist at the Royal Stoke University Hospital. He qualified as a doctor in 1974 from Manchester University. He joined the medical committee of the British Sub-Aqua Club in 1977 and was later its chairman for 10 years. Subsequently he was chair of the UK Sport Diving Medical Committee. He was medical officer on a number of international diving expeditions in the 1970s and 1980s. He has more than 200 scientific publications. His main diving-related research interests deal with the role of right-to-left shunts in decompression illness and immersion pulmonary edema.

Peter Germonpre, MD

Dr. Germonpre is a military physician in the Belgian Defence Medical Services where he trained in emergency and disaster medicine, sports medicine, diving medicine, and aerospace medicine. He presently serves as Medical director of the Centre for Hyperbaric Oxygen Therapy in the Military Hospital Brussels which he founded and developed.

His areas of interest in diving medicine and safety are focused towards patent foramen ovale and pulmonary risk factors; preconditioning of divers to reduce DCS risk; bubble detection techniques; (in hyperbaric medicine) – intensive care HBO, sudden deafness and acoustic trauma, evidence based hyperbaric medicine.

He is involved in the OXYNET Project (www.oxynet.org; COST B14 Action of the European Commission) and the PHYPODE Project (www.phypode.org; Marie Curie FP Action of the European Commission). He is also a board member of the Scott Haldane Foundation (www.scotthaldane.org; The Netherlands) which conducts courses in diving medicine for occupational and other physicians according to the EDTC/ECHM Curricula. He recently organized and conducted a NATO Introductory Course in Hyperbaric Medicine for military medical personnel in 2014-2015 (NATO HFM-RLS245 in Belgium, Portugal, and Florida US).

Phillip P. Foster, MD, PhD

Dr. Foster is a physician and research scientist who has achieved international acclaim for his exceptional and original research contributions that span a broad spectrum of biology of oxygen to applied operational or basic research for the National Aeronautics and Space Administration (NASA).

His research work has encompassed medicine, physiology, biology, biochemistry, mathematical/stochastic modeling and programming. Philip recently contributed to an extraordinary scientific achievement from basic research to innovative Human application: the success in hand-made assembly of the International Space Station in the most hostile environment that man ever had to face (spatial void, absence of gravity, extreme temperatures). Products and procedures were delivered to NASA. Dr. Foster received several international awards (competition across scientific fields) from NASA (Houston) (two awards), the Wellcome Trust (London), the European Space Agency (ESA) and Rouquayrol and Denayrouze Prize (Paris). Dr. Foster has over 410 citations for his journal articles, including Nature and Lancet including three textbooks and booklet. Dr. Foster's (nonprofit) Foundation is at www.BFOR-Foundation.org

Simon J. Mitchell, MB, ChB, PhD, DipDHM, FANZCA

Dr. Mitchell is an anesthesiologist and diving physician and is the Head of the Department of Anesthesiology at the University of Auckland. He has been a lifelong passionate diver and was a lead member of teams that were the first to locate, dive and identify three deep shipwrecks of high historical significance in Australia and New Zealand. At the time of one of these dives it was the deepest (600') ever undertaken to a wreck. He is widely published, particularly in the area of diving medicine, with over 120 scientific papers or book chapters which include (with Michael Bennett) the chapter on hyperbaric and diving medicine in Harrison's Principles of Internal Medicine. Simon was elected to Fellowship of the Explorers' Club of New York in 2006. He received the Albert R Behnke Award from the UHMS in 2010, the Eurotek Discovery Award in 2014, and the DAN/Rolex Diver of the Year Award in 2015

Marlowe W. Eldridge, MD

Dr. Eldridge is Professor of Pediatrics at the University of Wisconsin. He earned his medical degree from the University of New Mexico and was a postdoctoral fellow at the Lovelace Medical foundation. He completed his residency at Primary Children's Hospital of the University of Utah and also received fellowships at the National Institute of Environmental Health Sciences at the University of North Carolina and at the University of California San Francisco. He specializes in Pediatric Critical Care.

His research focuses on integrative cardiopulmonary physiology and pathophysiology. Of particular interest are cardiopulmonary interactions in congenital and acquired lung disease (bronchopulmonary dysplasia, congenital diaphragmatic hernia, asthma). Dr. Eldridge has made significant contributions to science particularly in the areas of preterm birth and cardiopulmonary physiology and pathophysiology; pulmonary gas exchange, and inducible intrapulmonary shunt pathways; pulmonary gas exchange, pulmonary hemodynamics and high altitude pulmonary edema; Asthma, inhaled endotoxin, airway inflammation and pulmonary gas exchange; and Doppler ultrasound, blood flow and preterm birth. He is widely published and has received many awards.

Željko Dujić, MD, PhD

Dr. Dujić is Professor of Physiology and Head of the Department of Integrative Physiology at the University of Split School of Medicine (USSM), Split, Croatia. He has held different national (Ministry, National Foundation for Science) and regional (Medical School, University of Split) professional positions and served as reviewer for various international journals, international funding agencies, opponent for PhD thesis defence in Sweden, national coordinator for OECD report to name a few.

Dr. Dujić received his medical degree from the University of Zagreb School of Medicine in Zagreb, Croatia and his PhD from the Graduate school of Biomedical Sciences, Medical College of Wisconsin, Milwaukee, USA. He has received National awards for scientific activities. Participated in various national and international research projects (see the current list at http://genom.mefst.hr/physiology/projects.html).

Richard D. Vann, PhD

Dr. Vann spent his career in environmental physiology or operational diving with emphasis on understanding the physiology of decompression sickness (DCS) and on developing procedures to avoid DCS. In 1986, he began studies for NASA to investigate how DCS risk during extravehicular activity (EVA) was influenced by exercise and simulated microgravity through their effects on bubble formation and nitrogen exchange. The results of this work became the foundation for an exercise prebreathe protocol used during EVA from the Space Station. Other interests at the Duke Hyperbaric Center included formulating statistical models of acute mountain sickness and CNS and pulmonary oxygen toxicity and developing efficient supplemental oxygen delivery systems for high altitude operations.

As Vice President for Research at the Divers Alert Network from 1992-2010, he investigated the causes of fatal and non-fatal diving injuries and published on dive computers, nitrox diving, flying after diving, prognostic factors in DCS therapy, flying with DCS, flying after DCS therapy, first aid oxygen at sea level for DCS, technical diving, rebreather diving, and the influence of elevated inspired oxygen on carbon dioxide narcosis. An investigation of depth-time recordings 120,000 dives demonstrated that the DCS risk of recreational dives is strongly dependent on dive conditions. In 1999, he established the DAN Research Internship Program to give students firsthand research experience to encourage their interest in diving research and medicine careers. He is currently an Assistant Professor Emeritus in the Anesthesiology Department at Duke and a consultant to DAN.

Luděk Šefc, PhD

Dr. Šefc is a Head of the Center for Advanced Preclinical Imaging (CAPI) and Assistant Professor at Institute of Pathophysiology of the First Faculty of Medicine, Charles University in Prague, Czech Republic. He is a leader of the group in the field of experimental hematology and stem cell research and because of his diving activities, he is also involved in diving medicine. Dr. Šefc started his diving career at the University Diving Club and became an instructor. He is a long-time member of Technical Committee of the Czech Divers Association, instructor trainer both for recreational and technical diving disciplines. He is a tutor of two PhD students (Jakub Honěk and Martin Šrámek) who coauthored the presented publication. He also participates in the popularization of diving and particularly diving medicine in public lectures and diving magazines. In 2004, he was diagnosed with a PFO, he suffered unprovoked DCI symptoms and was closed with an occluder. He is one of few divers that could closely observe PFO problems from both sides – as a patient and as a physician involved in its treatment.

Larry B. Goldstein, MD, FAAN, FANA, FAHA

Dr. Goldstein is professor and chair of the Department of Neurology and Co-Director of the Kentucky Neuroscience Institute at the University of Kentucky. He received his BA degree in 1977 from Brandeis University and MD from Mount Sinai School of Medicine in 1981. Dr. Goldstein focused his clinical, research, educational and service activities on stroke and related disorders. He has published over 650 peer review journal articles, reviews, editorials, book chapters, abstracts, and other professional papers. His research has spanned stroke-related laboratory based studies, clinical trials, quality of care and care delivery studies, as well as clinical effectiveness and epidemiological investigations.

He serves as a reviewer for numerous professional journals as well as national and international granting agencies. He is a member of the editorial boards, has served as editor of several medical journals, and lead various committees at numerous medical associations. Among his many awards, Dr. Goldstein was recently awarded the Order of the Long Leaf Pine by the governor of North Carolina in 2015 for his service to the state related to improving stroke care.

Douglas G. Ebersole, MD, FACC

Dr. Ebersole is a cardiologist at The Watson Clinic in Lakeland, Florida specializing in coronary and structural heart interventions and is a cardiology consultant for DAN. Along with Dr. Petar Denoble, he is co-investigator of the PFO research study that aims to determine the risk/benefit of PFO closure on diving. He is board certified in internal medicine, cardiology, and interventional cardiology. He is an avid technical diver experienced in rebreather and cave diving. He has lectured around the world on diving medicine and authored numerous publications in peer-reviewed journals.

He completed his undergraduate studies in Mathematics at Duke University before going on to the University of Miami where he received his medical degree. He served in the medical corps of the US Army at Brooke Army Medical Center where he also did his Internal Medicine Residency and his Cardiology Fellowship. He was awarded the Meritorious Service Medal in 1996. Other awards for his work are the John W. McClure Cardiology Award for Clinical & Teaching Excellence, 1996 and the Commander's Award for Outstanding Research, BAMC, 1992. He is a member of the American College of Physicians, the American College of Cardiology and the Society for Cardiac Angiography and Interventions.

Ward L. Reed, MD, MPH, UHM

Dr. Reed is a hyperbaric medicine specialist at the Hyox Medical Treatment Facility in Marietta Georgia. Dr. Reed received his BA in Biochemistry from Bowdoin College and earned an MD and MPH from the University of North Carolina, Chapel Hill. He served in the US Navy in various medical capacities including command surgeon for the US Special Operations Command South (SOCSO), Homestead FL; as Department Head for Occupational & Environmental Medicine and Director of Public Health for the Naval Hospital, Pensacola, FL; as Director of the Hyperbaric Program at the Naval Aerospace Medicine Institute, Pensacola, FL; Group Surgeon at the IMEF Headquarters Group, Camp Pendleton, CA; and as Undersea Medical Officer of the Naval Special Warfare Group, San Diego CA, and the Explosive Ordnance Disposal Mobile Unit Five, Agana, Guam. Dr. Reed has authored numerous papers in medical journals and other publications.

Michael Bennett, MB BS, FANZCA, DipDHM, MD, MM Clin Epi

Academic Medical Director, Department of Anaesthesia and Senior Staff Specialist, Department of Diving and Hyperbaric Med, Prince of Wales Hospital, Sydney, Australia; past President, South Pacific Underwater Medicine Society (SPUMS), and past Vice President of UHMS. Professor Bennett has published widely and specializes in the evidence-basis for indications in the field of DHM.

Keshav Nayak, MD

A native of Doylestown, Pennsylvania, Dr. Nayak graduated from Haverford College in Haverford, PA with a Bachelor of Science in Biology. He completed medical school at PennState University School of Medicine, in Hershey, PA and then joined the United States Navy Medical Corps in 1997. Currently, he is the Director of the Cardiac Cathlabs at Naval Medical Center San Diego, and was promoted to permanent rank of Navy Captain in September 2015. Dr. Nayak, by virtue of being an adult interventional cardiologist in the US Navy, has accrued a great amount of experience in evaluating and treating PFOs in military divers. He is proposing a prospective study of relative risk of DCI in Navy divers with PFOs.

David Smart, BMedSci, MBBS(Hons-1), MD(UTas), FUHM, FACEM, FIFEM, FAICD, FACTM, DipDHM, CertDHM (ANZCA)

Dr. Smart is a clinical associate professor in Diving and Hyperbaric Medicine, Faculty of Health Sciences, University of Tasmania. He is also a Senior Visiting Specialist and Medical Co-director, Department of Diving and Hyperbaric Medicine, Royal Hobart Hospital, Tasmania, Australia and serves as Medical Consultant to the Tasmanian Underwater Centre, CSIRO and Tasmanian Professional Diving Industry. He is president of the South Pacific Underwater Medicine Society (SPUMS) as well as past chair of Scientific Committee Australasian College for Emergency Medicine.

His interests in research focus on: Development and validation of safe diving schedules for bounce-diving in Tasmania's Aquaculture Industry using Doppler analysis of decompression stress; Professional Diver Health Monitoring and safety; Doppler validation of sub-2400m ascent to altitude guidelines; Hookah Surface Supply Diving Safety; Hyperbaric Oxygen Treatment for Lower Limb Trauma; Evidence Based Medicine reviews in Diving and Hyperbaric Medicine; Sequential use of hyperbaric oxygen and radiotherapy for the treatment of solid tumours; and Development of Emergency Department Acuity Indices in real time.

Richard Moon, MD

Dr. Moon is an anesthesiologist and hyperbaric medicine specialist at Duke University in Durham, NC. He received his MD from McGill University, completed postgraduate training in internal medicine (Toronto), pulmonary medicine & critical care and anesthesiology (Duke University Medical Center). He is board certified in internal medicine, pulmonary medicine, anesthesiology and undersea & hyperbaric medicine. He is Medical Director of the Duke Center for Hyperbaric Medicine & Environmental Physiology.

PRE-COURSE: "PATENT FORAMEN OVALE AND FITNESS TO DIVE CONSENSUS WORKSHOP"

WEDNESDAY, 06/17/2015

At this workshop, we will consider conditions necessary for DCS to occur in divers with PFO, need for action to prevent it, and the risk-benefit of available options.

08:00-08:10	Greetings	James Holm & Petar Denoble
08:10-08:30	Opening remarks	Richard Moon & Alfred Bove
08:30-08:50	PFO and Diving Exposure - an Overvie	Alfred A. Bove
08:50-09:30	Clinical Experience of RLS in Divers with Decompression Illness	Peter T. Wilmshurst
09:30-09:55	Incidence of DCS in Divers with RLS - A Prospective Study	Peter Germonpre
09:55-10:20	PFO, White Matter Hyper Intensities & Altitude Exposures	Phillip P. Foster
10:20-10:35	Coffee break	
10:35-11:00	The Pathophysiology of Microbubbles Crossing a PFO or Other RLS in Decompression Sickness	Simon J. Mitchell
11:00-11:25	Inducible Intrapulmonary Shunt Pathways: Are They Important in DCS?	Marlowe W. Eldridge
11:25-11:50	VGE Arterialization in Divers with Closed Foramen Ovale	Zeljko Dujic
11:50-12:15	RLS and Probabilistic Decompression Modeling	Richard D. Vann
12:15-13:30	Lunch Break	
SOLUTIONS		
13:30-13:55	Efficacy of Trans-catheter Closure of PFO for DCS	Ludek Sefc
13:55-14:20	Patent Foramen Ovale and Cryptogenic Stroke	Larry B. Goldstein
14:20-14:45	Risk-benefit Analysis of PFO Closure - A Prospective Study	Douglas G. Ebersole
14:45-15:00	Coffee Break	
15:00-15:15	Current State of Knowledge - Quality of Evidence	Ward L. Reed
15:15-15:25	Clinical Evidence and Policy-making. Does the Data Help?	Michael Bennett
15:25-15:50	Current Operational Implications of PFO in Military Divers	Keshav Nayak
15:50-16:15	SPUMS Consensus on PFO and Diving	David Smart
CONSENSUS SESSION		
16:30-17:30	UHMS Consensus on PFO and Diving	Richard E. Moon

Patent Foramen Ovale and Diving – an Overview

Alfred A. Bove, MD, PhD, MACC, FUHM

Former Chief of Cardiology, Temple University Medical Center and Emeritus Professor of Medicine, Temple University Medical School

This presentation is designed to provide background on the issues involved with PFO with the goal of providing our participants with a baseline understanding of what is a PFO and some of the issues that are involved in assessing a diver with a PFO.

I would like to spend a few minutes on embryology. The cardiac structure in the fetus begins with a folding of the upper part of the heart in a pouch-like structure which then develops a septum. This is the septum primum. The septum primum develops from above and connects with the interventricular septum, but then very quickly fenestrates so that there are significant openings in it called the foramen ovale.

This foramen ovale allows oxygenated blood to flow from the placenta through the inferior vena cava and across the right atrium into the left atrium, thereby providing oxygenated blood to the fetal circulation. Over time, a second septum begins to form from below on the left side of the septum primum. This is the septum secundum that ultimately acts as a flap valve. The flap valve obviously needs to be open during fetal life. When there is no respiration, because of placental blood flow, the right atrial pressure is higher than the left atrial pressure, and the flap valve remains open until birth. At birth when the fetus starts to breathe, the left atrial pressure increases. The flap valve is pushed against the septum primum by the pressure difference between the atria, and begins to scar down over time. It ultimately becomes a closed, firm septum that separates the left and right atria.

In some proportion of the population, that septum does not completely fibrose against the septum primum and there is a potential for the flap valve to open when the right atrial pressure exceeds left atrial pressure. In a small proportion of the population, the septum secundum does not form and the result is an atrial septal defect. In a substantial portion of the population, there is a part of that oval rim that does not have the flap valve fully scarred over it, and the remaining patent orifice allows deoxygenated blood flow from right to left (right-to-left shunt) into arterial circulation when right atrial pressure exceeds left atrial pressure. There are uncommon syndromes, usually at the case report level, of significant arterial desaturation because of PFO flow from right to left initiated by changes in position. In some individuals, a change in position produces a significant right to left shunt and results in enough arterial hypoxemia to be symptomatic.

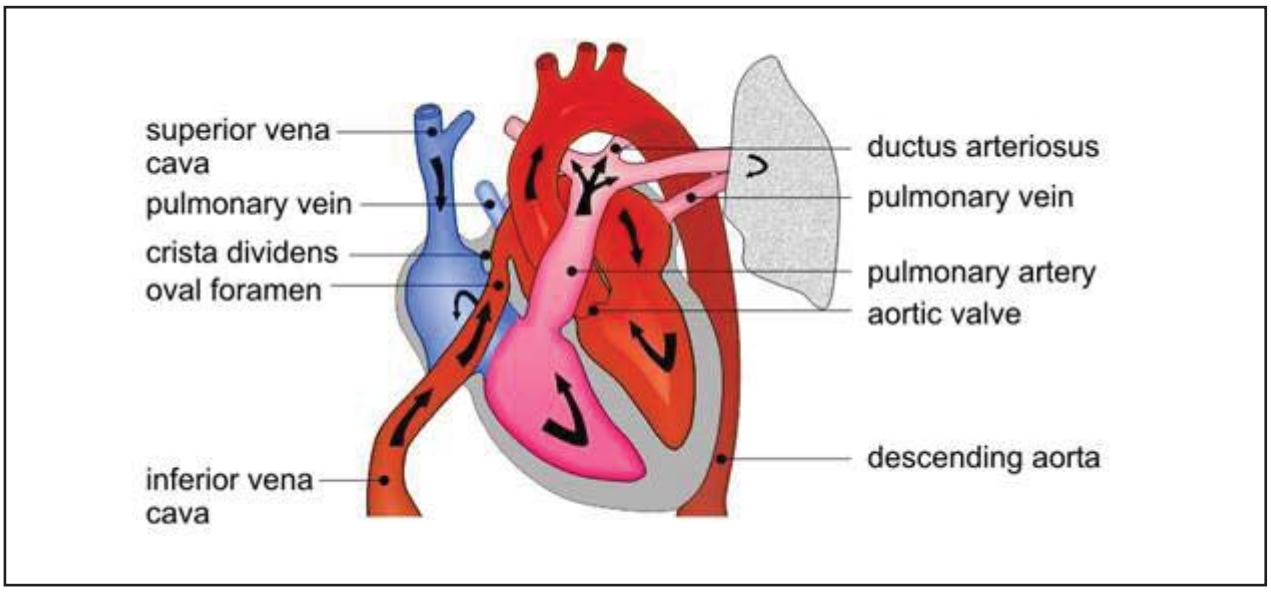

Figure 1. Schematic diagram of the fetal circulation showing flow from inferior vena cava through the foramen ovale (image source: https://maxrayne.wordpress.com/tag/cyanotic-univentricular-heart/)

Figure 1 shows a schematic of the fetal circulation. Placental blood flows up the inferior vena cava, streams across the right atrium, mixes a small amount with venous blood, but enters the foramen ovale, left atrium, and the arterial circulation to provide the fetus with oxygen in the arterial blood. When viewed from the pathologic perspective looking into the right atrium, you would see the oval opening with the septum secundum partially scarred down, but in many cases, this part remains open.

The size of foramen ovale opening can vary and there are different degrees of patency of the foramen ovale. Echocardiography is the gold standard for detection and quantitation of the PFO shunt. At times in the catheterization laboratory, while advancing a right heart catheter into the right atrium, it would suddenly appear in the left atrium. The catheter had crossed the patent foramen ovale because some are open enough that a catheter will pass spontaneously into the left atrium. The inadvertent passage of the catheter into the left atrium was helpful because we could sample arterial blood and left atrial pressure, but the echo is still the better way for screening and diagnosis of a PFO. An echocardiogram readily shows the right atrium and the left atrium and the flap valve of the foramen ovale. We use bubble contrast, micro bubbles or mini bubbles in saline injected into an antecubital vein to evaluate the shunt. The venous bubbles are very reflective of ultrasound and essentially act as an ultrasound contrast.

Figure 2 shows a thrombus moving through the PFO from the right into the left atrial chamber. [1] The diagram demonstrates the anatomy more clearly. You can see that there is an argument for paradoxical embolization usually to the brain when an image like this is recorded. These images provoke an emergency response in the echo lab when observed. It is clear from these isolated case reports that thrombi can cross a PFO and enter the left atrium causing significant arterial embolization. The pathologic study published a number of years ago by Hagen et al.,[2] provides a gold standard on postmortem observation. In over 8,000 patients they reported a 26% incidence of probe patent PFO. The incidence declined with age.

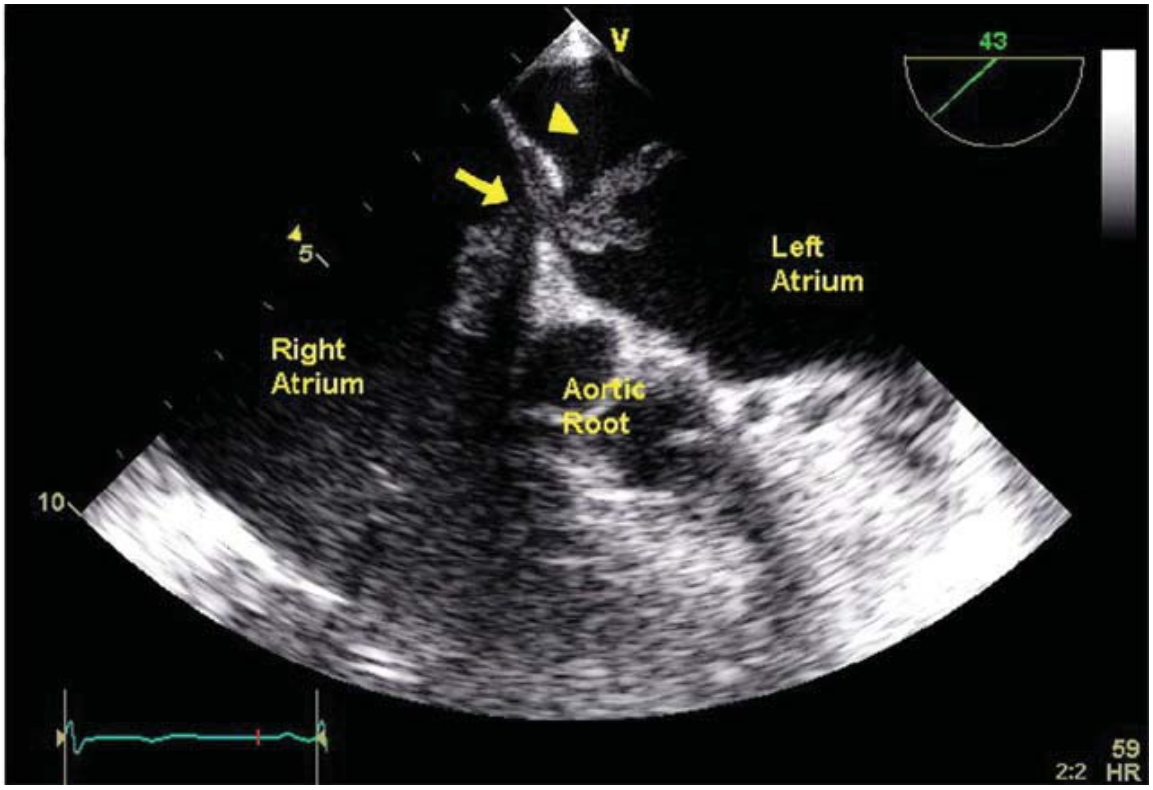

Figure 2. Echo image showing a thrombus situated part way thorough a patent foramen ovale (yellow arrow). Image source: Doufekias et al.[1]

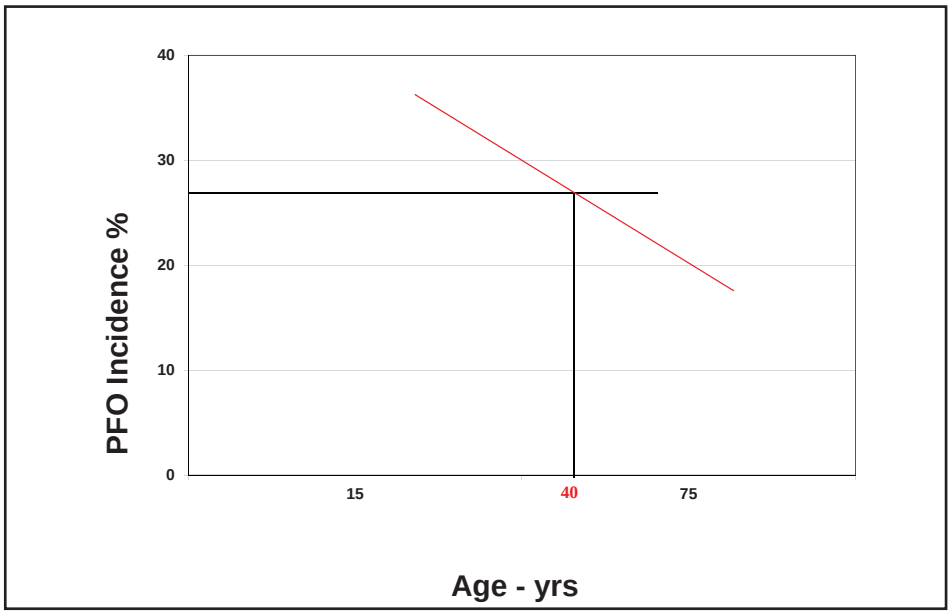

Figure 3. Estimated incidence of PFO vs. age based on data of Hagen et al.[2]

Figure 3 shows my estimate of the linear relationship with age. It is likely that the line flattens a bit in older age groups. And is likely not exactly linear. But the concept that they reported was that the foramen ovale and the scarring process goes on over a lifetime so the incidence of patency goes down with age. At 40 years old, it would be around 26%; and most studies report an incidence of 25 to 28% in the population.

How do we detect a PFO?

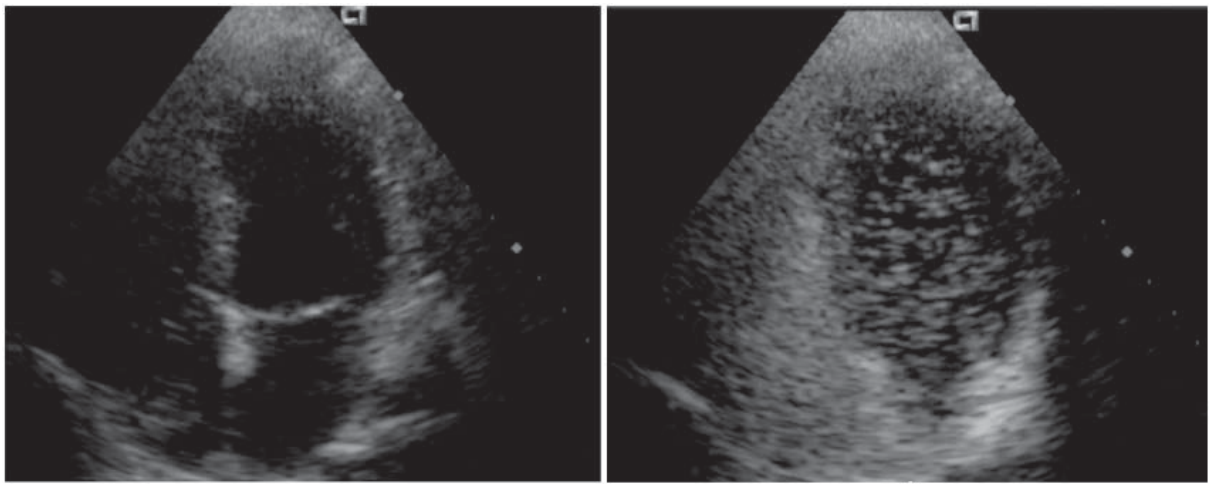

Figure 4. Echo images of the cardiac chambers. Left image - bubble contrast seen in the right heart chambers. Right image - after release of a Valsalva maneuver showing a large amount of bubbles in the left heart chambers

Figure 4 shows a single snapshot from a video four-chamber view from an individual with a PFO taken during injection of bubble contrast into the antecubital vein. Bubbles opacify the right atrium. The second image is recorded immediately post-release of a Valsalva maneuver and demonstrates a large amount of bubbles in the left atrium and the left ventricle. Bubbles appearing in the left atrium within two or three heartbeats following the appearance in the right atrium and right ventricle define a patent foramen ovale. The image indicates a large PFO because there are a large number of bubbles filling both the left atrium and the left ventricle.

There have been a number of clinical studies examining the role of a PFO in various embolic syndromes. Klotzsch et al.[3] reports findings from a group of patients with cryptogenic stroke. The study examined three ultrasound methods for detecting PFO. One is standard transthoracic echo (TTE) with the probe on the chest wall. In this group, there were 28% of subjects that showed a PFO. With transesophageal echo (TEE), which requires a probe in the esophagus but provides excellent images of the left atrium, the incidence was 41% in the same subjects. We usually consider TEE with bubble contrast to be the gold standard. A Doppler probe over the middle cerebral artery on the lateral side of the head produces a transcranial Doppler (TCD), which detects bubbles flowing through the middle cerebral artery following an injection into the antecubital vein again showing arterialization. The time relationship between the injection and the time bubbles appear is a measure of a PFO. The TEE is therefore most sensitive, transcranial Doppler the next most sensitive, and the transthoracic echo the least sensitive. Most clinical echocardiograms are TTEs. And the report of a 28% incidence in the general population comes primarily from transthoracic echo. From these observations, one could surmise that we may be missing some number of PFOs.

- Large PFO is most important for VGE arterialization
- The brain is the most commonly affected organ
- Not all divers with a large PFO get DCS

Dr. Germonpre is here today, and I would like to review his study from 1998 because it points out important relationships between the size of a PFO and clinical manifestations of DCS.[4] He quantitated PFOs into small and large shunts. He identified a group of divers with a cerebral (20 divers) and spinal cord (17 divers) symptoms. For each group he established a control group matched by age, gender and a history of dive exposure who never suffered DCS. Of the divers with cerebral symptoms, 70%, or 14, had a large shunt and 10% had a small shunt. So this would be 16 out of 20 divers with cerebral evidence of DCS who had a PFO; in the control group 5 out of 20 (25%) had a PFO which is close to reported data from the normal population. In a group of divers with spinal cord DCS, there were 17 cases. Six had PFOs and five of the six had large PFOs. This is a 35% incidence in these divers with spinal cord DCS. In the respective control group, 50% of the divers had a PFO, including six with a large PFO. The data from this study suggest that, a large PFO is most important and that the brain is the major organ involved (and not all divers with large PFOs develop DCS).

During our tenure at the Naval Medical Research Institute in 1971-73, John Hallenbeck, David Elliott, and I published studies on the venous component of spinal cord decompression sickness resulting from venous congestion.[5] We thought that besides arterial embolization, spinal DCS might have been a venous problem as well, which would support the concept that spinal cord DCS is not related to arterial embolization alone.

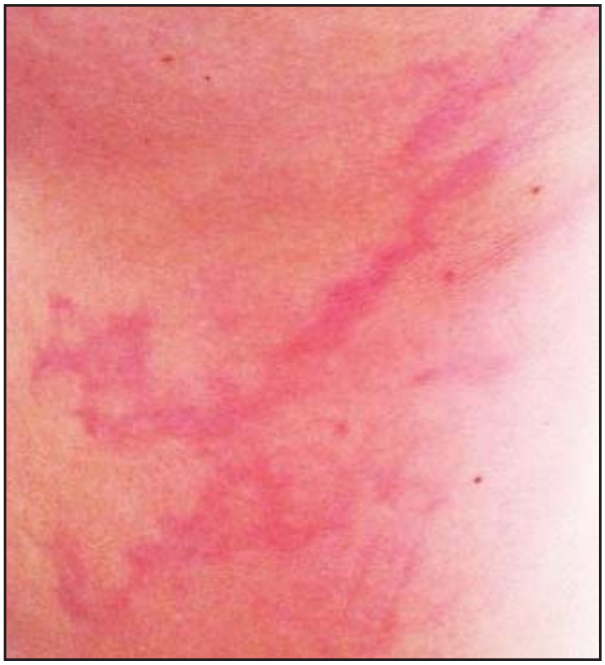

Figure 5. Typical skin rash of cutis marmorata

Peter Wilmshurst's study from 1990 was one of the landmark studies in identifying the effects of PFO.[6] He reported 109 divers with no symptoms of DCS of whom 24% had a PFO. A value close to what we expect in a normal population. In divers with early onset DCS within 30 minutes, and carefully eliminating divers with air embolism related to lung barotrauma, 66% had a PFO. With late onset DCS, 26% had a PFO, and with musculoskeletal DCS,

15% had a PFO. However, 86% of divers with cutaneous DCS had a PFO, which is a fascinating finding that has been corroborated in several other studies over a number of years. Although the numbers are small, it is still a very interesting finding that we still have yet to explain. The skin manifestations are labeled Cutis Marmorata. A typical presentation is shown in Figure 5.

PFO and Risk of DCS with Neurological Manifestations

Bove AA. Undersea and Hyperbaric Med. 25:175, 1998

	Risk	R/10,000 dives
P(DCS+/PFO+)	0.00047	4.7
P(DCS+/PFO-)	0.00019	1.9

Ratio = 2.52 ($p<0.001$)

I did a meta-analysis of the existing PFO and DCS data in 1998.[7] Let me emphasize the fact that we commonly report the incidence of PFO in patients with DCS. That is not the same as looking at the incidence of DCS in all divers with a PFO. One has to apply Bayes' theorem and consider the prior probability. It is possible to calculate the proper statistic from retrospective data on the incidence of PFO in divers with DCS and knowledge of the incidence of PFO in the general population. The calculation of DCS risk in a diver with a PFO is done using the Baye's formula that incorporates the probability of a PFO in the general population.

The calculation supports the concept that there is an increased risk of DCS in divers with a PFO. DCS risk is about 2.5 times greater in divers with a PFO, compared to divers without a PFO. However, the absolute incidence is 4.7 DCS cases in 10,000 dives, which is a very low incidence. This low risk of DCS with a PFO is not enough to justify screening and/or prophylactic closure.

Torti et al.[8] from Europe, studied prevalence of PFO in divers and its relation to the incidence of DCS. They found an overall prevalence of 28% which is the estimated prevalence in normal population. They defined three grades of PFO: small, midsize and large. Based on self-reported data, the incidence of DCS in a group of divers with no PFO was about 1.5 per 10,000 dives and in a group with the large PFO, around 9 per 10,000 dives. So this would be a 6 to 1 ratio. I calculated a 2.5 to 1 ratio in my meta-analysis, but it did not account for different grades of severity. For the most part, it is the large PFOs that seem to be associated with a high incidence of DCS, compared to small or medium-sized PFOs.

The Navy Experimental Diving Unit (NEDU)[9] was performing stressful air dives as part of a study of air decompression tables, and they observed six Type II DCS cases in 88 divers. The majority of the DCS cases were associates with grade 2 and grade 3 PFOs, and the DCS free divers most commonly had no PFO.

If we look at data on PFO closure, Billinger[10] did an interesting study on 104 divers who performed over 18,000 dives in 5 years. That is equivalent to three dives a month for five years. If you examined the neurologic events per 10,000 dives from the divers with no PFOs there were none. Incidence was 0.5 in 10,000 if the PFO had been closed; and 35.8 events per 10,000 dives with a patent orifice. Brain lesions identified by MRI imaging averaged 3.3 in the open PFO group versus just around 1 in the others. Lesions on MRI per 10,000 dives, were 104 with open PFO and 16 or 6 with no or closed PFO.

So there are a number of studies suggesting that the PFO does have effects on DCS incidence. And all these were not symptomatic divers, but they did report a higher number of neurologic events in divers with an open PFO.

I want to finish this review with the data of Honek et al.[11] This is an interesting study because it is one of the few studies that reports prospective, controlled data. They studied 183 European sport divers. Of 47 individuals with large PFOs, 70% had a history of DCS. In the remaining subjects with either no PFO or grade 1 or 2 PFO, there was an 8% incidence. Their population consisted of 118 divers without, 13 with a small, five with an intermediate and 47 PFOs. These were closed with a closure device. They exposed these divers to two dives in a chamber, an 18-meter dive for 80 minutes and a 50-meter dive for 20 minutes. From my standpoint, these, are stressful dives beyond what most sport divers would do in the United States. Thirty-four of these individuals were tested with the 18 meter protocol and 13 with the 50 meter protocol. In the 34 with a 60-foot for 80-minute dive, there were 21% that had symptoms of DCS with a large PFO that was open versus none when the PFO was closed. In the 165-foot for 20-minute dive, none of individuals the closed PFO, and 25% of divers with an open PFO had DCS related symptoms. These data, again, suggest that the large PFO is contributing to DCS in these dives.

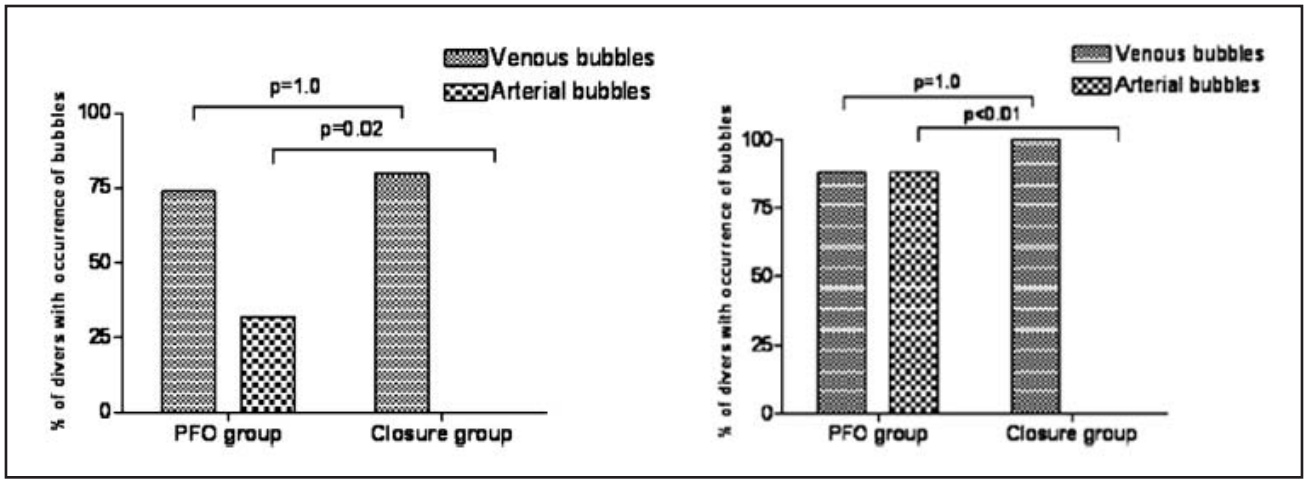

Figure 6. Bubble incidence in venous an arterial circulations following a 20 meter dive for 80 minutes (left panel) and a 50 meter dive for 20 minutes (right panel). Data from Honek et al.[10]

Now, if we look at the incidence of bubbles in these same subjects, this is a 60-foot dive for 80 minutes. Venous and arterial bubbles are shown in Figure 6. You can see there is a 70% incidence of venous gas emboli in the 60 fsw for 80-minute dive. There are no arterial emboli with the closed PFO while in the open PFO group, there is about a 25% incidence of arterialization. If you looked at the 165 fsw dive, you can note an 80-90% incidence of venous gas emboli. In the closed PFO group, there are none in the arterial side and in the open PFO group, about an 80% incidence of arterialization. So I think the message here is that stressful dives produce a lot of VGE, and whether you have a large atrial septal defect or you have a large PFO, the VGE are going to cross the PFO. We inject bubble contrast diagnostically in cardiology looking for the PFO following an injection of bubble contrast intravenously. We expect that bubbles will cross the atrial septum when there is a PFO. There is nothing different in destiny of the venous gas emboli produced by a decompression exposure versus intravenous injection. So I think the message here is, that a large PFO in the presence of large amounts of venous gas emboli is going to allow arterial embolization and the risk of a DCS event.

I will finish this review with a brief comment on altitude. At 8,000 ft. in a commercial aircraft with 3/4 ATA, passengers are very unlikely to bubble. The space shuttle and the U2 pilots however have significant decompression

Exposure to decreased pressure at altitude	
Commercial aircraft pressurized at 8000 ft	- 0.75 ATA
Space shuttle EVA spacesuit pressure	0.31 ATA
U2 pilots at 35,000 ft	0.24 ATA

exposures. The space shuttle protocol for EVAs, takes the astronauts to 0.3 ATA in a spacesuit. This exposure and concern for DCS drove a significant research effort to develop efficient DCS mitigation protocols.

Individuals performing EVAs in a spacesuit at 0.3 ATA use a prolonged exercise, 100% oxygen prebreathe, and are essentially denitrogenated before they enter this very low pressure environment. The protocols have been successful in avoiding decompression sickness in the EVA spacesuit environment. The U2 pilots are different. They are oftentimes on call. And when they are called to fly, they often must fly at very high altitudes without adequate time to complete a full prebreathe protocol. There has been some interesting concern about DCS in this group, which provoked a workshop several years ago and some recommendation for avoiding DCS. But these aviators have a significant risk when they are flying at very high altitudes because they don't have the opportunity to go through the very extensive prebreathe protocol that the astronauts do. The PFO issue in space has not been explored further because of the absence of DCS with use of their prebreathe protocols which have to date been an excellent solution to avoiding excess bubbling.

What are the controversies and questions?

What about spinal cord DCS? The data suggest that there is a lower incidence of spinal cord DCS versus cerebral DCS in divers with a PFO. Is this a blood flow issue? Is there a venous component to spinal involvement? Is there a VGE threshold that causes increased risk of DCS? How many bubbles must be present in the venous system in the presence of a PFO to demonstrate clinical pathology? What about inner ear DCS? There are several papers suggesting that inner ear DCS incidence is increased by a PFO. Does incidence vary over time? We saw data show- ing that PFO frequency declines with age. Several papers suggest that diving exposure actually prevents closure of a PFO. Comorbidities, particularly those that cause chronic elevation of right atrial pressure such as COPD with pulmonary hypertension, congenital heart disease with elevated right-sided pressures, will open or maintain a persistent PFO. There are some interesting data in chronic obstructive pulmonary disease (COPD) with PFOs suggesting that the PFO contributes significantly to hypoxemia in patients with chronic lung disease and pulmonary hypertension. What is the indication for PFO closure in divers? Should we discuss closure in hypobaric exposures?

Conclusions

In the US, sport diving limits usually do not produce significant venous gas emboli, but there are other divers who are exposed to riskier diving. Decompression diving is done by sport divers in Europe who more frequently perform extreme exposure dives. Commercial diving also creates more extreme exposures likely to produce large amounts of VGE.

In my opinion, the first step in prevention should be to minimize gas supersaturation and risk for venous gas emboli by controlling depth and time exposures. We could offer PFO closure to commercial or military divers who have had recurrent decompression sickness associated with riskier dive profiles. Peter Wilmshurst published a case series that suggests that PFO closure does improve their DCS risk. For altitude exposures, the oxygen prebreathe protocols have minimized decompression risk, but they are very time consuming. There are many unanswered questions that are open to discussion at this workshop.

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Clinical Experience of Right-to-Left Shunts in Divers with Decompression Illness

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Thank you very much for the opportunity to talk about my clinical experience of right-to-left shunts, particularly pulmonary arteriovenous malformations (AVMs) and persistent foramen ovale (PFOs) in divers with decompression illness (DCI).

Professor Bove mentioned the Mayo Clinic study by Hagen and colleagues in which the authors determined the prevalence of PFOs at post mortem examinations at 10 decade-intervals up to the age of 99.[1] They excluded children under the age of one year because everyone is born with a PFO and we know that PFOs close during childhood and adolescence. Figure 1 shows the relevant histogram from the paper by Hagen et al.

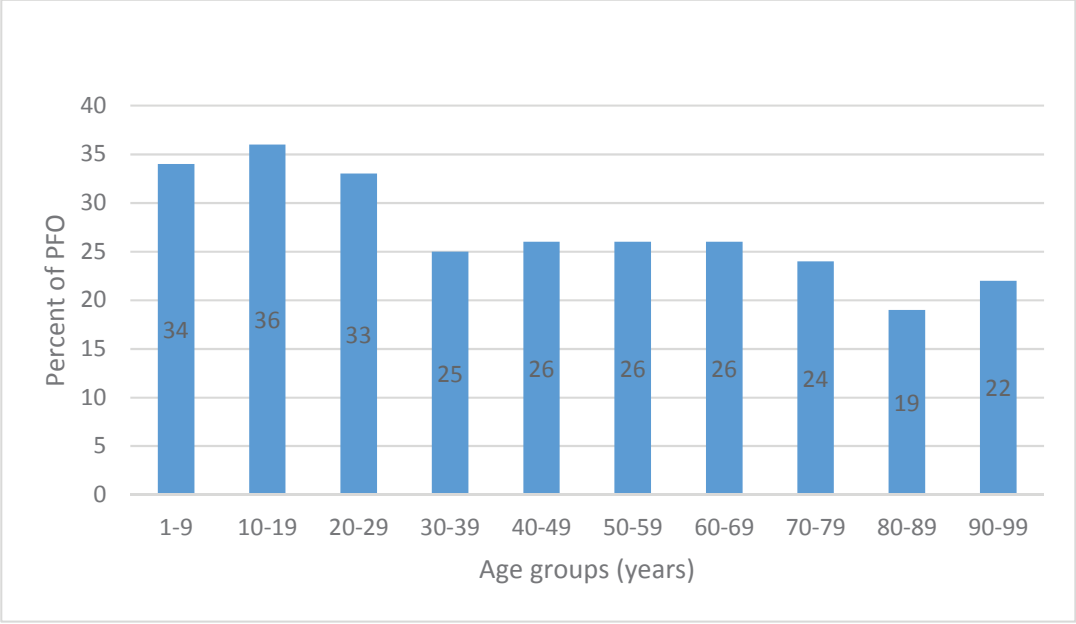

Figure 1. Incidence of PFO for age groups by decade-intervals. Overall foramen ovale were patent in 263 of 965 specimens

Paradoxical gas embolism in a scuba diver with an atrial septal defect

Wilmshurst PT, Ellis BG, Jenkins BS. BMJ 1986;293:1277

- Diver had done over 100 previous dives
- Dive preceding DCS: 38m for 15 minutes (his deepest dive)
- Two minutes after surfacing got abdominal discomfort, paraesthesia, dizziness and syncope
- Recompressed for cerebral and spinal DCS
- No evidence of barotrauma
- Signs of an ASD, confirmed at cardiac catheter and closed surgically

Patent foramen and decompression sickness in divers.

Moon RE, Camporesi EM, Kisslo JA. Lancet 1989;i:513-4.

- Out of 30 divers with DCS, 11 (37%) had a right-to-left shunt consistent with PFO
- All 11 shunts were in the 18 (61%) divers with serious DCS
- No shunt in those with mild DCS (joint & sensory)
- Shunts present in 9 out of 176 (5%) historic controls.
- P = 0.0001

The important thing is that there is a high prevalence of PFOs in young people, but prevalence declines to level off at about 25%. It is not a steady decline throughout life. It is an exponential decline that comes down to a plateau. Some people say that the prevalence of PFO goes down after the age of 80. If it were true, it probably would not matter much in the diving population, but it probably is not true. The two bars after age 80 are not individually significant compared with ages 30 to 79. In addition, in the upper age group the authors could not get 100 normal hearts which they wanted for each of the 10-year intervals. They could get 50 male and 50 female normal hearts for younger age groups, but they could not get that number for the very elderly. Therefore, the study had only 965 specimens, not 1,000 that the authors hoped to get. I believe that the prevalence of PFO starts at 100% at birth, decreases exponentially during childhood and levels off at around 25% during adult life. For each of the decade intervals, the prevalence of PFOs is the same for men and women.

In 1986, my colleagues and I published a case report describing a diver who had neurological decompression illness (DCI), or decompression sickness (DCS) as we called it then, and was found to have a large atrial septal defect (ASD).[2] Though he had ASD, he had done over 100 dives without any problems. So it is not just a matter of having a shunt and diving that gives you decompression illness. Something else is required.

On that particular day, he did the deepest dive he had ever done and, presumably, it was the one that gave him the biggest nitrogen load and the most venous bubbles. He got neurological symptoms a few minutes after surfacing and he had both cerebral and spinal DCS at the same time. It is unlikely that, when one gets a spinal event and a cerebral event almost instantaneously, there are two different disease processes occurring.

Three years later Richard Moon and colleagues reported in the Lancet a study of 30 divers who had DCS.[3] They reported that 11 of them had a right-to-left shunt on contrast echocardiography consistent with a PFO. All of the shunts were in the 18 divers with serious DCS and none were in those with mild DCS, namely joint pain

or purely sensory symptoms. They used historic controls, and their control group had a prevalence of PFO of only 5% (9 out of 176), which is very low.

The same year we published in the Lancet a blind comparison of 63 control divers who never had DCS and 61 who did have DCS.[4] Right-to-left shunts were found in 24% (15/63) of the controls and a statistically similar proportion of those with joint pain (1/6, 17%) and in those with neurological symptoms that came on more than 30 minutes after surfacing (4/24, 17%). The prevalence of shunts was significantly higher at 66% (19/29) in those divers who had neurological DCS starting within 30 minutes of surfacing. Of the ten with neurological symptoms that started within 30 minutes but who did not have a shunt, four had definite lung disease on testing.

Relation between interatrial shunts and decompression sickness in divers.

Wilmshurst PT, Byrne JC, Webb-Peploe MM. Lancet 1989;ii:1302-6.

Blind comparison of 63 control divers and 61 divers with DCS.

Groups	Shunt found in:
Controls	15/63 (24%)
Joint DCS	1/6 (17%)
Neurological DCS, onset >30 min post-dive	4/24 (17%)
Neurological DCS, onset <30min post-dive	19/29 (66%)*
Skin DCS	3/5 (60%) (3 also had neuro DCS)

*Significantly different from controls ($p<0.01$)

In that study, three of five divers with skin bends also had shunts. We also found that shunts were present more often when DCS occurred after non-provocative dives than after provocative dives. Provocative dive profiles were significantly more commonly associated with neurological DCS with onset more than 30 minutes after surfacing and joint pain than with neurological DCS with onset within 30 minutes of surfacing. In that study 17 divers had paraparesis and/or a sensory level consistent with a spinal bend, and nine of them had a shunt.

At the time, the results were considered controversial by some people in the UK. So I offered to do a replication study at another center under supervision of the Medical Research Council Decompression Sickness Panel. It was performed at the Diving Diseases Research Centre using their equipment. My technician and I performed the contrast echocardiograms blind to patient information. We confirmed and demonstrated what we had reported in the Lancet paper.[5]

The following year, at EUBS, we presented 109 control divers and 97 with DCS, who were divided into the same pre-defined subgroups, which we had used in our Lancet paper.[6] The prevalence of right-to-left shunts was 24% (26 of 109) in the control divers who had never had decompression illness. Shunts were present in a similar proportion in divers with joint DCS (3/20, 15%) and in a similar proportion in divers with late onset neurological symptoms (9/35, 26%) as in controls. Again, a significantly higher prevalence of shunts was found in those with neurological DCS with onset within 30 minutes of surfacing (33/50, 66%), and also in those with skin bends (86%) and cardiovascular symptoms (58%) such as shock, circulatory collapse, chest pain, breathlessness. Neurological DCS with onset more than 30 minutes after surfacing and joint DCS occurred after significantly more provocative dives than neurological bends with a latency of 30 minutes or less, than skin bends or than cardiovascular DCS.

Soon after that we published a study of divers with neurological DCS but looking at a shorter latency of onset, i.e. onset within five minutes of surfacing.[7] We had 38 divers who had such short latency of neurological symptoms. We excluded two because they had bullae on their chest x-ray. That left 36 divers with 40 episodes of neurological DCS. We subdivided those into 13 divers with bends after non-provocative dives who had a shunt; 11 divers with bends after non-provocative dives who had no shunt; and 12 divers with bends after provocative dives, four of whom also had a shunt.

None of the 13 divers in the group who had bends after they performed a safe dive and who had shunts had lung disease and there was a relatively low proportion of smokers, but ten of their bends had spinal manifestations.

Of the 11 divers who had 14 episodes of neurological DCS after a safe dive and who had no shunt, five had lung disease and six were smokers. Even in them there were two bends with spinal manifestations. So I believe that spinal decompression illness can be due to arterial gas embolism, even in cases when it is probable that the arterial gas embolism is caused by pulmonary barotrauma from bullae in the lungs.

It was around that time that we first started doing transcatheter closure of PFOs in divers who have had DCS. We started in commercial divers and used the button device.[8] Later we changed over to using Amplatzer devices[9], and we have now closed more than 300 PFOs and ASDs in divers with DCI.

Dr. Bryson and I reported our findings on the clinical features and causes of neurological DCI in 100 affected divers and 123 controls all of whom had contrast echo, a chest x-ray and flow volume loops.[10] We found that shunts graded medium or large were present in 52% of divers with neurological decompression illness, and in only 12.2% of controls. Half (26/52) of the divers who had either a medium size shunt or a large shunt had spinal decompression illness. But only one-quarter (12/48) of those who had no shunt or a small shunt had spinal decompression illness. In this study, 10% (5/52) of the significant shunts that we demonstrated were pulmonary.

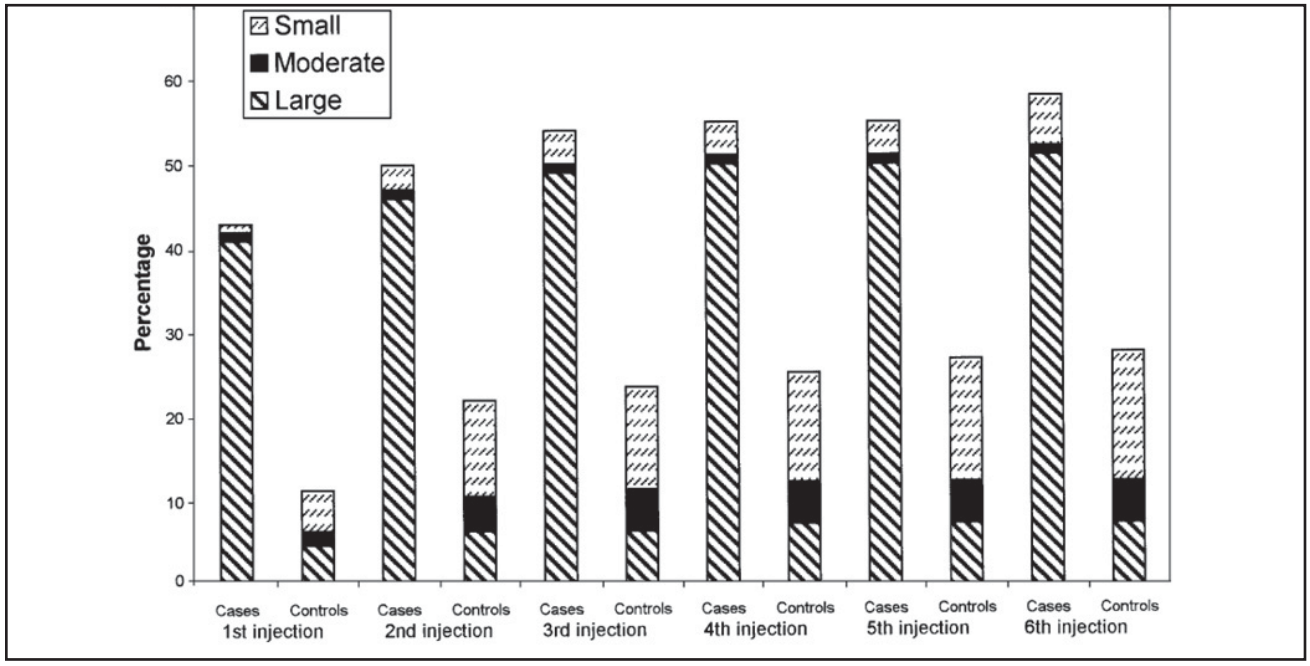

Figure 2. Comparison of prevalence and size of right-to-left shunts measured by contrast echocardiography in patients with neurological decompression illness and in controls

Figure 2 shows the cumulative rate of detection of right-to-left shunts by repeated contrast echocardiogram in divers with DCI and controls. In both groups, we did an initial injection with them at rest and breathing normally. Subsequent injections were with Valsalva maneuvers. Of the divers with neurological decompression illness, 41% had a large shunt at rest compared with five percent of the control divers.

With repeated contrast injections with Valsalva maneuvers, a few more large shunts were detected in the divers who had neurological decompression illness, but not many more small shunts. In contrast, in the control divers, repeated injections of contrast with Valsalva maneuvers did not greatly increase the number of large shunts, but more small shunts, which are probably not clinically significant, were detected.

The median latency of onset of neurological symptoms in the divers who had a shunt was 20 minutes after surfacing with very few divers with a shunt getting symptoms immediately after surfacing; and very few getting symptoms more than an hour after surfacing. In the majority of divers who did not have a shunt but had lung disease or had a provocative dive profile, the onset was immediately on surfacing or within five minutes with few having a latency greater than five minutes. In none of the divers in these groups was latency of symptom onset greater than eight hours after surfacing. In the few remaining divers who have had no shunt, no lung disease and no provocative profile, the latency of onset fell into two groups. There is a group with an early onset. They were smokers, but they had normal lung function. There was a second small group of divers whose latency of neurological symptoms was greater than eight hours. They all had subjective sensory symptoms alone and none of them responded to recompression.

Cantais and colleagues investigated 101 divers with DCI and 101 controls using transcranial Doppler with contrast.[11] They found that 24.8% of controls had a shunt, of which 11.9% had a major shunt. Major shunts were present in significantly more divers with cochleovestibular, cerebral and spinal bends than in controls, but major shunts were not more prevalent in those with joint pains. So they confirmed that DCI causing joint pain was not associated with shunts.

Table 1 shows the four studies of which I am aware that specifically looked at the presence of a large PFO or a large right-to-left shunt in divers with spinal decompression illness.[10-13]

Table 1. Prevalence of large PFO or right-to-left shunts in divers with spinal DCI

Reference	Spinal DCI (%)	Controls (%)
(12) Germonpre et al. Appl Physiol 1998	5/17 (29.4%)	6/16 (37.5%)
(10) Wilmshurst et al. Clin Sci 2000	26/38 (68%)	15/123 (12.2%)
(11) Cantais et al. Crit Care Med 2003	10/31 (32.3%)	12/101 (11.9%)
(13) Gempp et al. Int J Sports Med 2009	18/49 (37%)	8/49 (16%)
Totals	**59/135 (44%)**	**41/289 (14.2%)**

Germonpre and colleagues found no difference in the prevalence of large shunts in divers with spinal decompression illness and controls but the other three studies all found that large shunts were significantly more frequent in divers with spinal DCI than in controls. As previously stated, PFOs are present in a quarter of the adult population, and one would expect to find large shunts in a smaller proportion of the population than 25%. In the study by Germonpre et al.[12], the prevalence of large shunts in the control population was very high at 37.5%, whereas the other three studies had a lower and more consistent rates. The study by Germonpre et al. had a smaller control

group (n = 16) and study group (n = 17) than the other three studies. In the other three reports the control groups range from 49 to 123 individuals. The number of divers with spinal DCI were each two to three times greater than in the report by Germonpre et al. If we combine the data from the four studies we find that overall the prevalence of large shunts is 14.2% in the controls and three times greater (44%) in divers with spinal bends. So I believe that there is good evidence that large right-to-left shunts, such as PFOs, have a role in many spinal bends.

We reported a comparison of 61 divers with skin bends on one or more occasions and 123 historic controls.[14] In the control group, the prevalence of shunts of all sizes was 27.6% compared with 77% in the divers with skin bends.

As an aside, I suggest that this high detection rate at 77% shows that transthoracic contrast echocardiography does not fail to detect PFOs that are present.

Only six out of 123 (5%) in the control population had a large shunt at rest but 49% of divers with skin bends had a large shunt at rest. Skin bends usually occurred after non-provocative dives in those with a shunt but they usually occurred after deep dives; typically deeper than 50 meters and often on trimix, in divers without shunts.

Forty-four of the divers who had cutaneous decompression illness had other manifestations of DCI on the same or a different occasion. Thirty-five had neurological DCI and 29 of those had a shunt. One individual with a shunt had a painful swollen lipoma at the time that he had cutaneous and neurological DCI. I wish to return to him a bit later in my talk.

There is an exception to the general rule that joint pains are not associated with shunts. That is when pain occurs in a shoulder when there is an overlying skin bend. We found this repeatedly.

Divers who have had decompression illness and who attend my clinic get a contrast echocardiogram, a chest x-ray and measures of flow-volume loops blind to history. That is on arrival before the history is taken. The clinic is ongoing, but I want to talk about our data up to November 2007 for reasons which will become apparent later. Some also get a CT chest later, but that is not blind to history.

Of 636 divers who attended that clinic up to November 2007, 451 (71%) had a right-to-left shunt. Not all of the shunts were considered significant either because they were small or because we did not think that the symptoms and manifestations were typical of shunt-related DCI.

So 370/636 (58%) of divers who attend the clinic had a shunt we consider significant (defined as medium or large at rest or large with a Valsalva maneuver) and a history consistent with shunt-related decompression illness. Some divers had large shunts but we do not think they had shunt-related decompression illness. For example, a young woman, who had two episodes of severe neurological decompression illness. She got hemiparesis and became unconscious on ascent on one occasion and immediately after surfacing on the other occasion from dives shallower than 12 meters. She had been found to have a PFO elsewhere and it was planned that she would have that closed at another hospital. I spoke to her on the telephone. I advised her to come and see me. Her chest x-ray showed an obvious abnormality and her CT chest showed a very large congenital lung cyst that I am sure had caused arterial gas embolism secondary to pulmonary barotrauma. The cyst has been resected to improve her lung function.

We also had a middle-aged man, who was an experienced diver who had had cerebral decompression illness with rapid onset after ascent from an innocuous dive at 20 meters (66 feet). His contrast echo showed that he

had a very large shunt, but the story did not sound like shunt-related decompression illness because the dive was innocuous and symptoms were almost instantaneous on surfacing. He had bullae on CT chest. So we did not close his PFO.

Of our 370 divers with shunt-related decompression illness, we found that in 24 the shunt was pulmonary. One of them had a large pulmonary AVM and I occluded that. Most of the pulmonary AVMs we find cannot be occluded because they consist of multiple small AVMs. That left 346 divers with significant atrial shunts.

When divers have a history of shunt related decompression illness and a significant atrial shunt we advise them that they have three options to try to avoid or reduce their risk of recurrence of decompression illness. They can stop diving. They can dive more conservatively in ways that we talk to them about. Or they can have PFO closure.

Up to November 2007, 207 divers had opted to have PFO closure and seven of them had closure procedures with a device that does not require sizing. So we do not have the size data. Up to November 2007, we had performed 200 atrial shunt closure procedures in divers who had a history of shunt related DCI and in whom we had size (diameter) measurements (I chose 200 because that makes working out percentages very easy).

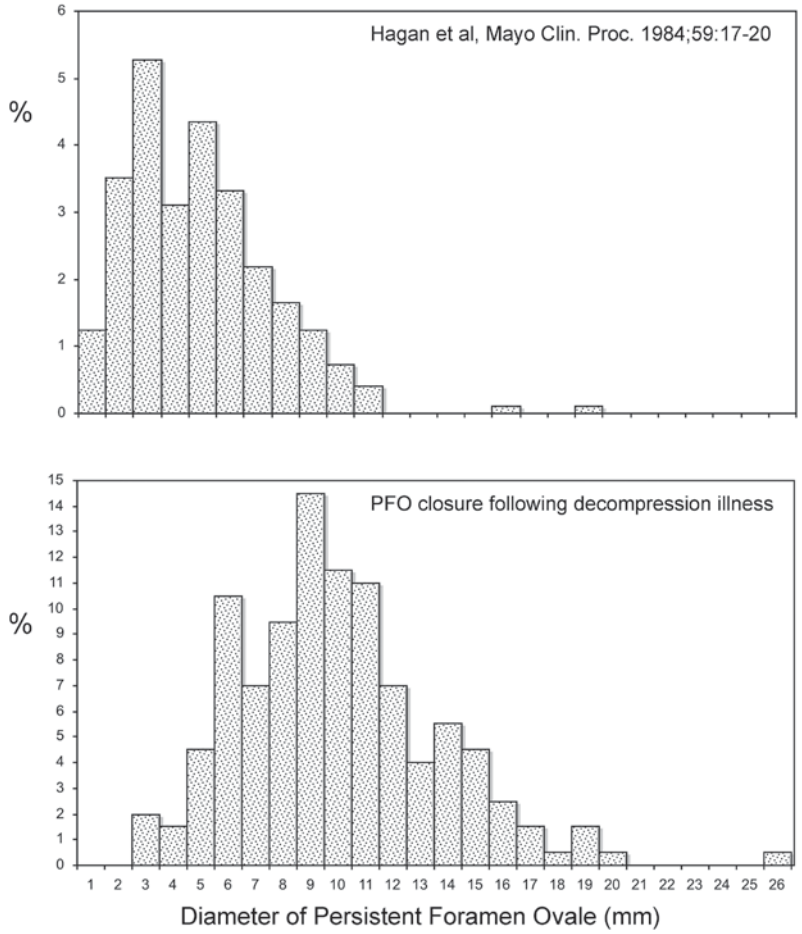

Figure 3. Histograms showing the distribution of diameters of persistent foramen ovale (PFO) in the general population from Hagen et al.[1] (upper panel) and the distribution of the diameters of PFO and atrial septal defects in divers with shunt related DCI (lower panel)

Eleven of the 200 had a secundum ASD and 189 had a PFO. Figure 3 shows a comparison of the diameters of the atrial defects that we had closed and the PFO diameter measurements in the publication by Hagan et al.[1]

The distribution curves are obviously different. Hagen et al. found that in the general population, the peak PFO diameter is around about 3-5 mm diameter. Hagen found that only 1.3% of the population have a PFO that is a centimeter diameter or larger, but we found that in divers with shunt-related decompression illness, the median PFO diameter is a centimeter.[15] This means that half of divers with shunt related decompression illness have a PFO that is a centimeter diameter or larger. So the greatest risk of shunt related decompression illness is in those with the largest PFOs, not the entire 25% of the population of divers with a PFO.

Some of our 200 divers with shunt related DCI had different manifestations of decompression illness on different occasions or on the same occasion. 150 (75%) had neurological decompression illness on one or more occasions; 12 (6%) had cardiovascular decompression illness; and 99 (49.5%) had skin bends.

In addition, 63 (31.5%) had a history of migraine visual aura after dives and 104 (52%) had migraine with aura in their everyday life. This compares with a prevalence of migraine with aura of 4% in the general population. Other studies have shown that about half the people who have a large right-to-left shunt, whether that is a large PFO or a pulmonary AVM, have migraine with aura. In addition, three of the divers who had closure of an atrial shunt following shunt-related DCI had a cryptogenic stroke confirmed on CT brain scan at a young age.

Our current data on divers with skin bends is that we have investigated 280 divers with skin bends and 79% have a significant shunt. The remaining 21% have nearly always done a provocative dive usually deeper than 50 meters (164 feet) and often on trimix. Many of those with skin bends have had recurrent skin bends before they seek referral and quite a few have had more than ten skin bends before they seek referral. Often they attributed the rash to suit-squeeze or an allergic reaction.

One female diver had about a dozen skin bends in her first 40 dives as an amateur diver. We closed her PFO eight years ago. She now works as a commercial diver doing much deeper air dives than she did during her training without problems. In her case and others, it is clear that PFO closure following skin bends prevents recurrence.

I mentioned the diver whose decompression illness was accompanied by an enlarged, painful lipoma. Trevett and colleagues reported two women whose DCI manifested as breast pain and who had a large PFO.[16] We also saw eight women who have had DCI manifesting as breast pain with swelling on one or more occasions and each had a large PFO and none of them had recurrence following PFO closure.

We have investigated 39 divers who have had one or more lymphatic bends and 30 (77%) had a significant shunt. Generally, the dives that preceded their lymphatic bends were not provocative.

There were nine divers with lymphatic bends who either have no shunt in five or a small pulmonary shunt in four. I suspect that their small pulmonary shunts may have been significant. Their lymphatic bends were after deep trimix dives when I think there may well have been more bubbling that overwhelmed their pulmonary filter.

What is the mechanism for shunt mediated decompression illness? I have done many thousands of contrast echoes, and I have never managed to produce a bend in anyone. So contrast echo does not produce decompression illness. Therefore, it is not just bubbles going across a PFO or pulmonary AVM that gives you DCI. It is something in addition. We know that you need a large right-to-left shunt. The dive must liberate many venous bubbles. I believe that the additional factor is that the tissues embolized must be supersaturated with dissolved inert gas

Postulated mechanism for shunt-mediated DCI

Wilmshurst P et all. Lancet 1989;1:731

Shunt-mediated DCI needs:

1. A large right-to-left shunt
2. The dive must liberate many venous bubbles
3. The tissues are supersaturated with nitrogen at time invaded and able to amplify bubble emboli

at the time they are invaded in order that they can amplify the embolic bubbles. As a result the clinical manifestations are determined more by which tissues are supersaturated at the time bubbles cross a shunt than by where the bubbles go. Bubbles do not just go up to the brain. They go everywhere. It is those tissues that are supersaturated at the time when bubbles cross from right-to-left that determines which types of manifestations result. That is what we proposed in the Lancet in 1989.

In summary, large PFOs and other types of large right-to-left shunts were associated with a greatly increased risk of decompression illness. Migraine with aura is a marker of increased prevalence of such large shunts. Small shunts are either not associated with an increased risk of decompression illness or have only a small risk. It would require a very large study to detect whether small shunts carry a small increase in risk. The type of shunt (i.e. whether it is atrial or pulmonary) is often misdiagnosed by doctors. I am often referred patients (both divers and stroke patients) to give an opinion because a cardiologist has done a study and has seen bubbles in their left heart but when they tried to close "the PFO" they could not cross the atrial septum. In fact a PFO that has caused paradoxical gas embolism or paradoxical thromboembolism is always easy to cross. When you pass a guide wire up the inferior vena cava it often goes straight across. If you do not get across quickly, you should ask is there a causative atrial shunt. In most cases when I am referred a patient in whom a cardiologist failed to cross a PFO, it is because they had misdiagnosed a pulmonary AVM as a PFO. Closing a PFO is relatively easy, although complications can occur. But deciding whether you should close a PFO can be more difficult. Finally, if you close a PFO, it is essential to make sure that you have closed it by doing a contrast echo later before allowing a diver to return to diving.

Thanks very much.

Financial conflicts of interest: None (I am a cardiologist and I do interventional procedures for the National Health Service but I do not do any interventions privately).

Acknowledgements: I would like to acknowledge the contributions of Chris Byrne, Michael Webb-Peploe, Simon Nightingale, Lindsay Morrison, Kevin Walsh, Matthew Pearson, Philip Bryson, Craig Davidson, Geraldine O'Connell, David Treacher, Alex Crowther, Stephen Smith, who I have worked with and have been co-authors of publications with me.

DISCUSSION

RICHARD MOON: We have enough time for a couple of questions.

Peter, I'm going to ask you a couple of questions. One is that you have shown that early onset bends are related to a PFO. Late onset neurological bends are not. But the onset time, of course, is related to the severity. Is it fair to say that some of those late onset neurological bends were sensory only and not motor or am I misspeaking?

PETER WILMSHURST: I would have to look back at the data. I cannot remember. It is in our Lancet paper in 1989. We tabulated neurological bends according to whether there was motor or sensory manifestations. So I would have to look back at the paper.

JAMES HOLM: Two questions that came to light. One is I think you make a strong case for a transthoracic (echocardiogram) being the superior method. It will miss some small ones possibly, but that may be good. And that you can do aggressive, provocative maneuvers, which you can't do in transesophageal. First, can you describe your procedure for what you consider the gold standard for transthoracic echo and what provocative maneuvers you do? The second question is, I noticed in some of your cases it's very clear that people had some pulmonary pathology. What screening do you do before doing an occlusion device on patients to ensure they don't have pulmonary pathology, such as spiral CT, spirometry, chest x-ray, et cetera?

PETER WILMSHURST: We do a chest x-ray and we do flow volume loops on everyone. And we only do CT chest if we think it is relevant really.

JAMES HOLM: And with regards to the first question, can you describe your protocol for transthoracic and your provocative maneuvers?

PETER WILMSHURST: We use bubble contrast. You have to produce a lot of bubbles to make sure that there are enough bubbles to completely opacify the right heart. I inject the bubble contrast into the left antecubital vein. I have done a study looking at femoral vein injection, and that is not superior to left antecubital vein injection in our experience. We inject into the left antecubital vein because very occasionally there are other abnormalities that can be missed by injecting into a right antecubital vein, such as drainage to the left atrium via a left sided superior cava and coronary sinus and sometimes via anomalous systemic venous connections into the back of the left atrium. So you have to inject into the left antecubital vein whenever possible.

You have to make sure you have got a lot of bubbles that arrive at the right atrium as a bolus. We do it by injecting with the arm elevated. That way venous drainage to the right atrium is aided by gravity. So we have the arm above the level of the heart when we inject the bolus. You have to make sure that the whole in the right atrium is filled with contrast so that there is complete "white-out". Sometimes you get streaming of blood from the inferior vena cava against the atrial septum and you have to eliminate that so that contrast is against the atrial septum. We do a first injection at rest and we do a long run to pick up pulmonary shunts. Then we do injections with Valsalva maneuvers a couple of times and we do injections with sniffing.

Typically shunting across a PFO appears in boluses in the left atrium. Typically when there is shunting at rest, you get boluses of bubbles crossing to the left atrium when the person breathes in. Shunting is promoted by whatever causes the right heart flow to increase relative to the left heart flow. You get that on release of a Valsalva maneuver. Sniffing is the maneuver that causes the greatest rate of change of intrathoracic pressure.

JAMES HOLM: Is that the standard, the sniffing, because many times just ordering a contrast echo, I think it's unclear that what they should do. Should we tell them exactly what to do? And do you need to confirm the septal motion, I mean, paradoxical septal motion?

PETER WILMSHURST: The septum moves with a sniff. If you are using a four-chamber view and you do it properly, when a person sniffs, the septum moves towards the left atrium, and if there is a large PFO you see bubbles shoot across to the left atrium. That is a trick I learned from a study in a snotty-nosed child who had a stroke. I could not find a shunt when I did a contrast echo with a Valsalva maneuver or at rest. I did another contrast injection. Coincidentally at that moment the child sniffed, and the whole of his left heart opacified. I have used the technique ever since then and I have found a number of people who were Valsalva negative but sniff positive and who had a large PFO.

DAVID DOOLETTE: Peter, in one of your summary slides which you outlined the mechanism, for PFO-related DCS the first step is lots of VGE, which makes sense. But in a lot of your talk you talked about DCS being associated with non-provocative dives so lots of VGE in non-provocative dives, I'm having difficulty reconciling that. So I'm wondering what you're calling non-provocative dives in your series.

PETER WILMSHURST: We consider a dive non-provocative if it was permitted using standard tables or a decompression computer used by the diver. Of course, some dives that are inside a table are more provocative than others. I gave some examples of people with lung disease who had got neurological symptoms after ascending from 12 meters (39 feet) and from 20 meters (66 feet). They are very non-provocative. However a typical shunt related neurological bend in the UK might be a spinal bends after a dive to about 30 meters (98 feet) for about 20 minutes with a square profile, which is just within the no-stop time on a computer. Many UK wreck dives are at around 30 meters and have such profiles. The divers spend 20 minutes there, and when they come up, they have more venous bubbles than a diver who had dived to 12 meters (39 feet) and they get their symptoms.

SPEAKER: I have two questions. My first question is about the migraine with aura. What was the reference for the statistics you laid out there that 52 percent of patients with PFO related DCS had also migraine visual aura? Do you remember?

PETER WILMSHURST: There are two papers. (Wilmshurst P, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. Clin Sci. 2001;100:215-20. and Wilmshurst PT, Pearson MJ, Nightingale S. Re-evaluation of the relationship between migraine and persistent foramen ovale and other right-to-left shunts. Clin Sci. 2005;108:365-7).

SPEAKER: Were you the first author on both of those?

PETER WILMSHURST: Yes. But there are other studies that found similar sorts of rates with other types of right-to-left shunts. Migraine with aura also has a high prevalence in people with cyanotic congenital heart disease, 58%. It has a high prevalence, 53%, in people with pulmonary AVMs and hereditary hemorrhagic telangiectasia. So the figure is 50-60% for all types of large right-to-left shunts. However, there are some people who have large shunts who never get migraine with aura. If you are interested in that, I have written a review which covers the topic. (Wilmshurst P, Nightingale S. The role of cardiac and pulmonary pathology in migraine: a hypothesis. Headache 2006; 46: 429-434).

SPEAKER: May I ask my second question? I've always been curious about this. That we're doing this test with the provocative bubble studies to look for a PFO, but bubbles are bad, right? Have you ever had a patient that had developed symptoms similar to DCS after the transthoracic contrasted echo study itself?

PETER WILMSHURST: No. But there are a fair number of people with a right-to-left shunt who get migraine aura very soon after contrast echocardiography. It is only the ones with right-to-left shunts who get that. Many of them say that it is like the migraine aura that they get with their migraine, but they do not usually get a migraine headache. They usually get the aura alone. It is usually a visual aura but sometimes there are tingly fingers or face, which they say is like the aura with their migraine. We put them on oxygen, it goes in five minutes.

RICHARD MOON: Thank you, Peter. I apologize in advance for any technical problems, which we hope will be fixed during the break. I suspect we will have many more questions than we have time for. So if you have a question that you would like answered at some point, please write it down on a piece of paper and give it to either Dr. Bove or myself and we'll collate those questions and address them during the break at the end.

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Right-to-Left Shunting, White Matter Hyperintensities: From Altitude to Diving

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Introduction

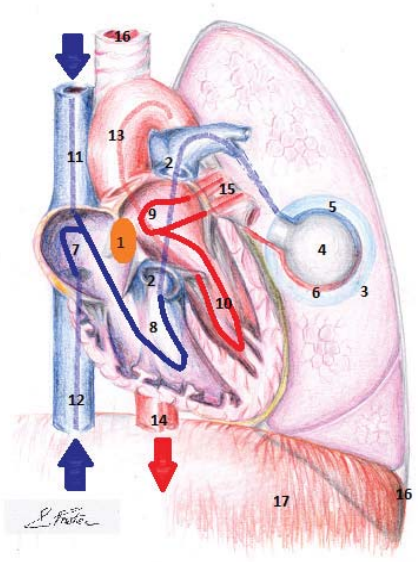
White matter hyperintensities, WMHs ("leukoaraiosis"), with a prevalence ranging within 10-20% in the middle age to 90% over eighty years of age[1] are commonly observed by magnetic resonance imaging (MRI) or computed tomography (CT) in brains of elderly individuals and patients with stroke and dementia. The histopathology of WMH is a neuronal degeneration with myelin pallor, demyelination (halo-like rarefaction), axonal loss, and microglial activation.[2,3] Such lesions affect long-distance white matter tracts, and are a hallmark of small vessel disease likely resulting from non-clinical cerebrovascular events. Hypoperfusion of the white matter has been suspected to cause an alteration of the blood-brain barrier, resulting in a chronic leakage of plasma into the white matter and then producing lesions deeply within the white matter (WMH).[4,5] Risk factors include all etiologies of potential cerebral hypoperfusion, mainly with advancing age and systemic arterial hypertension, but vascular disease, diabetes, smoking have also been associated with an increased incidence of WMHs. The origin of the potential presence of WMHs in divers, pilots and astronauts seems to be associated with cumulative decompression exposures albeit the underlying mechanisms are still unclear. The occurrence of right-to-left shunting (RLS) from right to left atrium causes paradoxical systemic embolization of venous bubbles from supersatured tissues with nitrogen per and post-decompression during altitude or hyperbaric exposures.[6] The presence of a patent foramen ovale, PFO, is an important risk factor of systemic arterialization of decompression venous bubbles for potential embolization in the central nervous system (CNS),[7,8,9] with cerebral[10] and vestibular localizations.[11] The presence of a PFO seems to be the main driver for RLS of decompression venous bubbles with enhancement by certain maneuvers such as Valsalva or Valsalva-derived (coughing, breath-holding, glottis shutting). Underlying mechanisms and phases of RLS are currently thought to constitute an essential foundation in the genesis of systemic embolic arterialization affecting the CNS. The influence of transmural pressure gradients (P_{TM}) within the thorax across structures of the cardiorespiratory system [heart chambers, major vessels, lungs, pleural space, rib cage] and other major vessels such as cerebral vessels play a crucial role albeit a relationship between arterial embolism and WMH appears to be indirect. The incidence, distribution, number, volume and aspect of WMHs are also different in diving, altitude and microgravity environments, as a direct cause-effect relationship is still unclear and under evaluation. In microgravity, WMHs have not yet been correlated to the presence of decompression microbubbles. However, based on WMH differences within three environments exposing individuals to different

forces and pressures, a logical deduction is that (P_{TM}'s) applying across structures of the thorax and the CNS most likely play a role in the genesis of WMHs.

Physiopathology of right to left atrial positive pressure gradient

1. Transmural pressure gradients during relaxation of the respiratory system

The left atrial pressure (LAP) is greater than the right atrial pressure (RAP) throughout the cardiac cycle. Maneuvers provoking changes in cardiorespiratory transmural pressure gradients P_{TM} gradients may affect the normal LAP > RAP paradigm. Such maneuvers involve active participation by straining of respiratory muscles or glottis modifying the P_{TM} in the respiratory system [lungs, pleural space and rib cage]. The net result will be a change of P_{TM} in the cardiovascular system. The breathing movements and Valsalva maneuver influence the hemodynamics within the thorax, heart's four chambers, vena cava (VC), aorta (AO), pulmonary artery (PA), pulmonary veins (PV) and pulmonary capillaries.[12,13] The four chambers of the heart and the vessels of the cardiorespiratory system during relaxation of the respiratory system at FRC (functional residual capacity) are illustrated in Figure 1. At FRC, static transmural pressure gradients, P_{TM}'s, of the respiratory system are equal to zero, inward and outward P_{TM} being equal and no force moves the system now immobile in a relaxation stage. The gradients are vectors and the algebraic summing is computed to evaluate the resulting vector.



1. Patent foramen ovale, PFO: orange, closed position
2. Pulmonary artery, PA.
3. Portion of lung parenchyma and terminal branching magnified shown in light blue (scale: few microns)
4. Single alveolus magnified, grey [1-3 microns]
5. Capillary from PA, venous blood
6. Capillary to pulmonary veins, PV, arterial blood
7. Right atrium, RA
8. Right ventricle, RV
9. Left atrium, LA
10. Left ventricle
11. Superior vena cava, SVC
12. Inferior vena cava, IVC
13. Ascending aorta, AO
14. Descending aorta, AO
15. Pulmonary veins, PV
16. Trachea
17. Diaphragm

Figure 1. Relaxation of the respiratory system. 3D Image: frontal slicing across four chambers, the top part of the heart is removed. Section of the pulmonary artery, bottom and top pulled away from each other. Portion of Aorta is sectioned and removed. Blood flow in removed portion or within vessels is in watercolor; visible blood flows in the inferior part of the heart is in solid lines. No air is moving in the relaxed respiratory system.

2. Transmural pressure gradients during inspiration

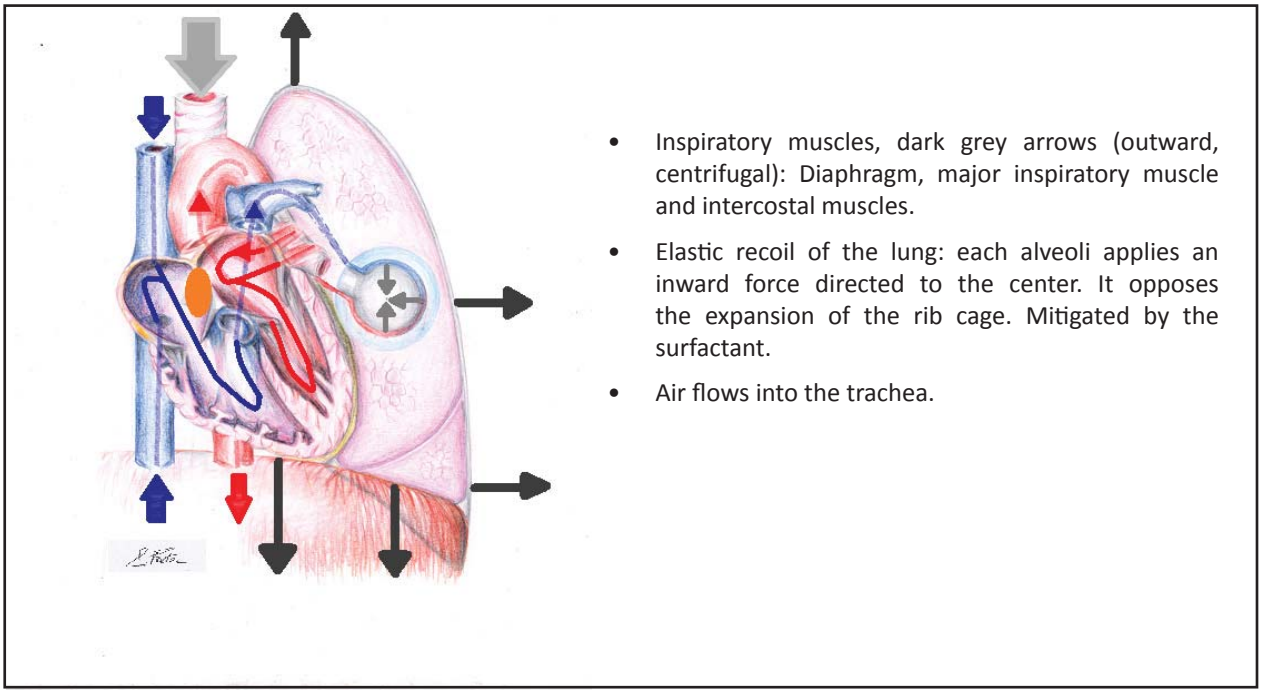
Figure 2 depicts the transmural pressures during the normal inspiration midway toward maximal inspiration. The unbalance of forces applying pressures in the respiratory system are represented by arrows, dark grey for outward pressures [diaphragm, intercostal muscles, sternocleidomastoid and scalene muscles]

tending to pull outwardly the lungs and alveoli and generating the transpulmonary pressure, P_{TMP}. The P_{TMP} gradient has a positive sign, by arbitrary convention (vector) since it applies in the positive direction from the center of the alveoli to the "virtual" intra-pleural space. The intra-pleural space is at a very low pressure, lower than atmospheric pressure and has a negative sign; this virtual space "sticks" the lungs to the rib cage. Contractions of respiratory muscles are the sole generators of pressure gradients applying on the respiratory system and necessary to breathing. The elastic recoil of the lungs is pictured by light grey arrows and has an inward (negative) direction in the convention.

$P_{TMP} = P_A - P_{PL}$ [transpulmonary pressure gradient]

$P_{TMT} = P_{PL} - P_B$ [transthoracic pressure gradient]

$P_{TMR} = P_A - P_B$ [transmural pressure gradient of the whole respiratory system]



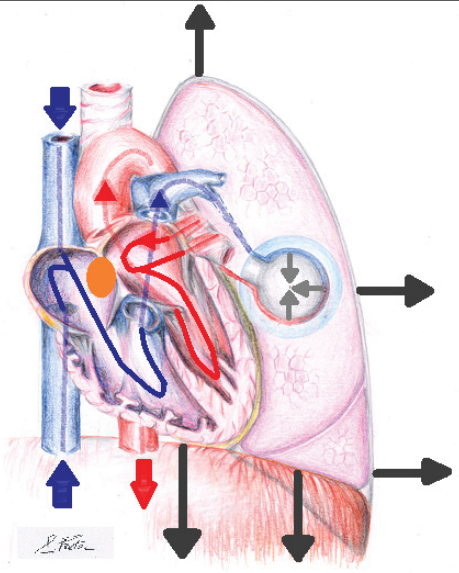
- Inspiratory muscles, dark grey arrows (outward, centrifugal): Diaphragm, major inspiratory muscle and intercostal muscles.
- Elastic recoil of the lung: each alveoli applies an inward force directed to the center. It opposes the expansion of the rib cage. Mitigated by the surfactant.
- Air flows into the trachea.

Figure 2. Transmural pressure gradients, P_{TM}, midway of inspiration.

3. Transmural pressure gradients during Valsalva

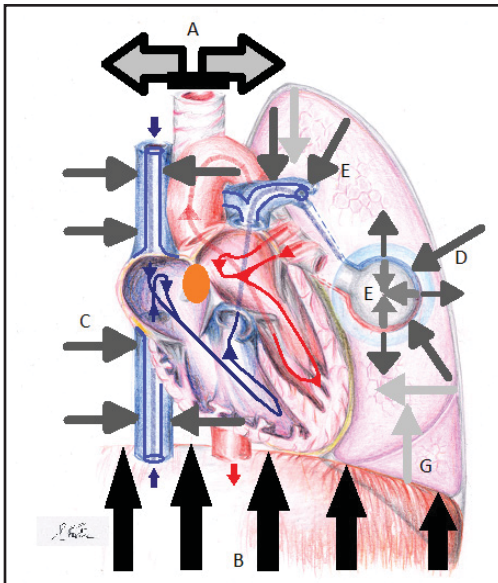
At the end, when the maximal inspiration is attained, air is no longer inspired, as seen in Figure 3; this stage is sometimes described as Phase 0 (Valsalva and other maneuvers) and Phase I is the onset of the straining of abdominal muscles and shutting of glottis (Figure 3). Those contractions are not yet significantly affecting P_{TM}'s in the respiratory system. Continuation of the strain, Phase II, by forceful contraction of abdominal wall muscles and unachieved expiration against a closed glottis, compress the abdominal organs cranially (upward) into the diaphragm, pushing the diaphragm upwardly, portrayed by grey arrows (B), on Fig. 4, and then reducing the volume of the thoracic cavity. Internal intercostal muscles contract during this blocked forceful expiration. The P_{TM}'s are illustrated by grey arrows (D) and apply pressure in the inward direction to the alveoli. According to Boyle's law, the volume of air contained in each alveolus, albeit compressible applies an outward pressure gradient from the center of the alveolus, shown as grey arrows (E). The latter overall pressure of all alveoli generates an increase in intrathoracic pressure which then applies a P_{TM} to the four chambers of the heart and the vessels within the thorax or their intra-thoracic portion; grey arrows (C and E) represent the P_{TM} applying on major intra-thoracic vessels. Within seconds,

the cross-sectional area and circumference of the superior vena cava (SVC) decrease considerably persisting throughout the strain phase, and frequently resulting in near total obliteration of the vessel lumen as seen by echocardiography[14], CT Scan[13] and MRI.[15, 12] The flow decreased in major intra-thoracic vessels, with a parallel increase of pressure in the superior VC [× 6 times, from 8 + 5 to 32 + 12 mm Hg].[14] The vessel collapsibility reconstructed in 3D shows a flattening of the inferior VC during this phase of Valsalva, adopting an ellipsoid cross-sectional shape.[13] The increased intrathoracic pressure generates transmural gradient P_{TM} [grey arrows (C and E)] on major intra-thoracic vessels and compresses the vessel lumina, with a peak during the late strain of the Valsalva maneuver (Phase III, Figure 4). The lumen of the SVC decreased sharply and molded its shape from triangular to almost circular at early recovery (Phase IV).[12] The mean peak velocity (V, $cm.s^{-1}$) of blood & flow (BF, ml per beat) in the ascending AO decreases sharply from resting baseline down to the late Valsalva (Phase III) and further down to a minimum (V: - 30%, BF: 62%) during the early recovery (Phase IV) with an overshoot in the late recovery (end of Phase).[12] A concomitant decrease of the AO diameter is observed (- 17% area, mm^2) from the same study. In SVC, reductions are more dramatic with a nadir of flow during Phase II (BF: 100%, 0 $cm.s^{-1}$) and a reduction in diameter (- 37%). Volume reduction of intra-thoracic vessels and cardiac chambers may sometimes result in a momentary circulatory arrest for a few seconds with contemporary decrease of cardiac output.[16]



- No motion of air. The centripetal forces of the elastic recoil of the lungs are at a maximum preparing for the expiration and sufficient by themselves to generate a spontaneous expiration.
- Phase 0 is immediately preceding the Valsalva maneuver. All inspiratory muscles are at their maximum contraction levels. Arrows represent vectors and no motion of the rib cage is noticed.
- Phase I is the early stage of forceful contraction of abdominal wall muscles and unachieved expiration against a closed glottis.

Figure 3. Transmural pressure gradients, P_{TM}, maximal inspiration. Phase 0 & Phase I.



A. Shutting of glottis
B. Forceful contraction of abdominal wall muscles. Pushing against internal abdominal organs, and indirectly pushing the diaphragm upwardly to compress the thorax above.
C. Transmission of pressure from the inflated (alveoli) lungs toward the vessel walls. Generation of PTM across SVC & IVC, light grey arrows. Light grey arrows, centrifugal (directed in the outward direction from center of alveoli).
D. Each inflated alveolus is applying pressure towards adjacent alveoli, contraction of the internal intercostal muscles via the rib cage. Grey arrows with an inward direction (centripetal).
E. The spontaneous elastic recoil of each alveolus is contributing to the retraction of the lung and the forceful (unachieved) expiration.

The PFO is closed. The reduction of blood flows and pressure is observed in intra-thoracic vessels. The diameters of all vessels are reduced [shown by fine pencil lines] and the area molds from circular to ellipsoidal. SVC and IVC are reduced more than AO and may even be stopped. The jugular veins are turgescent. The cardiac output may be reduced by 50% of its resting baseline value.

Figure 4. Transmural pressure gradients, PTM, at maximal levels: unbalance. Continuation of the strain, Phase II.

4. Relaxation of transmural pressure gradients at the release of Valsalva

As soon as the strain pressure is released, by relaxation of abdominal wall muscles and opening the glottis, it allows free-exhalation of air by starting the expiration (Figure 5, Phase III). The sudden drop of central venous pressure causes the expansion of IVC (inferior vena cava) and SVC, which is immediately followed by an increased flow of blood accumulated in the venous reservoir (Pstras et al., 2016). The P_{TM} across all intra-thoracic vessel walls is alleviated [absence of grey arrows C and E on Figure 5] while returning to their normal diameter. As IVC and SVC, PA and PV return to their normal diameter (Figure 5). During a few seconds, following an overshoot with abrupt and massive inflow of blood into SVC-IVC, the output of the left ventricle becomes lower than the output of right ventricle, which is used in part for filling up the pulmonary bed. Simultaneously RAP becomes greater LAP. During this brief period to time, if the PFO is present, it may open up and produce a RLS with a temporary mixing of venous and oxygenated blood as shown on Figure 5. In patients with pulmonary vascular disease, an abnormal response may be observed by absence of recovery (phase IV).[17] The augmentation of resistance of the pulmonary vascular bed may increase the PA pressure (PAP). The capillary wedge pressure, PWCP, then becomes lower than PAP resulting in lasting greater gradient [RAP > LAP], potentiating a RLS across a PFO. Early stages of pulmonary vascular diseases may be infra-clinical and observed in almost all underlying pulmonary diseases (COPD, asthma, interstitial lung diseases, etc.). Measurement by right heart catheterization of the mean PAP allows to evaluate the presence of a pulmonary arterial hypertension, PAH. We consider the PAP as normal to an upper limit of exercise-induced mPAP at 30 mm Hg,[18, 19] for a cardiac output of less than 10 $L \cdot min^{-1}$ or a total pulmonary vascular resistance at exercise of less than 3 Wood units.[20] However, the diagnosis of PAH is more complex in patients with heart and/or lung disease. Mean PAP may promptly increase with exercise in the presence of increased PVR, such as in COPD or increased LAP due to left heart failure or mitral stenosis.[20] Athletes may also express higher PAP during intense exercise as this would be considered as a normal response in

highly trained individuals. A study, in patients seen at the cat. lab. for coronary artery disease, myocardial infarction, cardiomyopathy or COPD, clearly showed that the most efficient maneuver for the larger P_{TMP} gradient producing a reversal was the Valsalva [RAP > PCWP] compared with coughing, breath-hold, and 20° head-down tilt.[17] Figure 6 also illustrates the potential sinuous transpulmonary passage of microbubbles through asymptomatic pulmonary arteriovenous malformations or hepatopulmonary syndrome. These entities are difficult to diagnose since they may be sub-clinical. Venous gas microbubbles following the path of a transpulmonary passage, another variety of RLS, travel a relatively long distance to be arterialized and require several heart cycles to be detected unlike the direct crossing of a PFO which is rapidly detected.

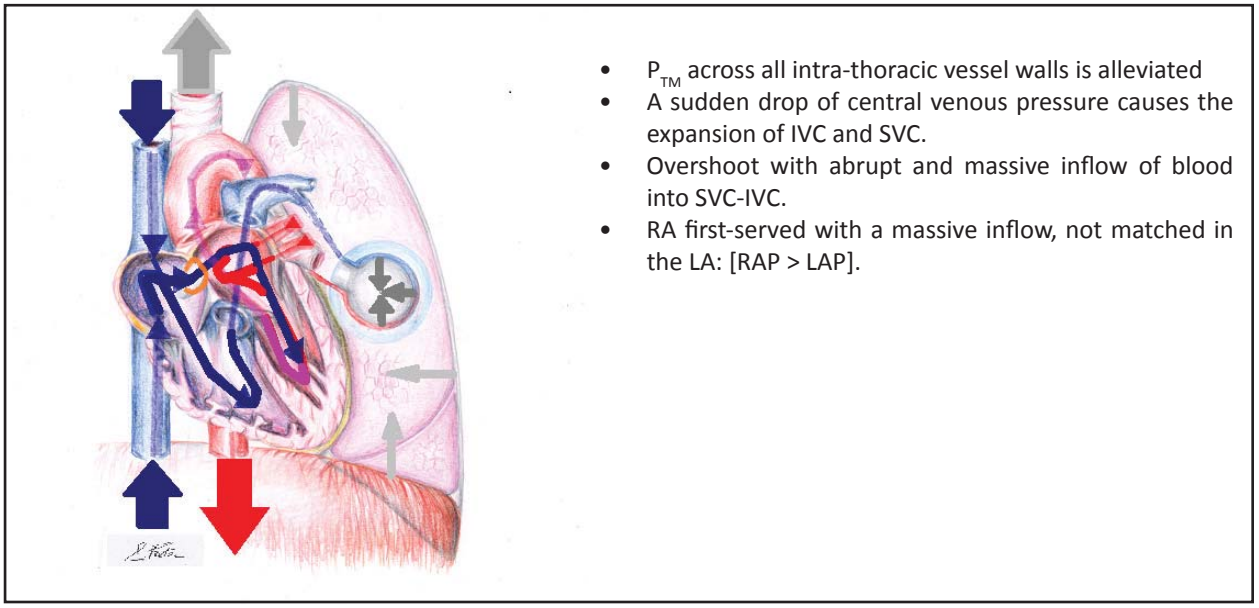
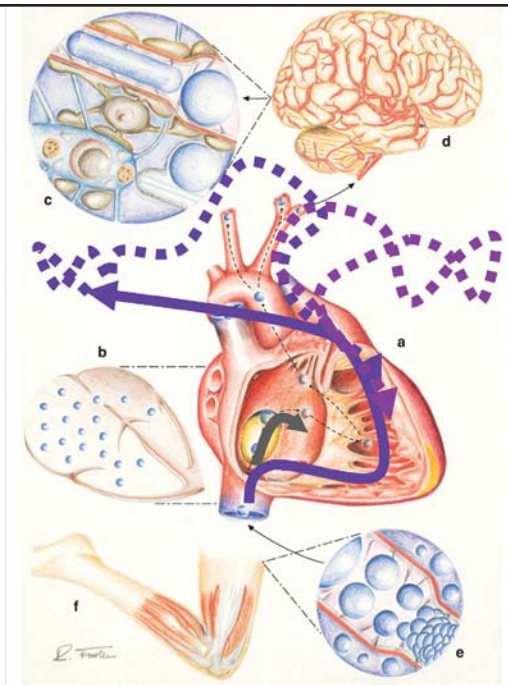


Figure 5. Releasing of the Valsava strain, Phase III and Recovery, Phase IV: Right-to-left shunting across a PFO. Transmural pressure gradients, P_{TM}, are released except across the PFO which may open during Phase IV.



Path/Blood Velocity via Pulmonary Circulation or PFO

$$PVR = \frac{mPAP - LAP}{Q}$$

$$\frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla)\mathbf{u} - \nu \Delta \mathbf{u} + \frac{1}{\rho} \nabla p = \mathbf{f}$$

u: vector-valued function (flow-velocity), function x & t.

$\nu = \frac{\mu}{\rho}$: kinematic velocity

Navier-Stokes Equation

Figure 6. Right-to-left shunting, RLS across a PFO & transpulmonary passage with sinuous long trajectory within the lungs simulated by a dotted purple line. Paradoxical arterial embolization to the brain represented during exercise. Modified from Foster and Butler.[33] The Navier –Stokes equation [see appendix for explanation].

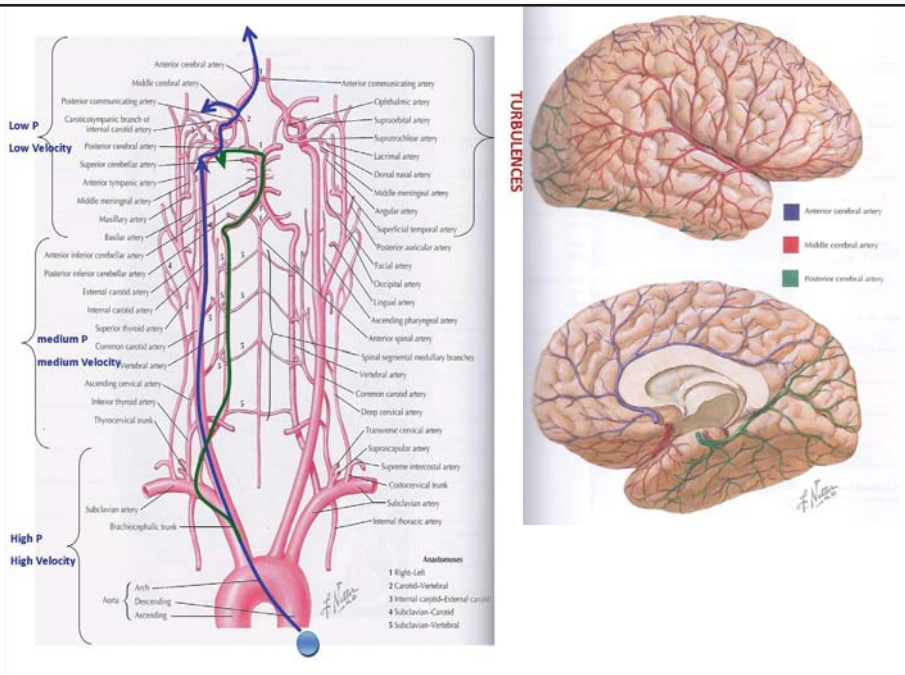


Figure 7. Trajectory of microemboli in the cerebral circulation. Modified from Felten and Shetty.[34]

Intra-thoracic and intra-cranial transmural pressure gradients for U-2 pilots & astronauts

In *U-2* pilots, thereafter 2006, the risk of decompression sickness (DCS) per flight was approximately 0.23%, out of which 44% of incidents were diagnosed as neurological-DCS and ranged from mild to permanent cognitive impairment, confusion and unresponsiveness.[3] Structural MRI images [3D high-resolution, fluid-attenuated inversion recovery (FLAIR)] revealed higher volume of WMHs in the frontal, insula, limbic, sub-lobar, and temporal regions and a higher number of WMHs in the insula, limbic, temporal, and sub-lobar areas in *U-2* pilots compared to matching controls. The occipital and parietal regions did not show any differences. The detection of a potential PFO was not necessary since this is not a disqualifier for the *USAF* Flying Class II Certification.[21] The nature of potential microemboli is not definite with three potential origins: decompression gas microbubbles, micro-thrombi, micro- or nanoparticles. All WMHs are located deeply within long-distance white matter tracts[3] suggesting an indirect phenomenon occurring at a distance from a presumed arteriolar occlusion by arterial microbubbles. However, the presence of WMH is not synonym of cognitive impairment albeit a large number and volume of WMHs is associated with a lower cognitive test performance.[21] WMH burden and age were positively correlated but not significant and could not be explained by age alone.[22] Decompression, not age seemed to be a factor associated with WMHs. In line with previous findings, in which cerebral microembolism occurs more frequently (transcranial Doppler ultrasound) in the middle than the anterior cerebral artery territory,[23] which may explain the uneven distribution of cerebral infarcts along these arterial territories, a similar microembolic distribution was found in *U-2* pilots.[22] In patients initially consulting for transient monocular blindness [retinal ischemia] at the neurolaboratory, cerebral microembolic signals are frequently detected on the side of retinal ischemia and associated with severe stenosis or occlusion of the ipsilateral carotid artery the week following the onset of symptoms.[23] In microgravity, a high incidence of ophthalmic alterations [OA] such as optic nerve sheath compartment syndrome, disc edema, choroidal folds, globe flattening, cotton wool spots, and hyperopic shifts are observed[25-28] and may be related to intracerebral compartmental volume distribution changes [ICV]. The distribution of WMHs found after exposure to microgravity appears to follow a specific pattern and is currently under investigation. It is unknown whether OA-ICV changes and WMH are independent or related phenomena. However, the asymmetry of OA, absence of elevated intraocular pressure in microgravity, persistence of elevated intra-cranial pressure days or weeks upon return to one-G are suggesting complex multi-system modifications unlike classic pathological intracranial pressure changes. The microgravity-induced changes of transmural pressure gradients (P_{TM}) within the thorax across structures of the cardiorespiratory system and other major vessels such as cerebral vessels certainly play a key role albeit the specific mechanism of OA-ICV alterations is unknown.

Privileged pressure transfer and trajectory of microemboli in the cerebral circulation: Hypothesis

This mathematical and theoretical modeling of the trajectory of microemboli towards and within the cerebral circulation is based on the Navier-Sokes equation. A direct trajectory may be privileged for micro-embolization rather than an indirect sinuous course around bifurcations. Therefore, the most direct trajectory appears to be guided within the (right) brachiocephalic trunk, with a wider diameter, higher pressure, higher velocity than the left side with a branching in two arteries (common left carotid artery and subclavian artery) of smaller diameters, lower pressures and velocities, according to the Navier-Sokes equation. A greater number of microemboli will travel faster on the right side. Right at the entrance of the circle of Willis, the most direct trajectory for the blood and microparticles is definitely the middle cerebral artery, MCA, which offers the less resistance with minimal bifurcation, then the anterior cerebral artery, ACA, offers a little more resistance (lesser diameter and more sinuosity). In contrast, the vertebra-basilar system is the most indirect communication between the cardiorespiratory system and the brain and supplies “directly” the posterior cerebral artery, PCA. The blood flow distribution, according to the Navier-Sokes equation, privileges the cerebral arteries in this order: 1. MCA; 2. ACA; and 3. PCA. This is the distribution of microemboli found in aforementioned patients and WMHs in *U-2* pilots. The asymmetrical observation of occurrence of OA in astronauts suggest a predominance of the right side in terms of (P_{TM}) modifications

within the major vessels such as cerebral vessels. The ophthalmic artery is also the first branch of the internal carotid artery. In astronauts, it is possible that the sole P_{TMP} gradients in both systems, cardiorespiratory and cerebral, associated with hypercapnia, and other factors provoke the OA without the presence of microemboli.

Susceptibility-resistance and genotype

An individual susceptibility to OA has been found and intergenic single nucleotide polymorphisms (SNPs) are under evaluation. The presence of SNPs such as *MTRR 66 GG* [methionine synthase reductase] minor allele is associated with the presence of severe spaceflight-induced OA.29 Presence of *MTRR 66 AA* or *SHMT 1420 TT* [serine hydroxymethyltransferase] genotypes in astronauts provides a resistance and none expressed severe OA.29 Interestingly, the *MTRR 66 AA* is also protecting against oxidative stress. A resistance to WMH is also the striking finding feature of a specific subgroup of U-2 pilots [approximately 10 out of N = 105, or 9.5%] who are extremely resistant and do not express WMHs, determined by number and volume, after exposure to a high decompression burden of cumulated hours greater than 1,500 hrs.[22]

Summary

Environmental-induced changes of transmural pressure gradients (P_{TM}) within the thorax across structures of the cardiorespiratory system and other major vessels such as cerebral vessels may produce detrimental changes in the CNS. In divers, maneuvers such as Valsalva provoke modifications of intra-thoracic (P_{TM}) gradients further opening a PFO, allowing RLS and paradoxical systemic arterialization of decompression venous gas microbubbles during a brief period of releasing the Valsalva. This phenomenon is possibly enhanced by early infra-clinical stages of PAH (COPD, asthma, ILD, atelectasis, pneumonia, pulmonary edema, heart valve defects, etc.) increasing PAP and hence RAP [RAP > LAP]. In astronauts, the combination of a cascade of microgravity-induced alterations in (P_{TM}) across structures of both systems, cardiorespiratory and cerebral, associated with other factors such as hypercapnia is suspected to produce OA and ICV modifications and might also potentially cause WMHs; WMHs have not yet been related to the presence of cerebral gas microemboli or a PFO. In the Space Program, investigations are currently ongoing to evaluate OA-ICV and WMHs. In *U-2* pilots, neurological DCS is associated with an increase in number and volume of WMHs although it had not been related to a higher incidence of PFOs. Spaceflight is a fascinating environment associating microgravity with hypobaric decompressions during extravehicular activities and exposes the body to the most dramatic modifications of (P_{TM}) gradients. However, other factors such as hypercapnia, stress, circadian rhythms immune system alterations, hormonal changes may directly affect the ICV. There is also a growing line of evidence that there is a susceptibility or a strong resistance to the occurrence of cerebral outcomes [OA-ICV] related to the presence of certain genotypes.

Appendix: Series of small-open connected volumes of arterial blood from heart to brain

Let Ω_i, be a series of open and small connected volumes (*in* arterial systemic circulation) from heart to brain microcirculation [heart → brain], filled with arterial blood. Fluid mechanics has been extensively studied.[30]

Fluid mechanics may also be studied in each very small micro-volume, Ω_i, in the [heart → brain] axis and at the end-organ level within a cerebral small artery or arteriole. Fluids mechanics are relevant to evaluate the blood flow at each bifurcation and at the end-organ level. However, fewer studies describe the end-organ level blood flow fluctuations since local micro-measurements are more invasive and less practical. In a 3D space, ds designates an elementary volume (dx_1, dx_2, dx_3). By splitting in small units, consider ω_0 a fixed subdomain (very little volume) of Ω_i; we denote $\partial\omega_0$ the boundary of ω_0 by γ_0. The mass of ω_0 is given by $-\frac{\mathrm{d}}{\mathrm{d}t}\int_{\omega_0}\rho\mathrm{d}x$, while the total mass exiting, ω_0, through the area γ_0, per time unit, is given by $\int_{\gamma_0}\rho\mathbf{u}\cdot\mathbf{n}\mathrm{d}\gamma_0$. Clearly, by the *mass balance equation*, one may obtain[31]

$$-\frac{\mathrm{d}}{\mathrm{d}t}\int_{\omega_0}\rho\mathrm{d}x=\int_{\gamma_0}\rho\mathbf{u}\cdot\mathbf{n}\mathrm{d}\gamma_0, \quad (1)$$

Where

- The vector-valued function $\mathbf{u}\left(=\{\mathbf{u_i}\}_{i=1}^3\right)$, designates the *flow velocity*, which is also a function of x and t;
- **n** denotes the *unit normal vector* on γ_0, outward to ω_0;
- $\mathrm{d}\gamma_0$ is the elementary *surface measure* on γ_0.
- ρ is the *mass density* (of blood), μ is the *dynamic viscosity*.
- $\Delta\left(=\nabla^2=\sum_{i=1}^3\frac{\partial^2}{\partial x_i^2}\right)$ is the *Laplace operator.*
- The notation $\nabla\cdot\mathrm{V}$ is used for the *divergence* $\sum_{i=1}^3\frac{\partial V_i}{\partial x_i}$ of the vector-valued function $\mathrm{V}=\left(V_i\right)_{i=1}^3$.
- **f** denotes a *density of volume forces*, applied to blood, per mass unit.

An isothermal flow (central temperature body temperature is constant), of a viscous incompressible Newtonian fluid which is taking place in Ω_i, during the time [0, t_{Final}], follows the *conservation of mass* and *momentum equation*, and is modeled by the following Navier-Stokes equations[30, 32]

$$\frac{\partial\mathbf{u}}{\partial t}+(\mathbf{u}\cdot\nabla)\mathbf{u}-\nu\Delta\mathbf{u}+\frac{1}{\rho}\nabla p=\mathbf{f} \text{ in } \Omega_i\times(0,t_{Final}), \quad (2)$$

$$\nabla\cdot\mathbf{u}=0 \text{ in } \Omega_i\times(0,t_{Final}), \quad (3)$$

where $\nu=\frac{\mu}{\rho}$ is the kinematic viscosity.

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Incidence of DCS in Divers with RLS – A Prospective Study

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I am here to talk about a prospective study examining the incidence or the risk of decompression problems in divers with right-to-left shunt (RLS). This is, to my knowledge, the only prospective study being conducted on this important topic.

When we talk about Right-to-Left Shunts (RLS), obviously, Patent Foramen Ovale (PFO) is by far the most prevalent right-to-left shunt in humans. However, intrapulmonary arteriovenous anastomoses (IPAVA) have been recently researched as a potential shunt after diving or physical effort.[1] We also know from Fred Bove's talk that relative risk (RR) arising from a certain condition is very difficult to determine from retrospective studies as these only yield odds ratios (OR) which can be quite similar in magnitude but not equal to RR.

Relative Risk (RR) for DCI when diving with PFO not known (retrospective studies – only Odds Ratios)

Risk for DCI dependent on type of diving

Is the risk clinically significantly higher in divers with PFO than in "normal" recreational divers?

Complicating things even further is the fact that obviously, DCI is dependent on the type of diving. Some types of diving produce high risks for decompression sickness whereas others have a very low risk. What we were interested in was to find out if the risk of DCS is clinically significantly higher in divers with RLS than in average recreational diving populations.

In his meta analysis from 1998, Fred Bove[2] showed that the risk for DCS in military divers is 1.3, in sport divers is 2.5, and in commercial divers 2.09 per 10,000 dives. The overall risk was about 2.28 per 10,000 with an odds ratio for DCS if you have a PFO of about 2.5; 1.93 if only severe forms of DCS are considered. This indicates roughly a doubling of the risk.

Prospective study in recreational divers

- Power analysis based on Odds Ratios from retrospective studies
- Screening test for RLS to be developed
- Blinding of research subjects as to result of screening test
- Ethical Committee approval
- Duration of study – drop-outs for data collection
- Data collection accuracy
  - Exposure: number and types of dives
  - Outcome: absence or presence of DCS

The Swiss study of Sandra Torti[3] shows a similar pattern with a higher risk according to the size of the PFO. The overall risk of DCS is similar to Bove's figures, 2.5 per 10,000; but the odds ratios for major DCS, which was defined as DCS taking longer than 24 hours to resolve or having been treated in a recompression chamber, was higher (4.8 to 5.7) than the 2.5 that Fred Bove reported.

The aim of the DAN Europe study was to establish the Relative Risk of DCS in recreational divers with right-to-left shunt.

The feasibility of such a study needed to be ascertained first. A power analysis was made based on available retrospective data. We had to develop a screening test that we could use on a large number of divers without much problems. We had to address the fact that if we test divers and we tell them whether they have a right-to-left shunt or not, they might change their diving behavior and so "falsify" the study by diving much safer then they normally would, or inversely, divers who were told they do not have shunt might feel overly "protected" and dive more risky (in an extreme scenario, we could end up seeing divers without RLS having more DCS than divers with RLS, which is not really the idea). Ethical committee approval obviously was needed and we would have to take into account the probably large number of drop-outs ("lost to follow-up") as the study would take years to complete. Finally, we would have to make sure the data were collected with a maximum of accuracy, both with regard to exposure (number and types of dives performed) and outcome (absence or presence of DCI).

Sample size

Best case scenario:

50,120 dives or

200 divers (50 dives/year, 5 years)

Worst case scenario

200,517 dives or

3752 divers (52 dives/year, 5 years)

Sample size calculations

We assumed the odds ratio for DCS when having RLS to be four, which is higher than reported by Bove but lower than what was later reported in the Swiss study. We assumed the prevalence of PFO in the general divers' population to be 25%. PFO is more prevalent in the young and less prevalent in the older people[4], it is not an exact figure, so having a single rounded number is convenient and possible for these sample size calculations.

For our best case scenario we assumed a risk of DCS over all of 1 in 10,000. For the 95% power of the study and no dropouts at the end of the study, we needed a total of 50,000 dives or 200 divers (each performing an average of 50 dives/year over 5 years). In a worst case scenario with a 50 percent dropout and a power of 80%, we would need 200,000 dives or about 4,000 divers over a period of five years.

Development of the screening test

In order to have an acceptable screening test for RLS, it needs to be minimally invasive, low tech, low cost, and have a good sensitivity/specificity ratio. We developed and described the Carotid Artery Doppler test[5], injecting agitated saline intravenously, similarly to a classical contrast echocardiography for detection of PFO. The straining maneuver we used was not really a true Valsalva maneuver, but rather a voluntary intrathoracic pressure increase (blocking the respiration and "bearing down") for a number of seconds, followed by an abrupt release of pressure. We inject the agitated saline solution just before release of the straining, and listened to the change of acoustic signal over the carotid artery using continuous 8 MHz Doppler.

This test was validated on a group of 33 patients, single blinded comparison with contrast transesophageal echocardiography, and yielded a very good Sensitivity (100%) but a number of false positives, which gave us a Specificity of 88%. A French group[6] replicated our validation test on 200 patients with transesophageal contrast echo, and found similar good figures for sensitivity and specificity (sensitivity 89%, specificity 97%).

Recruitment of investigators and subjects

A dedicated page on the DAN Europe website was set up to recruit investigators who were all diving medicine physicians. We developed a study package with a PowerPoint presentation, printed forms, report files, etc. We organized "Carotid Artery Doppler" training workshops, because, even if the test is relatively easy to perform, it needs some training to make sure there are no "false negatives". All the materials were developed in Dutch, French, English, German, and Italian, those being the primary "target" areas in Europe (in Europe, over 25 different languages are spoken, so we would only develop specific language materials if a sufficiently high yield would ensue). During the workshop, every investigator received a hands-on training on about 10 divers so they could reliably report the results of the test. Furthermore, round the clock telephone and e-mail support was provided.

We used the DAN Europe website and personal contacts to recruit divers and organized the "research sessions" with about 10 to 12 divers at a time. These divers were given a 1.5 hrs long presentation on diving decompression risks; on how risk for DCI is dependent, not only on gas load but also on many other, often unknown factors; about PFO and how it would increase the risk for DCS; and on the importance of conservative, low-bubble diving to reduce the risk of DCI. Then they were informed again that while they would be tested for RLS, they would not be told the result of the test; and we would simply encourage them to "dive safely". [7]

Testing

Each testing was performed individually, the subjects going through the informed consent process one at time. During the test, subjects wore headphones with loud music so they couldn't hear the test screening signals. First, we did a few "simulated injections", to practice the straining maneuver. And then we did up to three saline injections with a properly performed straining maneuver (see Figure 1).

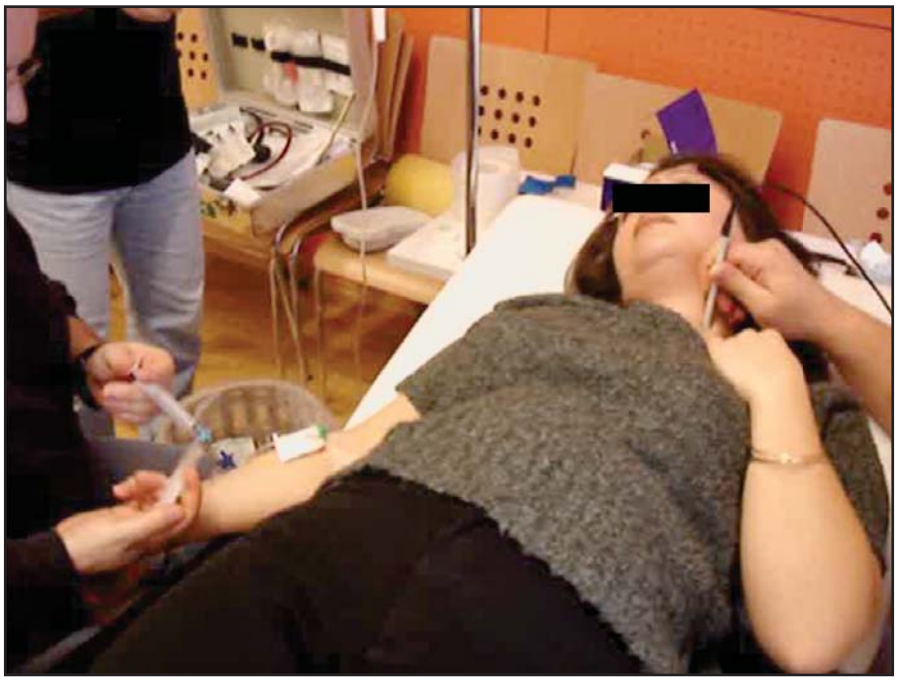

Figure 1. Carotid Doppler Test

During the development of the test, we verified that the sounds that are heard are actual bubbles passing into the carotid artery. Using a 2-D duplex scanning, bubbles could be seen passing the beam of the Doppler probe and producing the distinctive sound (see Figure 2).

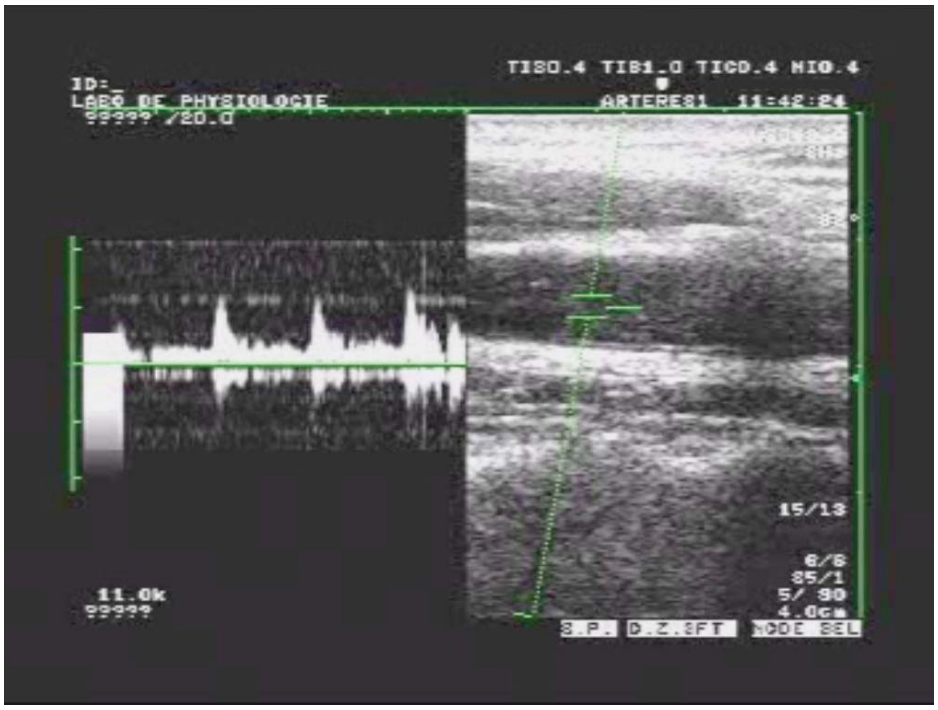

Figure 2. 2-D Doppler over the carotid artery demonstrating bubbles passing

Results

The study had a recruitment period of about eight years (2001-2009). During that period, 15 investigators were recruited and trained, but only seven have provided final data. Three provided data on less than 10 divers after their initial training. Two more investigators are still finishing up their data collection and will be included in the final analysis. Three of the investigators had decided not to blind the divers to the result. This is now a separate group that will be analyzed separately.

The results presented below are to be considered only preliminary as some data are still being analyzed. However, some interesting trends can be noted.

Out of 430 divers recruited, a little less than 60% were effectively blinded to the result. The mean age of the test subjects was 37 years, and 25% were female. In about 21% of subjects we had a positive carotid Doppler test, indicating a RLS. This was the initial data collection.

Each participating diver was contacted again after a period of 7 to 10 years, and was sent a "final questionnaire" enquiring on their diving experience (number and types of dives), the DCS or diving incidents they might have had, and a number of other questions to make the questionnaires both detailed but not too cumbersome to fill in.

As expected, a large number of divers could not be located anymore, even though telephone numbers, postal address, e-mail and other data had been recorded. So far, only 31.5% of participants returned the questionnaire. Efforts to retrieve more questionnaires will be continued through the end of 2015.

The majority of the return data were received from "blinded" divers. Of the "non-blinded" divers only 11% responded. There were some divers who stopped diving after the test, and that may or may not have been because the test was positive. One diver had his PFO closed after detecting it with the Carotid Doppler test.

The total number of dives that we collected in this way was 61,565 (the final number will obviously be a bit higher). Demographics were quite similar between RLS-positive and RLS-negative divers. Sex distribution and age are quite similar. There were no significant differences in height and weight, smoking habits, or study duration (7.5 vs 7.7 years).

The diving experience before and the number of dives after the tests was not significantly different, although RLS positive divers tended to have fewer dives before the test (272 vs 517 dives, NS). Most divers used dive computers for decompression management, most of them used the popular dive computer brands. Some divers still use tables, some divers use "technical" dive computers, but the majority can be considered recreational divers.

In the questionnaire we inquired what kind of dives they had done during the study period. We arbitrarily divided the dives into "decompression air dives", "no-decompression air dives", "decompression nitrox dives", "no-decompression nitrox dives", "technical dives" and "nitrox on air tables/computer" dives, giving a detailed description of each type of diving activity.

We also tried to make a second categorization between "recreational dives", "sports dives" (deep square dives, such as on wrecks or deep reefs), "deep dives" (over 40 meters), and "low risk dives". Again, there is not much difference between the two groups in this respect.

Now, what is interesting to see is the decompression sickness. The DCS was confirmed in little less than 10% shunt-negative and in about 30% shunt positive divers. If all cases of possible decompression illness are taken into account (people saying I had some symptoms, but maybe it was DCS, maybe not), the figures are a little bit comparable. A total incidence in the shunt-positive divers seems to be about double the one from the shunt-negative divers.

Relative Risk

Relative Risk for DCS when diving with RLS

Confirmed DCS: 3.15 (CI 1.33-7.4) p=0.009

All DCS (Confirmed + Possible): 1.89 (CI 0.94-3.8) p=0.07

DCS incidence

RLS+: 5.5/10,000

RLS-: 2.06/10,000

Nine percent of RLS negative divers and 29% of RLS positive divers had experienced a "confirmed" episode of DCS during the study period. The incidence per 10,000 dives was 2.06 and 5.35 respectively, giving a Relative Risk of 3.15 (CI 1.33-7.4, p=0.009). Some divers reported symptoms, without having been treated for DCS and a detailed description of these symptoms failed to positively identify those as DCS. If also those cases of "possible DCS" are taken into account the incidence in RLS negative divers is 18% and in RLS positive divers 33%. The incidence per 10,000 dives is a little less than twice as high for RLS positive divers (6.11/10,000 dives vs. 3.91/10,000 dives), giving a RR of 1.89 (CI 0.94-3.8, p=0.07).

Regarding the types of symptoms of DCS, it is interesting to note that although cutaneous symptoms (cutis marmorata) and vestibular or cochlear DCS are most commonly associated with the presence of arterialized gas bubbles (PFO), it appears to be a symptom of (possible) DCS in RLS negative divers as well. Spinal cord decompression sickness also occurred (once) in shunt-positive divers.

Scrutiny of the DCS cases, revealed that three of RLS positive divers that were treated with HBO, had performed a dive with maximum depth of 58, 54, 36 meters respectively (the 36 msw dive having 50 minutes bottom time on CCR). The dives of those cases that were not treated with recompression were, likewise, more provocative than can be expected from "recreational diving". One diver had severe vertigo and nausea after a 99 msw dive on air. Other DCS cases in the RLS positive group were repetitive decompression dives, square dive to 62 msw for 68 minutes on CCR, square decompression cold water dives.

In the shunt-negative group, four treated DCS occurred after deep trimix technical dives, and square decompression cold water dives. Thirteen dives resulting in untreated post-dive symptoms were on average 40 msw depth, which is not really recreational in nature; six of them were repetitive or decompression dives. Only two of those applied oxygen first aid, indicating that divers' denial is still very much present.

Table 1. Incidence of DCS

Decompression Sickness	RLS Positive	RLS Negative
n	24	108
Confirmed DCS	7	10
DCS (%)	29	9
DCS Incidence/10,000 dives	5.35	2.06
Possible DCS	1	9
Confirmed and possible DCS (%)	33	18
Total Incidence/10,000 Dives	6.11	3.91
HBO Treatment for DCS	3	6
Cutis Marmorata DCS	3	9
Vestibular/Cochlear/Visual DCS	5	4
Spinal Cord DCS	1	5

Discussion

This prospective Relative Risk evaluation of diving with RLS showed that indeed, the risk for (confirmed) DCS is approximately three times as high in divers with a RLS. If we take into account all reported symptoms possibly associated with DCS, the RR is about 1.9 which is much less. These figures are in line with previous, retrospective reports. However, it must be noted that most decompression sickness cases in the RLS positive group followed after dives that are beyond reasonably defined recreational diving safety limits.

Further analysis on these data is planned. We will invite all confirmed and possible DCS cases to perform a contrast echocardiography. With proper saline contrast and straining maneuver technique, almost all PFO cases can be diagnosed on transthoracic echocardiography, obviating the need for transesophageal echocardiography. This will confirm if divers who were classified "RLS negative" are, or are still, RLS negative. There are indications that patency of the foramen ovale may increase over the time.[8]

At the end of 2015, the data collection will be closed and all figures will be "finalized". At this time only 31% of all the divers have responded, the study is still largely under powered according to our initial sample size calculations. With the initially assumed DCI incidence of 1 in 10,000, we have only 40% power and we would need about 210,000 dives to attain 80% power. However, if we redo the sample size calculations using the actual incidence of DCS in this cohort (2.76 in 10,000), then we have already a 92% power at this time. So even with these data we have a well-powered study to support our conclusions.

Finally, we will analyze the divers that weren't blinded to the result and compare them to those that were blinded. Both the response rate (11.3% vs 45.5%) and the proportion of divers with DCS (5% vs 13.9%) were much lower in the non-blinded group than in the group that has been blinded. That leads us to think that, indeed, if you tell somebody that he has a shunt, he/she will subconsciously or consciously adapt their diving behavior, be just a little bit more careful and not have any or less decompression bubbles. This has been published by Klingmann et al in 2012.[9] They have found that just by informing divers (with or without a PFO) about the risk for venous gas emboli, the risk of subsequent decompression sickness is reduced to almost zero. Even with large PFOs, this risk reduction was achieved just by educating the divers.

Conclusions

In conclusion, based on this preliminary analysis, we suggest a Relative Risk of DCS for recreational diving with a RLS to be 1.9 (all DCS) to 3.15 (confirmed DCS). However, the absolute risk is low (2.76/10,000 dives all divers, 2.06/10,000 RLS negative and 5.5/10,000 RLS positive) and even more, most of these DCS cases happen outside what we would consider safe recreational diving.

Systematic screening of recreational divers for RLS does not appear warranted.

Thank you very much.

DISCUSSION

RICHARD MOON: Thank you, Peter. Given the delays due to technical problems, we're reasonably well on time, but we do have time for a couple of questions if anybody has one.

TOM NEUMAN: You're absolutely to be commended for trying to do an immense piece of work. Could you comment upon the observation that of your RLS positive people, 42% were using the dive computer and only 29% of the RLS negative people were using the dive computer? It seems to me that one could make the argument that a dive computer is dangerous because of the increased incidence of DCS in that group.

Similarly, you see a tremendous difference in people who are using nitrox dives on air. Well, the percentages are low, but still it's almost twice as many or 80 percent more using nitrox dives on the air tables in the RLS negative group. So what you've got are a number of other confounding variables, and I wonder if you could comment on that, and especially comment on the observation that most of these dives were well outside what we consider safe diving. So, I mean, you sort of shrug your shoulders and say, well, is there any big surprise that these people got decompression sickness.

PETER GERMONPRE: On the nitrox on air tables, I cannot really comment because, as I say, the numbers are so low that it's actually not significant and probably it's also changing. These are the numbers of dives performed with nitrox on air. So it might be that one diver consistently uses nitrox on air tables; whereas, another one just does it occasionally.

TOM NEUMAN: Or just tables versus computers. Because much more in the RLS negative group are using tables.

PETER GERMONPRE: I'm not sure if we can figure that out from this database. There is a different database from DAN Europe comparing computers with Buhlmann algorithm versus computer with RGBM algorithm, which gave an unselected contribution of dive profiles with their outcome gave a similar risk for these two models. So I would say that this looks to me as if it's a coincidence. I don't think this study will be able to answer that question. We don't have the correlation between what has been dove with which computer. So I have to disappointment you on that. I'm sorry about that.

PETER WILMSHURST: If I could ask about your decision which people you said were right-to-left shunt positive. Did you have to have a set number of bubbles detected in your carotid before you --

PETER GERMONPRE: That's a good question, Peter. I'm sorry. You want to elaborate on the question?

PETER WILMSHURST: I was just going to say that I have looked at this in divers where we're sure — that divers had shunt-related decompression illness and they've got a large PFO. In those divers when you inject, you see so many bubbles that you can't actually hear the heartbeat. And those people actually get bent. We get about 100 DCS cases a year in the UK. And the majority are bent inside the tables or computer.

PETER GERMONPRE: If you'll look at the validation studies on carotid Doppler test, it is so that only the ones that have a large shunt produce an audible signal in the carotid artery. So if you have these great one shunts with a few bubbles, five, six, 10 to 15 bubbles passing, usually you don't hear them in a reliable way. So you have to have a large shower of bubbles to hear the bubbling signal there. We think indeed that they are the larger shunts.

Now, we use only grade 0, I and II. The Swiss have added a grade III, meaning a spontaneous shunting without any provocative maneuvers. As you said, the flow patterns in the right atrium are so if you inject in the femoral vein instead of in the antecubital vein, you'd have much more positive test without straining maneuver[10] than if you're injecting the antecubital vein. So we don't make that difference between grade spontaneous shunting or shunting only after Valsalva maneuver. For divers, the distinction would be like “no shunt”, a “very small shunt” which is probably insignificant in diving, and a “large shunt” which is everything else.

RICHARD MOON: Thank you, Peter. One comment. Your prevalence of decompression illness is very similar to Dick Vann's project dive exploration prevalence. So I think that is pretty firm. Thank you very much, Peter.

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The Pathophysiology of Microbubbles Crossing a PFO or Other Right to Left Shunts in Decompression Sickness

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David Doolette and I have been asked to speak about pathophysiology of microbubbles crossing a patent (or "persistent") foramen ovale (PFO), or a pulmonary shunt, from the veins to the arterial circulation.

Venous bubbles are often formed early after decompression. These bubbles have been studied and characterized. Brian Hills and Bruce Butler (1981)[1] measured them in decompressed dogs noting that they fall typically in a range of 30 to 60 microns diameter. They pointed out that this is a size range that they would expect to be filtered by the pulmonary capillaries and therefore prevented from reaching the arterial circulation.

On that background, there is published evidence for an association between a PFO, particularly a large PFO, and cutaneous decompression sickness (DCS), spinal DCS, inner ear DCS and cerebral DCS. The link between PFO and cutaneous and inner ear DCS is probably the strongest, but all of these DCS variants have been associated with PFO by at least one or more studies.

The most plausible reason for this association can be illustrated with a simple diagram. Specifically, these bubbles that are formed in the veins early after decompression and normally filtered out by the lungs may enter the systemic circulation via a PFO or a pulmonary shunt, and they can then distribute to tissues where they presumably cause problems.

How do these tiny, 30 to 60-micron bubbles cause harm?

Let's drop into a Q & A format now. The first and obvious question is how do these tiny, 30 to 60-micron bubbles cause harm? There are several possibilities. This animation shows bubbles formed on the venous side of tissue

capillary beds crossing a PFO, and they then impact on the arterial side of these capillary beds in a variety of tissues such as the brain. A well-perfused organ like the brain will receive a high proportion of any bubbles that cross a PFO.

We know from work by Des Gorman[2] that bubbles (especially small bubbles) don't arrest, even in the microcirculation. They redistribute. Intuitively that seems a good thing, but it's not a wholly benign process. Des and also Drew Dutka[3] conducted very similar studies that showed what happens to cerebral blood flow after bubbles pass through the microvessels of the brain. Des's data comes from a study in rabbits exposed to two different aliquots of intra-carotid air: 25 microliters or 400 microliters. Whereas the cerebral blood flow in rabbits exposed only to saline did not change, there was a progressive (and similar) decline in flow over 60 minutes after exposure to both doses of air.

It is clear that none of these bubbles lodge and produce an immediate obstruction to flow, they actually redistribute. But over time after the bubble exposure the cerebral blood flow declines. The interesting thing is that the effect could be obliterated in leukopenic rabbits[4] or dogs[3] implying that there's an inflammatory process incited by the redistribution of these small bubbles.

Now, it's true that the 25 and 400 microliter aliquots of air were not delivered to the brain in tiny bubbles of 30-60 micron size, but nevertheless what is clear from these data is that there's not a discernable difference in effect between the two air doses. The point is that even small amounts of gas going through these small vessels will produce these kind of changes.

So in respect of the first question you could say that in the brain, if exposure to these tiny bubbles crosses some poorly-defined threshold (which presumably relates to the number and size of bubbles) then these inflammatory changes could produce a decrease in flow, and symptoms.

Why in many inner ear DCS cases seemingly related to PFO, is only the inner ear affected?

Another question that arises, and whose answer is important in interpreting how these bubbles might affect organs receiving less blood flow, is: since the brain and the inner ear share a common blood supply, why do many of the PFO-related inner ear cases only have inner ear symptoms? If bubbles are arriving in the inner ear, they must also be arriving in the brain. So why in many cases is the inner ear affected, but (seemingly) not the brain.

This is a table from a paper that David and I have recently published in DHM[5]. We've combined all the relevant case series of inner ear decompression sickness, and about 74% of cases present with isolate inner ear symptoms, nothing else. And yet 80% of these cases have a large spontaneously shunting PFO. So they're seemingly "PFO-related" cases.

The obvious problem with that hypothesis is that the labyrinthine artery (into which arterial bubbles would have to pass) is a tiny branch of the basilar artery. It is therefore implausible that bubbles in the basilar artery would distribute only to the inner ear. Indeed, we would expect that most bubbles would go to the brain and only a few to the inner ear. And yet these divers are presenting with just inner ear symptoms.

In trying to explain this David and I invoked a hypothesis first proposed in respect of the spinal cord by Peter Wilmshurst and applied it to the inner ear. Thus, if even a few small bubbles arrive in a tissue that remains super-saturated, those bubbles could be caused to grow by inwardly diffusing inert gas.

To summarize this paradigm, these tiny bubbles are formed in tissue capillary beds, pass to the right heart in the venous system, pass through a PFO, and impact in a tissue that remains supersaturated. Such a tissue has a high tension of dissolved nitrogen and that nitrogen would diffuse into the bubble making it bigger and, therefore, more likely to cause problems. This can explain how even a small number of tiny bubbles reaching a supersaturated tissue could cause harm to that tissue, whereas larger numbers of bubbles reaching a non-supersaturated tissue might remain clinically silent.

Inner ear supersaturation time table

David and I addressed the plausibility of this hypothesis in respect of the inner ear in a paper in JAP in 2009.[6] We considered a 30m air dive, square profile, 25 minutes with a direct ascent to the surface (at 18m/min). This profile was chosen to be similar to those that seem to cause inner ear DCS during air diving. We compared the dissolved gas tensions in the brain and the inner ear during and after this dive. The brain quickly develops a higher gas tension at depth because it's such a well perfused tissue, but for the same reason it outgasses very quickly during decompression. Using our previously published model for inert gas kinetics in the inner ear,[7] we showed that the inner ear does not develop the same gas tension as the brain, but because of slower outgassing there's a 30 minute period after the dive in which the inner ear remains supersaturated. So any bubbles arterialized across a PFO and arriving within that window would have a potential to grow and cause problems. We recently showed that about 75 percent of inner ear DCS cases have symptom onset within the first 30 minutes after the dive;[5] that is, within the residual supersaturation window we predict occurs in the inner ear after a typical dive.

The other requirement for the "supersaturation" hypothesis to be valid is that venous bubbles must appear within the window of organ vulnerability. In the case of the inner ear, this means within the first 30 minutes after surfacing. Blogg and Gennser[8] have demonstrated venous bubbles within that first 30 minutes under various diving conditions. Their paper shows that short bounce dives, typical of the sort of dives that recreational divers are doing, do produce venous bubbles within that first 30 minutes.

Supersaturation-based vulnerability in other organs

We believe it's likely that this sort of supersaturation-based vulnerability also applies to other target organs. I've pointed out that PFO is more prevalent amongst divers who have suffered cerebral, spinal, cutaneous and inner ear DCS. That implicates small, arterial bubbles shunted from the veins in these forms of DCS. The vulnerability of the brain is probably explained by its luxury perfusion. Because of this, it will not be supersaturated after typical dives, but it will receive a large proportion of any small bubbles that shunt across a PFO.

In contrast, the spinal cord white matter, the skin and the inner ear are less well perfused. They'll receive fewer bubbles and sometimes none (in the case of the inner ear that would be very plausible). But the inner ear (and probably the other tissues implicated) is supersaturated for a period after the dive and any arriving bubbles will be prone to grow because of the inward diffusion of the supersaturated gas. That's the fundamental basis of our paradigm for explaining the relationship between PFO and these forms of DCS.

There's some circumstantial supporting evidence for these hypotheses. For example: a PFO seems most prevalent amongst the early onset cases even though venous bubbling typically continues for hours after diving. When you look at the later onset cases, PFO is less prevalent. This indicates that there's something influential going on early after the dive, like residual supersaturation in the target tissues.

The other thing that has also been pointed out this morning is that it's rare to get symptoms after a strongly positive bubble contrast study. That's despite the fact that usual methods of bubble contrast generation actually produce

bubbles in a very similar size range[8] to the venous bubbles measured by Butler and Hills[1] after decompression in dogs.

Thus, in a strongly positive bubble contrast echo, the bubbles are the same size and there are substantial showers of them passing into the systemic circulation, and yet we don't see decompression sickness symptoms in subjects undergoing the test. To the best of our knowledge there's never been a report of inner ear, spinal or cutaneous symptoms after a positive bubble contrast echo. However, occasional cerebral symptoms are reported.[10,11] There is about 11 cases in the literature where symptoms have occurred after a bubble contrast echo, but they're all cerebral. This is consistent with and supportive of my previous commentary. These bubbles can cause cerebral symptoms if enough of them distribute to the cerebral circulation. Thus, the brain is vulnerable because of the high proportion of arterial bubbles it receives. But the other organs (inner ear, spinal cord and skin) are not affected in positive bubble contrast echocardiography because they're not supersaturated with inert gas when you're sitting in a doctor's surgery.

Factors necessary for RLS to contribute to DCS

Finally, I want to finish by asking this question: How can someone with an undiscovered PFO dive for years, often performing hundreds of dives, without problems and then suffer DCS that appears related to their PFO? This is a question that gets asked frequently. I think the answer to that question can be answered by incorporating some of the pathophysiology discussed so far into the Swiss Cheese model that Reason proposed to illustrate how multiple factors have line up in order for an adverse outcome to occur.

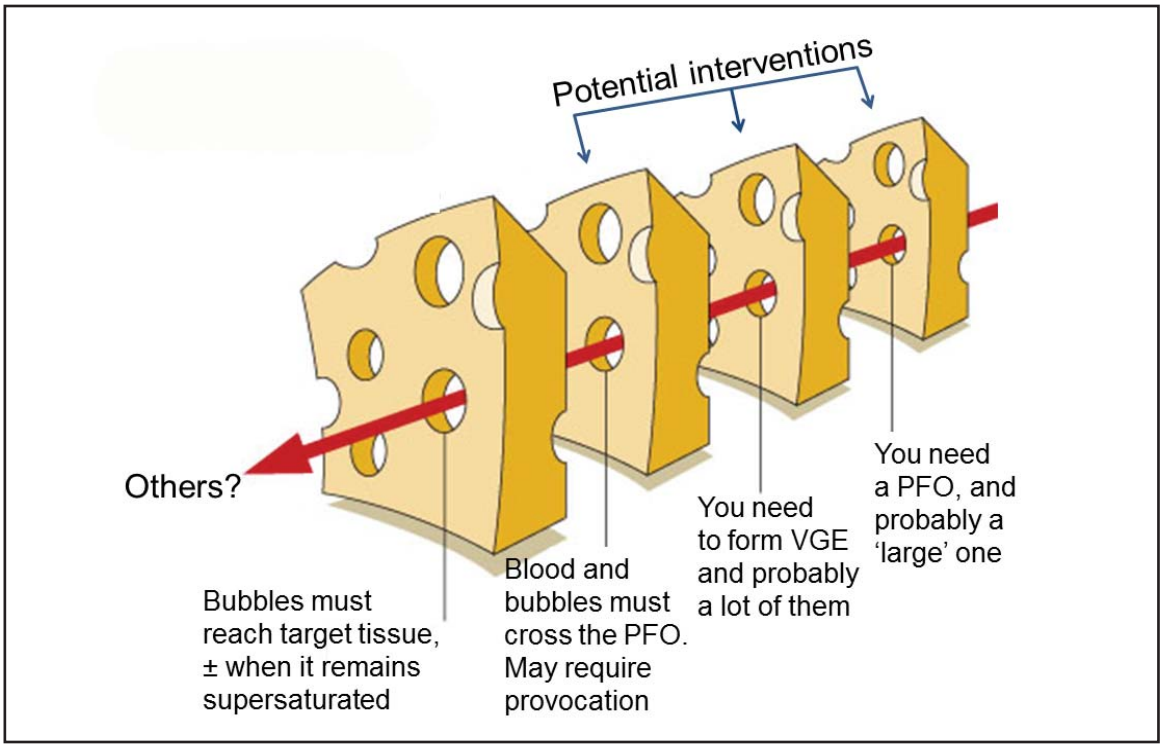

Figure 1. A four stage Swiss cheese model for PFO in DCS

For a start, and most obviously, if a PFO is going to be an issue in diving, you need to have one and probably it needs to be a large one. There's reasonable support for that. Torti et al.[12] calculated the risk of major neurological DCS per 10,000 dives among subjects stratified by size of PFO. The stratification had 4 categories: no PFO; grade I in which there was shunting of only a small number of bubbles on provocation; grade III in which there was spontaneously shunting of bubbles with no provocation; and grade II was somewhere in between. What seems clear is that a grade III (spontaneously shunting) PFO that allows a lot of bubbles to cross is a definite risk factor (~10 cases of serious DCS per 10,000 dives), whereas a small PFO was not different to no PFO and almost certainly doesn't increase risk (~1 case of serious DCS per 10,000 dives). So size matters. You have got to have a PFO and it has got to be big.

Then you have got to form venous gas emboli (VGE), and you've probably got to form a lot of them. There is some supporting evidence for that statement also. One example is the simple positive venous gas emboli vs DCS risk correlations in unselected populations which contain people with PFOs. It's not hard evidence, but these correlations exist. A second example is that relevant cases often arise after provocative dives. In the inner ear DCS series that we present in our recent paper[5] the median maximum depth is 35 meters. Thirty-five meters is a deep recreational air dive. And these inner ear cases hardly ever occur in dives that are shallower than 18 meters. So these more provocative dives (by that I mean more likely to produce large numbers of VGE), seem to be more prevalent amongst these cases.

A final piece of evidence supportive of the contention that VGE numbers are important is the apparent success of risk mitigation strategies that are designed to reduce VGE. Cristoph Klingman[13] published a small study in which he demonstrated a reduction in the risk of diving with a PFO if divers did things that were likely to reduce the number of VGE, like diving nitrox but using air tables or padding decompression stops a little more. So there is certainly some circumstantial supporting evidence suggesting that high numbers of VGE are important.

The third "hole in the swiss cheese" is that blood and bubbles must cross the PFO. And that does not necessarily happen after every dive, especially in the PFOs that require some provocation to cause right to left shunting. Provocation can be lifting or straining after a dive or exercising after a dive. These are things that divers do and they often do it at exactly the wrong time. For example about 30 minutes after a dive when VGE numbers are beginning to peak a diver might pull an anchor up or lift their equipment into the back of a car.

And then finally, as I have discussed at some length, the "final hole in the swiss cheese" that has got to line up is that the bubbles may need to reach a target tissue when it remains supersaturated with inert gas in order for that tissue to be most vulnerable to injury.

There may be other things that we do not know about, but that's our current sense of the risk factors that have got to line up for PFO to influence risk of DCS. The Swiss Cheese diagram helps explain the question that Moon and Bove[14] put in their 2004 editorial in UHM where they posed the question, PFOs are common and venous bubbles are common, so why don't we see more neurological DCS? It could be that the answer is that having a PFO and venous bubbles are not the only issues; there are still these other two factors that have got to line up for the PFO to be a problem. These factors may help us explain the disconnect between a common alleged risk factor (PFO) and a relatively rare disease (DCS) that Moon and Bove pointed out.

I should briefly mention the extent to which we could expect PFOs shunting from right to left to disturb inert gas exchange to a point where it might disadvantage a diver. We do not believe that disturbance of nitrogen elimination is a plausible explanation for the significance of a PFO in DCS. Dr. Eldridge may comment on this, but he published a paper in 2011[15] in which he showed that even in a group of subjects where the PFOs were mostly

spontaneously shunting, the shunt fraction was about 1.5 percent. This would not significantly impair nitrogen elimination.

Potential interventions to mitigate the contribution of a PFO to risk of DCS include having a PFO fixed, reducing the production of VGE after a dive, and encouraging divers not to do things that are provocative for right to left shunting across a PFO after a dive. That's not the subject of my talk, and I'll leave it to other people to discuss later. So happy to take any questions if I've got any time.

DISCUSSION

DR. ALFRED BOVE: Let me ask the first question. You've done some work on anti-inflammatory medication and decompression sickness and so on. And Peter and I were talking in the lobby because there's another issue. And that is all the mediators that are released when we have bubbles in the venous system and the PFO allowing those mediators to cross. So what would you put in your swiss cheese diagram regarding considering the non-bubble effects, the secondary bubble effects on vasoreactivity. For example, some of the mediators are vasorestrictors, so you could reduce blood flow in the inner ear by vasoconstricting rather than having a bubble.

DR. SIMON MITCHELL: I didn't put that in there, to some extent, Fred, because although over the years we've all talked about all of those things like platelet activation and complement activation, we've never really honed down on hard evidence for a role for those processes in human DCS. However, I acknowledge it, and I think you're right, and you probably have to put that in there as a potential positive effect of reducing formation of venous gas emboli. That is where it would fit in. It’s potentially relevant whether you've got a PFO or not. Those mediators can be formed in the veins and presumably unless there are things that are actually actively metabolized in the lungs which do protect the systemic circulation from some vasoactive substances, they can probably just get through the lungs as well. So I'm not sure of the relevance of that to PFO.

GARY LATSON: I was going to comment that another hole in your swiss cheese is that the target tissue must produce symptoms in order for it to be a clinical case of DCS. If that target tissue is a silent area of the brain or spinal cord or another organ.

DR. SIMON MITCHELL: I agree with that.

GARY LATSON: That might be the white matter lesions that cumulatively over time start to see it.

DR. SIMON MITCHELL: I totally agree.

DAVID DOOLETTE: You need another hour on the potential interventions. It's easy to reach the surface without your central nervous system supersaturated. You do a safety stop, for instance. That may be the only thing that safety stop actually does in recreational dive or you do adequate recompression. So that's another way you can intervene.

DR. SIMON MITCHELL: The obvious intervention in the 4th hole in the Swiss Cheese is making sure that your vulnerable tissues aren't supersaturated. Thank you, David.

BILL BATEMAN: I very much like your swiss cheese model there, Simon. The first part I think we need to remind ourselves that in the first piece of cheese is we're talking about PFO when we really actually mean shunt. We've already heard that shunt can come from other places too. In the context of this workshop, admittedly, PFO is the most important.

The second piece of cheese above a VGE I would submit that we probably need to think of that as bubbles rather than just VGE. And that's particularly important in the context of inner ear decompression illness where it may be that the bubble does not come from the blood but from a minute episode of barotrauma where we wouldn't expect inner ear barotrauma, per se, because of the risk factor, just a minute enough bubble to form a nucleation sinus where there's a significant inert gas load like you described, a small bubble becomes bigger.

DR. SIMON MITCHELL. I agree with that, Bill. I'm focusing on the role of PFO here. For spinal decompression, as Fred has pointed out, it can be venous congestion, it can be bubbles forming in the tissue itself, it can be bubbles getting to the spinal cord in the arterial blood. I have not given an over-arching view of the pathophysiology of DCS. I've focused on the role of right-to-left shunting of VGE. And I certainly take your first point about pulmonary shunts being in there as well.

BILL BATEMAN: And last but not least, you said it but I would certainly hope you'd include it in your swiss cheese, that the bubbles must reach a vulnerable target tissue, and that may bring in what you were saying early on about the hypersensitivity of particular tissues depending on the situation.

DR. SIMON MITCHELL: I agree. I kind of meant that with target tissue rather than just any tissue, you're absolutely right, and Gary's point was very similar.

AUDIENCE MEMBER: Thank you very much for this very interesting presentation. For what consent you're reasoning, would you expect a difference for the same exposure, a difference in conclusion for helium dives versus air dives?

DR. SIMON MITCHELL: Well, I'm not sure I'd expect any difference, to be honest. How you form your VGE is irrelevant to me. I have proposed a paradigm to explain how VGE can become pathophysiologically significant. The whole helium versus nitrogen thing is another debate, and it's actually been reasonably well informed by some recent work that's been published by David Doolette. And perhaps we can take this discussion off line, and I can point you to the various references that speak to the differences between helium and nitrogen. Basically, it's how many bubbles you form. Once those bubbles are formed, the processes I have described are what we think make them relevant.

AUDIENCE MEMBER: My question more concerns the target tissue itself.

DR. SIMON MITCHELL: Is there a difference between helium and nitrogen in the way they effect tissues? I'm not aware of any data that would illuminate the answer to that question.

DR. ALFRED BOVE: Thank you, again, Simon.

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Inducible Intrapulmonary Arteriovenous Shunt Pathways: Are they important in DCS?

Marlowe W. Eldridge, MD
Professor of Pediatrics, University of Wisconsin

I want to thank the organizers for inviting me and allowing me to crash your party with some new thoughts and new ideas about how bubbles may move from right to left and not have to have any inter cardiac defects. I have no disclosures except for sometimes I do crazy things. My objectives for this presentation are:

1. Provide some evidence that intrapulmonary arteriovenous shunt pathways (IPAVS) do exist.
2. Provide evidence that IPAVS are large, distinct, shunt pathways.
3. Explore mechanisms of regulation that may be important in DCS.

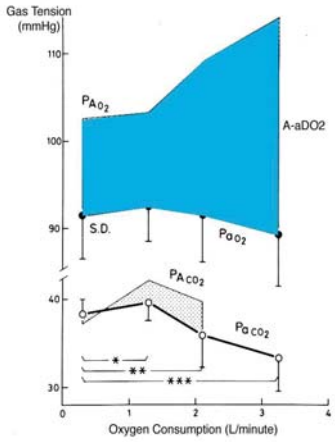
How many of you actually learned about intrapulmonary shunt pathways in medical school? It was something not mentioned. It was something that was just totally passed over. When I got involved in these studies, we were actually addressing a different problem and that is, lead athletes often develop exercise-induced arterial hypoxemia. In other words, the lung is not the most efficient with gas exchange particularly as exercise increases.

The way we were looking at this, and this was very controversial at the time, at least for a couple of different labs, was that as you increase your exercise, the alveolar oxygen tension rises and the arterial oxygen tension drops. By definition, an inefficiency in gas exchange.[1]

As outlined in Figure 1, the reasons you can have gas exchange dysfunction are ventilation perfusion inequality; diffusion limitation; right-to-left shunts; intracardiac shunts including PFO and other atrial or ventricular septal defects; post-pulmonary venous admixture through the Thebesian and the bronchial circulation de-saturated blood delivered back to the left heart; and intrapulmonary shunts, whether they be physiologic with atelectasis and alveolar flooding. Atelectasis will not occur in exercise, but there was some potential for alveolar flooding. Or you can have anatomic intrapulmonary shunt pathways.

I worked with Peter Wagner's laboratory a while ago and learned about multi-inert gas elimination technique (MIGET)[2] and applied it to addressing ventilation perfusion question. MIDGET has 56 compartment model. Special gas here, sulfur hexafluoride, and its' partitioning coefficient of the dissolved and the gas phase, is used to measure intrapulmonary shunts. And how we looked at this was that you can have the measured the difference between the alveolar and the arterial blood oxygen tensions (A-aDO2), which goes up. And then you can have that that's predicted by MIGET. There were some issues with this.[3]

Potential contributors to the gas exchange dysfunction seen with exercise include:



- Ventilation/Perfusion inequality
- Diffusion limitation
- Right-to-Left shunt
  - Intracardiac shunts
    - Patent Foramen Ovale (PFO)
    - Atrial or Ventricular Septal Defect
  - Post-pulmonary venous admixture
    - Thebesian circulation
    - Bronchial circulation
  - Intrapulmonary shunts
    - Physiologic (atelectasis and alveolar flooding)
    - Anatomic (intrapulmonary shunting)

Figure 1. Potential contributors to the gas exchange dysfunction seen with exercise

So when I went to the Rankin lab and started working with Jerry Dempsey, we started to re-address this question because, one, I knew the limitations of MIGET. I had worked with it. And also in previous years, Gledhill, who had worked with Dr. Dempsey, had suggested that a two percent shunt would explain all of this difference he predicted.[1] And then we started exploring the literature looking for morphological studies showing arteriovenous intrapulmonary shunts (Weibel, von Hayek).[4,5] We found one morphologic study that suggested that arterial venous intrapulmonary shunts do exist. There's also a whole stack of papers that said, no, they don't. And then there was some early microsphere studies that suggest that large micron microspheres up to 200 microns could actually be forced passed the pulmonary circulation in isolated lung preps.[6,7,8,9]

These were all situations where the lungs were really not in a good state. They were preserved lungs, et cetera. And it took a lot of pressure for some of these large microns to get passed through. But we said, let's take advantage. If intrapulmonary shunt pathways do exist and they can contribute to the gas exchange abnormalities that we see, let's use the whole fact that the lung is a biological filter. It will filter out microbubbles, particles, thrombi, parasites. It's one of the roles of the lung. It's not just gas exchange. And let's take advantage of that to see if we can determine whether there's intrapulmonary shunt pathways during exercise.

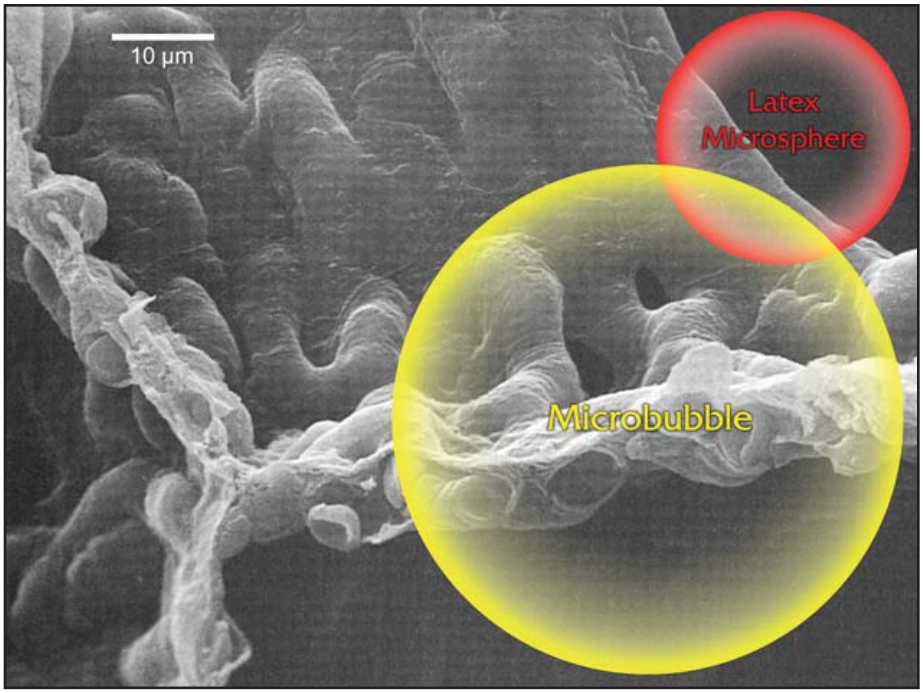


Figure 2. Pulmonary capillary filter

Exercise opens IPAVS

We used contrast echocardiography, just like what everybody has been talking about, except now we're doing it during exercise protocol. And the initial study we just looked at 26 subjects and found that three of those had PFOs. We did the Valsalva-based studies. They were a broad range of VO_2 maxes from slugs to lead athletes. American cross country champion was one of the subjects.

We did this incremental exercise with bubble injections at the last 30 seconds or so, and then an apical four-chamber view. We were quite surprised by how good images we could actually get during exercise.[10]

This is a classic negative study. All of you know about this so I don't need to go through too much. If there's a septal defect, the bubbles show up really quickly, within three cardiac cycles. And if it's coming through the intrapulmonary shunt pathway, it will be late and be about five seconds or so.

Low workload, no bubbles. As we increase the workload 230 watts, we start to see the bubbles in the left side. And then as we increase the workload towards maximum, there were even more bubbles. Interestingly, when subject stops exercising, the passage of bubbles disappears.

With this study, we showed that exercise created a shunt pattern in more subjects than we really expected. We expected just to see the high-end exercises that developed arterial hypoxemia to be the ones that would shunt. But we saw there was a nice distribution of shunts, almost a bell-shaped curve, with maybe a tendency for some to shunt at the higher workloads. There was a couple of subjects that did not shunt during exercise.

This issue was controversial at the time. Lots of points/counterpoints, going back; are these pulmonary shunts real or are they important. Was this an artifact of the methods that we used?

So we went to another method, again, using the lung as a biological filter, technetium-99m (99mTc)-labeled macroaggregated albumin (MAA). Using various methods of calculation, we have shown that shunt fraction was around two percent and that there was a relationship between a magnitude of shunt following a PO_2 during the exercise.[11,12]

Hypoxia enhances opening of IPAVS

I am more of an altitude physiologist rather than a diving physiologist. So we were very interested in what happened with different oxygen tensions, and actually postulated that those few individuals that don't open up their shunts during exercise would be the ones most vulnerable to high altitude pulmonary edema. That they would over-circulate various regions of the lung, and that these shunt pathways were actually protective pop-off valves. So we did a very similar study as the original one, but we had the subjects exercise at normoxia and hypoxia, and then we also did blood gas analyses.

We actually postulated that hypoxia would prevent the openings of these pathways. And we were absolutely, unequivocally wrong. They actually increased — we had never before seen shunting during rest, and here we saw in some subjects shunting during rest during hypoxia and everyone shunted earlier during hypoxic exercise. And everyone shunted for many minutes afterwards. It seems like oxygen tension was an important factor in regulating these pathways.

Hyperoxia closes the IPAVS

So we decided, well, what happens with hyperoxia? We have shown in exercising subjects in normoxia shunts and no shunts when breathing oxygen. So clearly some oxygen signaling mechanism is involved but we didn’t figure it yet.

Mixed venous O_2 tension may regulate opening of intrapulmonary shunts

For further studies we went to an animal model. Basically, we put a rat in an echmo circuit and injected solid microspheres, 25 microns at different stages of venous oxygen tension, and found that as the mixed venous oxygen tension fell towards 22, that was when the shunting occurred. So there wasn't shunting and then there was shunting. So there seems to be a trigger at a mixed venous oxygen tension at least in rats of around 22. It wasn't the alveolar side, but it was on the backside of the venous side. So definitely a regulation related to oxygen tension.[14]

There's a lot more studies out there that we did, but I wanted to hit the highlights.

Catecholamine infusion opens IPAVS at rest

Andy Lovering who was a post-doc in the lab and had done a lot of the earlier stuff with me went off to Oregon and continued this work. He and his graduate student looked at catecholamines. Two things, venous oxygen tension comes down right about the 60% maximum, and catecholamines start to rise. He actually just took healthy, normal subjects with no PFOs and laid them down, and did an epinephrine infusion. As the epinephrine infusion increase, there were more and more bubbles. If they gave subjects 100% oxygen, pretty much bubbles were wiped out. Dopamine had a similar effect but not as profound. So two things, oxygen tension and some kind of oxygen signaling mechanism, and catecholamines or an adrenergic kind of mechanism are helping to control these vascular events.[15]

Adrenergic regulaton of IPAVS

Melissa Bates again in the animal lab, a rat model, similar kind of study as described before, looked at normoxia. No cell fractions, essentially zero. Hypoxia, lots of microspheres across the pulmonary bed and into the circulation. Normoxia plus isoproterenol, way up there. Hypoxia and a beta blocker brings it down. Isoproterenol plus propranolol totally abolishes the movement of microspheres across the circulation. And isoproterenol plus hyperoxia, hyperoxia helps isoproterenol.

So these are conflicting mechanisms. I don't know exactly why this would be the case, but there's definitely things to think about, oxygen tension and catecholamine surges particularly had adrenergic effects (unpublished).

Over-embolization opens IPAVS

Another question to think about is what is the bubble load that goes into the pulmonary circulation? Could the bubble load be enough to override and open up these pathways? In another study that Dr. Bates did, we embolized the lung with small microspheres, around eight microns, large numbers of them so that the downstream resistance was very high, and then injected larger microspheres like 25 microns and then collected. We showed that with the embolization the number of large microspheres passing through increases. We actually saw seven micron microspheres get across a rat lung.

Then in some of those lungs we did a high resolution contrast CT. The images show that the distal circulation has been embolized out and in larger, more proximal, vessels we saw a bridging between large vessel. We've also done similar kinds of studies in pigs, and I have similar CT scans.

IPAVS are a remnant fetal vascular network

We think that intrapulmonary shunts are normally closed at rest, but they're there. They're similar to the PFO in that they're a remnant fetal vascular network that allows the oxygenated blood to bypass the nonworking capillaries of the fetal lung and then get to deliver oxygenated blood to the systemic circulation.

Up to now we have shown that oxygen tension, beta adrenergic control, and the distal vascular resistance seem to be important in recruiting and opening IPAVS by exercise.

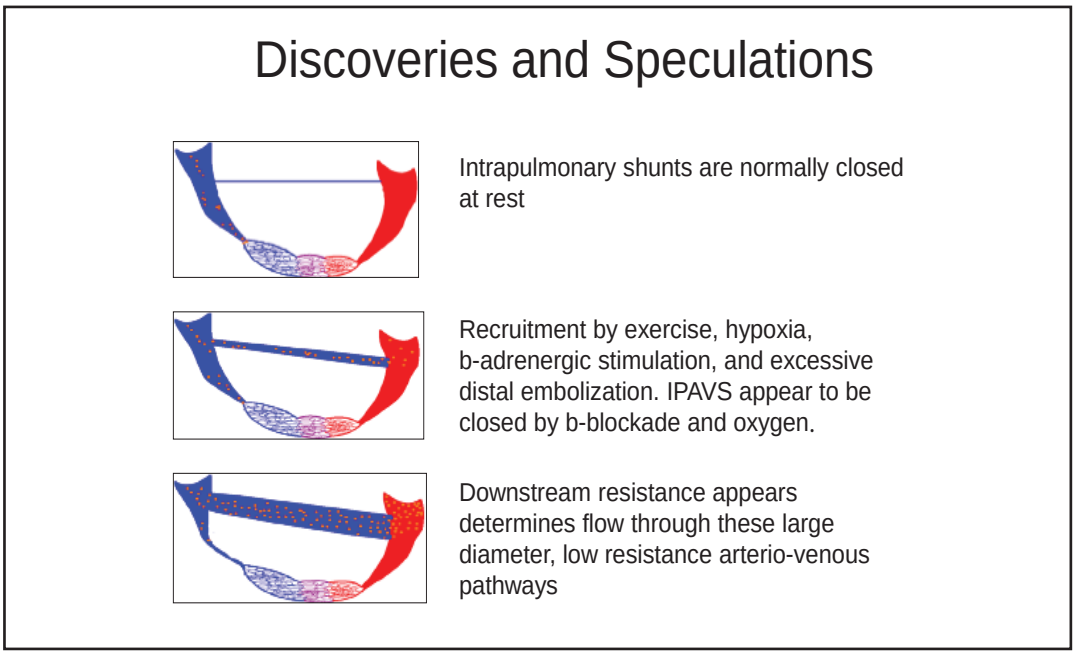


Figure 3. Discoveries and speculations

It's not just exercise but the physiologic effects of exercise. It's not cardiac output and high pressures. We've got some good data to suggest that it's not that. Dr. Lovering would disagree, but that's always nice to have former post-docs disagree with you. It worked in my case.

Excessive distal embolization may be important in that they seem to be regulated by beta blockade and high oxygen tension. I think in this scenario it's really important to think about what the downstream resistance is. What is that bubble load downstream? If the bubble load is high enough downstream, it may open these pathways to allow those venous gas bubbles to cross over into the left side.

And certainly scenarios of high catecholamines occur in dive situations. Pretty hard exercise can occur in dive situations. So those are my thoughts and speculations. It takes a lot of people to do these things of studies and lots of support. I will entertain questions now.

DISCUSSION

DR. ALFRED BOVE: Thank you. It brings another insight to the things we do in diving medicine because you're describing an awful lot of pulmonary regulatory things. Oxygen effects on pulmonary muscle and catecholamine effects, among other things, and the effects of pressure itself in the arterial circulation. So things we have to learn about more because they involve some of the things we deal with.

DR. PETER WILMSHURST: I want to make two points. One is about the timing of shunting with pulmonary arteriovenous malformations (AVMs). In fact, on contrast echo you can get very early shunting with pulmonary AVMs, very large pulmonary AVMs you can get it within one heartbeat of the right heart. And what I've written about in European Respiratory Journal is that, in fact, the way to tell the difference between a pulmonary AVM and an intracardiac shunt is actually not to look at what happens at the beginning but to look at the end. Because when you inject the contrast and it's all gone through the right heart, if the bubbles are still appearing in the left heart, they must be coming from the lungs because they can't be coming from an empty right heart. So that's one thing.

And the other point I was going to make is that this is very like something we described in 1996 in pregnant women who get desaturated during pregnancy and they have pulmonary shunts. If you do a contrast echo at rest, they have pulmonary shunts and it gets worse when they exercise and it goes away when they're no longer pregnant.

DR. MARLOWE ELDRIDGE: First of all, yes, I agree totally with your pulmonary AVM. And we actually used similar kind of criteria to exclude those individuals and identify them in all of our series. On one individual, we can actually prove that he had a pulmonary AVM. That was what prompted me to use this. So very important comment. And we did take that into account.

I'm not sure what happens in pregnancy. There's probably many regulatory mechanisms and mediators that can open these pathways. Catecholamine syndrome is certainly a very important scenario that clearly shows that there's an ability to open these pathways in a variety of circumstances. You're describing pregnancy. We've seen it in a child with asthma who was intubated, was very sick. I agree they're important. Probably clinically important in many different scenarios.

DR. ALFRED BOVE: Let me take the prerogative of limiting the questions because we're already out of lunch at this point. Could I ask the other speakers to please write your questions down? We'll try to answer them later on. Thank you.

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VGE Arterialization in Divers with Closed Foramen Ovale

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Professor of physiology and Head of the Department of Integrative Physiology at the University of Split School of Medicine (USSM), Split, Croatia.

The data presented were collected under field diving conditions in order to evaluate the physiological factors affecting a diver's body such as water immersion, cold, exercise, work of breathing, mental stress and hyperoxia. In addition to venous gas emboli (VGE), as one of the older hypothesis for decompression stress, newer mechanisms will be discussed as well such as arterial endothelial dysfunction and increased microparticles formation in the post-dive period. Since I am physiologist and not involved in treating DCS, I will discuss asymptomatic physiological changes that were investigated by my lab during the last 20 years.

VGE grading in our studies was performed by using Dr. Brubakk and Eftedal's scale, recently modified by Dr. Pollock and us (Table 1). Related to technology for performing imaging studies, we started with precordial Doppler, but then moved to portable echo machines like Logiq Book and lately to Vivid Q for field work and also e9 for lab work. It is important to have high resolution units in order to make adequate quantification of the bubble load to the heart post-dive.

Also over the years we worked on procedures for reducing a gas bubble load such as a single high intensity interval training 24 hours before diving or nitroglycerine administration before a dive.[1,2] This was extended by others to pre-dive sauna, hydration, whole body vibration, oxygen prebreathe, etc.[3]

Coming to today's talk about VGE arterialization in patent foramen ovale (PFO) negative divers, this work was initiated with a case report in which first grade 5 VGE in the right heart was detected in a PFO negative diver, together with grade 4 in the left heart. What was amazing is the fact that this diver although producing huge quantity of VGE was asymptomatic and did not present any decompression stress (DCS) symptoms. Since PFO was excluded as a potential cross over pathway, the only remaining shunting mechanism was intrapulmonary shunts or arteriovenous anastomoses (IPAVAs).

In the next few studies, we were again surprised by large VGE post-dive that were not associated with DCS. This conclusion was reached after a trimix dive series in which a high bubbling load lasted up to 90 minutes post-dive. In five out of seven divers, VGE arterialized at some point. At the time, we were not testing for PFO and one of

these divers had small grade 1 PFO.[4] In this study we also showed that there was an increased pulmonary artery pressure post-dive. So this was really the first time that raised our interest related to very high VGEs and potential for arterialization.

Table 1. VGE grading scale

Eftedal		Dujic		Pollock	
Grade	**Description**	**Grade**	**Description**	**Grade**	**Description**
0	No bubbles	0	No bubbles	0	No observable bubbles
1	Occasional bubbles	1	Occasional bubbles	1	Occasional bubbles
2	At least one bubble/4th cycle	2	At least one bubble/4th cycle	2	At least one bubble every four cycle
3	At least one bubble/cycle	3	At least one bubble/cycle	3	At least one bubble every cardiac cycle
4	Continuous bubbling, at least one bubble/cm^2 in all frames	4-I	1 – 2 bubbles/cm^2 in all frames	4	At least one bubble/cm^2 in every image
	Continuous bubbling, at least one bubble/cm^2 in all frames	4-II	At least three bubbles/cm^2 in all frames	5	At least two bubbles/cm^2 in every image
5	"White-out", individual bubbles cannot be seen	4-III	Near complete white-out	6	At least 80% of visible lumen obscured by bubble cloud; single bubbles cannot be discriminated

In the follow-up study done together with Dr. Brubakk and the Norwegian Labor Directorate, we tested some new air diving procedures, with depths of 18, 24 and 33 meters of sea water (msw) [59, 79, 108 fsw] and with long bottom time (up to 60-70 minutes). In 12 divers (only one PFO positive) grade 4 was present in 56 out of 69 dives and the arterialization was shown in 5 out of 12 divers. When comparing the two studies, more arterialization occurred in the trimix dives.[5]

We found that in order to arterialize, VGE bubble grades need to be 4-II or higher. So you really need to be a "bubble producer", someone who produces bubbles in most dive profiles, in order to have the potential for arterialization. After years of working with divers, we have found 15 bubble producers that we call on when we want to see effects on bubble production and especially the reduction of the VGEs.

Summary on VGE arterializations

- Crossover of VGE to systemic circulation paralleled with high bubble amounts in the right heart
- Gas bubbles arterializations detected in 9/10 trimix divers with grade 4 and 11/56 air dives with grade 4
- Arterialization occurs only with grade 4-II or higher

The next question that we raised was, if exercise in the laboratory setting recruits IPAVAs and causes arterialization of exogenous bubbles given as a bolus, can this occur with VGEs post-dive? The second question was can 100% oxygen, which is used as a first-aid treatment in DCS, close these shunts? These issues were investigated in PFO negative divers. We found that in the laboratory setting, some subjects arterialized at very low level of exercise intensity (below 20% of VO_2 max), which is equivalent to swimming or carrying equipment. Still, some subjects that arterialized

in the laboratory did not shunt in the field due to much smaller bubble load. When subjects started to shunt post-dive, 100% oxygen closed all these shunts as it did in the lab.[6]

Incidence of arterialization increased around 40% with exercise compared to the resting condition. Also, the lowest VGE grades that accompanied the arterialization dropped from 4B to 3, which is a very common bubble grade. The dive profile that we used in this air dive was 18 meters (59 feet), 47 minutes bottom time - rather moderate frequent recreational dive. IPAVAs once they were opened by exercise, if you stop exercise, they are closed within 88 seconds. If you give 100% oxygen, then the opening is reduced to 46 seconds.

Exercise after diving and arterialization

- Exercise increased incidence of arterialization from 13 to 52% via recruitment of IPAVAs
- Fifty percent of arterialization cases occurred with exercise of light to moderate intensity
- Arterialization with exercise occurred at lower VGE grade than at rest. The lowest VGE associated with arterialization was 3

The next question was whether VGEs that cross over via IPAVAs post-dive can be found in the brain circulation (evaluated with transcranial Doppler, TCD) and whether the number of hits is larger in the posterior or anterior brain circulation? We were expecting with exercise that more and more hits will reach the posterior circulation based on the fact that with increased exercise intensity posterior perfusion is prioritized. Hits in the TCD signals are called microembolic signals (MES).[7]

To answer that question, 20 divers performed laboratory and field exercises post-dive. We found a very small number of MES in either anterior or posterior brain circulation, which was a surprise. The explanation for such a small number of TCD hits was cardiac output redistribution towards the active muscle bed during whole body dynamic exercise. We are planning to do a follow-up study with hypoxic stimulus to recruit IPAVAs and then we may expect more hits in the brain. Still, although the number of bubbles that is reaching the brain is small, if you reach a sensitive area or hypersensitive area of the brain, then these bubbles can be clinically relevant.

Based on our research, individual risk factors are important in determining a diver's decompression stress. These include: a) high bubble production on different dive profiles, b) PFO presence or IPAVA recruitment, and c) CO_2 retention. The last risk factor still has to be investigated, for now it only an attractive idea.

- Presence of high VGE post-dive do not necessarily result in arterialization
- Exercise induced IPAVA recruitment is load dependent
- Increased AGE load with exercise induced cross-over does not lead to substantial microembolic signals

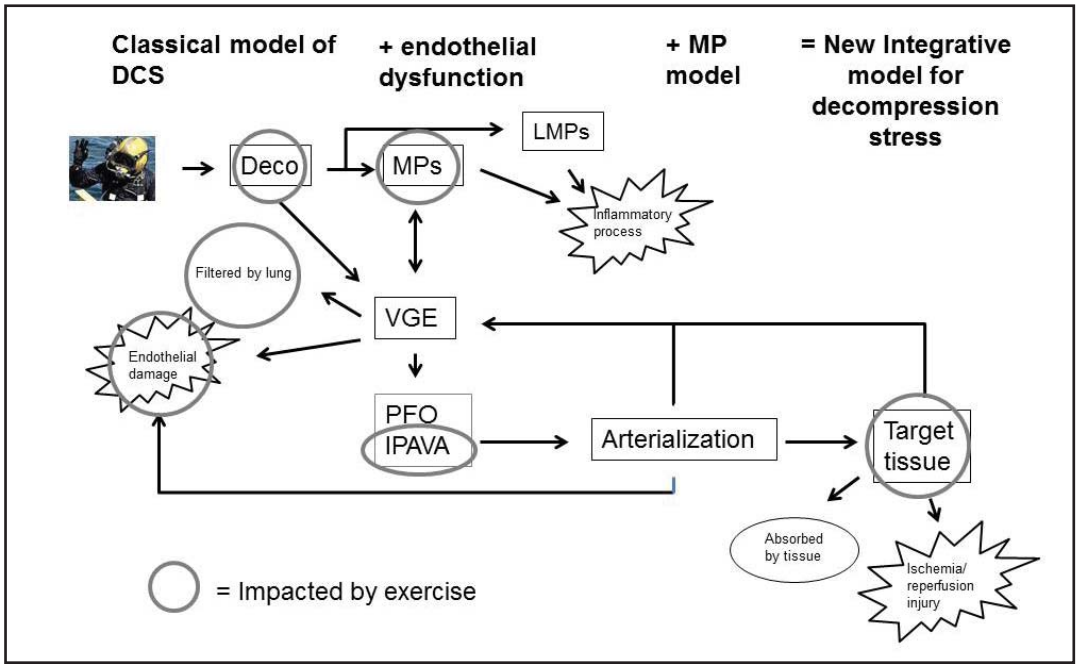

Figure 1. Pathophysiological processes involved in decompression illness

And this is just the story about the classical model of DCS related to VGEs, PFO or IPAVAs, arterialization and embolization of the target tissue (Figure 1).[8] New so called integrative model of decompression stress includes endothelial dysfunction and increased production of microparticles post-dive. The total number of microparticles as well as subtypes are increased by diving, and are very high in DCS cases. Since microparticles can potentiate the inflammatory process, they should be included in the new model for decompression stress (Figure 1). VGEs, endothelial function and microparticles can be positively affected by pre-dive exercise (circled marks); thus, it is possible in vulnerable individuals (bubble producers, easy shunters or CO_2 retainers) to ameliorate decompression stress.

DISCUSSION:

DR. ALFRED BOVE: We probably have time for one question before we move on. Anybody have any specific question they'd like to ask?

PHILLIP FOSTER: It was very interesting. Because in divers or people just sitting on ground level, they use a lot of their muscles which is not found in astronauts and pilots, they don't use that. So it's draining a lot of blood into the vertebral circulation. So it outlines that physical exercise is playing a major role in decompression. You have also added information as we have that exercise is playing a major role in the shunting. So exercise is a key.

DR. ZELJKO DUJIC: There are many more results of course. This was really a reduced presentation just for this topic. But exercise can really modify VGEs, microparticles response and so on. So it can cause really good preconditioning effects. I thank you for the comment.

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Vascular Gas Emboli And Probabilistic Decompression Models

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Decompression Safety and the AGE Hypothesis

Decompression sickness (DCS) associated with modern decompression procedures is a rare injury that is generally mild with manifestations including joint pain and peripheral paresthesia that are usually easy to treat and, if untreated, often resolve spontaneously.[22] Serious decompression injury presents with paralysis, motor weakness, and cerebral dysfunction that are more difficult to treat, more likely to result in lasting injury, and a greater threat to diving safety.

The correlation of serious DCS with right-to-left cardiac shunt (RLS) discussed at this workshop suggests methods that might allow safer decompression by reducing the occurrence of arterial gas emboli (AGE) and, thereby, decreasing the risk of serious injury. We refer to this body of evidence under the name, “AGE hypothesis,” which includes the arterialization of venous gas emboli (VGE) through either the heart or lungs leading to the potential for CNS bubble growth and serious injury.

AGE, Autochthonous Bubbles, and Serious DCS

A series of reports from 1988 to 1992 investigated the involvement of AGE and space occupying lesions (SOL) in the pathogenesis of cerebral and spinal DCS in animal models. Dives to 300 fsw for 15 min produced SOL in canine spinal cords. Cord function was monitored by somatosensory evoked potentials (SEP), and cords were fixed for examination after post-dive loss of SEP. SEP loss in dived animals was considered pathonomic of DCS. SOL were found within myelin sheaves of axons and compressed surrounding tissue but without capillary involvement indicating they were extravascular.[9] SOL were replaced by hemorrhage over 2-8 hours, which evolved into necrotic foci (Francis, personal communication).[11] The authors concluded that SOL were in situ, extravascular autochthonous bubbles and were responsible for loss of SEP in spinal DCS.

These animals fell into two groups: one with SOL and rapid SEP loss, and the other with no SOL and delayed SEP loss.[7] Testing was also performed on undived dogs with clamped aortas and undived dogs given continuous intra-arterial infusion of bubbles. These were observed to produce no SOL and delayed SEP loss suggesting to the authors that short delay to SEP loss was associated with autochthonous bubbles and long delay with AGE. Further studies supported the conclusion that spinal DCS was correlated with both autochthonous and intravascular gas bubbles.[27]

Similar investigations of cerebral DCS in a canine model found lesions in the cerebral white matter including congestion, pericapillary hemorrhage, edema, and acute ischemia indicating that AGE were the origin of bubble growth in cases of acute cerebral DCS.[1] A subsequent study by Pearson et al. used a cranial window to record events in the pial circulation and their correlation with cerebral and spinal SEP.[28] The initial event in the loss of cerebral SEP was AGE followed by complete occlusion of pial arterial and venous circulation. Cerebral SEP was affected before spinal SEP indicating greater vulnerability of the brain.

To investigate depth thresholds for SOL formation independent of AGE, animals were sacrificed at pressure to preclude AGE from entering the systemic circulation. Hardman et al. (1992) dived shoats (pigs) for 24 hours and found depth thresholds for bubble formation in the brain and spinal cord of 10-15 msw.[12] Francis et al. dived dogs for four hours and counted spinal SOLs >100 µm.[6] These are shown in Figure 1 and indicate a threshold for 100 µm spinal SOL of 26-30 msw, 15 msw deeper than for Hardman's shoats, but dives longer than four hours might have shifted the threshold curve of Figure 1 to the left.

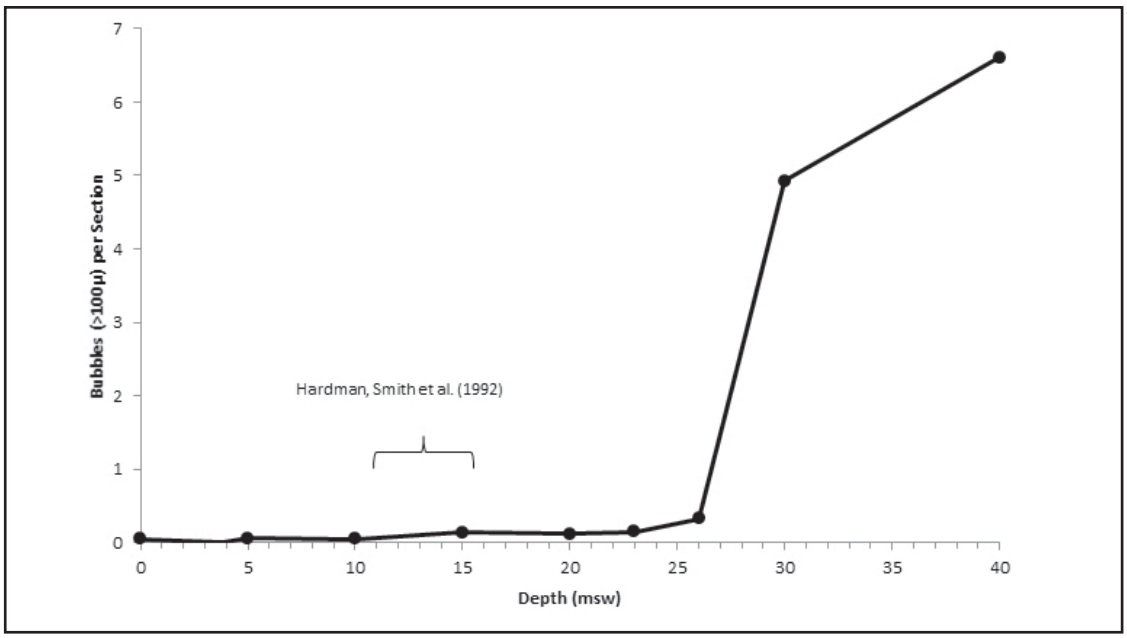

Figure 1. The number of bubbles >100 µm forming in canine spinal cord after 4 hour dives at various depths.[6] The depth range for SOL formation in shoats after 24 hour dives is also indicated[12]

VGE and DCS in Humans

The relationships of VGE and DCS in humans for 24-48 hour air saturation dives[4,33] and for altitude exposures[37-39] are shown in Figures 2a and 2b. In Figure 2a, the x-axis is dive depth in msw, and the y-axis is the percentage of VGE or DCS. There were 111 divers in the VGE group 4, and 550 dives in the DCS group which included 22 cases of DCS, all mild except for one CNS manifestation.[33] In Figure 2b, the x-axis is feet of altitude, and the VGE and DCS data were from a population of 193 research subjects[36-39] in which DCS manifestations other than joint pain were rare.[39] The percentages of VGE and DCS increased with altitude and depth for both saturation dives and altitude exposures (equivalent to sea level "saturation dives"). VGE occurred at shallower depths, lower altitudes, and were more prevalent than DCS.

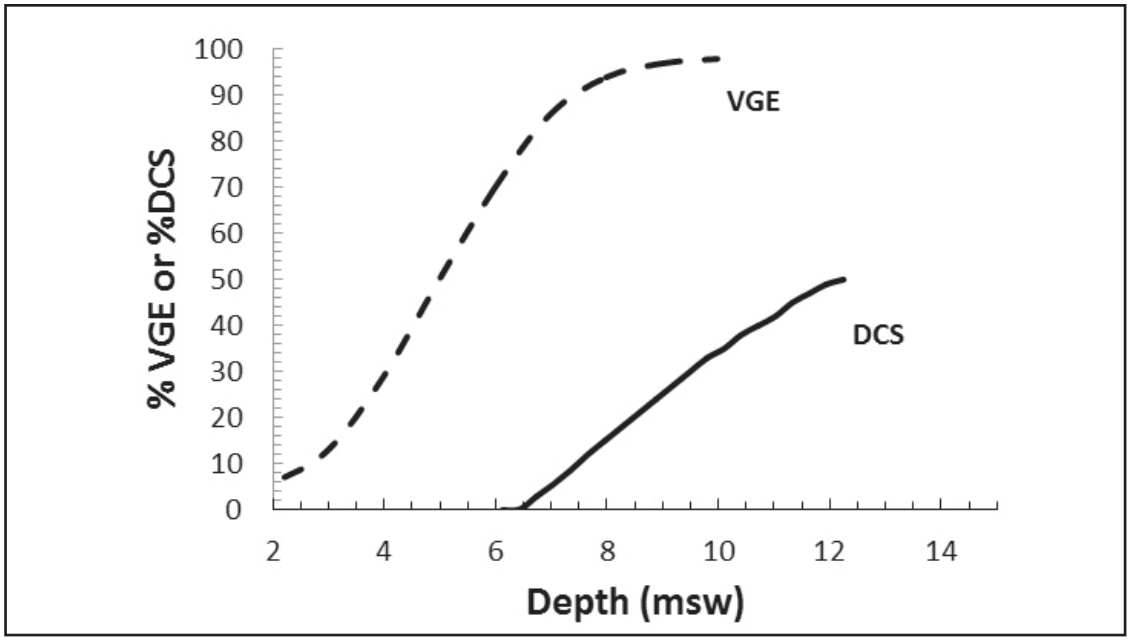

Figure 2a. Saturation dives[4, 33]

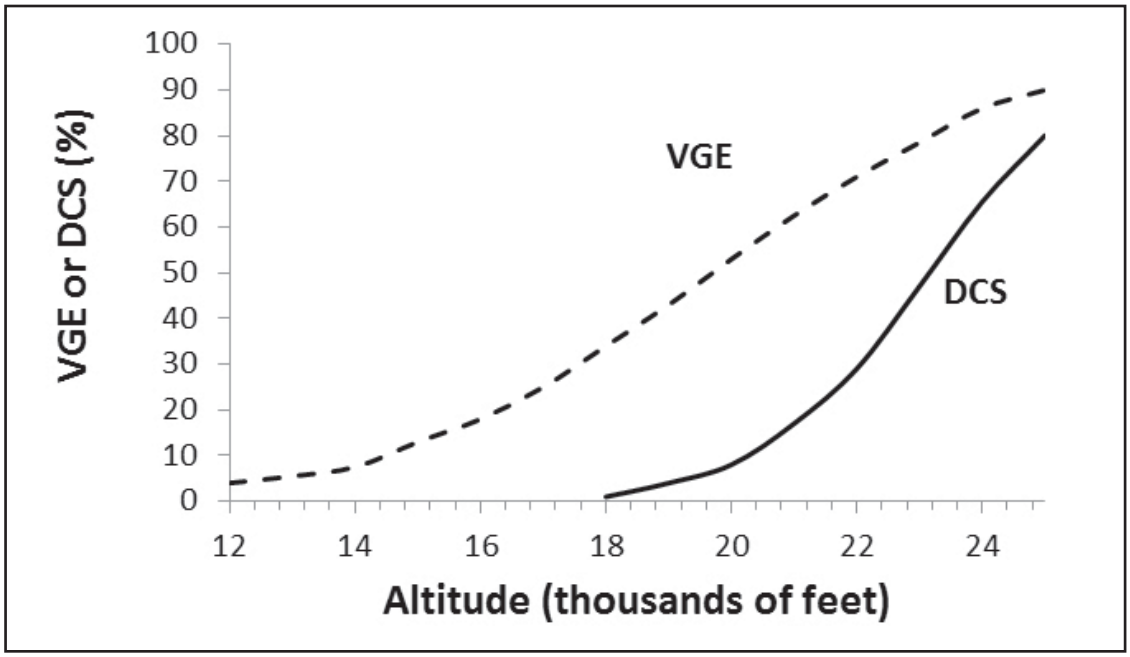

Figure 2b. Altitude exposure subjects[37-39]

Figure 2. The relationships of VGE and DCS in humans for (a) air saturation dives and (b) altitude exposure

Conditions for AGE

Figures 2a and 2b demonstrate that VGE were present much earlier (i.e., at lower diving or altitude exposure pressures) than DCS for both hyperbaric and hypobaric decompression in humans. Autochthonous bubble formation in animals (Figure 1) requires more decompression than observed for mostly mild DCS in humans (Figure 2a) although this comparison is made for different species. These observations suggest that AGE can appear independently of autochthonous bubbles if supersaturation pressures are high enough for VGE but lower than autochthonous bubble formation thresholds. (Note that this does not preclude autochthonous bubble formation if supersaturations are sufficiently high.) Once AGE are present, the entire systemic circulation could be seeded leading to interesting pathological consequences.

Several case studies are informative. Laboratory tests of extravehicular activity (EVA) spaceflight protocols at Duke investigated the effect of exercise during oxygen prebreathe on prebreathe time.[2,9] The hypothesis was that exercise would accelerate nitrogen elimination and reduce the prebreathe time needed for low DCS incidence during subsequent decompression to 30,000 feet. There was no DCS in 45 trials with 4 hours of pre-breathe exercise, but when the exercise level was increased and prebreathe reduced to two hours, one of the three subjects tested developed grade 4 VGE and collapsed after two hours at 30,000 feet. He was subsequently found to have a resting PFO. Despite a total of four hours of oxygen breathing, late occurring AGE may have initiated intravascular bubble growth from residual cerebral nitrogen consistent with the AGE hypothesis.

Operational occurrence suggesting involvement of the AGE hypothesis might explain the serious DCS in U-2 pilots who fly in excess of 70,000 feet while wearing suits pressurized to 29,000 feet.[13-16] The pilots breathed oxygen before and during flight, but despite long oxygen periods that might eliminate most nitrogen from well-perfused brain, there were four of five life-threatening cases at one operating location and two cases of pulmonary DCS. The U-2 exposures and their DCS severity were beyond the VGE and DCS of Figure 2b in which DCS was generally mild, VGE were common, and oxygen was not breathed. Should VGE have escaped the pulmonary filter in the heart or lungs, however, AGE distributed to the brain might have expanded by inward diffusion of residual dissolved nitrogen. No cardiac defects were found in seven pilots who were tested for RLS by bubble contrast[13] suggesting a pulmonary origin for AGE, particularly since pulmonary DCS was present in two cases.

AGE and Autochthonous Bubbles in the Skin and Inner Ear

In skin, both AGE and autochthonous bubbles appear associated with cutaneous DCS. Lambertsen observed autochthonous bubbles in pigs and humans resulting from counterdiffusion.[17,18] Independent of decompression, autochthonous bubbles appear to form when ultrasound is applied to the skin (sonophoresis).[19, 20, 24, 25,29] VGE from non-cutaneous tissues that are arterialized in the heart or lungs may seed otherwise bubble-free skin causing cutis marmorata.[40] VGE entering the central circulation from other tissues would augment VGE reaching the heart.

AGE and autochthonous bubbles are also proposed to initiate cochlear DCS.[3,21,23] Divers having inner ear DCS and RLS implicate AGE involvement, but gas exchange in the inner ear is slower than in the brain resulting in higher supersaturations, so autochthonous bubble formation is also possible. Mixed gas diving with helium to nitrogen gas switches augments inner ear supersaturation as a result of counterdiffusion given the unique anatomy of the inner ear. The vestibular system appears to be at lower risk than the cochlea because it is better perfused and, therefore, washes out inert gas faster.

VGE Load and VGE Threshold for AGE

Previous sections described the empirical rationale and evidence for the arterialization of VGE and the formation of autochthonous bubbles. This section describes a theoretical rationale for the VGE load and the VGE threshold at which AGE might occur. Adopting Flook's definition, the VGE load is the gas fraction in the central circulation or the volume percent of bubbles in mL of gas per 100 mL of blood.[5] By extension of this definition, AGE might occur if the VGE load exceeded a threshold value after which AGE might seed systemic tissues via the arterial circulation. Bubble growth and resolution would occur according to the chosen mathematics, but mathematical models are not a topic for discussion here.

If the RLS status of each diver in a population were known from bubble contrast testing, separate thresholds could be estimated for divers having and not having RLS. Absent this knowledge, the same VGE threshold must be adopted for the heart and lungs of every diver which renders models of the AGE hypothesis less sensitive. Nonetheless, exposures that result in high VGE loads and serious DCS could be identified and, if desired, high VGE loads could be purposely avoided in future decompressions to implicitly reduce the chances of AGE in the entire population whatever might be the AGE source.

Unpredictability and Model Parameters

The unpredictably of DCS and VGE and their tenuous statistical relationship are well-known sources of uncertainty. If information were available relating specific divers and dive profiles to VGE and DCS outcomes, these might allow us to convert uncertainty to risk through the semi-quantitative relationship,

$$\text{RISK} \approx \text{PROBABILITY} * \text{SEVERITY}.$$

Probability can be estimated quantitatively but severity must be assigned subjective values such as "mild" and "serious" we have done here.

We can think of DCS (or VGE) probability by analogy with the pressure of a gas confined in a rigid container. The molecules are distributed over a wide range of velocities, and the pressure on the walls of the container represents the average of their impacts on the walls. By analogy, the DCS probability of divers represents the "average" of a population whose individual probabilities are distributed over a wide range of unknown DCS probabilities. Individual molecules, or by analogy, individual divers are not necessarily characteristic of the entire population and cannot be expected to represent the entire population, but the average probability is a useful macroscopic representation of the whole. An important difference is that gases usually involve millions of molecules whereas diving populations generally involve only hundreds and rarely thousands of divers. One cannot predict the behavior of a population from a single diver, but the contributions of all divers in the population may give rise to a meaningful average if the model is reasonably accurate.

The parameter values of probabilistic decompression models that underlie the methods described here are not determined a priori but found empirically by fitting models to dive trial data. In this fashion, two models may be compared statistically to determine if one describes the data better than another. Interested readers are directed to Weathersby[35] and the survival analysis workshop.[10]

Dive Trial and Inert Gas Data

Most dive trial or altitude exposure data includes only DCS outcomes, not VGE Doppler bubble scores. DCS data are usable for model calibration, but assigned Doppler VGE scores offer interesting advantages. For example, computed VGE loads could be grouped according to bubble scores assigned during Doppler monitoring and would serve as decision aids concerning VGE loads to avoid if the risk of arterialized VGE is to be limited.

This approach uses the AGE hypothesis indirectly but is simple and intuitive while still providing a tool for managing decompression risk. Direct use of the AGE hypothesis involves comparing the VGE load with the VGE threshold for AGE as described above and computing the ensuing bubble volumes in cerebral/spinal tissues and the corresponding probabilities of serious and mild DCS. This would provide optimal fidelity to the pathological mechanism embodied by the AGE hypothesis.

A further application of the AGE hypothesis applies to assessment of differences between inert gases as illustrated in the work of CAPT Ed Thalmann, MC, USN with the Mark 16 closed circuit rebreather.[31, 32] One dive series used nitrogen-oxygen and the other used helium-oxygen. The inspired oxygen partial pressure was controlled to a 0.7 atm set-point during the dives, but the inert gases were not switched during the dives. The use of a single inert gas is typical for Navy rebreather diving but not so for much non-Navy diving where gas switches from helium-oxygen to nitrogen-oxygen or oxygen are common. Maintaining the same inert gas, however, illustrated possible differences between nitrogen and helium regarding serious DCS.

Table 1 indicates the overall DCS incidence was 5.4% for nitrogen and 3.6% for helium, but when cases were separated into mild and serious, mild DCS was higher for nitrogen (5.4%) than for helium (2.3%) whereas the opposite was true for serious DCS (0.8% vs 1.4%). The divers were monitored with Doppler ultrasound, but the Doppler data were not analyzed until 2003.[28] Nitrogen dives had 24.6% grades 3 and 4 VGE while helium dives had 42.8% grades 3 or 4 VGE. Given that serious DCS was more common with helium, this suggested that helium bubbles might be smaller or more numerous than nitrogen bubbles leading to a greater likelihood of AGE. These concepts could be investigated using the VGE load and VGE threshold for AGE appearance.

Table 1. Nitrogen-oxygen and helium-oxygen dive trials[30-32]

	47 DCS in 873 N_2/O_2 dives	55 DCS in 1,508 He/O_2 dives
% DCS	5.4	3.6
% mild DCS	4.6	2.3
% serious DCS	0.8	1.4
% III&IV VGE	24.6	42.8

The US Navy has conducted only limited dive trials in which divers were monitored by Doppler for VGE scores. Exposure data that contain both VGE and DCS data are available, however, in Defense Research and Development Canada records[26], NASA and Air Force trials[39], and Duke Hyperbaric Center records.[34]

Conclusion

In concept, the AGE hypothesis appears to be amenable to probabilistic modeling and may provide tools for analyzing decompression data and for controlling the risk of serious injury. The next step is to test these suppositions by programming the theory and comparing its predictions to dive trial data.

Acknowledgements

The authors thank the following for helpful reviews and suggestions during the preparation of the manuscript: Frank Butler, Stephen McGuire, Ronald Nishi, Neal Pollock, David Southerland, Hugh Van Liew, and James Webb. James Francis and Edward Flynn were particularly helpful in pointing out and interpreting important references.

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Efficacy of Trans-catheter Closure of PFO for DCS

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Introduction

In the Czech Republic, we have screened about 600 divers for PFO since 2004. The results of the study are being prepared for publication. Briefly, most divers practiced safe diving within non-decompression limits or decompression dives without violation of decompression regimen. Nevertheless, there occurred infrequently unprovoked decompression sickness in some divers. Divers with a history of decompression sickness (DCS) had very high incidence of PFO, predominantly large shunts - PFO grade 3 according to the International Consensus Criteria[1]. Incidence of DCS in the group of PFO 3-positive divers correlated with the number of dives. The more these PFO divers dived, the higher was the probability of unprovoked DCS.

Case report

Male diver, 44-year-old diving instructor, has been diving for 20 years with over 2,500 dives without incidence of DCS. Suddenly, in 2003, after a series of non-decompression recreational dives, he had DCS manifested by thorax and upper extremity skin rash, pain, itching, bruising and altered sensitivity.

Four weeks later he tried to dive again, but after two consecutive non-decompression dives, he again had a rash and extreme fatigue. Within the next four months, every repetitive diving attempt provoked DCS.

Contrast Transthoracic Echocardiography (TTE) revealed intracardiac shunt, and Transcranial Doppler (TCD) and Transesophageal Echocardiography (TEE) confirmed PFO grade 3. The patient was indicated for PFO closure. In the beginning of 2004, PFO closure using Amplatzer occluder was performed without any complications (Figure 1). One month after closure, TCD confirmed no shunt. Six weeks after the closure, he performed a series of dives (30 dives within 9 days, even deep dives) with no signs of DCS. During the 11-year follow-up, he performed more than 2,000 additional dives without recurrence of DCS.

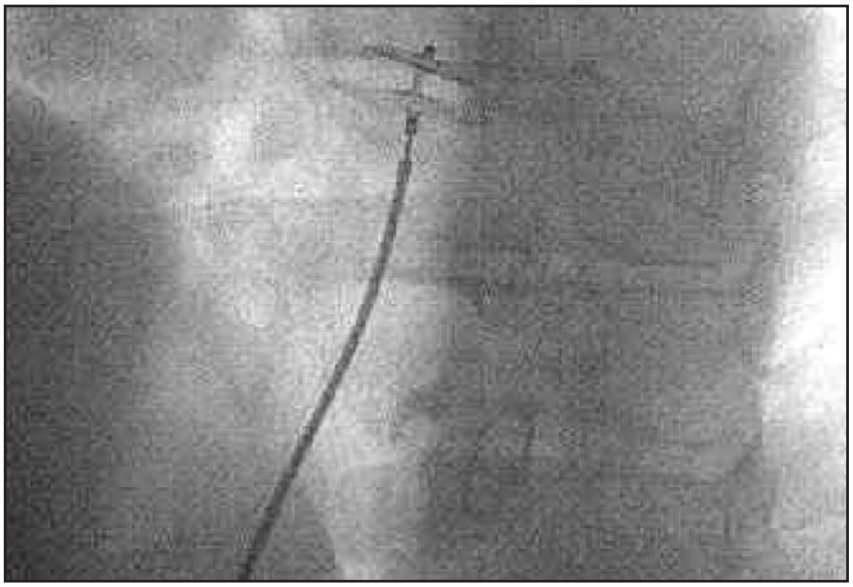

Figure 1. Amplatzer occluder placed in position

That was my own experience. In summary, I dived extensively for 20 years without any DCS. Then suddenly appeared an unprovoked DCS. Without closing, further diving would have been impossible. After the closure, I continued diving and all DCS problems disappeared immediately. Until the closure, I mostly did recreational diving. Thereafter, I practice more technical diving including deep diving, decompression diving, long cave dives, all without any recurrence of DCS.

Efficacy of trans-catheter closure of PFO in divers

We performed a study on PFO divers using simulated dives in a decompression chamber. The aim of the study was to measure the efficacy of catheter-based PFO closure against arterialization of bubbles occurring during and after the dive. We hypothesized that catheter-based closure might prevent arterialization of bubbles and reduce the risk of DCS.

The study[2] enrolled 47 divers with PFO grade 3 according to the ICC grading. Among them, 20 divers (a closure group) were already closed and 27 divers had PFO grade 3 without closure (PFO group). Two types of occluders were implanted and no major complication occurred after the surgery.

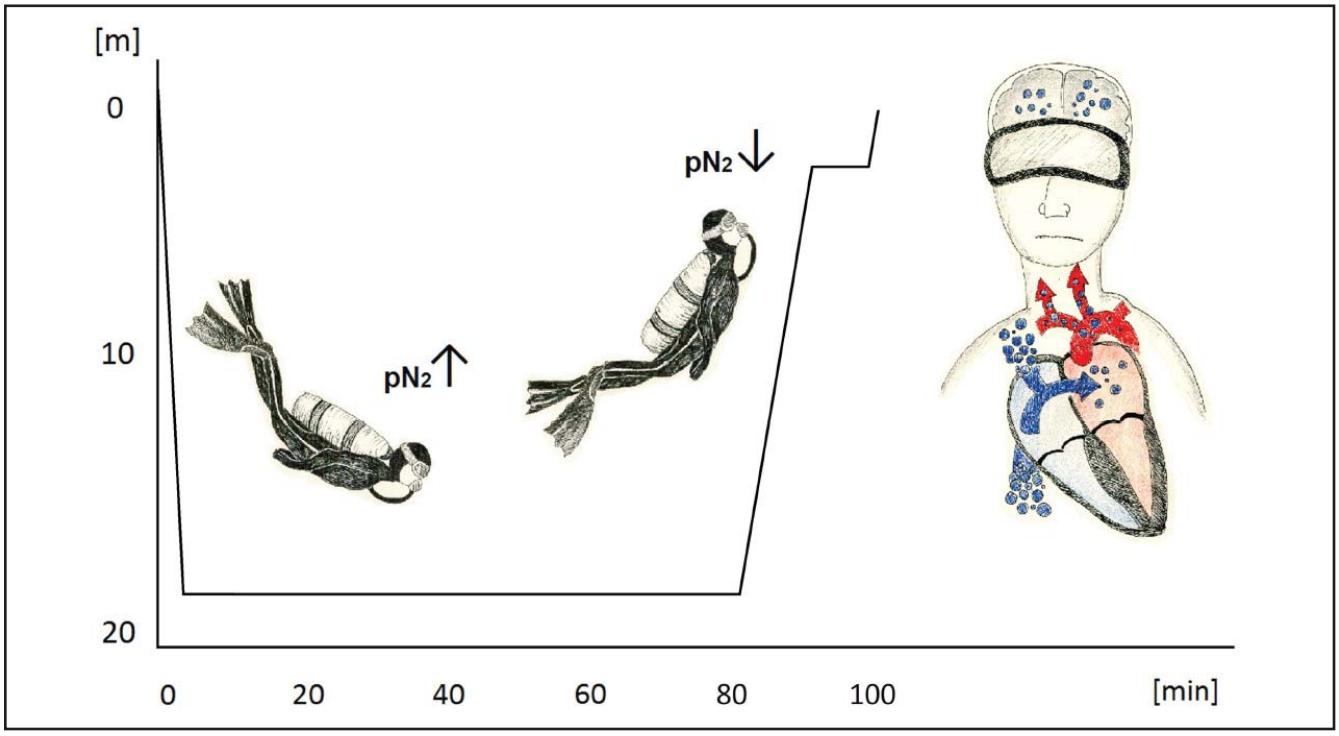

Figure 2. Pathophysiology of bubble formation and embolization in decompression sickness, conditions of Dive A (18 meters / 80 min)[3]

We simulated two types of dives in the hyperbaric chamber, the decompression procedures were performed according to US NAVY 1996 decompression tables. The first dive (Dive A), was a dry dive (Figure 2). A long, shallow dive to 18 meters for 80 minutes was done by 34 divers. The second dive (Dive B) was a very provocative decompression wet dive, performed in a wet decompression chamber to 50 meters for 20 minutes (13 divers). We screened the divers for venous and arterial bubbles after the dives.

Venous bubbles were detected by TTE within 60 minutes after surfacing. Usually we observed a shower of venous bubbles (Figure 3).

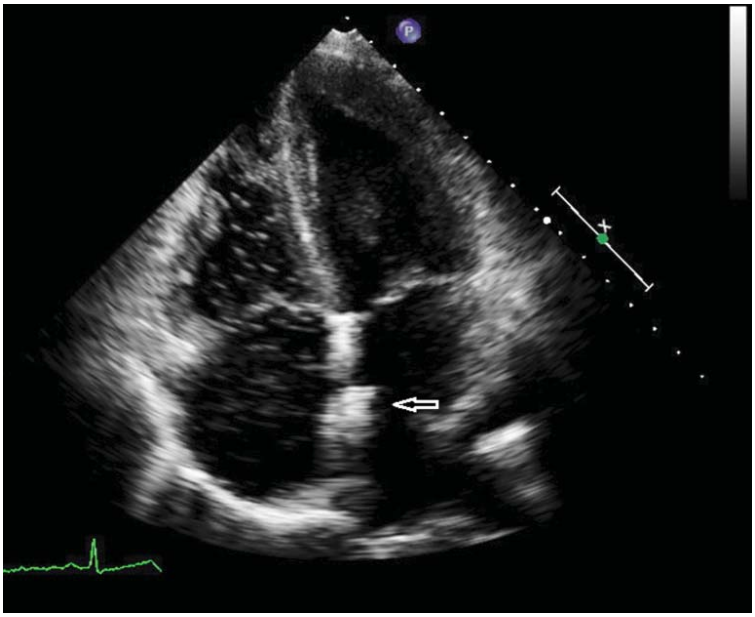

Figure 3. Echocardiographic appearance of post-dive venous nitrogen bubbles by transthoracic echocardiography - arrow shows the occluder in the diver from "closure group" (representative picture)

Arterialization of bubbles was screened by Transcranial Color-coded Sonography (TCCS), both natively and after Valsalva maneuver within 60 min after the dive as well (Figure 4). If we found hits, there were usually tens of high-intensity transient signals (hits) except of two divers after the deep dive with a shower.

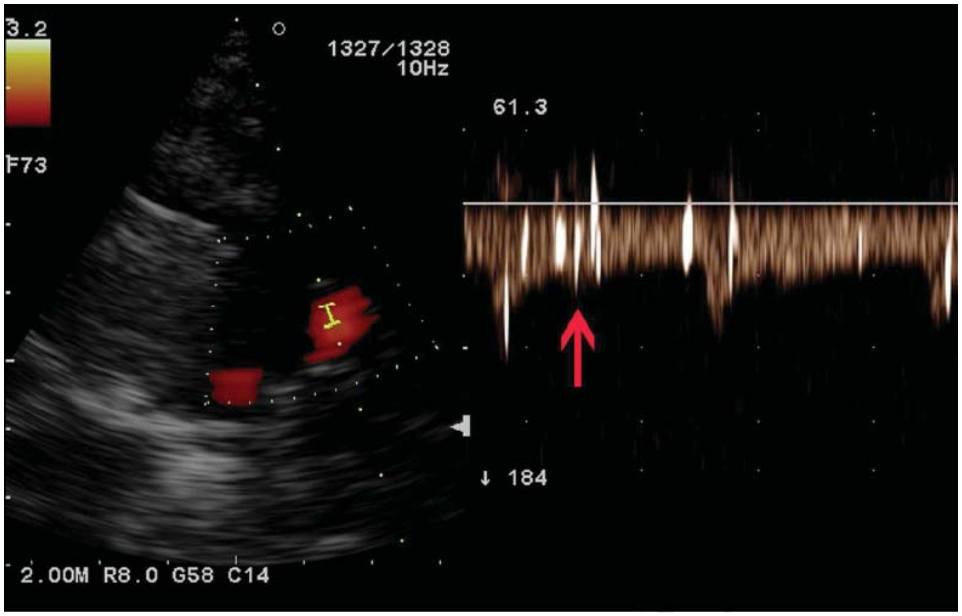

Figure 4. Arterial gas emboli visualized by transcranial color-coded sonography: post-dive arterial gas emboli apparent as high-intensity transient signals (hits - arrow) in the Doppler spectrum in the middle cerebral artery in a diver with a patent foramen ovale[3]

Results from the long, shallow Dive A are shown in Figure 5. The dive provoked venous bubbles in 74% and 80% of divers, and 43% vs. 0% these divers with venous gas embolism (VGE) arterialized these bubbles into the left atrium in PFO and closure groups, respectively.

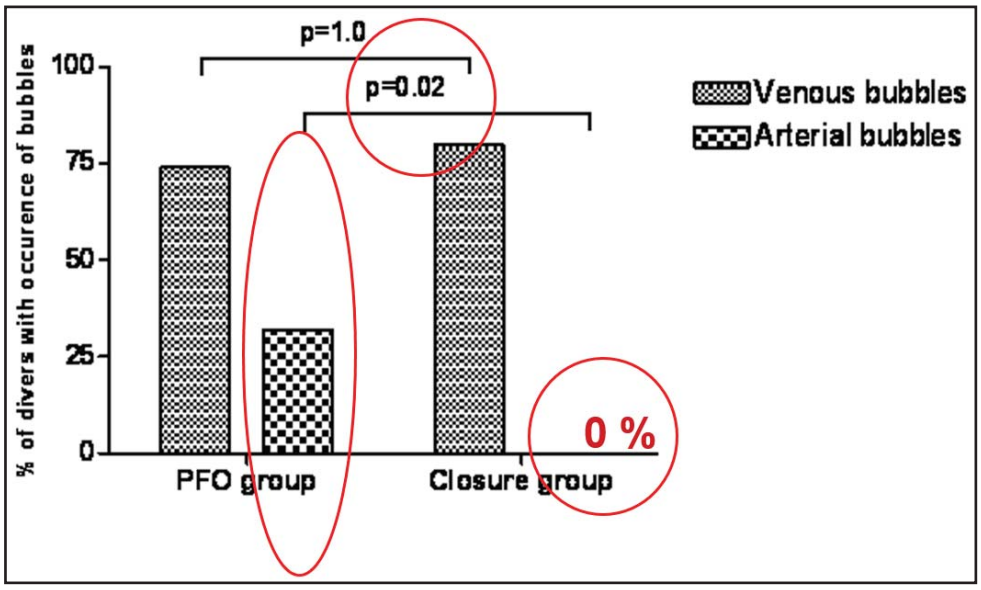

Figure 5. The proportion of divers with the occurrence of venous and arterial bubbles after Dive A in divers with patent foramen ovale (PFO group) and divers treated with a catheter-based patent foramen ovale closure (closure group)[2]

Figure 6 demonstrates bubble appearance after a deep wet Dive B. PFO divers (88%) developed venous bubbles and all of them arterialized these bubbles. In the closure group, 100% of divers had venous bubbles but none had arterial bubbles.

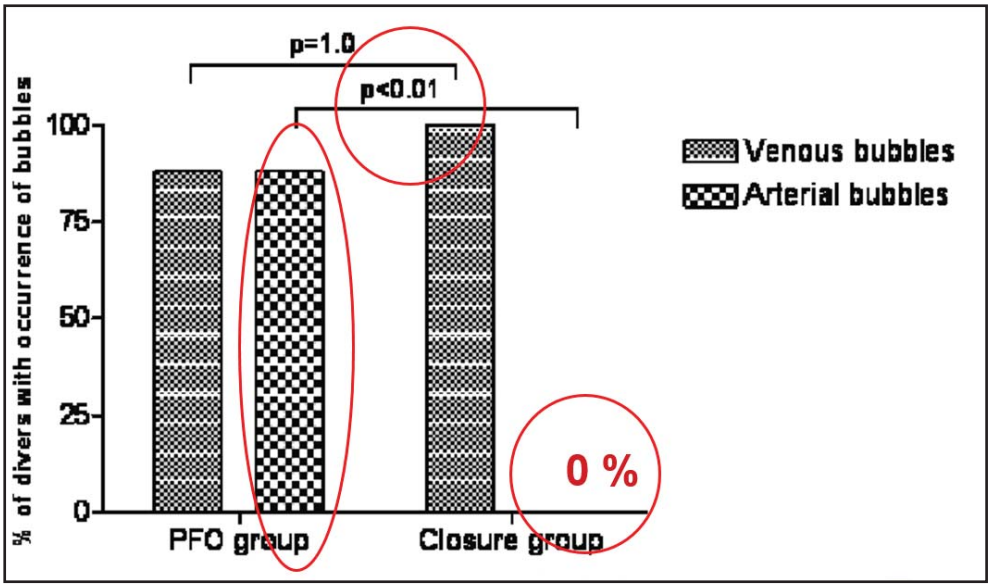

Figure 6. The proportion of divers with the occurrence of venous and arterial bubbles after Dive B in divers with patent foramen ovale (PFO group) and divers treated with a catheter-based patent foramen ovale closure (closure group)[2]

Mild neurological symptoms of DCS (headache, unusual fatigue, transitory visual disturbances, dizziness) were present in 28% of divers in the PFO groups after surfacing from both Dives A and B. No divers in the closure group reported DCS.

PFO has been found to be associated with high incidence of neurological and cutaneous forms of DCS.[4] The PFO prevalence is high, and venous bubbles occur after most dives. Divers with PFO might experience unprovoked DCS due to paradoxical embolization. We have demonstrated that in conditions of two simulated dive types, catheter-based PFO closure was associated with the elimination of arterial bubbles. These results suggest that PFO occlusion might lead to a reduction of unprovoked DCS incidence in divers.

Effect of conservative dive profiles on arterialization of bubbles

The question is, does conservative diving, avoiding decompression regimens diminish arterialization of post-dive venous bubbles? If yes, PFO grade 3 divers could dive in a conservative manner to significantly reduce the risk of unprovoked DCS.

We identified 19 divers with PFO 3 (PFO deco group) for a decompression dive to 18 meters for 80 minutes, the same as was the shallow dive in our previous study. Fifteen divers after PFO closure (closure group) performed the same decompression dive. Thirteen divers with open PFO performed a non-decompression dive for 51 minutes to 18 meters (PFO non-deco group).

Venous bubbles were detected in 74% and 80% of divers in the PFO-deco and closure groups, respectively. After a conservative dive (PFO non-deco group), only 31% of divers developed venous bubbles. In the PFO deco and PFO none-deco groups, we observed 43% and 47% of divers with venous bubbles that arterialized these bubbles. No arterial bubbles were found in the closure group that performed the same decompression dive as the PFO deco group (Figure 7).

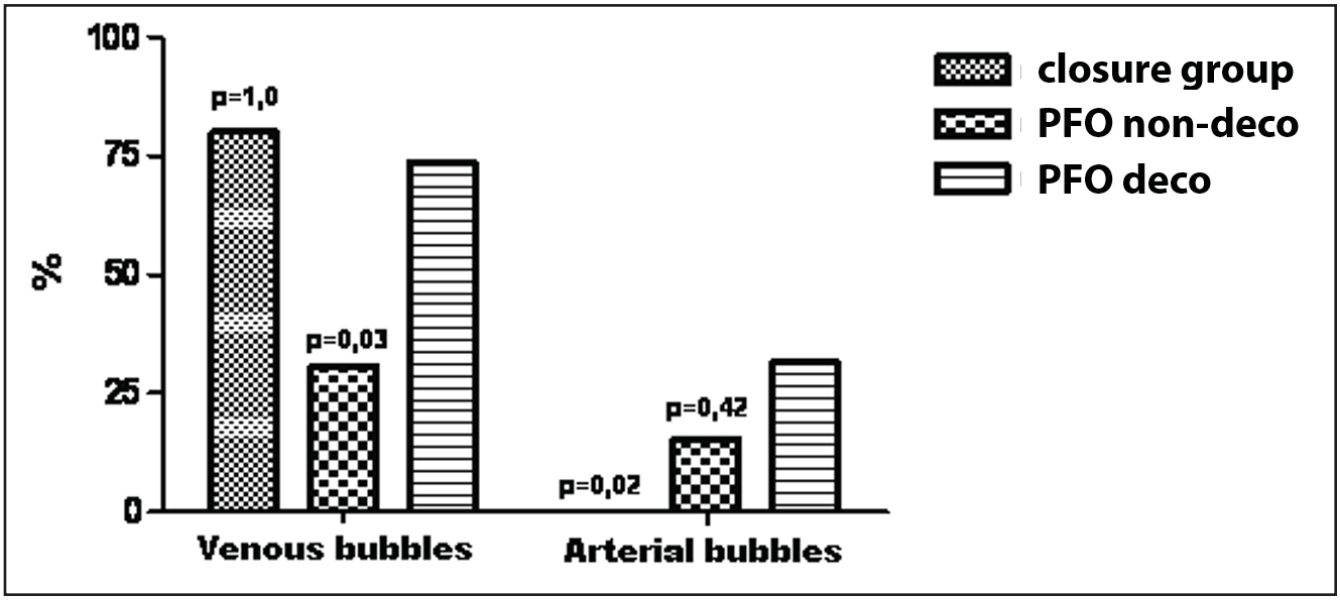

Figure 7. Arterialization of post-dive venous bubbles in PFO divers after decompression and nondecompression diving profiles

Our data revealed that conservative non-decompression diving regimens did not eliminate arterialization of bubbles through the PFO. A similar high proportion of divers with venous bubbles arterialized these bubbles to the left atrium after both decompression and non-decompression dives. There was no difference in the occurrence of VGE between the PFO and closure groups but the PFO closure again completely eliminated arterialization of venous bubbles. A conservative, non-decompression diving diminished a portion of divers with venous bubbles but did not prevent their arterialization in divers with PFO.

Acknowledgement

This **r**esearch was supported by MHCZ–DRO, University Hospital Motol, Prague, Czech Republic 00064203; SVV 2014-260 033 from the Charles University in Prague; and PRVOUK-P24/LF1/3 of the Charles University in Prague, First Faculty of Medicine.

DISCUSSION

RICHARD MOON: We probably have time for one or two questions. I have one question. The earlier data you showed with 80% of your divers with PFO having DCS versus the data we've seen earlier, which is in the order of 10 incidences per 10,000 dives, there's obviously some selection going on in your population.

LUDEK SEFC: Our study that I mentioned in the introduction was not a randomized study. Part of the divers already experienced DCS and this was the reason why they applied to be enrolled. It is seen on the incidence of divers with PFOs in the study (41%) which is higher than data published for randomized population (27%).

Nevertheless, we suppose that a PFO diver can dive a long time without any problems. In contrast to nondivers, an increase of the PFO size has been reported in divers over the time. If a defect develops, PFO grade 3, the unprovoked DCS can appear. The more dives that a PFO 3 diver realizes, the higher risk occurs. We really expect that PFO 3 is a very high risk for those divers who dive a lot, extensively, for professional divers, instructors, military divers, and also for technical divers. We have found also many unprovoked DCS in recreational divers with PFO 3.

DAVID SMART: What did you do with your cases of DCS? How did you treat them?

LUDEK SEFC: When the patients experienced decompression sickness after the chamber dive, they are immediately transferred back to the compression chamber and treated according to decompression tables.

DR. PETAR DENOBLE: Did you do anything to control for pulmonary shunts in the divers that you closed or divers who participated in your study?

LUDEK SEFC: Yes. Every diver was screened by TCD. It can clearly distinguish between cardiac, intracardiac and pulmonary shunt according to the time of appearing arterial bubbles after contrast injection. After PFO closure, we performed TCD one month, six months, and one year after the closure. Few divers had some bubbles one month after the closure, but all were without bubbles in the later periods. Of course, we did not look for exercise-induced intrapulmonary arteriovenous shunts, just for native lung shunts which we could see without stimulation by exercise.

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Patent Foramen Ovale and Cryptogenic Stroke

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Abstract

The diagnostic evaluation of patients who have had an otherwise cryptogenic stroke in the setting of a patent foramen ovale is complicated and the optimal treatment is uncertain. The risk of recurrent stroke in this setting is generally low. There is no evidence that warfarin is superior to aspirin for reducing the risk of recurrence, and there has been no statistically significant benefit of PFO closure in clinical trials, with no FDA-approved device for this purpose.

The current state of knowledge about the role of patent foramen ovale (PFO) and the pathogenesis of cryptogenic stroke and its treatment may best be described as a morass. The problem is in part related to the definition of cryptogenic stroke and in part due to uncertainty regarding the pathophysiologic role of PFOs.

Using the Trial of ORG10172 criteria, ischemic stroke can be considered in terms of six broad pathophysiogical categories: 1, large vessel atherosclerosis; 2, cardiogenic embolism; 3, lacunar; 4, other determined etiology; 5, undetermined etiology; and 6, multiple possible etiologies.[1] For each type, a diagnosis may be probable or possible. Stroke of undetermined etiology (i.e., cryptogenic stroke) can occur in the setting of having either an incomplete or a complete evaluation. One population-based study found that, based on race-ethnicity, 40-50% of ischemic strokes are cryptogenic.[2] The components of a "complete evaluation," however, are not completely defined, and subject to change. For example, studies now show that many patients, including those with PFO and otherwise stroke of unknown cause, may have atrial fibrillation (i.e., a high-risk cardioembolic source) with prolonged ambulatory monitoring.[3,4] These patients with previously occult atrial fibrillation would no longer be considered "cryptogenic." Prolonged cardiac monitoring has become part of the standard post-stroke evaluation of patients in whom the cause of stroke is not apparent.

Stroke in a patient with a potential medium-risk source of embolism (including PFO) and no other possible cause is classified as having a possible cardioembolic stroke.[5] Using this criteria, patients with stroke and no identified cause who have a PFO might not be considered "cryptogenic," although the term "cryptogenic stroke in the setting of PFO" is often used. What remains unclear is the frequency that the PFO is actually involved in the mechanism of the stroke or is an incidental finding. One way of approaching this problem is to determine a patient's PFO-attributable recurrence risk (i.e., the proportion of recurrent stroke avoided if the PFO is eliminated).[6] The attributable recurrence risk depends on the probability that index stroke is related to the PFO and the risk of

recurrence. One study found that the chances that a PFO is the cause of an otherwise cryptogenic stroke is 40-percent lower in smokers, 35-percent lower in those with diabetes, 32-percent lower in those with a deep infarction, 32% lower in hypertensives, 28% lower with each 10-year increase in age, and 22% lower in those with prior stroke or TIA.[6] A score (RoPE) was developed based on the presence or absence of these factors. It was found that the more likely the stroke was related to the PFO, the less likely the patient would have a recurrent event.

The optimal management of patients with truly cryptogenic stroke in the setting of PFO is also uncertain. Presuming that the stroke is related to thrombus formation, treatment with either an platelet antiaggregant such as aspirin or an anticoagulant (i.e., warfarin) is generally considered. A meta-analysis found that the choice of antithrombotic therapy did not affect the risk of recurrence.[7]

Three clinical trials (CLOSURE I, PC Trial, RESPECT) have been conducted evaluating the use of transcatheter PFO closure as means of preventing recurrent stroke in patients with a PFO (Table 1).[8-10] In CLOSURE I, there was no reduction in the primary endpoint (Table 1) among those who underwent PFO closure (Hazard ratio, HR=0.78, 95% CI 0.45-1.35, p=0.37).[8] There was no heterogeneity based on the presence or absence of an atrial septal aneurysm, the size of the shunt (trace, moderate or large) or the type of entry event (stroke vs. TIA). Major vascular complications (3.2% vs. 0%, p<0.001) and new onset atrial fibrillation (5.7% vs. 0.7%, p<0.001) were more common in the subjects who had PFO closure.

Table 1. Clinical trials of transcatheter PFO closure for prevention of recurrent stroke

	CLOSURE I	PC Trial	RESPECT
Medical Treatment	Warfarin or Aspirin or Warfarin+ASA	Warfarin or Aspirin or Thienopyridine	Warfarin or Aspirin or Clopidogrel or ASA+Dipyridamole
Total N	909	414	980
Closure:Med	1:1	1:1	1:1
Primary Endpoint	TIA/Stroke/30-d all cause mortality/2-yr neurologic mortality	TIA/non-fatal stroke/death/periph. embolism	Non-fatal stroke/fatal stroke/ 30-d all cause mortality
Follow-up	2-years	Mean 4.1-years	Mean 2.6-years

Modified from Pineda et al.[11]

The PC trial and RESPECT used a different PFO closure device than CLOSURE I. The PC trial failed to show benefit of PFO closure (HR for primary endpoint=0.63, 95% CI 0.24-1.62, p=0.34) Meier, 2013, 7406. There was no heterogeneity based on the presence or absence of an atrial septal aneurysm, age younger vs, older than 45-years, or the type of entry event (stroke vs. TIA). The frequencies of serious adverse events and atrial fibrillation were similar between the groups.

The intention-to-treat analysis for the trial's primary endpoint was negative in RESPECT (HR 0.49, 95% CI 0.22-1.11, p=0.08).[10] Per protocol (received the randomly assigned treatment, adhered to protocol-mandated medical treatment, no major inclusion or exclusion violation; HR=0.37, 95% CI 0.14-0.96, p=0.03) and as treated (received a protocol-approved treatment, adhered to protocol-mandated medical treatment, classified according to the treatment actually received; HR=0.27, 95% CI 0.10-0.75, p<0.007) pre-specified secondary analyses, however, were hopeful. Although not significant, those with an atrial septal aneurysm and having a large shunt tended to have greater benefit.

A meta-analysis combining the results of the three trials based on intention-to-treat found no significant benefit of transcatheter PFO closure for reducing stroke or TIA (Odds ratio, OR=0.70, 95% CI 0.47-1.05, p=0.08) or stroke (OR=0.65, 95% CI 0.36-1.20, p=0.17).[11]

In summary, whether a PFO is causally related to stroke in the majority of patients is uncertain, but when no other cause is evident, the risk of recurrence is low. Treatment with an antiplatelet drug or warfarin are equally efficacious, although warfarin is generally avoided owing to the required dietary restrictions and monitoring. There is no significant benefit based on the intent-to-treat analyses for the study primary endpoint for any of the three completed randomized trials of transcatheter PFO closure, no significant benefit when the data from the three trials are combined, and there remains no FDA-approved device for this purpose. Secondary analyses of data from the RESPECT trial, however, are hopeful and it is reasonable to consider closure in patients who have had a recurrent event despite medical therapy.

Disclosures:
Site PI & Neurology Executive Committee RESPECT (St. Jude)
*Unappr*oved treatments: No FDA-approved device for PFO closure for stroke prevention

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Risk-benefit Analysis of PFO Closure - A Prospective Study

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The reason I became interested in this field is I have been diving since 1974. And like Simon in the back, I do a lot of technical diving. So my peer group, who know I am a cardiologist, started coming to me about 10 years ago asking about PFO and people who were found to have PFOs and asked if they should have these closed. That piqued my interest in trying to set up some form of clinical, as opposed to basic science research to answer that question.

We have been talking about some divers who see more than their fair share of DCS. From the London Hyperbaric Chamber, Dr. King mentioned that one of his patients had 400 episodes of DCS out of 600 dives. Now, I don't know about you, but if I had 400 episodes of DCS in 600 dives, I would pick up golf.

My interest in this field was piqued by a friend of mine who came to me with this story. She said she was diving within the no decompression limits, and she noticed that if she used 34% nitrox rather than 36%, she had about 60 episodes of DCS. This is a working dive master. Later, she had this lymphatic episode of a golf ball-sized lump on her breast and that caused her to get a PFO test. She had a markedly positive TEE that I performed on her. We had a long discussion with her about stopping diving, diving more conservatively, and what that would involve versus closing it. Finally, we opted to close the PFO.

She wanted this done because she said she had an "undeserved" incident of DCS. Well, nobody "deserves" to get bent. I mean, we have to put this in perspective. We all know there's no absolutely safe dive, but small differences can result in large differences in risk. For this reason, in our study, we actually have asked all the divers to provide their dive computers to be downloaded to the database so we can really see what their risks are.

Here's an example of a diver who was in our study.

Expected or Unexpected?

- Experienced technical and cave diver in her late twenties, developed breast and shoulder pain with skin rash and mottling, 40 minutes after dive
- Diver maintained that she did same dive 4 days ago. Two dives and their estimated DCS risks are shown above.

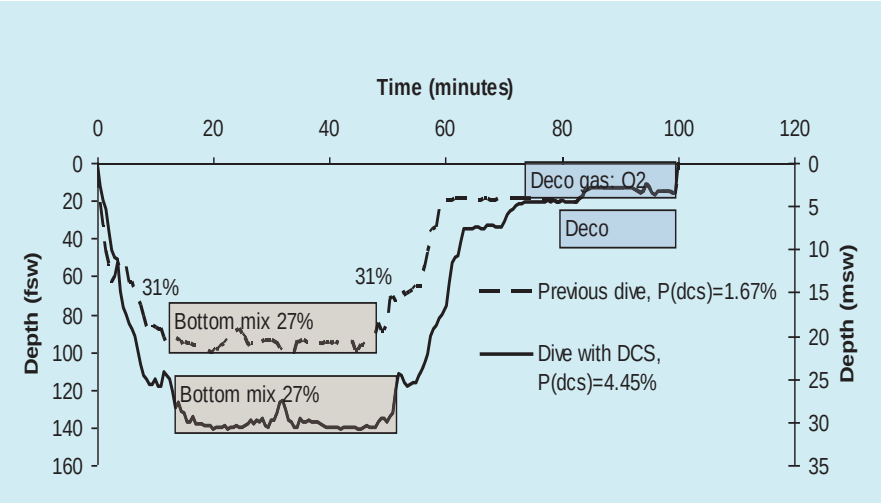

Figure 1. Dive profile comparison of diver who experienced DCS symptoms

This is an experienced technical diver. She said that she had an episode of DCS, but the day before she had done exactly the same dive, in her mind, and without any symptom. Figure 1 shows the dive computer recorded dive profiles from both related dives. Although similar in patterns, the dive that was followed with symptoms was shallower, of less duration and with more oxygen used at the decompression stop. Actually, the probability of decompression illness estimated by Wayne Gerth model (reference) was nearly three-fold higher for DCS dive than for previous dive. So again, we need to be aware of the fact that when people say they've done the same dive a hundred times, it may not really be the same dive.

Transcatheter closure of PFO

-Efficacy	86 – 100%
- Recurrent neurological and peripheral embolic events	0 – 3.8% per year

The success of PFO closure is quite high and the complication rate is quite low. In cases of PFO closure for cryptogenic stroke, recurrent episodes with closure of PFOs is somewhere in the 0 to 3.8% range. And success rates should be on the order of 99 or 100%. The serious complication rate in good hands should be minuscule. This is a procedure that takes about 30 minutes. You go home the same day. The major complication rate is bleeding from the groin and that should be about one percent. There are a few percentage of people who will get some palpitations, some premature atrial complexes (PAC), and the occasional atrial fibrillation for a few weeks after the procedure presumably because you've got this device rubbing up against the atrial septum making it a

bit irritable electrically. The device I have used is the Amplatzer device. They come in a variety of sizes. I will tell you that 90% of the time you use the 25 millimeter device.

Let me give you an example of what actually goes into this procedure.

This is a patient who was enrolled in our study. He is a 35-year-old technical diver. He had multiple episodes of skin bends and had two episodes of neurological bends with transient paralysis. Despite that, he went on a dive trip to Truk which is a long ways from anywhere. On that trip he again had paralysis, but he was lucky and recovered. He was getting concerned because it was his second episode of post-dive paralysis, and he had a trip to Bikini Atoll planned for the following summer. For anyone who doesn't know where that is, it makes going to Truk Lagoon look like a walk in the park. It is 36 hours of air and land travel and then you have another 36-hour boat ride to follow and so on and so forth. So he was very concerned.

I performed a TEE and found a very large right-to-left shunt at rest. This was even without Valsalva. So I thought that he would benefit from closure and he decided to do it. I perform closure under control of intracardiac echo, as opposed to transesophageal echo. It's a little more comfortable for the patient. Figure 3 shows the intracardiac echo catheter in the right atrium and the left atrial disk deployed in the left atrium.

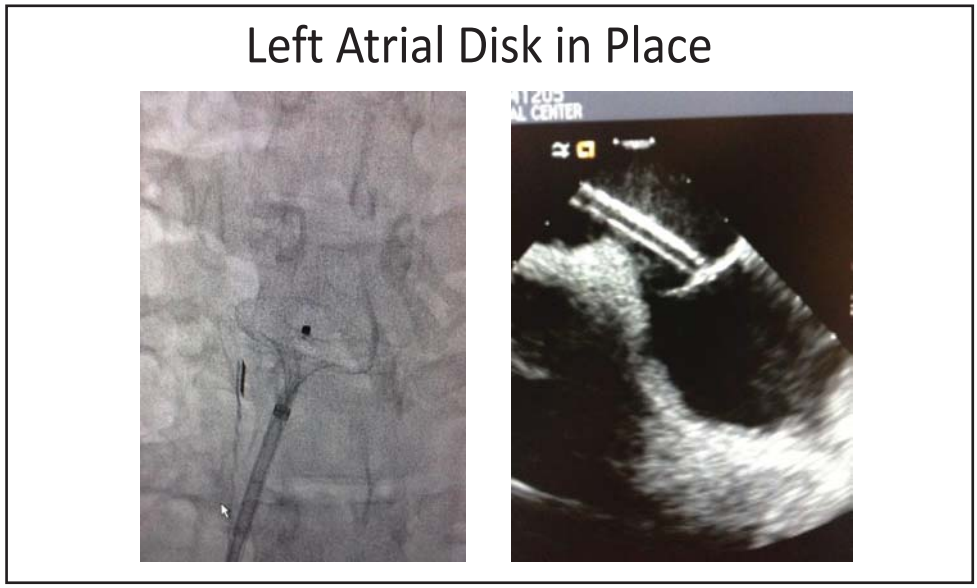

Figure 3. Fluoroscopy (A) and intracardiac echo image of deployment of the left atrial disk (B)

We then deploy the right atrial disk and then vary position and stability with a "push-pull" technique. Figure 3A shows completely deployed. Figures 4 and 5 show what it looks like on the follow-up transthoracic echo the next day.

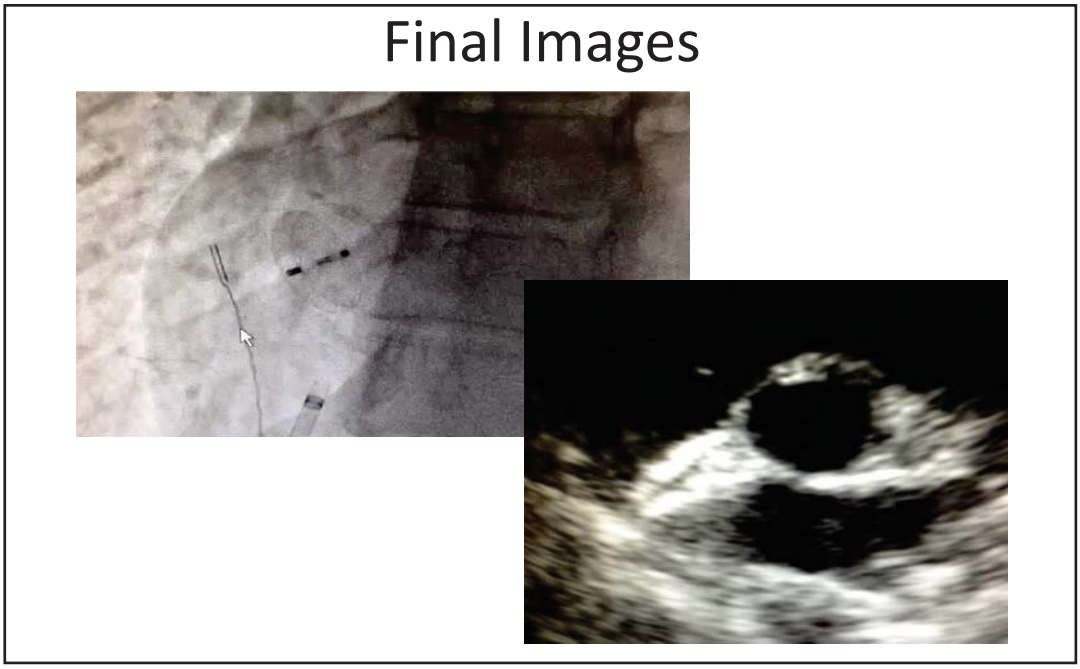

Figure 4. Fluoroscopic (A) and intracardiac image of device deployed (B)

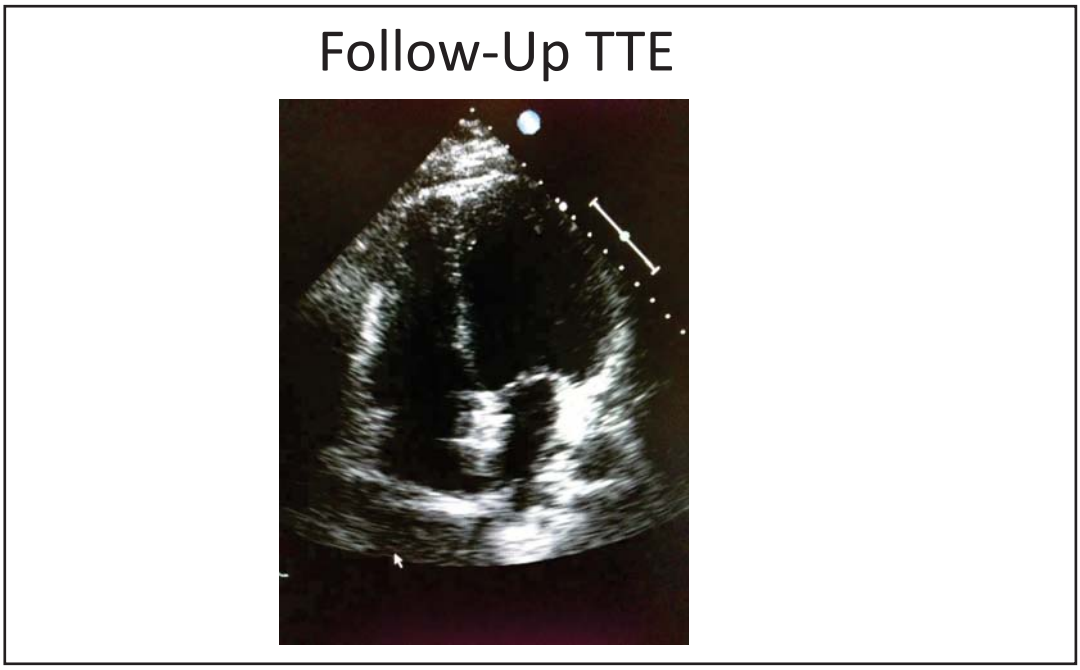

Figure 5. Follow-up transthoracic echo image of the device

This is a procedure that can be done very easily. It has a very low complication rate. The question really is who needs to have this done.

Ideally, we would like to have a randomized study with several hundred divers from all over the world, taken care of by a variety of different physicians, who get randomized to either a PFO closure or a sham procedure. There would be a follow-up with physicians who are blinded to what happened. You'd have input to include decompression events procedural complications, and then a very long-term follow-up.

The problem is, this is not realistic. Dr. Denoble and I sat down about five years ago to try and design this study and said, what can we realistically come up with without the funding to do any kind of large, multi-national, randomized study? So what we came up was the following.

DAN Study: Closure vs Non-Closure

- Research question
  - Who is better off, divers with PFO who continue diving (conservatively) or divers who close their PFO before returning to diving?
- Voluntary enrollment
  - Decision about closure independent
  - Status of PFO verified by cardiologist
  - Outcomes self-reported
- Follow-up five years

We designed an observational study. Our research question was: Who is better off, divers with PFO who leave their PFO as is and continue diving more conservatively, or divers who opt to have their PFO closed before they continue diving?

Most of participants were identified either by them finding the DAN website or seeing the study referenced on various social media forums. The minimum enrollment criteria were that they are certified divers and have been diagnosed with PFO. We then sent them the forms which are all located on the DAN website.

It is not a randomized study which has a large number of limitations. So the patients decided which strategy they were going to have; did they leave the PFO open or did they opt to close it? One of the first questions is, are divers in those two groups going to be similar, which we think probably would not be.

Another important question is will they change their diving habits? That is going to change the long-term follow-up. There were lots of biases here. There was a bias of reporting procedural complications. There was a recruitment bias because some people would choose to be closed or choose not to be closed for a variety of reasons.

The status of PFO was verified by cardiology. And the outcomes, unfortunately, were self-reported. And there's an annual follow-up through DAN once a year for five years where the patients are contacted and asked to download their dives and what kind of problems they may or may not have had over the last year.

Enrollment started back in 2010. We had a big push initially because a lot of people were interested. The rate of enrollment has declined over the years. We're currently at 65 divers, 34 of whom have opted to have their PFO closed. The other 31 have continued to dive with it open. Basically, you had to be 18 years old, have a diagnosed PFO, and be medically cleared for diving.

Annually we contact these people and find out how they're doing. First question is, are they still diving; if yes, how many dives are they doing; what type of diving are they doing. Then if they've had DCS, how were they treated. If they had a closure before they were enrolled or during the follow-up, what complications did they have as a result of the procedure.

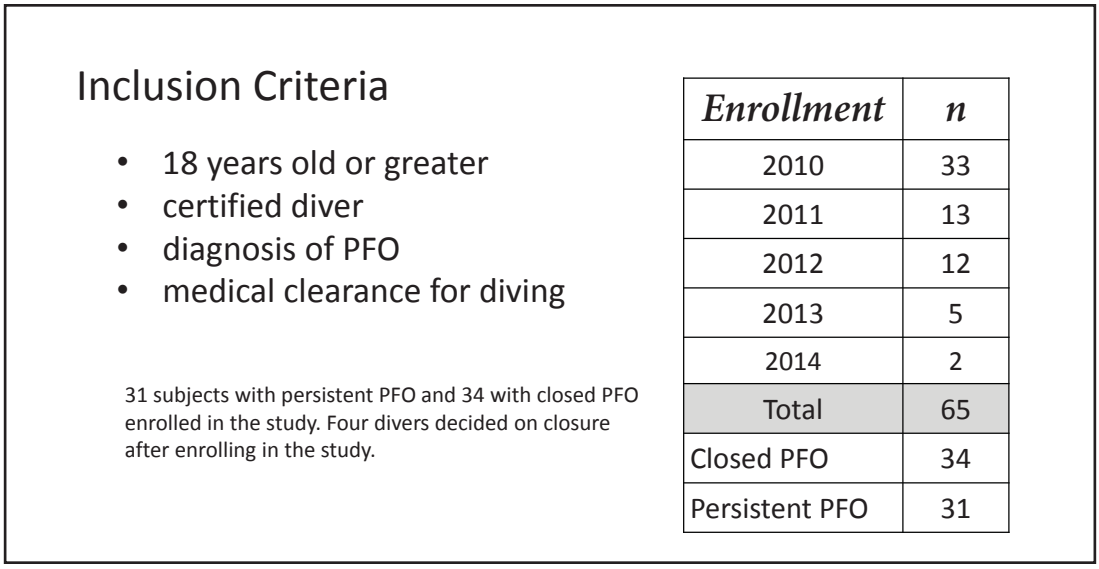

Figure 6. Inclusion Criteria

The mean age in the closed PFO versus the persistent PFO group is about the same. The years of diving before diagnosis in the closed group is a little bit more and they've been doing more dives after closure.

Table 1. Subject demographics

Measure	Closed PFO (n=33)	Persistent PFO (n=22)
Mean age	45 (28-63)	49 (31-65)
Percent of females	48%	41%
Years diving before diagnosis (mean)	10.4 (1-34)	7.8 (2-23)
Years diving after diagnosis (mean)	4.6 (0-10)	4.3 (1-16)
Number of dives before diagnosis/closure (mean)	709 (20-5400)	284 (0-1025)
Number of DCI episodes (mean)	6	1.5

The people who opted for closure are far more likely to be the people who have been diving longer, diving more, and possibly diving more aggressively. There's more technical and cave divers in the closure group as opposed to the persistent PFO group. Most people had between one and three episodes. There were some people who had multiple episodes. Divers who opted to have their PFO closed prior to being enrolled in the trial had far more DCS episodes than the people who opted to leave it open.

Sixty-five people have been enrolled so far. We have follow-up on 55 of these. Sixty-five total enrollees, 55 follow-ups, 22 in the PFO open group and 33 in the closure group. The question then is how these divers differ. We have follow-up mean of about 2.7 years, about 4.7 since the closure, since the diagnosis. We've excluded a few people. Of those 65, we made it 55 because some people quit diving, some had incomplete enrollment forms, and some people have been noncompliant with our follow-up.

So what have we found?

Table 2. Preliminary results

PRELIMINARY RESULTS (2.7 years follow-up)	
Closure Group	**Persistent PFO Group**
33 subjects	22 subjects
Mean # dives 105 dives/subject	Mean # dives 76 dives/subject
1 episode of DCS in 3,465 dives	3 episodes of DCS in 1,672 dives
Event rate 2.9 events per 10,000 dives	Event rate of 18 events per 10,000 dives

In the closure group a few people have stopped diving. You'll notice that the mean number of dives is larger in the closure group. Interestingly, despite a larger number of people in the closure group who tend to be diving more aggressive dives, there's only one episode of DCS here. Whereas, in the smaller group with persistent foramen ovale doing fewer dives, the number of episodes was three.

So if we look at 2.7 years of follow-up in the closure group there were 33 subjects with a mean number of 100 dives per subject, with one episode of DCS in 3,465 dives (2.9/10,000 dives). Whereas, in the persistent PFO group, there were 22 subjects with a mean number of dives of 76, which would mean there were 3 episodes in 1,672 dives or an event rate of 18 per 10,000 dives. Again, these are all self-reported results.

So this is where the study is at the moment. We're halfway through follow-up. We're still actively enrolling patients and we are looking for a five-year follow-up. If anyone is interested in participating in the study they can contact me at debersole@watsonclinic.com and/or download the enrollment forms at www.dan.org/pfostudy.

Current State of Knowledge - Quality of Evidence

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Introduction

The discussions and information presented to this point has been concentrated on the relationship between a patent foramen ovale and decompression illness. A reasonable place to start this very brief review is to explore why there is such an interest in this relationship. Both conditions had been known for a long period of time before there was a significant interest in the association between the two.

The first development was the advent and wide use, in the research setting, of precordial Doppler detection venous bubbles. This allowed investigators to see that there were bubbles present in the venous blood stream in after many non-eventful hyperbaric exposures. In divers who were routinely exposed to more aggressive profiles venous bubbles may be present in all nearly all hyperbaric exposures.

The second development was the wider availability of 2-D echocardiography with the resolution to reliably detect the presence of a patent foramen ovale. Smaller, cheaper, and easier to use echocardiography hardware made screening by echocardiography made screening a more realistic possibility.

The third was the availability of transcranial color Doppler flow detection. This made detection of bubbles in the arterial circulation near the organ of interest, i.e, the brain, possible.

The fourth and most important reason was the development and availability of a technique to fix the observed defect that was acceptable in terms of both cost and risk. Prior to the availability of percutaneous techniques, closure of a patent forman ovale required a thoracotomy. For the purposes of decreasing the likelihood of DCS (an event that could be avoided by other means) open heart surgery would not have been an acceptable proposition for nearly all individuals. Once percutaneous closure techniques were available and perceived to be safe and effective enough, proving the link between DCS and PFO and then repairing the lesion would allow a significant increase in safety without having to significantly alter behavior.

And lastly, and perhaps most importantly, if the association between PFO and DCS could be proved, an explanation to a subset of DCS patient may be possible. Individuals who have been treated for DCS are often desperate for an explanation as to why the diving accident happened on this day, at this time, on this profile when it didn't happen to anyone else, they hadn't done anything differently.

If the association could be proven between patent foramen ovale and a significantly increased risk of DCS (especially serious cases of DCS) it would allow diving medical physicians to do two important things: First give

the previously injured diver the answer that they desire, and then later be able to correct the problem with a high-tech medical procedure.

Elements of Causation

The desire to make the connection for a causal relationship between decompression sickness and the presence of a patent foramen ovale was, and still is, strong. In the intervening years there has been a significant volume of literature on this topic, much of which has been introduced in other topics of these proceedings. The process for relating two events is called causation.

The statistical and methodological requirements for causation are still being debated. The most widely accepted criteria for a causal link between two phenomena were put forward by Austin Bradford Hill 50 years ago in 1965. [1] Hill proposed seven tests which can link two events. There is no specific number of the seven which must be met, but the greater number of the criteria that are met, the stronger the evidence to support causation.

1. **Strength**

   Generally, the stronger the statistical association between a small statistical association does not mean there is not a causal effect. Although the larger the association, the more likely it is to be causal.

2. **Consistency**

   If the same effect is seen by multiple investigators in multiple sites with different populations, it is more likely that a causal link exists.

3. **Specificity.**

   Causation is likely to be present if the disease or phenomena occurs only in a specific population at a specific site and specific disease with no other explanation. The more specific the association between cause and effect, the more likely it is to be causal. The best example of this is mesothelioma and asbestos. The specific relationship between mesothelioma and asbestos is so strong that the discovery of mesothelioma is proof of a prior asbestosis exposure.

4. **Temporality**

   Obviously, the cause has to precede the effect.

5. **Biological gradient**

   This is otherwise known as dose response. It means that greater exposures should lead to greater incidence of the effect. Biological gradients can be complicated by the presence of threshold effects: low exposures have no perceptible effect on outcome until some level is reached, then a dose-response may be seen.

6. **Plausibility**

   A plausible mechanism between the phenomena should exist. Plausibility can be somewhat problematic, in that insufficient scientific and technological knowledge may prevent a correct causal relationship from being formed. A Cuban physician, Dr. Carlos Finlay, not only correctly identified Yellow Fever as being transmitted by mosquitoes, in 1881 he correctly identified the precise vector, Aedes aegytyi. Unfortunately, the state of the science was such that his explanation lacked biological plausibility and another 20 years would pass before the science was able to catch up.

7. Coherence

The term coherence, in this setting, is an agreement between laboratory basic science and what is observed clinically.

Experimental Evidence

Are there animal models or direct experiments which can be used to demonstrate the proposed connection between the proposed cause and effect? Experimental evidence can be difficult to obtain when either there are no acceptable models, or significantly complicated when latencies may be measured in decades.

Analogy

Do similar exposures result in the same effect? Or does the same exposure result in a series of effects which are all closely linked? For example, given the fact that there are carcinogens in cigarette smoke, the carcinogenesis which occurs in the lung has an analogous exposure to other tissues exposed to the substance (the epithelium of the bladder, for instance).

Types of Epidemiological Studies

It is appropriate at this point to review the different types of evidence which are put forward to establish a link between a potential cause and a potential effect. There have been several types of reports cited thus far and a brief review of the relative strengths of the experimental designs is helpful. These are listed in ascending order of strength, and in the usual order of chronological appearance.

Case Reports

Case reports are the lowest form of evidence which exists: this is one individual publishing observations about a single case. These are usually the earliest types of studies published on any phenomena. They are considered to be hypothesis generating, rather than proving. They are considered highly susceptible to observer bias, susceptible to confounding from temporally related but not causal factors.

Case Series

Like a case report, except several of them. The level of evidence is considered somewhat higher, but still low level. These are unsurprisingly also highly susceptible to observer bias.

Cross Sectional Studies

These are very common in the epidemiological literature. A population is sampled, and characterized as to an exposure/risk factor of interest, and the state of the population as regards an outcome in question. An association between exposure and outcome is more direct, but cross sectional studies suffer from major limitations which include:

- *The sample is observed at one moment in time.* Changes through time cannot be ascertained, and this may alter the association as it really is vice what it is observed (healthy worker phenomena).
- *The study is highly sensitive for selection bias*: The results obtained in one setting (a rural primary care clinic) may give different results than those taken in another (tertiary care referral center in a major city).
- *Temporality cannot be determined.* In a cross sectional study, since it only is a snapshot of one moment in time, it is difficult to ascertain causation - which came first? In addition, two observations associated with a third (not recognized) exposure may appear to be related, but that relationship is incidental.

Case Control Studies

Case control studies, as the name implies, seek to compare a population with an outcome or condition of interest, with a population where the condition is not present. Case control studies have fallen out of favor of late. However, if the control population is well selected, they can be an extremely powerful pool to help identify causation. The problem arises in selecting an appropriate control population. The control population must be in all respects similar to the case population the only difference being the presence of the condition or outcome of interest.

Cohort Studies

Cohort studies, (clinical trials, both randomized and non-randomized are a subset of cohort studies) are the most powerful tools in order establish epidemiologic causation. Cohort studies follow a collection of individuals through time and observe outcomes. Members of the cohort are identified (and in the case of clinical trials an intervention is performed) as to the presence of a risk factor of interest initially. They are then followed through time and observed and classified as to the development of the outcome of interest.

Clinical trials are a subset of cohort studies. The "cohort" is the recruited population, and the investigators control which members of the cohort receive the exposure/intervention and which do not. Ideally (if the cohort is well selected and randomized) all potential confounders (including those which are not recognized or able to be measured) will be the same in both elements of the study.

Moving from the elements of causation, and the major types of epidemiologic linking, it is easier to look at the evidence which has been published to date. There has been a significant amount of evidence in the peer reviewed scientific literature about the relationship between a patent foramen ovale and the development of decompression sickness. Many of the early important papers and much of the important recent research has already been examined as part of the proceedings. We will review, with a critical eye, some of the existing evidence on the topic.

One paper has been referred to three times thus far today, is worth a deeper investigation. This is the Swiss paper by Torti published in 2004.[2] This is a cross-sectional design studying the risk of DCI in those with and without PFO. The study recruited a total of 230 volunteer divers. Prospective subjects were excluded from the study if they admitted did not follow either decompression tables and/or computer guidance, but there was no auditing of logs or computer profiles to verify compliance.

Nearly all of the divers in this study were recreational. As most of the studies that have been quoted today there were less than 10% professional divers in this study. The rather significant bias in this, and most of the studies cited thus far, limit the ability to make conclusions or recommendations regarding commercial or military divers.

PFO was determined by transesophageal echocardiography. Intracardiac shunt was determined by injection of Physiogel agitated with air. The presence of DCS was determined by questionnaire response. This was performed prior to the subject undergoing TEE, eliminating a potential element of bias, as individuals who learned they have a PFO may be more likely to retrospectively report events than one who was classified as normal.

Minor DCS was classified as: limb pain, cutaneous erythema, abnormal fatigue, headache, dizziness, paresthesias, and tinnitus. Minor events were scored based on frequency: never, rarely, every three or four exposures, every other dive or more. Major events were limb weakness, cutaneous sensory level, impaired bowel or bladder function, paresis or paraplegia, blurred vision, dysarthria, amnesia, hemiplegia or loss of consciousness post dive.

Table 1. Characteristics of divers with PFO and without PFO

	PFO (63)	No PFO (167)	p
Lifetime dives	650 (250-1200)	400 (214-800)	0.009
Years diving	11±8	9±7	0.25
Diving depth (m)	29±9	28±9	0.83
Dives>40m	50 (10-150)	40 (8-100)	0.10
Air only	41 (65%)	136 (81%)	0.01
Valsalva for pressure equalization	20 (32)	39 (23)	0.06

Table 1 shows the diver characteristics of the two groups in the study: those who were shown to have a PFO and those that did not. These results immediately demonstrate some of the problems inherent with cross-sectional studies. An examination of the diver characteristics show that the PFO group and the non-PFO group are not exactly the same. The PFO group is more experienced: they demonstrate approximately 50% more dives, have been diving for two years longer, and are more likely to use mixtures other than air. All of these factors are associated with being a more experienced diver. There is one other notable finding, which also demonstrates an element of case control studies, individuals in the PFO group were more likely to use the Valsalva maneuver to equalize their ears on descent. This could be a cause, an effect or is just a spurious association which was noted incidentally.

The overall risk of DCI was one case for every 2.5×10^4 exposures. This figure has been seen in multiple studies quoted thus far, between one in five per 10,000 exposures. In the results of this study, all grades of PFO were associated with increased risk of DCI.

The rates here are unadjusted for any factor. Using a backwards stepwise Poisson regression (Poisson regressions are similar to a logistic regression, but used in cases where the outcome is extremely rare) the only significant factor in the analysis was number of dives reported. The corrected odds ratio for DCS in the presence of a PFO was 4.5. This increased to a corrected odds ratio of 5.3 for major DCI, and 12.7 for being treated in a recompression chamber.

So this study is representative of several of the cross-sectional designs. It only describes the population sample but only at that one point in time. Note the population was exclusively sport divers. The main outcome variable was determined by subject report rather than any objective criteria. Despite this, the overall frequency of DCI, however, was consistent with other studies.

Analogy: Cryptogenic Stroke, PFO, and DCS

The Torti data demonstrate the potential difficulties which arise when one attempts to undertake a clinical trial for PFO closure and DCS. Even though the risk factor isn't that uncommon, the outcome measure is quite rare. As a result, in order to obtain sufficient statistical power in an acceptable time frame a large sample size is necessary. That sample size may well be beyond what could be feasibly financially and logistically possible.

Given this limitation, it may possible perform clinical trials in other conditions analogous to decompression stress with right to left shunting and make inferences to DCS. One such condition is cryptogenic stroke.

Cryptogenic stroke has been examined in other presentations in this collection. It is defined as phenomena CVA from a presumed embolic source but no clear source of that embolism in the left heart. The cryptogenic stroke story is in many ways similar to the DCS story. The PFO occluders in use for the secondary prevention of DCS in individuals with a PFO and a significant right to left shunt were designed for use as secondary prevention (perhaps even primary prevention) of cryptogenic stroke. There had been a large body of case control/cross sectional data which implicated PFO with RLS in cryptogenic strokes. However, there was no clear consensus that closing an otherwise asymptomatic (e.g. not hemodynamically significant) PFO was of long term benefit. As such, there were calls for randomized clinical trials for the use of PFO occluders in cryptogenic stroke.[3]

The difference, of course, between cryptogenic stroke and DCS was the potential size of the market. There is a relatively small active diving population, and the population with a significant right to left shunt is a fraction of that. The potential population at risk for cryptogenic stroke would be the entire population with a PFO and a significant right to left shunt. As such there was both the interest and funding necessary to undertake such an endeavor.

Three major prospective clinical trials were undertaken, the results were published at nearly the same time. The RESPECT trial, which has been previously touched upon, was published in the New England Journal of Medicine in 2013.[4]

Patients were eligible for enrollment they presented with cryptogenic stroke, as defined as focal neurologic defect for >24 hours with neuroimaging correlation, and a PFO noted on the TEE with right to left shunting as defined by infused microbubbles visualized in the left atrium within three cardiac cycles after appearance in right atrium. Patients were excluded from the study if, using a broad series of criteria, a source for the stroke could be identified or inferred. Potential subjects were excluded if they had identifiable large vessel disease, noted clear other source, identifiable small vessel disease, or hypercoagulable state. Eligible patients were randomized to either standard therapy (anticoagulation with either aspirin, warfarin, clopidogrel, or aspirin and dipyridamole) or closure of the identified PFO with the Amplatzer device. Patients in the closure group also received strong antiplatelet therapy for 1 month, then mild antiplatelet therapy (aspirin) for an additional 5 months.

A total of nearly 100 patients were enrolled, with a slightly greater number in the intervention cohort than the standard care cohort, with about 2.5 years of follow up per patient. There was a significant difference in dropout rate in between the two groups.

Of the 499 patients assigned to the intervention group, 464 underwent the procedure. Of those 99.1% of the subjects assigned to the intervention group had the device implanted. The rate of procedural success (implantation without serious adverse events as 96.1% (note: bad things can happen).

In the intention to treat analysis (the one considered least likely to contain bias) there was a small, but not statistically significant reduction in the primary end point.

In the intention-to-treat cohort there were 25 primary end-point events, nine occurred in patients who were assigned to the closure group and 16 in patients assigned to the medical-therapy group. Three patients with recurrent ischemic stroke who had been randomly assigned to the closure group did not have a device in place at the time of the recurrent stroke. Since this was an intention-to-treat analysis, in the analysis they were treated as having failed closure.

The as-treated cohort included all patients who received a protocol-approved treatment and adhered to it. In this cohort, patients were classified according to the treatment they actually received, regardless of the randomization assignment. The results of the as-treated cohort did show a statistically significant decrease of about one event per every 100 patient years (0.39 vs 1.45, p=0.007).

So, where does that leave things? It depends upon where you stand. The editorials at the time of release had the title: “Something for everyone”. That is more or less correct. If one is looking for data to support the closure of PFOs in the presence of cryptogenic stroke, this provides support for that. While the strictest interpretation of the data (intention to treat) did not show a statistically significant decrease in stroke rate, there was a decrease in events. There was a statistically significant difference in the per-protocol and as treated analysis, the difference being 3 patients who had an event prior to the intervention happening.

If one is looking for data that does not support the interventionist approach to PFO and cryptogenic stroke this (and other) studies support the proposition that, overall, closure did not have a statistically significant difference in the intention to treat analysis, even when looking at the best analysis for the interventionists, the difference was about one event per 100 patient years, not a huge clinical difference.

Summary: another look at the Hill Criteria

So, where do we stand on the Hill criteria, with an eye toward the data that has been presented?

Strength

We'll start with strength of association. There is a relatively strong statistical correlation between PFO and DCS increased risk. The effect seen is consistent upon multiple studies by multiple investigators done at multiple periods of time. A meta-analysis published in 2009[5] showed a combined OR for neurological DCS of 4.23 (3.05-5.87), with the odds ratio increasing to 6.49 (4.34-9.71) when limited to high grade PFO. Unfortunately, it's not very specific. There are many other elements which cause increased risk of DCS.

Consistency

While the magnitude of the increase of risk varies, there have been no significant study which has either shown no risk or a decrease in risk of DCS associated with a right-to-left shut from a patent foramen ovale.

Specificity

Specificity is where the relationship probably begins to break down. There are many factors involved in the development of the clinical syndrome known as neurological decompression illness. The strongest is the exposure to increased pressures of inert gas; all others, including PFO are a distant second. In addition, there are some significant other factors associated with the development of DCS, both known and unknown.

Temporality

Temporality does appear to favor causality, as the overall status of the diver does not significantly change during the course of the exposure. This said, there are some clues that perhaps frequent forced Valsalva may both increase the prevalence of PFO as well as increase right to left shunting when bubble may be present in the right side of the heart (however, under normal conditions one would not expect the need for forceful Valsalva during the decompression phase of an exposure with the special exception of surface decompression).

Biological Gradient

Biological gradient does appear to be fairly strong both in Torti and most of the other studies which we have discussed today. The strongest increase in risk was seen in the highest grades of PFO. Low or minimal PFOs appeared to create a negligible increase in risk.

Plausibility

As was pointed out in the start of this paper, the interest in PFO and DCS came about because of the near overwhelming amount of face validity that the concept has. Intravascular bubbles are a precondition to the development of DCS. Intravascular bubbles on the left side of the circulation are a problem.

Now, the last three are where there are definitely problems, at least a little bit.

Experimental Evidence

In other sections there have been a few experiments which show that individuals with high grade PFO do have increased number of transcranial Doppler signals following experimental hyperbaric exposures. This is suggestive of a relationship, but there is not clear experimental evidence that using controlled hyperbaric exposures using known subjects results in a higher incidence of DCS.

Analogy

In analogy, the best analogous condition of cryptogenic stroke is in the same situation we are, which is in a morass. There was a large amount of data which indicated that patients with PFO resulting in a significant right to left shunt had a higher incidence of cryptogenic stroke. Some early data had indicated that closing the PFO decreased the risk of stroke. Unfortunately, three large multicenter randomized clinical trials failed to show a clear, convincing effect in decreasing the incidence of recurrent stroke.

Coherence

In this case, there are no relevant animal models, so coherence is not applicable.

Taken on the whole, Hill criteria would tend to favor PFO with right to left shunting as a causal element for the development of neurological decompression sickness. The criteria are not completely covered, and there are significant gaps in the data available, as well as some contradictory findings when analogous conditions are considered.

So in summary, there is a significant amount of data which support the contention that PFO, especially when associated with a high amount of right-to-left shunt, is associated with increased risk of neurological DCS. The data is by no means conclusive, and there are significant areas where data is not available, particularly when non-recreational divers are considered. There are significant, possibly unsurmountable, difficulties which would be associated with conducting the desired blinded, randomized, longitudinal studies to finally put the causation issue to rest. In addition, even if one takes the causation issue as a given, the data from the cryptogenic stroke trials indicate that closing the PFO may not solve the problem as well as the initial look may indicate.

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Evidence Synthesis and the Australian Experience

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Introduction

Ward Reed and I were tasked with reviewing the clinical evidence around the risks of diving with a persistent foramen ovale (PFO). Dr. Ward has done a great job on reprising for us many of the studies that have been mentioned a number of times already today. I am going to try not to repeat the same information too often. I am also going to spend a couple of minutes talking about our experience at Prince of Wales where we have recently published our retrospective analysis of relevant kinds of patients just to try and put what we've been saying into a real and evolving clinical context. I quite openly want to show you the results one might expect in the real world, where there may be less than perfect performance in diagnosing and advising these patients.

I have no commercial interest whatsoever. I am not important enough and I have too little influence on my colleagues to be worth sponsoring for anything.

Evidence review

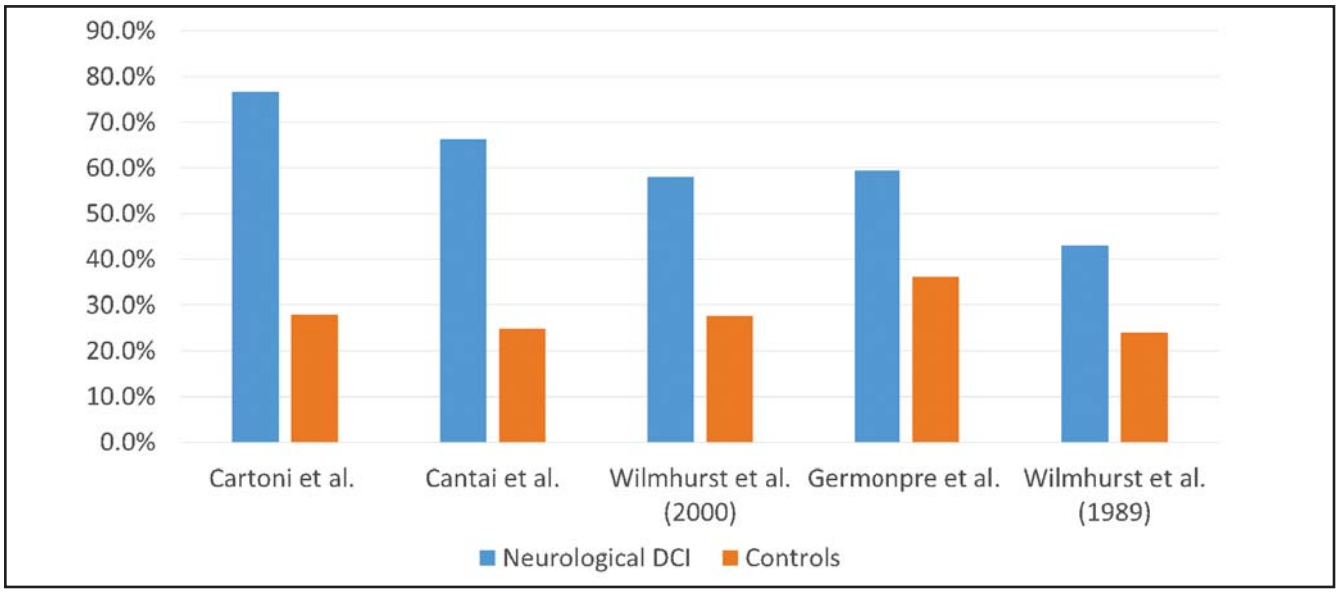

Figure 1. The prevalence of PFO in divers with a history of neurological decompression illness compared to a control group in five published case-control studies[1]

The main body of work we've been discussing today has fortunately been already reviewed in a meta-analysis by Olivier Lairez et al.[1] These authors found five comparative trials suitable for inclusion in their meta-analysis. In all cases, these studies looked for evidence of PFO in cohorts of divers with neurological DCS and compared the prevalence of PFO in similar cohorts of divers with no such history.

The individual results are summarized in Figure 1. Each of these case-control studies suggests the prevalence of PFO is higher in those who have suffered an episode of neurological decompression sickness (DCS) than in controls. The results of primary interest to us are shown in Figures 2 and 3.

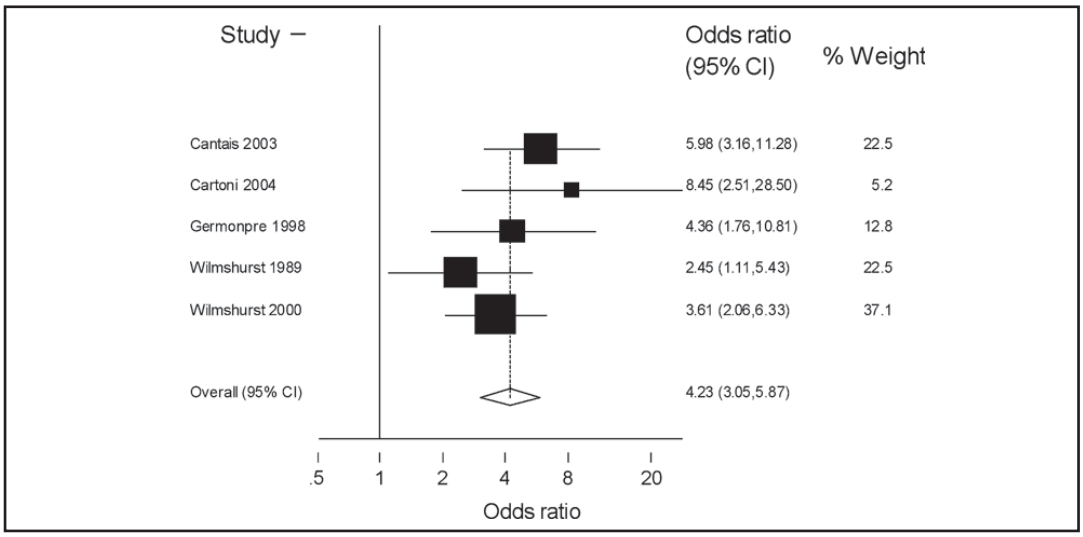

Figure 2. The odds of having an episode of neurological decompression illness with any demonstrated right-to-left shunt compared to no shunt in a group of control divers[1]

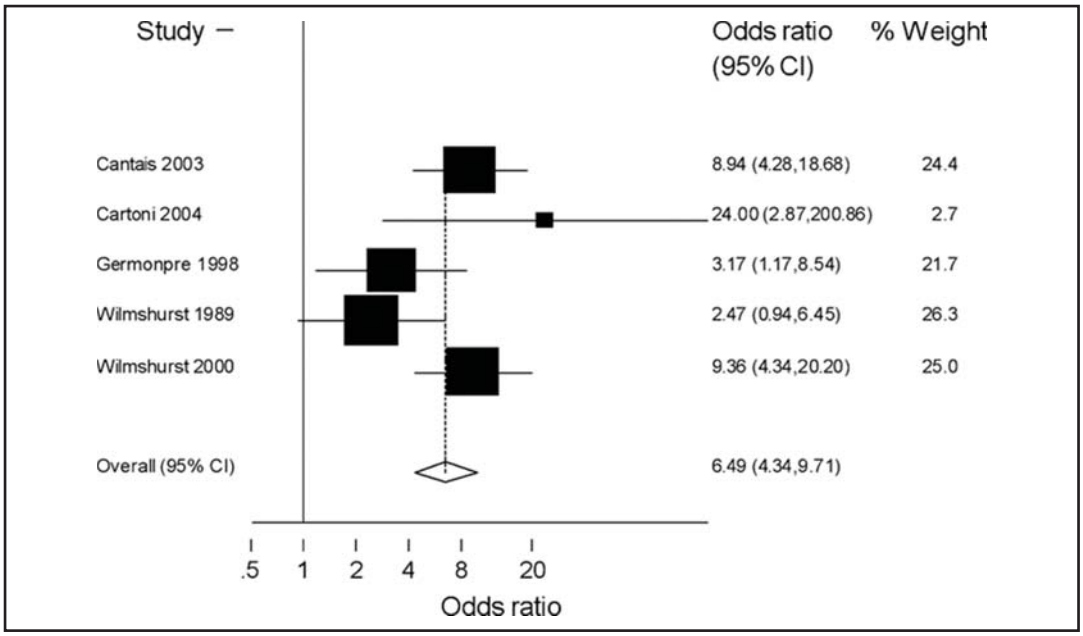

Figure 3. The odds of having an episode of neurological decompression illness with a high grade (large) right-to-left shunt compared to no shunt in a group of control divers[1]

As you can see, these figures quantify the pooled odds of having a PFO when comparing the two groups. When you meta-analyze these data, there are obviously individual study variations, and that's not surprising. These are not randomized data, and each of these case-control studies is likely to be subject to some bias. It is not surprising that in different countries at different times, using different techniques and different criteria of diagnosis you're going to find a lot of variation.

Nevertheless, when you pool these data with standard statistical techniques, those with a history of neurological DCS are more likely to have a demonstrable right-to-left shunt on testing compared to divers with no such history (Odds Ratio (OR) 4.23). If the analysis is confined to the detection of a high-grade shunt, the odds rise (OR 6.49). This is taken to imply that larger PFOs, across which bubbles are more likely to pass, are highly represented in a group of divers susceptible to serious DCS – a supposition entirely consistent with the hypothesis that it is the passage of bubbles that causes the clinical appearance of serious DCS in these divers.

This is definitely a case where we should express effect sizes in odds rather than risk. True risk needs to be determined from randomized control trials where we know the true incidence of serious DCS from equal diving exposure in each group. In these observational studies it's much more appropriate to talk about an association, rather than causation. This literature shows a strong association between large PFOs and an increased chance of serious decompression illness. We cannot be sure the link is causative.

Interpretation

One might take the OR of 6.5 to mean it's very important we screen divers to eliminate this potential problem. Neurological DCS can be devastating, even fatal, in a small minority of cases.

An important question we should first ask ourselves, however, is just how many divers do we need to screen in order to avoid getting one episode of DCS. We can't answer that at our current state of knowledge, but we can get an estimate based on the data we've just discussed – with the addition of some assumptions. I freely admit these assumptions may be, in some of your minds, way off base. We can play around with those assumptions during our discussions to come and see if it changes our minds about the usefulness of screening.

So let's assume the incidence of significant DCS is about five in 10,000 dives. Let's also assume the incidence of a larger PFO is around 5% of the population. Note we are not making any attempt to raise the prevalence – that is, to choose a subset of divers where we might expect a higher rate of positive testing for PFO. My third assumption then, is that we (as a first step at least) are contemplating a blanket testing of all prospective divers. In truth, we will want to find a way of selecting out those most likely to be at risk, or in whom the consequences are likely to be very severe.

Using our base assumptions above however, we can calculate we would need to screen approximately 1,000 prospective divers and deal with 50 PFOs in order to prevent one significant neurological DCS event. This is a potentially misleading use of observational data, but the best estimate we can make at this time.

Screening 1,000 divers is a lot of work. In Australia, the cost of 1,000 simple echocardiograms is about $230,000 AUD – without specific bubble contrast maneuvers. Add the cost of 50 PFO closures at approximately $1,200.00 AUD each and the total cost to prevent a single episode of significant neurological DCS is (very conservatively) well over $300,000 AUD.

I think it's appropriate to suggest, as we go into the discussion later on and we look at David Smart's summary of the SPUMS position in this area, that most of us will agree screening of the general recreational diving population is inappropriate from those sort of figures. Perhaps we will find some debate about that.

The Prince of Wales Hospital Experience

One day three or four years ago, the head of cardiology at POWH came down and put one question to us: "How do you do it? How do you select individuals for PFO testing? Not only do your patients have a high positivity rate, but there is a very high prevalence of large PFOs in your group. No other group sent for testing has anything approaching your hit rate."

That observation led to one of the cardiology fellows looking at our experiences over the period from January 2004 (when we moved to the present site) and May 2013.[2] Over that period we referred 75 such patients. In general and in common with a lot of colleagues in this room, we would refer divers following significant neurological DCS, cutaneous DCS or what we've heard referred to several times today as "undeserved bends."

I share the reticence of many here today with the use of that latter term. I am not sure exactly what it means and I am not sure my colleagues are any surer than I am. I use it here to indicate a diver sent for PFO testing following a peripheral bend that seemed out of proportion to the diving they'd been doing.

The proportion of our patients that go for bubble studies in our big cardiology department is a very small proportion of the total (about 1.5%). Our divers were very different from the usual run of patients presenting to the cardiology department for these studies. When looking for the source of emboli, bubble-contrast echo was positive in 21% of cases, in a collective bag of miscellaneous indications only 10% were positive, while in divers more than half (52%) were positive. Following an episode of DCS we were often correct in our assumption that they may well have a PFO (Figure 4).

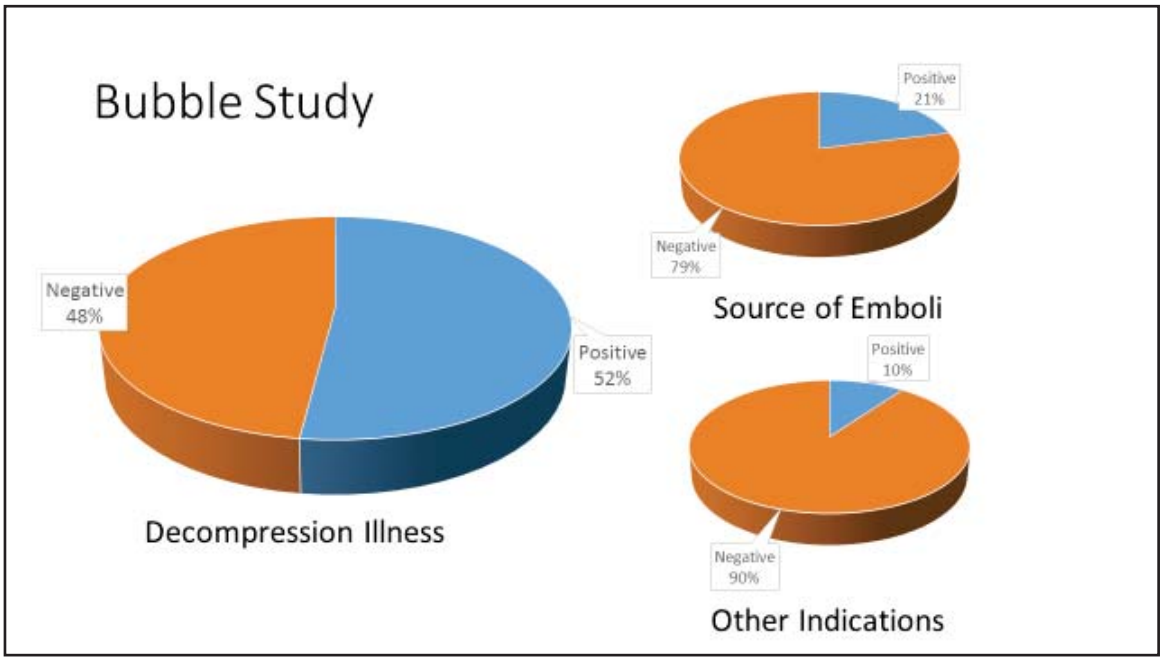

Figure 4. The proportion of individuals with positive and negative bubble contrast studies in three different patient groups (discs not to scale)[2]

A few characteristics of that group. The average age was nearly 40 and 61% were male. Most of them had one episode before they were tested but there was a few who had two or three (mean episodes of DCS 1.3). Interestingly, as we've seen from some of the others' figures earlier today, the median number of dives prior to the episode that precipitated the visit to the cardiologist was 93. And they were not trivial dives. As noted by Dr. Reed, these divers often have significant depth/time profiles – here the average precipitant dive was 31 meters for 35 minutes duration. Separating our group into those who subsequently proved to have a PFO and those who did not does not reveal any clear characteristic that would predict this status.

If we separate those with 'major' and 'minor' DCS signs and symptoms, our cohort confirms those with major DCS signs and symptoms are more likely to have a PFO confirmed than those with minor symptoms (72% versus 28% respectively).

Conclusion

Both the published data and the POWH experience suggest a large PFO is highly associated with serious neurological and cutaneous DCS. There is little support for the widespread testing of unselected divers, but equally little published consensus on appropriate, cost-effective selection procedures. The South Pacific Underwater Medicine Society (SPUMS) has recently produced a set of guidelines that may assist in this area.

I recommend to the group to think carefully about whether these SPUMS guidelines are a step in the right direction. If we can use them as a template for our discussion, maybe we can move fairly quickly to an appropriate UHMS/DAN approach. With that respectful suggestion to the chairpeople I thank you very much.

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Current Operational Implications of PFO in Military Divers

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Good afternoon, everybody. Thank you Dr. Bove and Dr. Denoble for having me here. I am honored to be presenting today. I share a great passion for patent foramen ovale (PFO). As a Navy interventionalist, I am referred many patients with PFOs and as such I have to evaluate the significance of PFO in active duty Navy divers and pilots, so it is quite exciting to present my military experience in this forum.

I will start by presenting an interesting case, not your typical PFO case, which will serve as a good foundation for discussing the role of PFO and PFO closures in active duty US Navy divers. I also will review our current US Navy policies which are published in specific military documents, namely MANMED (CH15, Arts.102,105) and MILPERSMAN. I will end this presentation by making a case for the 'at-risk PFO' and discuss a prospective study we are proposing to conduct in US Navy divers.

Our case is that of a 35-year-old active duty Navy SEAL who is status-post PFO closure. He had a 25mm GORE Helex device closure prior to my arrival at the hospital. The patient was referred to me six months later for palpitations. A trans-thoracic echocardiogram (TTE) performed showed a positive bubble study. A repeat trans-esophageal echocardiogram (TEE) was performed and showed a residual shunt inferior to the occluder device. Except for that one episode of palpitations, the patient was completely asymptomatic. In fact, during the first visit with me he was back to ultramarathoning. Like most Navy SEALS, my patient was highly fit and could run 50 to 100 miles without limitation. So here I found myself evaluating an entirely asymptomatic individual with a small minimal residual shunt. What would you do?

As a Navy interventionalist, I was faced with the responsibility to judge the patient's fitness for full military duty. By definition, a residual shunt made him unfit to return to combat duty assignments. I met him a few times over the next three months and performed serial echoes to document any change in shunt size. However, the shunt remained the same size. The patient wanted to return to combat SEAL assignments across the world, so much so, that he requested surgical correction for an asymptomatic residual shunt. At this point, I offered him repeat closure based on the indication to return to full world-wide deployable duty, per our Navy guidelines as we understood it then, and the purported decompression illness (DCI) risk.

Let us review the patient's imaging data: on CT and MR imaging, there was no fracture or displacement of the initial device. By CTA and TEE the residual defect measured to be less than five millimeters and adjacent to the previous occluder device. The residual defect was inferior and anterior to the previous occluder device.

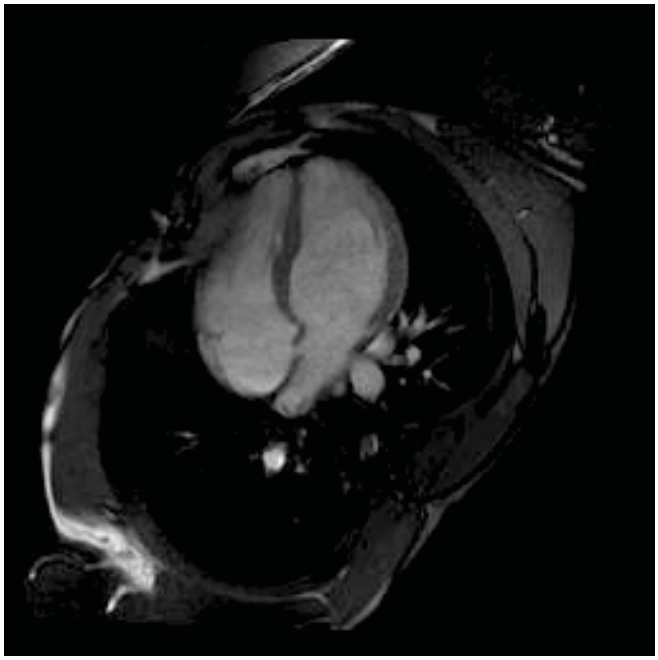

Figure 1. Preoperative MRI showing residual shunt

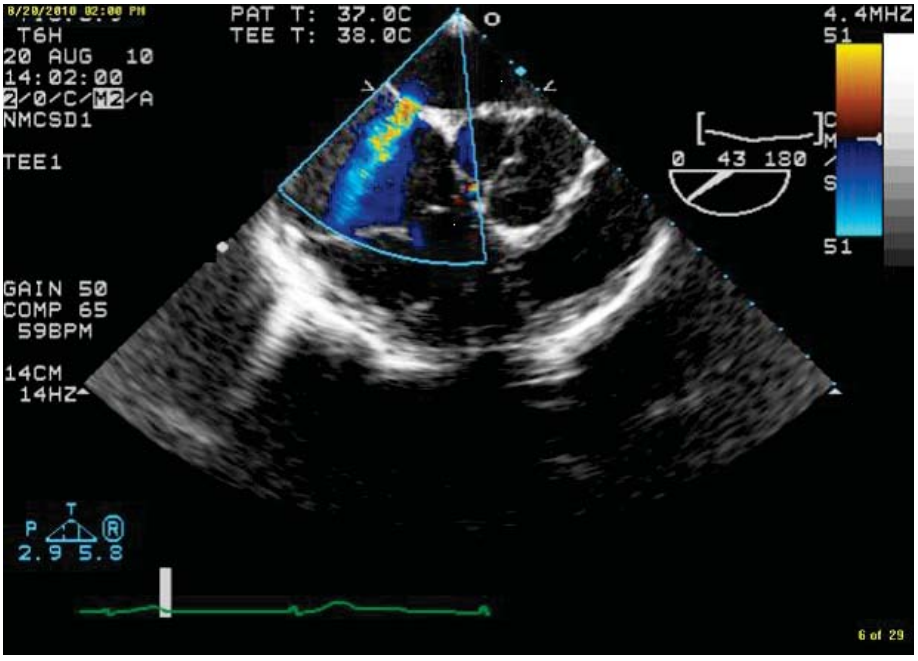

Figure 2. Preoperative TEE demonstrating residual shunt

We proceeded to the cardiac catheterization laboratory. Initially, we used the traditional crossover methods. The lesion could not be crossed easily. I used an RCB guiding catheter instead to advance our traditional stiff wire across the shunt. I was able to put a second GORE Helex device after multiple throws shaping the left atrial disc such that it did not interfere with mitral valve function. As suggested in Figures 3 and 4, the patient may have in fact had a multi-fenestrated defect with residual ASD. He had complete closure in the cath lab, and six months later was fit for full duty and back to combat duty assignments.

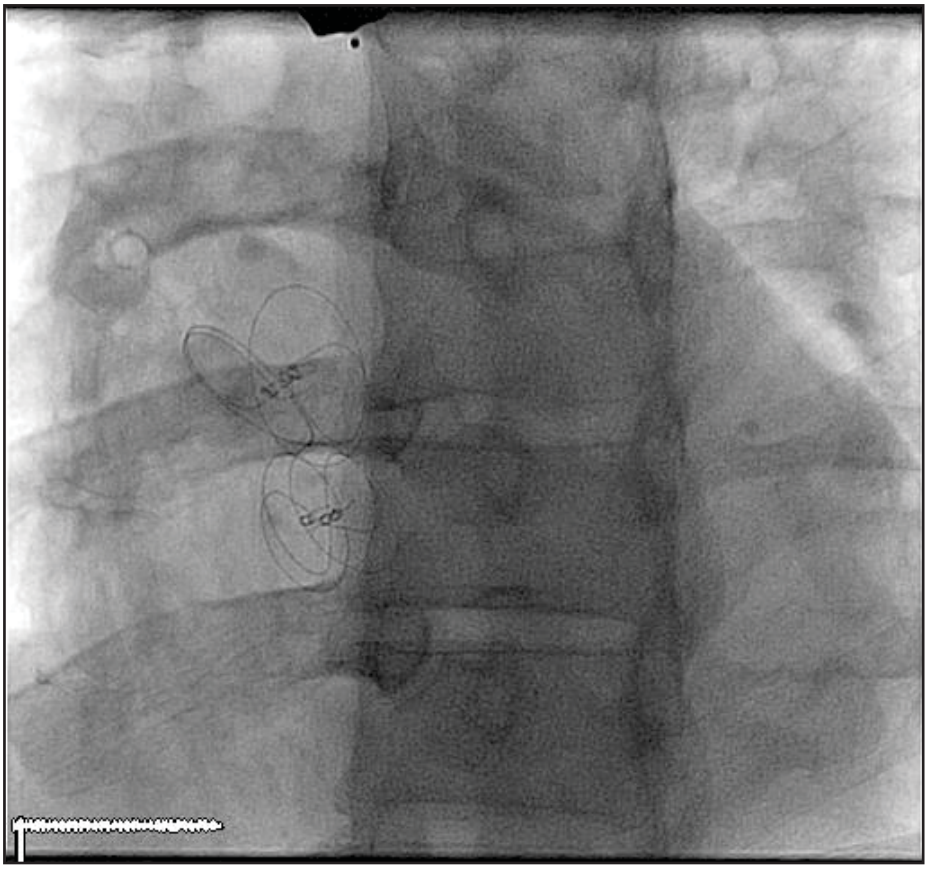

Figure 3. Flouroscopic image of two intercalated Gore HELEX devices

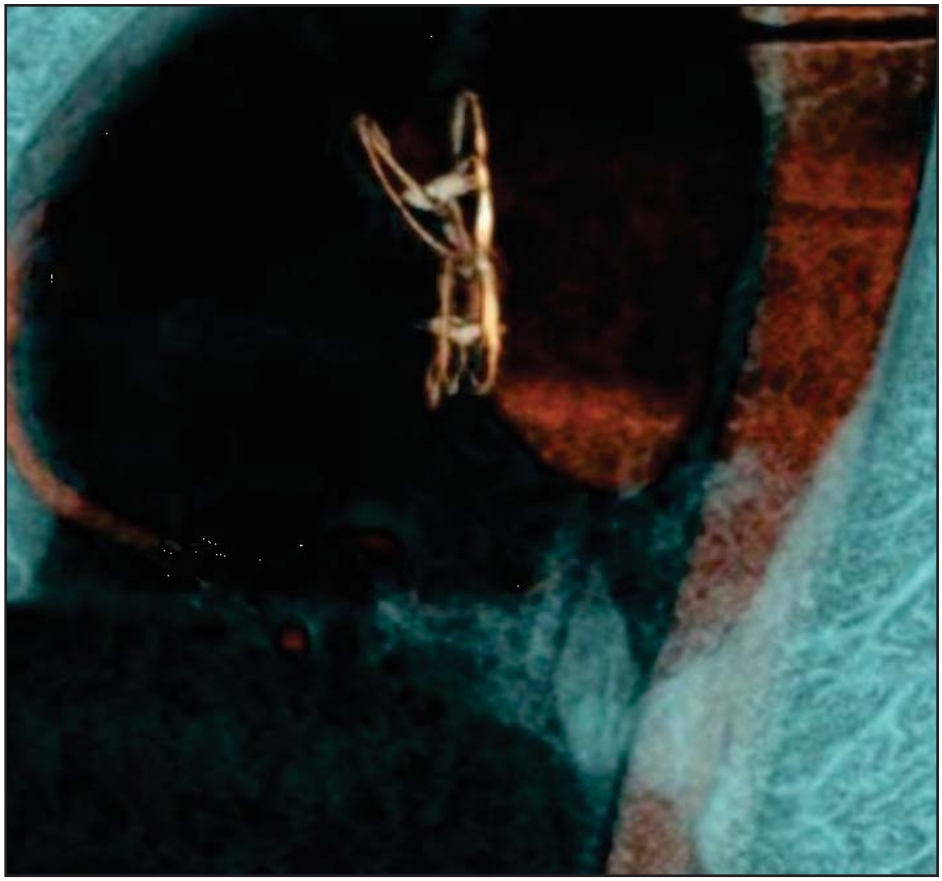

Figure 4. Color rendered CTA image of the second GORE Helex device intercalated with the first device

So that is a good foundation for what our Naval Undersea Medical Institute and BUMED guidelines mandate for medical clearance when entering into dive training. These guidelines originate within the M3B3 office. The two documents, MANMED (CH15, Arts.102,105) and MILPERSMAN, are nearly 10 years old and are overdue for revision. In these documents, there is no mention of routine use of echo to evaluate for PFO in a prospective diver. The first time an echo is used is after the first DCI event in a diver.

At that time, clinical workup ensues to include echo, TEE, MRI, CTA, according to the cardiologist's discretion. The diver is put on a no diving protocol until percutaneous closure and/or a waiver is completed to return to full duty and if the shunt is completely abolished.

Where does the guidance for how to handle PFOs in divers come for the Navy? We have seen this a couple times today and I'll go through it quickly. Many of you may not know that Dr. Bove is a retired US Navy captain. In the late '90s, Drs. Bove and Moon were asked by the US Navy to provide guidance on the clinical significance of PFO in divers. They advised the US Navy that routine use echo for screening divers was not indicated. PFO increases risk of all DCS, however, the absolute risk is small, and did not warrant routine use of echo in US Navy divers.

Another paper that is frequently referenced by our BUMED guidelines is Torti's paper[1] which corroborates Dr. Bove's original paper[2] in that the absolute risk of DCI is very low. This paper also showed further evidence that the risk ratio for DCI increased with shunt size of PFO and that a small PFO has the same risk as no PFO.

I should point out that the risk seen in larger PFOs calls for analyzing PFO shunt size and architecture with the most accurate and sensitive imaging tool, preferably a TEE. Our BUMED guidelines also refer to the following papers to justify safe and efficacious use of device therapy to treat divers and perhaps get them back to diving safely.[3]

Current BUMED (M3B3) guidelines for medical clearance when entering into dive training

- No routine use of echo to evaluate for PFO
- Expert clinical work-up after DCI event
  - Echo/TTE/MRI/CTA
  - No diving
  - Consider percutaneous closure and waiver to return to full duty if shunt is completely abolished.

Finally, Honek's paper[4] is cited by our BUMED officials as an example that large PFOs have an increased incidence of clinical DCS, and subsequent closure can completely eliminate arterial gas embolization. The question of whether prophylactic or prospective evaluation of PFO is beneficial in divers still remains and it is largely an unanswered question.

This is exactly why we are proposing a prospective study of relative risk of DCI in US Navy divers. This study is in collaboration with Captain Robinson who is at this symposium and also retired captain Bove.

Prospective study of relative risk of DCI in Navy divers with PFO

Objectives:

- Describe relative risk of DCI in Divers with PFO
  - Prospective longitudinal study of divers with PFO
  - Does relative risk increase during a diver's career
  - Do PFO's get larger as divers age and dive more?
- Improve Force-wide clinical recommendation for at-risk PFO (pathogenic PFO)
  - Benefits the Navy to preserve health of divers
- Avoidance of punitive measures or closure when simple PFO discovered
  - Benefits the Navy to preserve force strength and retention

We are aiming to describe relative risk of DCI in divers with PFO, and as such, this is a prospective longitudinal study.

Our seminal question is whether the relative risk of DCI increases during a diver's career? Do PFOs get larger as divers age and dive more? As you can imagine, this is quite a controversial topic within the non-medical community of Navy divers. Just as Dr. Bove opened the conference today, NASA does not want to answer this question, neither does the diving community. It is such a rare event and if we are so safe, why would anyone want to screen out Navy divers based on presence of a PFO. In embarking on this project, we have made it clear that such a study would improve force-wide clinical recommendations for at-risk PFOs or pathogenic PFO. It benefits the Navy to preserve the health of our divers. Even if it is avoiding one event, it is an important study and also avoid unnecessary punitive measures or closure when a simple PFO is discovered. This will also benefit the Navy to preserve force strength and retention. These are basic components of the study: Survey tool, echo with bubble

study, and periodic surveys. We are fortunate to select our patient population to be newly-inducted student divers who will be strictly monitored and can be expected to adhere to decompression tables. And, therefore, events will be genuinely decompression events, the so-called unexpected or undeserved hits.

This study is proposed to be conducted at a joint command training site. Captain Robinson is going to be senior medical officer in a few weeks there. It encompasses all branches of the US military, including Navy, Army, Air Force, Marine Corps, Coast Guard, Navy divers and EOD, undergoing the full spectrum of diving conditions, and in concert with NEDU.

At the diving training site, there are approximately 1,500 student divers per year, each undergoing at least 50 dives per year, leading to a total of 75,000 or more dives/year.

Survey Tool

Screening
- Dive history: demographics, medical history
- Symptoms: minor/major

Personal reporting
- Personal Dive log/Dive conditions
- New events reported per routine

Surveillance
- Repeat survey during dive physical every 5 years
- Pilot SMART phone APP use to increase compliance

The screening survey tool will collect dive history, diver demographics, medical history, and then symptoms. We will require personal reporting using their dive log, and new events are to be reported per routine medical workups. Surveillance survey would happen at a dive physical every five years. We are also aiming to pilot a smart phone app used to increase compliance for all enrolled divers to remain in the study and not lost to follow-up.

The initial echo will be done with a standardized protocol including bubble study with Valsalva, trained by a PFO center, and perhaps done by the same team throughout the year.

All subjects will be blinded to the result. The core lab will review for uniformity of the data set and classify shunts as specified. And the repeat echo will be done every five years at the dive physical.

There will be DCI event fallout, and undergo routine review as per protocol now and consideration for PFO closure. A return to duty after that and continued in the study with surveillance echoes.

A question was raised when we presented this for conditional approval regarding incidental findings during the echo, such as hypertrophic cardiomyopathy, or bicuspid aortic stenosis. And my response was that these conditions would need treatment regardless of when they were found. And perhaps during the training period, divers would fall out due to these conditions.

I would like to raise the question here whether we can describe an ‘at-risk PFO’ similar to what we see for young patients with cryptogenic stroke. I understand that it is not the PFO, but rather the nitrogen bubbles in DCI. As seen in the position paper by Pristipino[5], a case is made for multidisciplinary team evaluation by cardiologists, neurologists, neuroradiologists, to assign treatment based on risk of both anatomic and clinical factors. I would ask you to humor my request whether we can develop a “Risk of paradoxical Embolism in Divers”: RoPED risk

score – where the higher the score, the more the pathogenic PFO and the lower the score, the PFO is just an innocent, incidental bystander.[6]

We modified the RoPE score, originally used for estimation of risk of stroke due to paradoxical embolism, to use it for estimation of DCI risk score in divers with PFO. We will need to elucidate anatomical features of PFO that will confer high risk when married to diving criteria that are deemed high risk, such that a high Ro-PED score would be equivalent to high risk of DCI for our divers.

In summary, there is no current evidence to support a Navy-wide PFO evaluation or screening program. I hope that, in the near future, I have more data to review with you to generate a Ro-PED score to drive prospective closures in divers with PFOs being shown as at-risk, pathogenic PFO, with high grade shunting and in high risk diving.

Thank you very much. Special thanks to Captain Robinson who is here as the other uniformed attendee, Captain Waters who is our BUMED expert, and retired Captain Bove.

RoPED Score
(Risk of Paradoxical Embolism in Divers)

DCI risk score with PFO:

1. Anatomy of PFO (By TTE or TEE)
   - Large defect
   - Resting shunt
   - ASA
   - Prominent EC/CN
   - Size of Tunnel
2. Cortical infarct on neuro-imaging
3. History of DCI
4. History of CVA
5. Deep diving
6. Repetitive diving
7. Decompression diving
8. Cold water technical diving

DISCUSSION:

DR. ALFRED BOVE: We can have a question or two before we get to our last presentation.

DR. RICHARD MOON: Are you proposing to insert an occluded device in anybody who has had a neurological event and one or more of those risk factors after a single event?

DR. KESHAV NAYAK: No, not at all. Are you referring to this slide (RoPED Score) right here?

DR. RICHARD MOON: Right.

DR. KESHAV NAYAK: No. It would be a consensus evaluation based on a combination of risk factors that includes high risk anatomy and high risk diving. Remember, the proposed RoPED Score on this slide is purely a hypothetical risk score that I hope we can derive from completing a prospective study.

DR. LATSON: Didn't you say the current standard for BUMED was if they had a DCI in parallel with a PFO shunt, in order to return to diving they had to have the shunt closed?

DR. KESHAV NAYAK: Correct. If a PFO is implicated as the causative etiology of the DCI event, PFO closure is at the discretion of the expert clinician and return to duty can be achieved if the shunt is completely closed.

DR. LATSON: So the fact of it is that's the policy.

DR. RICHARD MOON: So what that means is that a large number of people who have had one of those events but happen to have a PFO, a large percentage of those the PFO is actually not related.

DR. KESHAV NAYAK: In terms of size and event, whether it is causally related or not. That is partially the debate.

RICHARD MOON: After a single event, the data we've seen earlier from Dr. Wilmshurst suggests that if you look at people who had an early onset severe neurological event, about 50 to 60 percent will have a right-to-left shunt.

DR. KESHAV NAYAK: I am not debating that. I think this slide may have been misunderstood. This is purely a speculative proposal after completion of the study to generate a DCI risk score.

DR. RICHARD MOON: My point is that after a single event, you can't tell whether somebody's event is related to a PFO or not. A third of the population have a shunt, arguably 10 percent have a large shunt. And so you end up if you use an algorithm like that, you end up closing a lot of PFOs that may not be related.

DR. KESHAV NAYAK: That may be, in fact, true, and that is where I think this study is necessary to point that out. And it is more of a suggestion that can we come up with a RoPED score, not necessarily that we are going to close every PFO that has a DCI event.

CAPT. ROBINSON: That's what we're trying to avoid. We're trying to come up with some more actual data to prevent that from happening.

DR. KESHAV NAYAK: Currently, I can share with you the indications for closure are relatively weak and that's where this study would improve that.

DR. SIMON MITCHELL: My comments kind of get to the same points. My understanding is that if there is any form of DCS in a Navy diver, so that includes a musculoskeletal event, that mandates a PFO test, even though musculoskeletal DCS has never been associated with a PFO. And then if you find a PFO, it must be closed before the diver can return. And my point, on that background, and I can't imagine why you've gone down the road to such a policy, but on that background, why on earth would any junior diver at the beginning of their career in their right mind consent to being part of that study where they may have a PFO discovered? They're gambling on the outcome on the basis of your trial.

CAPT. ROBINSON: I need to clarify something here. For those that volunteer to be part of this study, there is no repercussions to be part of the study-- there is a sanctuary. So they are blinded from the results. And the PFO, whether it exists or not, will not be closed and will not be treated. So we are proposing a prospective, long-term study, for five years if not longer to study event leads, to justify whether we need -- so the folks that actually end up falling out are the ones that have true events. What Dr. Latson just mentioned, there was a time when if a diver had an event, whatever event it is, whether it's minor and you're found to have even a simple PFO, a low-risk PFO that we have proven has no clinical consequences, will be closed for that diver if he or she wants to return to diving. That's current standard. And nobody in this room was involved in formulating that. That's why I think doing this study will change those recommendations, and that's where I hope that point can be crossed. The real-life happenings now in my clinic, there are divers who choose not to dive again after that, such an event, in the Navy, and they move to different jobs within the military.

DR. ALFRED BOVE: Let me recite a short piece of history. Richard and I were asked a number of years ago to give some advice to the supervisor of diving on this topic. And we made it very clear that there was no justification to close PFOs routinely in divers, and recommended strongly that the Navy fund a prospective, noncommittal trial just to get the data. The consequence of that, and I was not aware, the consequence of that, somebody wrote regulations at BUMED that were totally counter to that advice, and that's what exists today. So we still need the prospective trial to try to undue those regulations. I have no idea where the regulations came from. I don't think it came from any of us that are in the world of diving medicine at this point.

DR. PETER WILMSHURST: I didn't understand your scoring in the sense that you've got your – I don't know if you can go back to the score. You've got things on there that aren't been shown to have any relationship to DCI. They may have been shown to have a relationship to stroke in some studies, but not really to DCS, like atrial septal aneurysms or --

DR. KESHAV NAYAK: Correct. Those are purely speculative goals—that is not part of the study. It is a question whether we can develop something similar. And that was a question that was raised for the audience here, that can we mirror what our neurologists have done for cryptogenic stroke with a RoPED score. Are there criteria. And those are up for debate, completely out of this study. Are there specific criteria that we can find and elucidate and specify to make up a RoPED score. Those are not the actual components of the RoPED score. I simply put those up there for a debate and obviously has already created a stir!!

DR. RICHARD MOON: Very short question.

DR. GERMONPRE: Two short questions, if I may. I think it might be very well possible to devise such a score, so I urge you to continue thinking about that. We have a little bit better record than Michael Bennett in referring our divers to a cardiologist.

Second comment is that I've tried to do a similar study in the Belgium Navy, and whether it's because we're Belgian and not Americans, I've never succeeded in that. First of all, divers are going to be afraid that their records will be exposed at one point in time. And secondly, the authorities did not want to do it because they were afraid that one diver might find a good lawyer and get rich because he had DCI and had PFO.

So I really think this is a study that you need to try to do.

DR. KESHAV NAYAK: Thank you Dr. Germonpre. With your help I hope we are successful. I want to thank Captain Robinson, Captain Bove who have been instrumental in putting this together. I will have to convince everybody involved that this is data that is required. And perhaps with UHMS support, we can complete this study in the next few years.

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SPUMS Consensus on PFO and Diving

Summary of the Joint position statement on persistent (patent) foramen ovale (PFO) and diving. South Pacific Underwater Medicine Society (SPUMS) and the United Kingdom Sports Diving Medical Committee (UKSDMC).

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SPUMS held its 2014 conference with the theme of persistent (or patent) foramen ovale and diving. My first assignment 24 hours after being elected SPUMS President in May 2014 was to chair a workshop on PFO and diving. The findings will be published this week in *Diving and Hyperbaric Medicine Journal*. [1] The conference was also attended by specialist members of the United Kingdom Sports Diving Medical Committee (UKSDMC). My presentation today will not be a literature review. The supporting literature has been summarized today. I'll just present the findings of the 2014 SPUMS workshop.

I'd like to acknowledge my co-authors, Simon Mitchell, Peter Wilmshurst, Mark Turner and Neil Banham who was the convener of the conference last year. I also acknowledge all the participants of the workshop held at the 43rd SPUMS Annual Scientific Meeting, and subsequently members of the UKSDMC. There are no financial or other conflicts of interest to declare.

So why should we develop a position statement specifically for PFO?
We had many inquiries from our members regarding PFO in divers. One of the key questions was whether or not we should do routine testing for PFO at diver health assessments. We needed to provide guidance to our physician members of our organization and also to try to make sense of the growing quantity of PFO literature. During the week of the SPUMS conference we had multiple presentations on PFO. Speakers presented literature summaries, large case series, individual case presentations, including personal recaps from SPUMS members.

The presentations examined the issues and medical conundrums that needed to be answered. The key issues and conundrums evolving from the week's presentations were distilled by authors Smart and Mitchell, prior to the workshop. Smart chaired the workshop with panel members Wilmshurst, Turner, Mitchell and Banham. Each PFO issue was then presented to the workshop delegates for discussion and consensus. After the workshop, the consensus was presented to UK Sports Diving Medical Committee for further input and refinement. Note that Wilmshurst and Turner were both expert members on the UKSDMC; hence there was quite a degree of

input from their committee representatives during the development of the position statement. The joint position statement was finalized, formatted and referenced for publication in *Diving and Hyperbaric Medicine Journal*.

Persistent or patent? Given that we've gone into cahoots with the English, we needed to make sure that our definitions were correct from the Oxford English dictionary. *Persistent* is defined as "*continuing to exist or occur over a prolonged period"*, as opposed to patent which is defined as "*being open and unobstructed and failing to close"*. An analogy for PFO is the "planets lining up". Adverse events from PFO's generally don't occur unless multiple factors are in alignment to cause bubbles to cross from right to left. The workshop participants chose *persistent* because many foramen ovale are physiologically inactive until the planets do line up and produce the shunting of bubbles, followed by clinical DCS.

I will now summarize the questions that were asked and then provide the solutions that resulted from the workshop.
The questions were:

1. Is routine testing for persistent foramen ovale required at the time of the initial or periodic dive medical?
2. In what circumstances should physicians consider testing divers for PFO?
3. If testing is performed, who should undertake the testing and how should the testing for PFO be undertaken?
4. What constitutes a positive PFO testing result?
5. How does that correlate with risk of DCS?
6. Following the diagnosis of a PFO, what options are available to the diver?
7. How should these options be assessed based on the clinical setting and the risk profile?
8. Following closure of PFO what criteria must be satisfied before a diver returns to diving?
   - I think that is actually one area that hasn't been covered in much detail today at the conference. For example, how long after a PFO closure should a diver wait before returning to diving? Should we keep them on medication or stop medication post-closure before we allow them to dive? What testing should we do to clear them for returning to diving post PFO closure?
9. And finally, for the above questions, what references are available to support the consensus solutions, classified by level of evidence?
   It seems that the definition of various levels of medical evidence changes over time, but the broad categories are always the same. On this occasion, category 4 evidence was defined as expert consensus of SPUMS and UKSDMC if higher levels of evidence were not available.

The answers to the above questions constitute the joint position statement on persistent (patent) foramen ovale and diving from SPUMS and the UKSDMC being published in *Diving and Hyperbaric Medicine Journal.* They are summarized below:

PFO Testing

First of all, routine testing for persistent foramen ovale (also referred to as "patent" foramen ovale) at the time of dive medical fitness assessment (either initial or periodic) is *not indicated*, based on level IV evidence.

When should physicians consider testing for PFO?

Investigating for PFO should be considered in any of the following circumstances: a history of DCS with, cerebral, spinal, vestibulocochlear or cutaneous manifestations. Consider investigating with a current or past history of migraine with aura, also a history of cryptogenic stroke, and a history of persistent foramen ovale or atrial septal

defect in a first degree relative. That's another area we haven't touched on today. There are some genetic risk factors for PFO. All of the above factors are supported by level IIa evidence.

Where and how should PFO testing be performed?

Testing for PFO should be performed in centers well practiced in the technique. That's our expert advice (Level IV). Testing must include bubble contrast, ideally combined with transthoracic echocardiogram and provocation maneuvers. (Level IIa evidence) The transthoracic echocardiogram is more sensitive because it is undertaken with a cooperative patient who can perform provocation maneuvers such as sniffing, Valsalva and elevation of limbs.

Two dimensional and color-flow echocardiography without bubble contrast is not adequate. (Level IIa evidence) I've seen an example of that just recently. At the Hobart Hyperbaric facility, a patient was treated after sustaining an iatrogenic gas embolism. After recovering from a cystoscopic procedure, he was in a sitting position when a central line was disconnected by staff. The line wasn't clamped off. He became quadriparetic within 30 seconds of the disconnection of the central line, and lost the ability to speak. Initially the gas embolism wasn't recognized – it was thought that he had sustained an allergic reaction to medication and became confused.

Eventually the anesthetist was called and when he saw the disconnected central line, he went very pale himself. The patient was immediately laid supine. Our hyperbaric team was consulted and the patient transported to us. He recounted to hyperbaric staff, "*I felt my mind and my muscles melt*". He was treated for cerebral arterial gas embolism, which was suspected to be due to a PFO. He has recovered fully.

Post HBO treatment, the physicians in their wisdom ordered standard trans esophageal echo without bubble contrast. This did not demonstrate a PFO. The Hyperbaric team disagreed with them respectfully. A bubble contrast echocardiogram was then requested and shunting was observed without provocation – a big PFO. This is an example of making sure that you do the right tests. The patient is now being assessed for closure due to stroke risk.

The testing must include the use of provocation maneuvers to promote the right-to-left shunt, including Valsalva release and sniffing, as already discussed above. Provocation should be undertaken when the right atrium is densely opacified by bubble contrast (Level IIa evidence).

If the testing for PFO is positive, what are the risks for the diver?

Spontaneous unprovoked shunt or a large provoked shunt represents an unequivocal risk of DCI. (Level IIa evidence) Smaller shunts are associated with lower but poorly defined risk of DCI. The clinical setting is important for interpretation. So a smaller shunt where someone has had a really serious episode of neurological DCI has already proven their risk and would be assessed differently from someone else who has come in with a history perhaps of migraine with aura. The risk in the latter case is more difficult to quantify. All the information must be taken into account.

What options does the diver have if a PFO is detected?

The options for the diver are fairly simple. Stop diving (level IV evidence), dive conservatively (level IV evidence), or close the PFO (level III evidence). The diver options should be in considered in consultation with a diving physician (level IV evidence). For the second option, we provided some recommendations regarding diving conservatively; these have been empirical but they are based on trying to reduce risk. The options include single dive days, diving well inside decompression limits, diving less than 18 meters, using decompression stops where not mandated

and use of nitrox on air tables. They're just general recommendations and have been kept deliberately broad rather than trying to be too specific. The third option is to close the PFO.

The options outlined in the previous statement require careful consideration of the risks and the benefits in a clinical setting that led to the testing. (Level IV evidence), the author has personal experience with this. PFOs are common enough to affect almost everyone. One of the author's daughters has a PFO. She trained as a diver at 13. She then started getting migraine with aura when she was around 15 (not related to diving). A PFO was identified at bubble contrast echocardiogram. Being a teenager, she wanted the migraines with aura fixed, her DCI risk and everything else fixed with one fell swoop of a cardiologist. After considerable debate, the family decided on option two and elected to risk-mitigate her diving practices.

Following closure of PFO what criteria must be satisfied before a diver returns to diving?

Our workshop concluded that following closure of a PFO, before returning to diving, the diver requires a repeat bubble contrast echocardiogram to confirm closure. Diving should not be resumed until satisfactory closure of the PFO has been confirmed, and the diver has ceased potent antiplatelet medication. This is generally a minimum of three months after the procedure (level III evidence).

SPUMS Consensus

The SPUMS/UKSDMC position statement reflects the available literature at the time of publication and is regarded as a live document. There have been papers presented at this workshop which have been published after the SPUMS/UKSDMC position statement was developed. It usually takes six to 12 months of working through a position statement before it is finally published. The position statement will be subject to review and revision as new information becomes available. Hopefully this position statement is of assistance to today's workshop. If our job has been done correctly, we should all be on a similar page, or at least the same planet, anyway.

REFERENCE:

1. Smart D, Mitchell S, Wilmshurst P, Turner M, Banham N. Joint position statement on persistent foramen ovale (PFO) and diving. South Pacific Underwater Medicine Society(SPUMS) and the United Kingdom Sports Diving Medical Committee (UKSDMC). *Diving and Hyperbaric Medicine*. 2015; 45(2) 129-131.

Panel Discussion

DR. ALFRED BOVE: As of now, the panel discussion has begun. Richard assembled a series of questions that I think we reviewed and created a consensus or a good start for developing some conversation on a consensus and a guideline similar to the SPUMS. I will say I've been working on the guidelines of the American Heart Association American College of Cardiology. We now have guidelines from the European Society of Cardiology, guidelines from the Canadian Society of Cardiology and a variety of other places. They don't always agree. So I think there's a precedent for specific organizations creating guidelines or recommendations. They don't always necessarily totally agree. But I think when you look, the consensus across most of the guidelines that I would be witnessing are close enough that they all are saying pretty much the same thing. So I think if we create a consensus, it's going to sound a lot like your SPUMS consensus. I guess the question is why don't we just put our name on it and plagiarize it.

Why don't we go ahead and put the slides up. One written question was submitted about what about return to diving in a patient with a small PFO. I guess that will come up as a point for discussion. The question is, if you identify small PFO in an asymptomatic diver, how do you deal with that? Or, if you identify a small PFO in a diver that's had DCS of different levels, minor, major, what do you tell diver?

Another question that was raised was, are there any contributions from shunting from, for example, bronchial base. Again, I think we as diving physicians don't think much about the nuances of the pulmonary circulation, but it is an important area to think about when we deal with this kind of an issue.

I'll raise the question about the role of vasoactive mediators release by activated platelets in the symptomatic responses in patients with PFO. Some of those, particularly serotonin (5-HT) are potent vasoconstrictors, and that might be something to provide an understanding of, for example, the aura of migraine. So there are a couple of things for discussion that are worth bringing up at this point.

Richard, while we're doing that, why don't you read the first question so we can start the conversation.

DR. RICHARD MOON: So the first question, you all have a copy of it, is the association between PFO and some types of DCS of the cause and effect nature, i.e. seething of the arterial circulation with bubbles or just merely correlated with some other factor like genetic, in other words, true. True and unrelated.

DR. ALFRED BOVE: I think one can see the context of this question knowing that of all the divers in the world 25% or 30% have a PFO. So I think Richard's question is valid. Is this an observation that PFO is just highly prevalent in the population and we expect to see a large number of decompression syndromes related to PFO simply because it's there or is there clearly a cause and effect relationship? I'd appreciate some comments. We've seen some compelling data today suggesting that we do see a cause/effect relationship. Is anybody willing to challenge that?

DR. RICHARD MOON: I think, Fred, if I can just interject, the main evidence that it's not true and unrelated is the fact that we've now seen evidence that closing a PFO changes the pattern of decompression illness; it appears that likelihood of getting decompression illness is reduced. So I think to the extent that the data are clear, that's (causal relationship) pretty clear. If you get rid of the germ and the disease goes away, then cause and effect is established.

I put this up only to make sure that we're all agreed on that. If anybody has any differing opinions, please shout it out now.

DR. GARY LATSON: I think it would have to go somewhat in the vein or if you're looking at it from the scientific perspective, it's not proven beyond a shadow of a doubt statistically, it's not cause and effect data; it's not prospective data. But I think if you're looking at it from the weight of the evidence, I think the weight of the evidence strongly favors the association. It's kind of like criminal court versus civil court. So for the scientists in the group, they can certainly make an argument that the causation effect is not established (beyond the doubt). But for the physicians in the group that have to treat patients day in and day out, I think that the presumption of the evidence is you have to presume some relationship.

TOM NEUMAN: I would echo what Gary says. I can think of several reasons that the observations that have been made have been made without a causal relationship. I think the evidence strongly suggests a causal relationship between PFO and certain forms of DCS. On the other hand, I think the evidence is pretty strong that it's not related to a simple limb bend. So I'm basically echoing what Gary said.

DR. ALFRED BOVE: Does anybody object to the concept that there's a dose-response relationship between depth and time and the amount of venous gas emboli that one might find in the circulation after decompression? That is, the longer the depth-time exposure, the higher number of venous gas emboli you'd expect to find. Is anybody willing to challenge that concept?

DAVID DOOLETTE: Yeah. Absolutely. It is the (entire) profile, not just the depth-time exposure. I just want to challenge the simplistic notion that it's depth-time. It's related to the profile how much decompression you do.

DR. ALFRED BOVE: What would be an alternative? What I'm gathering is that you'd think that the profile itself rather than just the nitrogen load would be also conducive to generating risk. So a 100-foot dive for one minute could be a bubble-producing dive versus a, let's say, a 100-foot dive for 30 minutes? Is that the concept that the profile itself can produce bubbles?

DAVID DOOLETTE: No. I was just challenging the simplistic notion that you can describe it in such a simple way as the depth-time exposure. It's a lot more complicated than that, how much decompression is done. I think it's going to be if you're trying to get towards some sort of statement where dives of 30 minutes duration might result in VGE that can cause PFO-related DCS in dives, but minutes duration can't, I don't think you can go there because it's more than just the depth, just the time. It's the way, how much decompression is done.

DR. ALFRED BOVE: But I guess then the question is: Is it reasonable to advise somebody, regardless of whether they have a PFO or not, that they dive conservatively? Can we make that statement to limit their diving exposure to avoid risk for DCS with or without a PFO? Is that a valid statement?

DAVID DOOLETTE: I think you can make that statement, but it has to be along the lines of what David Smart and some other people outlined. You might have to say do more decompression than is prescribed either by using nitrox or on air tables or limit your bottom time to very well inside the no stop limits or add safety stops and that sort of thing. I think coming out and saying decompression dives are no riskier than no decompression dives or 30-minute dives are riskier than 10-minute dives, it's not that simple.

DR. ALFRED BOVE: One of my colleagues in cardiology said level of evidence is a bunch of experts sitting around the bar with glasses of beer trying to come up with a consensus.

GLEN HAWKINS: The other thing is I think Simon brought it up beautifully that all the evidence is circumstantial for both PFO versus DCI. One thing we've not really taken into account is the size of the PFO as well as the gas load. So I think there's more things involved because people can have a big gas load but a small PFO. They may not get into problems. It's fairly obvious that a large proportion of the population has potentially some form of PFO, but we don't get a massive amount of DCI or DCS with a lot of very provocative diving. It's not just gas load or having a PFO or not. It's a combination effect. A very small PFO is the same as the risk of no PFO at all.

DR. RICHARD MOON: We're going to get to that later, Glen. Thank you for bringing that up.

DR.LUDEK SEFC: This is about my own experience with PFO and DCS. It's known that patients who suffered one DCS hit are more susceptible for another one. After being diagnosed with PFO, I tried to dive very conservatively, to moderate depths, much shorter times, not getting close to the non-decompression limits, but my DCS problems continued. Conservative diving did not help me. We are planning to do more experiments in decompression chamber to study how different types of conservative diving would affect occurrence of the bubbles. So far we have learned that even if we can diminish the number or incidence of venous bubbles, we still see arterialization. So it should be thoroughly thought over.

DR. RICHARD MOON: Thank you for making that point, which brings up another issue. It appears that there is a subpopulation of people who have repetitive events and do have a PFO, and, yet, bubbles are, if not ubiquitous, extremely common and PFOs are also extremely common. So given that we've got tens of thousands of people with PFOs and bubbles diving (who do not get DCS), the question comes up as to whether there's a third factor or a fourth factor that we haven't discovered yet.

One anecdotal observation of Fred is that he has a patient, I shouldn't talk about your own experience, Fred, but he has a patient who got recurrent cutis marmorata. Fred prescribed clopidogrel and the event stopped occurring, which suggests that there may be a platelet factor or a tissue factor that is important in this. Yes, Peter.

AUDIENCE MEMBER: I would like to make a suggestion, which is that, as we've heard, there's so many unknowns that we still don't know. We don't know when and how people are actually making VGE. Some people seem to make more, some people seem to make less. The dive profile, the ascent rate, etc., are all the factors that we can't figure in. Even with probabilistic bubbles it's very difficult to do that. Same thing goes for PFOs. There's different anatomies, different types of fenestration, long term or short term. There's so many things we don't know, we'll never be able to produce any recommendations based on hard, scientific, valid grade 1, grade 2 data. So here is an idea: why don't we sum up all the factors that we think may have an influence, like factors that produce VGE, factors that might increase the shunting through a PFO, and then recommended to divers (regardless) whether they have or have not a PFO just to try to limit those factors to decrease the risk. That will solve all the problems.

DR. ALFRED BOVE: We don't have Dr. Nishi here at the meeting, but we do have Dr. Bateman here at who is about 150 yards away from where Dr. Nishi worked for most of his life. My recollection is that Ron created a set of tables that he said were bubble free tables. Can you say a word about that? Is that true? Are there tables we can use that don't produce any bubbles?

BILL BATEMAN: No, (Ron didn't say "no bubbles". Ron was always very careful to say that the word "no" shouldn't exist in science or in medicine. Very low probability (of bubbles), yes. And this is actually a particular attribute (that we have to be aware of) of Canadian forces divers that may be helpful to the future study of this phenomenon. We parse all of our divers into shallow water divers who very rarely go deeper than 18 meters, so they limit it to no deep profiles only exceptionally going to 30 meters, and deep water divers, so much smaller number are the ones that do much deeper diving up to 100 meters of sea water using mixed gas and rebreathers, exotic stuff. It is that small and select population that we've chosen to carry out a routine bubble contrast transthoracic echo on. And thus, are violating principle one that the SPUMS criteria have.

As a routine, we are screening those people. In the last year we have made a joint operational, medical and command decision continue to screen our deep divers and not to disqualify those people (with PFO).

The number of divers we deal with is rather small. I see my colleagues in USA talking about 7,000 divers. In the five years we've been doing this we've got 70. So it's going to take us a long time to collect that data. But it's an opportunistic population. We may be able to have some insight on the kinds of things that we're talking about today.

The reason we are justifying it also is a unique aberrant of Canadian occupational health was that we can choose to carry on doing the study based on the occupational requirement of this at-risk population to make informed consent decisions on whether to participate in the table development of the likes of Dr. Nishi. So in a nutshell, no, we don't believe there is a completely low risk, but there probably is a lower-risk population and a higher-risk population, which we've arbitrarily picked and we have an opportunistic way to weigh ahead for our own population.

DR. LUDEK SEFC: I want to point out that maybe the number of DCS we are considering is underestimated. During diving trips, informally discussing with divers, I'm always surprised how many divers are talking about decompression incidence which they did not refer to a doctor. Skin rash - never mind. Headache can originate from something else. So my opinion is that the number of DCS episodes is much higher than published in the literature and referred to the physicians.

DR. RICHARD MOON: I think that's possible, although I think we've all agreed that the type of DCI that is associated with PFO, except perhaps for skin rash, is the more severe types that is less likely to be under recognized.

DR. LUDEK SEFC: I observed a lot of mild decompression incidents in practice. Usually these divers do not refer to the doctor. They breath oxygen, but it's never recorded.

DR. ALFRED BOVE: Dr. Moon has another meeting to go to so we'll continue on. Richard, go ahead.

DR. RICHARD VANN: To answer your comment or your question about no bubbles tables, I've looked into it. I'm sorry Ron is not here. He frowned on anything greater than grade 2. So when he finally formulated the tables, DCIM tables, he ensured that VGE higher than a grade 2 would be very rare within those tables. They were low bubble grade tables.

Now, Richard has gone away, but he had mentioned a third factor, and I know we're speaking about PFOs, or I guess we should say right-to-left shunt specifically here, but are we forgetting about a possible third factor of the lung as a source of AGE, which is more difficult to quantify and harder to measure? But it does muddy the water as far as answering the question is concerned.

DR. ALFRED BOVE: The lung in terms of.

RICHARD VANN: Being a source of AGE itself.

DR. ALFRED BOVE: Through shunts or through minor barotrauma?

DR. RICHARD VANN: Not through barotrauma, no. Shunts and there are other ways. If you have very small bubbles, they will get through the lung. If you overwhelm the lung's capacity as a filter, if you produce vasodilatation or have pulmonary oxygen toxicity. So there are a number of factors that are important there. And how does that fit in with assessment of what should be done regarding a PFO.

DR. ALFRED BOVE: We showed some interesting data today on the physiology of pulmonary let me call them AV shunts that are reduced by hyperoxia and increased by hypoxia, increased by CO_2 and decreased by other vasoconstrictors. So you can get the sense that things that cause vasoreactivity in a pulmonary shunt would either increase the flow through the shunt or decrease the flow through the shunt and, therefore, you're right, muddy the waters in terms of a cardiac level shunt. And that needs to be considered. Much more difficult to measure, among other things, because we don't have simple ways to look at pulmonary AV shunting.

I guess the question of how many bubbles are needed is, again, some of it based on the idea that we could provide advice to divers, particularly in the sport diving world, to dive with minimum risk for bubbles, that would be at least a concept that would be put forth. What I'm hearing is most people would say that makes sense, but there's some questions about whether it's absolutely valid. But, again, it's probabilities, not just black and white decision making. Go ahead. There's some other questions. Why don't you comment first?

AUDIENCE MEMBER: I wanted to make a couple comments on where we're evolving to, it seems like, since we're not going to advocate screening for the asymptomatic diver that's never had DCI, the time that we're likely to find the PFO is after the guy has had his first neurologic DCS. So what we're really struggling with is what our recommendation is for somebody who has been bent once? Are they truly at more risk for being bent a second time? Is there something that happens on that initial episode of DCS that makes it more likely? Just like when you have heat stroke. Once you've had heat stroke, you are more likely to get it again. So is there something like that going on in DCS that we don't yet understand. That's a possibility.

The other thing we struggle with is the history of why the Navy's policy is the way it is. I can give some historical perspective because I was involved in the discussions. I didn't make that policy. Please don't shoot me. But I do have some understanding of the logic that went into that policy and would be glad to share that if anybody is interested.

DR. ALFRED BOVE: It would be interesting to hear that sometime. Because, again, as I said, Richard (Moon) and I were asked to advise on that and we advised exactly the opposite of what the policy turned out to be and never got any commentary back on that.

DR. PETER WILMSHURST: I wasn't going to say this, but that's a good point. People who have heat stroke don't have a second episode because they had a first episode. They have a second episode because what caused the first episode is causing the second episode. Just as people who have a second myocardial infarction had the second myocardial infarction because they've got coronary disease which caused the first as well.

I think there's a lack of common sense here, if you don't mind me saying so. I mean, cerebral hemorrhage can occur in people with normal blood pressure, but it's more common in people with the high blood pressure, and it's more common in people with the highest blood pressure. If you have someone who has had a cerebral hemorrhage and their blood pressure is 350/150, you don't start thinking, well, maybe we shouldn't treat their blood pressure because they might have another reason.

I'd suggest, and I'm not a member of this society, but I suggest that you actually look at the SPUMS guidelines and see where you differ from them because there's already a guideline and you ought to look at them. That's what I think. That would be common sense.

DR. ALFRED BOVE: The thing is we have to create one first to see if it agrees or disagrees. That's what we're trying to start with today. I appreciate the comment.

PHILLIP FOSTER: I see many patients with arterial venous shunts. And I was thinking that we have a way to detect grade 1, 2, 3 PFO, contrast TTE, but there may be some other things we can do. You look at maybe a protocol that you have combining exercise and Valsalva and see what type of shunting (that may cause). So, of course, how much (bubbles) do you have in right side of your heart. Genotyping and micro particles may also help. To the risk of the opening of the PFO may correlate to a size of PFO so you don't have to do the occlusion in all the people. They (with small PFO) may not be susceptible.

So they're all routes that we should investigate. We can do this on a regular basis and it's cheap. Very, very cheap. It used to be very expensive, but now costs have been decreasing by ten times in two years. We may do some testing in the individual DCS related to grade 3 and 4.

DR. ALFRED BOVE: Thank you. I think one of the issues we have in the current research environment is funding for these kinds of studies because we don't have a population like the population of people with myocardial infarction in the United States or heart failure or hypertension. We've got a fairly small population. And trying to get funding for this is difficult. That's why we look to the military a little bit because it might be one of the places where we can do some of the experimental studies like that.

The recommendations are well taken if we can accomplish that. Go ahead, Michael.

MICHAEL BENNETT: I just wanted to make the point that, and I'm sure the vast majority of people in the room perfectly well understand that, but it's not coming across in our discussion very clearly, I think. And that is that what you do with divers is highly dependent upon what kind of divers they are. So we've heard an example of the Canadian military, which are I think a perfectly sensible decision to screen, and a true screening is test everybody, and have a plan for what you might do depending on the result. For those people who are going to be at high decompression stress, however, the Doolettes of the world wish to define it and we make input into

that. That's an extraordinarily different situation from most recreational divers where I think it's clear that we should never advocate screening. It's just simply the yield is too low. The reassurance is too high. We've all had, I'm sure, encounters with divers who believe that once they've had the PFO shut, they don't need to worry about decompression tables anymore.

Wherever this workshop is going, I mean, we might well consider to either not consider the whole gamut of diving or concentrate on one end of the spectrum or the other. That might be one way to go.

DR. ALFRED BOVE: Comment well appreciated. Most of the work I do now in terms of diving consulting is recreational divers asking whether they can dive with diabetes or stents or atrial fibrillation or pacemakers and so on and with PFOs. That's our bigger population, but certainly the recreational divers aren't the only divers. We have commercial and military divers, all of whom need some sort of support. It seems to me that considering the environment of the divers is essential to the decision making that we have to make here. So it's a comment well taken.

I think Richard put a question on here of, “Is there a minimum degree of shunting, that is, can we ignore a small grade 1 PFO and pretend it's not there? Is it only grade 3s?” So I'll leave that question open, but go ahead and make your comments and maybe you can make a comment about that question as well.

DR. NEAL POLLOCK: It's not that I want to go back to the idea of future susceptibility based on one event. We have to remember that some dives are very well so provocative that it doesn't matter what you have. So you have to evaluate that before you consider the PFO. In some dives it was absolutely certain that they would have DCS.

DR. LUDEK SEFC: I have two brief comments. First, there is one paper showing divers with small PFO during time open the PFO, increase in size. It was done just on a limited number of divers. So it was very important to confirm this because in the normal population with age, the number of PFO diminishes. In divers, it seems to be opposite.

The second comment is to think about Valsalva. It was demonstrated that Valsalva can open a PFO, but bubbles appear during ascent when divers do not perform Valsalva. There is higher incidence of DCS in experienced divers with a long record of diving. The most experienced divers do not perform Valsalva at all. Instead of this they perform Frenzel maneuver. With minimum effort and with minimum increase in the intrathoracic pressure. So we shouldn't overestimate Valsalva during the diving. Of course, it is very important in screening, but under the water, mostly not.

DR. ALFRED BOVE: Thank you. Having been a diver for a long time, I can't imagine being able to dive without being able to do a Valsalva maneuver at least three or four times in a given dive. You're right, everybody is going to do some degree of Valsalva maneuver, which is generally going to provoke a transient increase in right atrial pressure. I want to hear about the dynamics of the sniff as well.

DR. PETER WILMSHURST: I first want to say that PFOs do not open. I've looked at some of my divers 15 or 20 years after I did their first contrast echoes, the ones from the 1980s, there is no difference.

Secondly, Valsalvas, we do it all the time. When you're in the boat and you lift your bottle, you do a Valsalva. I do more Valsalvas in the year straining at stool than I do when diving. So let's, you know, forget about it. Anyway, so it's nonsense. We lift heavy things all the time. It's not Valsalva when you're -- or clearing your ears. It's nothing compared with picking up suitcases and so on, which you do all of the time and you don't call it Valsalva.

DR. ALFRED BOVE: Can you tell us a little bit about the right atrial dynamics of a sniff.

DR. PETER WILMSHURST: You just increase flow into the right atrium. That's what happens with a Valsalva. What you do when you do a Valsalva is you empty the heart. You increase intrathoracic pressure and you empty the heart. And when you release it, the blood flows preferentially back to the right heart because the lungs, the right heart and the left heart are all empty. Shunting occurs on release of the Valsalva when the right heart fills and the left heart is empty, so the atrial septum moves to the left. That's what happens. It isn't a pressure thing. It's a flow thing. It is that you have two empty chambers and one of them is suddenly filled with the release. And it fills up and it opens the flap.

DR. ALFRED BOVE: I understand that. I think you can't expect the surge of blood coming into the right atrium to occur in an isobaric, in a neutral pressure. I can't imagine that you could produce a shunt from right-to-left without the pressure in the right atrium being slightly higher than the pressure in the left atrium in that brief transient.

DR. PETER WILMSHURST: It is slightly higher, but it's mostly the flow directive is because of the increased flow. But, in fact, the pressure goes down on releases of the Valsalva in the chest. It isn't an increase in pressure. It's a reduction.

DR. ALFRED BOVE: You have a volume surge coming into the atrium on the right side relative to the left. I'm asking specifically about the sniff. Does it have the same dynamic?

DR. PETER WILMSHURST: It increases filling of the right side of the heart as inspiration does. That's why we know there's an ASD because you get fix splitting rather than moving splitting in the second answer.

DR. ALFRED BOVE: As a parenthetical statement, our guidelines people that talked about thoracic aortic aneurysm, I don't know if you're aware of this, but they warned about Valsalva maneuvers in people with thoracic aneurysms because that blood surge not only goes through the right heart, it goes through the left heart. And there's been incidence of aortic dissections induced by Valsalva maneuvers, which I think is an interesting secondary concept.

DAVID SMART: Number one, we didn't differentiate between occupational and recreational divers. And I agree the military could be a special case because of the high performance aspects. But what you're talking about is whether or not this is a risk of DCS based on the physiology of the heart, not the type of diving. Recreational divers are often just as radical as professional divers in terms of risk. That's the first one.

Second one is we also deliberately kept it broad because I think you're in danger, and this is with respect to when running it, you're in danger of bogging down in too much detail and getting tied up in knots with a position statement. So we managed to keep everything broad because of that.

DR. ALFRED BOVE: Thank you.

PHILLIP FOSTER: I just wanted to add something the echmo do that in COPD patients. We do that also in ARDS, acute respiratory distress syndrome. We need to remove the CO_2. That's too much on the arterial side. And we do that, it's like an arterial venous shunt peripheral, and we remove that. And those patients are experiencing a high level of strokes and TI, unexplained, probably bubbles, oxygen bubbles.

And there is another study also. Patients have a continuous flow with a mean blood pressure. And I have some slides that I didn't show this morning. If you want to look at some slide about arterial venous shunting. When you have those shunts, you show the differences. I don't know if you want to look at this now. Maybe it's too late. But what I'm thinking this is a measure issue, those bubble emboli, embolization of the bubbles in the brain. And we should have a protocol that really targets those individuals who are susceptible to that and I wonder if they are experiencing any mild fatigue, divers with fatigue, not waiting for DCS, just fatigue. Maybe an echo and a Valsalva, but doing something noninvasive and doing the detection at early stage to prevent any further DCS.

If you look at something else, what I showed this morning with the white matter hyper intensity in those U2 pilots, there's something striking. 90% of the pilots, active duty, responded they had all MRIs. Out of those 90% of pilots 80% had white matter hyperintensity more than control group. And they have not been screened for PFO, but they probably have incidence of PFO about 25% , 27% as it was described earlier. And it happens in more than the classic 25% PFO.

DR. ALFRED BOVE: I haven't had --

PHILLIP FOSTER: It's unpublished.

DR. ALFRED BOVE: I haven't had a patient with an LVAD (left ventricular assist device) come and ask me if they can go diving. I'm sure it's going to happen soon. But the dynamics is a very similar process. You can set that to shut down the diastolic pressure to very low levels, which in the presence of a PFO ought to induce a right-to-left shunt. And I don't recall seeing that happening at this point. So that's another interesting area of observation is whether an LVAD -- if you set the LVAD wrong, as you know, it will pull the left atrial pressure way down in compared to the right atrial pressure. If there's a PFO, it would likely open the PFO and cause a right-to-left shunt, not with bubbles but with desaturated blood. I haven't seen that happen at this point. And I think if we try to do a bubble study in an LVAD patient, somebody would object because you wouldn't want the bubbles going through the LVAD. So there's some interesting dynamics having to do with the balance between right and left atrial pressures that could be looked at in different models that might give us some insight to what's going on in the diving community.

PHILLIP FOSTER: So my job is to look at the relationship between the heart and the lungs in those patients and assess whether they're going to either transmit or seal the LVAD. The continuous blood flow is something in those patients who had systemic hypertension, which is also a risk of stroke and TI.

DR. ALFRED BOVE: Fortunately, I don't think we'll see that. They have to bring batteries with them and they don't work well in saltwater.

PETAR DENOBLE: Time is running out. It doesn't seem that we are close to position statement. I would propose that we put on the screen the SPUMS position statement and see where we agree or are we in disagreement because I think that's the only way to get some instructions for the people to derive position statement later.

DR. ALFRED BOVE: Sure.

DR. PETAR DENOBLE: Or if you have questions that would contribute to the position statement, I would rather discuss that than to open discussion for introduction of new evidence, new proposals, new ideas, because that's not taking us in the right direction.

DR. ALFRED BOVE: Well, we've got about 20 minutes. I don't know whether we could go through the entire SPUMS report and try to comment, but it would be worth putting some of the questions up. Go ahead.

AUDIENCE MEMBER: Toward that end, I think one of the important things we should do is define what, quote, recreational diving is. Because what I propose is diving within the limits of the traditional tables like the PADI or NAUI tables that are less than 130 feet, minutes, no decompression. Because if you just say "recreational diver," what Simon and Dave do for recreation is slightly different from what I do for recreation. So we have to be careful about that.

DR. ALFRED BOVE: Okay. I've found the definition of recreational divers in the United States is different than the definition of recreational divers in Europe, for example. Or let's just say that their limits for exposure are different, so the European recreational divers are doing more decompression diving, for example, which we aren't supposed to do in the U.S. So those are important distinctions.

I think I have Richard's computer so I don't think I have the PowerPoints on here. If we wanted to show SPUMS information.

WARD REED: I just wanted to clarify that these recommendations probably should be limited to recreational diving for the main reason that almost every study that we've discussed today has been done exclusively or almost exclusively with populations of recreational divers. Some had some technical divers in there. There were a few military and one or two working, what we would call, working divers. There's very little data that we've presented that came from the commercial diving field. Plus, when you read the SPUMS guidelines, they're very nice in that they're individualized to the risk tolerance of the diver and their practitioner; whereas, in the commercial world the risk tolerance is that of the diving supervisor and the commercial diving enterprise.

DR. ALFRED BOVE: It's a good recommendation. I'm interested in the fact that some of the things that were discovered in recreational divers and reported in recreational divers became standard policy to U.S. Navy, which, to me, is not an appropriate extension of the information. So I think your point is well taken that the community that you want to study ought to be the community that you make recommendations for. And if the military wants to make recommendations, they should do prospective studies. I think we heard about at least one attempt at trying to do a prospective study, and whether it's going to work or not is a different question. I don't disagree with that point of view.

TOM NEUMAN: In addition to clearly meeting a definition or defining what we consider recreational scuba diving, we might also consider making a recommendation that we define what we mean by DCS or decompression illness. I'm not trying to get into that right now. We've already heard in some of the reports that some people consider vague paresthesia that occur two, three and four days out after a dive neurologic DCS. Some people consider headaches manifestations of DCS. Some people consider fatigue as a manifestation of DCS. Until we're all, sort of, operating on the same playing field about what we're considering the signs and symptoms of the illness that we are trying to talk about, we're, sort of, beating our heads against a very hard wall.

DR. ALFRED BOVE: My recollection is there's a paper published by Neuman and co-workers on the definition of DCS. Is that the appropriate document to use at this point in time?

TOM NEUMAN: No, I don't think it is. One could make an argument that it might be, but that's a highly specific definition of DCS with somewhat limited sensitivity. I think it's a good definition of DCS. And if we're willing to say that we're only interested in knowing about the serious DCS that occurs related to a PFO, then I think it's a fine definition. But whatever definition we choose, and that's not what I'm trying to get at, it should be uniform across the board.

To me, hearing about some of the signs and symptoms, I say to myself, gosh, I would never consider that DCS. But if we all consider it DCS, that's fine; we're all looking at it the same way. So I think some sort of a recommendation within this framework ought to be made that we're all talking about the same thing no matter how we define it.

DR. ALFRED BOVE: So we had the big four, cerebral, spinal, audio vestibular and cutaneous as the key four that we should be looking at, not fatigue, not paresthesia --

TOM NEUMAN: Yeah, but is a headache cerebral DCS? I agree with you. You don't have to say no to me. But are there people who are considering that DCS? Are there people who are considering vague paresthesia spinal cord DCS or cerebral DCS? I agree with you, no. But there are some people who may be considering it.

DR. ALFRED BOVE: Really I think what you're saying is if we're going to define those four entities, we ought to clearly define them as clear cut clinical syndromes and not vague symptomatology and so on. I think that makes sense. I think that's going to be part of what we come up with as a consensus.

NO. 1

Routine screening for persistent foramen ovale (PFO) (also referred to as “patent” foramen ovale) at the time of dive medical fitness assessment (either initial or periodic) is not indicated. (IV)

PETER WILMSHURST: If you get to that in a couple of slides you will see it only says "consider" testing for a PFO in these conditions. And you can define that separately. Perhaps you ought to just work through these, since you've got very little time, work through them one at a time and see what people think.

DR. ALFRED BOVE: This is the first one. Anybody want to comment on that?

AUDIENCE MEMBER: Agreed.

AUDIENCE MEMBER: Agreed.

DR. ALFRED BOVE: If we can leave with one item. So number two,

Consider investigating for PFO under the following: DCS with cerebral spinal, vestibulocochlear, or cutaneous manifestations.

Again, as Tom points out, is a headache considered cerebral DCS?

DR. SIMON MITCHELL: Perhaps to get around some of Tom's anxieties, one fairly easy way around it would be to say that these specifically exclude those presentations defined as mild in the proceedings of the remote workshop, which excludes all of those things that Tom was talking about.

PETER WILMSHURST: If we said we won't treat myocardial infarction because some doctors misdiagnose it, we would be doing considerable harm. Just because some people don't know how to diagnose it doesn't mean those who do know how to diagnose it shouldn't treat it when they see it if they think that's the right thing to do.

DR. ALFRED BOVE: Of course. 80% of chest pain is not a myocardial infarction. And the beauty of the MI is we have components that we can presumably use for diagnosis. But here one of our biggest dilemmas in medicine is the patient with chest pain. It's the same situation as the patient with paresthesia. Is that neurologic or vasoconstriction or whatever.

NO. 2

Consider investigating for PFO under any of the following circumstances:

- History of decompression illness (DCI) with cerebral, spinal, vestibulocochlear or cutaneous manifestations (IIA)
- Current or past history of migraine with aura (IIA)
- History of cryptogenics stroke (IIA)
- History of PFO or ASD in a first degree relative (IIA)

TOM NEUMAN: Just because, and remember, we can misdiagnose DCS both positively and negatively. We cannot diagnose it when it's there and we can diagnose it when it's not there.

One of the other big things that I saw on this list of signs and symptoms that were considered cerebral DCS (and you really have to look at the individual cases, but, again, I think it's because it's important), the case definition for remote locations and mild really dealt with decompression illness and barotraumatic cerebral gas embolism would be included in the treatment algorithm there because that's very serious. I would argue strongly that barotraumatic cerebral gas embolism, in other words, our typical breath hold AGE, has to be excluded from this.

DR. ALFRED BOVE: Of course. That's right. So we have item No. 2 up here, and I'm kind of interested in the last three lines because it turns us into clinical neurologists rather than diving doctors. So I was wondering if we could at least agree on the first bullet in No. 2 and maybe leave the other ones alone for now. Anybody want to comment on that.

PHILLIP FOSTER: You asked a question about this. In the Air Force and NASA, most of the people that have been doing MRI, they've been doing MRI in 90% of the pilots, and very little of them had any DCS. There was no DCS case. At NASA there's no report of any astronaut having had DCS. We're currently doing MRI in astronauts for all mission unrelated to DCS. Number two, if you have those four categories, that is fine, but already the diver is going to experience something severe.

And if there are other symptoms, the early signs of DCS, some people mentioned fatigue, headaches, paresthesia, and other things, we may want to look a bit more in those divers. Maybe not a complete investigation. Maybe they should go and see their diving physician and ask the question. There should be a kind of a checking point. There should be a checking point, an assessment by a diving physician, like during the yearly visit they may have, you do a check.

PETAR DENOBLE: Do you agree with this or --

PHILLIP FOSTER: I somehow agree, but if you wait until they get to that, they're going to already have a problem.

NO. 3

Where and how to perform screenings for PFO:

- Perform in centers well-practiced in the technique (IV)
- Must include bubble contrast, ideally combined with transthoracic echocardiogram and provocation maneuvers (IIA)
- 2D and color-flow echocardiography without bubble contrast not adequate (IIA)
- Screening must include the use of provocation maneuvers to promote right-to-left shunt (Valsalva release and sniffing) (IIA)
- Provocation should be undertaken when the right atrium is densely opacified by bubble contrast (IIA)

DR. ALFRED BOVE: Let me take the first bullet point. Is there a consensus that that would make sense?

AUDIENCE MEMBER: Yes.

AUDIENCE MEMBER: Yes.

AUDIENCE MEMBER: Yes.

AUDIENCE MEMBER: Agreed.

DR. ALFRED BOVE: Let's move on. Maybe you could have the next person comment too. Could we do that? How do we perform screening for a PFO?
Now, being a cardiologist, I think this is wonderful because we own the echo machines and all that kind of stuff. How do we perform screening? We saw a very interesting way to screen with carotid Doppler and intravenous injection, which is pretty straightforward. Any comments on that? Do we have to go to a qualified PFO screening center with echocardiography or can we come up with something a little easier than that? Comments? Questions? Everybody agree we should do it with bubble contrast?

AUDIENCE MEMBERS: Yes.

DR. ALFRED BOVE: And everybody agree we should do it with a Valsalva maneuver?

AUDIENCE MEMBERS: Yes.

AUDIENCE MEMBER: I was going to say I think it's significant that you're saying transthoracic echo, which is noninvasive, low risk and low cost, versus transesophageal echo, which particularly in some patients involves sedation and significant risk. So I think that's one of the strong points of this recommendation.

DR. ALFRED BOVE: What's your thought about doing, let's say, carotid bubble study with intravenous bubble injection?

AUDIENCE MEMBER: I would be open-minded to it if it was done with good protocol.

DR. ALFRED BOVE: Number one, it's a lot cheaper and probably a little bit easier to do, perhaps more open to interpretation.

NO. 4

If PFO Screening is positive:

- Spontaneous unprovoked shunt or large provoked shunt represents unequivocal risk for DCI types referred to previously (IIA)
- Smaller shunts associated with lower but poorly defined risk of DCI (IIA)
- The clinical setting is important for interpretation (IV)

TOM NEUMAN: And do we have enough data to say that now.

ALFRED BOVE: Correct.

AUDIENCE MEMBER: I would definitely not recommend carotid Doppler screening as a screening for PFO. You could screen for right-to-left shunt in a moderate way.

DR. ALFRED BOVE: So we can't rule out intrapulmonary shunt. So I think you're right. That makes sense.
AUDIENCE MEMBER: Whereas, you might want to include a specification of the type of contrast used to prevent people from using the commercial echo-based or other things that produce too small bubbles, and use saline contrast with air and a little bit of blood.

DR. ALFRED BOVE: So let me just get a consensus by raise of hands. If you were going to send a patient for screening for PFO, would you look for a qualified echo center? How many people would do that versus anyplace at all?

AUDIENCE MEMBER: Hard part is identifying that center.

DR. ALFRED BOVE: Somehow you'd have to have some relationship with the people who are doing the echoes so you'd know they were doing the right protocol.

AUDIENCE MEMBER: Could you go back to the previous one, please. I was going to say only one consensus under which we recognize detection of PFO. As we know, the DCS risk is the sum of a lot of DCS factors. But what is important is in the population you can find very high bubble and low bubble. So that's probably something that we can detect the nature of people bubbling.

And I don't necessarily agree with one of the conclusions, that recreational divers don't produce a lot of VGE. I think that there is not a lot of proof and evidence about that. Because most of the studies focused in the past on rather severe dives. So VGE prediction close to the non decompression (no-decompression limits) needs is fully known. And we wouldn't be surprised by investigating the recreational population, people with rather low fitness to dive, you would be surprised about the level bubbles produced and the level of risk a few people can take when they dive.

So, for me, one of the conclusions was to avoid, for instance, to routinely detect PFO for people what this point is in this first slide. But my opinion is that for people that have similar bubbles, and in particular high bubbles, it would make sense to detect PFO to prevent them to DCS. So I would add here detect this population of high bubbling.

DR. ALFRED BOVE: We'll have to qualify this a little bit, but I think we've agreed on the first part of this statement with some qualifications.

MIKE BENNETT: I just wanted to make a comment about the how. I know from my experience in Australia that it would be very useful in any guideline that the UHMS could produce to go into some -- now, clearly there's a difference of opinion, and I'm not suggesting we should have one individual cardiologist's version of the truth, but there should be some fairly solid guideline about how we think the most successful ways of detecting are. One of the problems -- and I'll accept some of the responsibility -- one of the problems is we're not as good as you are in Belgium. It's not only our selection of patients, but our cardiology department's ability to detect a PFO when it's there is not at the same level as some of the people in this room, that is notably Dr. Wilmshurst, and something in the guideline about how it would be very useful to us.

DR. ALFRED BOVE: There's nine points. Let me move on here.

AUDIENCE MEMBER: Just one thing about the last one where you said screening for PFOs. That's the terminology. What you're really doing is not screening. When you say screening. You're testing for PFOs. You're trying to rule in or rule out. So I would really suggest changing that word. We don't screen for carotid stenosis. We test for it.

DR. ALFRED BOVE: The word "screening" should be changed to "testing."

How to perform testing for a PFO. And, again, I think we've agreed provocative maneuvers are important to include in the testing. And I think Peter Wilmshurst pointed out that you want to do provocative maneuvers when there's bubbles in the right atrium. Does anybody have any other suggestions for that? We'll use the word "testing" not "screening," but provocative maneuvers in the presence of bubble contrast.

AUDIENCE MEMBER: Add a reference to a good journal article or instructional article that an echo technologist

could pull up on the web and get the protocol.

AUDIENCE MEMBER:There are two papers that you might want to include. One is in 2004 and the other one is by Johnson in 2006, that specifically deal with the technique of injecting maneuvers and the false negatives.

DR. ALFRED BOVE: I'm not going to write them down. I'm going to send you an email to send me the references. Let's go on.

If the PFO screening -- let's use the word testing. If testing for PFO is positive in the patients selected, what do we do with the information?

EDMOND KAY: I just want to make a comment that there's no reference to the timing of the bubbles that appear in the left heart. In cases where I've ordered these tests and I usually use transcranial, but I've used all of the tests, I have never yet gotten a notation about delayed bubble at a counting in the left heart which would be pulmonary shunting.

DR. ALFRED BOVE: I think in some of the papers describing this. Outside the world of diving testing for PFO there is a description of the, number one, size, number of bubbles or size of the PFO, and the timing of the presence of bubbles in the left atrium. So we have literature like that, that we should incorporate into our commentary here.

EDMOND KAY: What I'm saying is I don't get it. I don't get that in my report when I order it.

AUDIENCE MEMBER: That's why you get an expert to do it.

TOM NEUMAN: This is from Gary Latson and me. We both feel that the word "unequivocal" is pretty strong. That's an awfully big word for such a little amount of hard data.

DR. ALFRED BOVE: Okay. Fine. Semantics? What would you use "increased" or just take the word all altogether?

TOM NEUMAN: Just take it out. Probably. Potentially. Unequivocal is, I mean, you're setting yourself up to be shown wrong.

DR. ALFRED BOVE: I don't see that as a problem. In this statement the word "unequivocal" is questionable and there should be some look at the thesaurus to come up with a word that's a little more acceptable.

NO. 5

Diver options if diagnosed with a PFO considered to have increased DCI risk:

- Stop diving (IV)
- Dive conservatively (IV)
- Close the PFO (III)

AUDIENCE MEMBER: Just to be completely correct, you might want to add to that first point "in diving with VGE present." Because if you do diving without VGE, then a large shunt without hemodynamic consequence, it doesn't matter.

DR. ALFRED BOVE: Anybody else have any objections to those statements? Take the word "unequivocal" out. And I think it's important to, yes, to point out that it has to be within divers that have a VGE load in the presence of a large shunt.

The other two points, anybody have any objections to those? Let's move on here to try to get to No. 9.

Divers options. I started out asking questions about diving conservatively, and I thought I heard a lot of disagreement on whether we could tell a diver how to dive conservatively. Here's three points. Stop diving. I don't think that's too hard to figure out. What about the second point? Is there some consensus that you could advise somebody on how to dive conservatively to lower risk of DCS?

DAVID DOOLETTE: I think you may have misinterpreted what I said about that earlier. Because you can tell people to dive more conservatively, more decompression.

AUDIENCE MEMBER: I would just point out conservative, there is better than level four evidence for that. It's a small study by Christoph Klingman that show recommendation to dive conservatively reduces incidence of DCS in people with PFOs. So that's level three evidence.

DR. ALFRED BOVE: So in point no. 5, would anybody want to modify that or can we leave it the way it is?

DAVID SMART: There are more data than is on that slide in relation to dive conservatively. And I can read it out if you like. Otherwise, I can email it to you.

"Dive more conservatively. There are various strategies that might be employed to reduce the risk of significant venous bubble formation after diving with a subsequent right-to-left shunting which sends the bubbles. The appropriateness of this approach and the strategies chosen need to be considered on an individual basis and a discussion with a diving medicine expert. Examples include reducing dive times to well inside accepted no-decompression limits, restricting dives to less than 15 minutes, performing only one dive per day, use of nitrox with air dive planning tools, intentional decompression stop, avoidance of heavy exercise, and unnecessary lifting or straining for at least three hours after diving (level four evidence)."

AUDIENCE MEMBER: I would say I completely agree with all those, except saying a specific depth to limit it at 15 meters is a pretty small depth. I think people can dive pretty safely and comfortably at slightly higher depths. That's about the only thing I would take issue with. Otherwise, I think it's well worded.

TOM NEUMAN: I don't think we have the data for the lifting and straining within three hours yet. If we go back to level four, that's fine. But if we switch to dive conservatively, we don't have level three evidence to that.

ALFRED BOVE: No. 6, talk to somebody that knows about diving. Seems to be a reasonable statement. I don't think anybody in this room would disagree with that. I'll say No. 6 is something that goes without saying.

No. 6 implies also that there's a diving physician involved in this to go through the risk and benefits in the clinical

NO. 6

The above options should be considered in consultation with a Diving Physician (IV)

setting. I think, you know, I find many times that patients go to physicians that don't have any understanding of diving and get a very, very, sort of, skewed point of view because of a given physician's perceptions of diving rather than knowledge of diving. So it seems to me that this ought to include conversation with an expert of some sort.

AUDIENCE MEMBER: Bringing the element of perhaps institutional setting as well because it brings in an issue that all of us have been raising or multiple people have been raising, is that the decision will partly depend upon the organization that ordered the screening in the first place, and particularly their tolerance of that risk and acceptance thereof. So it's not just clinical between doctor and patient. There's a third, at least as important, element.

AUDIENCE MEMBER: With regard to this point, I might suggest that we also or you also put down that there are potential other causes that must be researched. And I remember Peter Wilmshurst (presented) a case with a diver who not only had a PFO but also pulmonary bullae or blebs or didn't have a PFO but did have a pulmonary bullae or blebs. So I would recommend that apart from doing a PFO testing, you also do a comprehensive pulmonary testing possibly including a high-resolution CT scan because normal x-rays they were frequently invisible.

DR. ALFRED BOVE: Again, I think it begs the issue of having somebody that understands diving medicine to deal with the individual who is raising the question. Because if there is concern for pulmonary components of this, then the physician should make the judgment to do that.

NO. 7

The options outlined in statement 5 require careful consideration of the risks and benefits and the clinical setting that led to screening (IV)

Let me move on to No. 8. No. 8 is the last one, as it turns out.

Diving should not be resumed until satisfactory closure is confirmed. Following closure of a PFO, divers should have a repeat bubble contrast echo showing shunt closure and wait three months before they return to diving.

It goes without saying if the shunt is closed, there's going to be some tests to make sure it's closed. I would think it would be inappropriate for somebody who closes a PFO during a procedure not to come back either at the end of the procedure or the next day and test to see if the PFO is closed. So I wouldn't see any reason to argue about that. I guess the question I would ask is the three months. Anybody have any specific comments about that?
PHILLIP FOSTER: I think it's fair. I think it's the best you can do, especially having the dive physician overseeing everything. The diving physician will be a key player following up with patients. And you see patient may have right-to-left shunting in those patients who have atelectasis. So the role of the diving physician will be a key here. You put it in 7th position or 6th position, you should put at the very end so it's highlighted.

NO. 8

Following closure of a PFO and before returning to diving, the diver requires a repeat bubble contrast echocardiogram demonstrating shunt closure, a minimum of three months after the closure (III)

Diving should not be resumed until satisfactory closure of the PFO is confirmed, and the other diver has ceased potent antiplatelet medication (Aspirin is acceptable) (III)

DR. ALFRED BOVE: Let's hear from the other folks about this question about testing. Comments?

AUDIENCE MEMBER: I wanted to make one comment here and that's simple that it's an observation. Let's say you put in a patch and you reduce a massive grade 4 shunt with an atrial septal aneurysm down to almost complete closure with a trivial trickle of bubbles. Does that warrant putting in another device? I personally think that the Navy probably forced a clinical procedure on a guy that, you know, there's no data on two closure devices and what the long-term risk of that is compared to the very, very small risk that that guy had of DCS. A bigger issue is lead poisoning.

So I think that we have to be careful about saying the shunt has to be absolutely completely obliterated. It's a clinical judgment that a cardiologist and a diving physician can make.

DR. ALFRED BOVE: If you look in the non-diving literature, the incidence of residual shunting after a closure device is around to 15%, so it's not zero. There is a percentage of individuals that have a residual very small shunt. It's probably not important. But if you wanted to say all those things should be close to no shunt at all, you're going to generate a lot of extra procedures and risks.

AUDIENCE MEMBER: How long does it take for the endothelium to grow over a shunt?

PETER WILMSHURST: I was going to say two things. It is a waste of time doing a contrast echo at the end of the procedure because lots of people have massive shunts at the end of the procedure and the devices realign. So firstly they realign and flatten, and then they endothelialize, which takes a matter of weeks. So there's no point in doing it before a couple of months.

But if you look on color flow when you're doing a procedure, if you see a residual shunt on color flow, and it doesn't look as though it's going to realign, then you might want to put a second device in, a different sort of device. So it's a matter of -- but that's experience, and that's why you use people that know how to do the procedures really.

I mean, I haven't ever put -- two of my patients got three devices in their atrial septum. We're not too worried about a few bubbles getting across because we don't think that either they've got a normal risk, the same risk as someone with an intact atrial septum, or it's so marginally different that it probably doesn't make any difference.

AUDIENCE MEMBER: My comment exactly. If you have somebody who had a large shunt and you put a device in and you end with a grade 1 shunt with just some bubbles, basically he goes back to a risk which is equivalent to having no shunt at all. I don't quite agree -- if you say "satisfactory closure," then you're open to all options. If you say "complete closure," I think it's a little bit too harsh.

DR. ALFRED BOVE: I think the point is well taken, that we should wait for endothelialization before we make any decision on what the residual shunt is. That sounds like a reasonable thing to conclude.

DR. LUDEK SEFC: We screen for persistence of PFO one month after closure and if it's negative, we allow diving. Until now we had no references of problems.

KESHAV NAYAK: For the Navy we wait six months before return to full duty.

I wanted to ask a question about potent antiplatelet medication. What is the standard for everyone in the room? For us in the U.S. it's therapy for six months. That coincides with the echo.

PETER WILMSHURST: We used to use aspirin alone like everyone else, but then we went over to using clopidogrel. We published on 180 closure procedures, not all divers, comparing aspirin and aspirin plus clopidogrel, but clopidogrel only for one month and then we stop it. Unless they get recurrence of migraine, then they go back on the clopidogrel for a couple of weeks and then they can usually stop it. Because you get this post-closure migraine in some patients. You probably see that as well. Not if you put them on clopidogrel for six months. All you get is the bleeding.

ALFRED BOVE: Thank you. I'm very much involved in the cardiology world and what we call dual antiplatelet therapy, lots of controversy on how you use it. Sounds like we might end up with that same controversy for PFO closure or ASD closure. I think some of that literature will show up in the non-diving world that we might be able to tap into as well. Aspirin or aspirin plus clopidogrel, whatever we want to call, a thienopyridine, antiplatelet drug, PY12, whatever it is, we could consider both things or aspirin alone, either one, I guess.

PETER WILMSHURST: Let the cardiologists decide.

AUDIENCE MEMBER: That's up to the cardiologists. Their position might change and our cardiologists shorten the time of antiplatelet because they pretend that it increases the rate of endothelialization so it gets patients healed quicker.

DR. ALFRED BOVE: It also increases the risk of bleeding if you're on antiplatelet therapy too long.

There were eight points. I think we've answered them.

AUDIENCE MEMBER: If I may go back to No. 4. It's not me, for someone who had to leave for another meeting. Stating that if PFO testing is negative, that doesn't preclude the risk for DCS. So it's important to mention that don't focus only on the PFO.

JAMES HOLM: My concern is if a diver has a PFO closure for recreational diving or technical diving, that they will think they’re somehow protected from decompression sickness.

AUDIENCE MEMBER: In addition to PFO testing, you know, we talked about intrapulmonary shunts. So these tests

can be done at the same time as PFO testing, but also with exercise. And, for example, we until now work with asymptomatic divers but without DCS, but it could be done as a part of the screening which is done after the first neurological DCS. The PFO and intrapulmonary shunts can be tested --

DR. ALFRED BOVE: Would you add TCD plus PFO?

AUDIENCE MEMBER: Contrast TTE plus TCD, for example. This could be done and then you cover both sides. Of course, the majority is PFO so that's we're discussing only PFO. These intrapulmonary shunts, we are getting some data. It's mostly asymptomatic subjects. But I think we should at least have an open mind that there are some other potential than PFO.

DR. ALFRED BOVE: I think it's worth a mention.

AUDIENCE MEMBER: And future research should be done to collect more data on people with DCS.

ALFRED BOVE: Let me thank everybody for being patient and hanging on for an extra 20 minutes. We have some work ahead to try to get something down in writing, but I think it's been a very good session. I appreciate all the speakers. I think we've got a very good overview of the topic, different points of view, and hopefully it will let us come up with something that is a recommendation. Although I have to recognize the fact that SPUMS has done a good job of doing this already. Thanks again, everybody, for being here. (End of session).

PFO Statement

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Introduction

Epidemiological studies have shown an association between PFO and certain types of neurological and cutaneous decompression sickness (DCS, see below). DCS risk in recreational divers has been reported as 3.6 cases per 10,000 dives, with 0.84 cases of neurological DCS per 10,000 dives, with a 4-fold increase in risk with PFO.[1] Thus, if DCS cases were random events, the overall risk of neurological DCS is low, even in the presence of a PFO. However, for some individuals PFO seems to be a greater risk than predicted.[2] Guidelines for PFO testing are aimed at identifying such individuals and managing their DCS risk.

The presumed mechanism by which PFO increases DCS risk is systemic translocation of venous gas emboli (VGE). Therefore, in order for PFO to have any influence on the probability of DCS the depth-time exposure must be sufficiently provocative to generate venous bubbles. While it is rarely known whether VGE exist after any given dive, the following data can help to provide relevant contextual information. A threshold depth of 20 fsw has been observed for DCS after direct ascent from saturation exposures.[3] Data from bounce dives suggest that depth-time exposures for single dives within the USN no-stop limits have a low rate of VGE.[4] Neurological manifestations after short, shallow dives, or after rapid ascent where a breath hold is suspected, is more likely to be due to pulmonary barotrauma and arterial gas embolism rather than arterialization of VGE via a PFO.

The following guidelines were developed from the joint position statement on persistent foramen ovale (PFO) and diving published by the South Pacific Underwater Medicine Society (SPUMS) and the United Kingdom Sports Diving (UKSDMC),[5] and a conference held in conjunction with the UHMS Annual Scientific Meeting in Montreal, Canada, June 2015.

Statement 1

Routine screening for patent foramen ovale (PFO) at the time of dive medical fitness assessment (either initial or periodic) is not indicated (IV).

Statement 2

Consideration should be given to testing for PFO under the following circumstances:

- A history of more than one episode of decompression sickness (DCS) with cerebral, spinal, vestibulocochlear or cutaneous manifestations (IIa). [6-12]

Non-cutaneous manifestations of "mild DCI" as defined in the Remote DCI Workshop Proceedings (Consensus Statements, In: Management of Mild or Marginal Decompression Illness in Remote Locations, Workshop Proceedings (May 24-25, 2004). Mitchell SJ, Doolette DJ, Wachholz CJ, Vann RD, Eds. Divers Alert Network, Durham, NC, 2005, pp. 6-9.) are not indications for PFO investigation. Headache as an isolated symptom after diving is not an indication for PFO investigation.

Statement 3

If testing for PFO is performed, then the following is recommended:

- That testing is undertaken by centers well practiced in the technique (IV).
- The testing must include bubble contrast, ideally combined with trans-thoracic echocardiogram (TTE) because this best facilitates cooperation with provocation maneuvers. Use of two-dimensional and color-flow echocardiography without bubble contrast is not adequate (IIa).[13,9,12]
- The testing must include the use of provocation manoeuvres to promote right-to-left shunt including Valsalva release and sniffing as described in the supporting references (both undertaken when the right atrium is densely opacified by bubble contrast) (IIa).[9,12]

Statement 4

Interpreting a positive PFO test result:

- A spontaneous shunt without provocation or a large, provoked shunt following diving when venous gas emboli are present is recognized as a risk factor for those forms of DCS listed in statement 2 (IIa).[6,9,12]
- Smaller shunts are associated with a lower but poorly defined risk of DCS. The significance of minor degrees of shunting needs to be interpreted in the clinical setting that led to testing (IIa).[6,9,12]
- Detection of a PFO after an episode of DCS does not guarantee that the PFO contributed to causation (IIa).

Statement 5

Following diagnosis of a PFO considered likely to be associated with increased DCS risk, the diver may consider the following options in consultation with a diving physician:

- Stop diving (IV).
- Dive more conservatively: There are various strategies that might be employed to reduce the risk of significant venous bubble formation after diving, or the subsequent right-to-left shunting of such bubbles across a PFO. The appropriateness of this approach, and the strategies chosen, need to be considered on an individual basis, and in discussion with a diving medicine expert (IIIb).[14]

  Examples include: reducing dive times to well inside accepted no-stop limits; performing only one dive per day; use of nitrox with air dive planning tools; intentional lengthening of a safety stop or decompression time at shallow stops; avoidance of heavy exercise and unnecessary lifting or straining for at least three

hours after diving (IV).

- Close the PFO (III).[15,2,16-19,12] It is emphasized, however, that closing a PFO after an episode of DCS cannot be considered to provide assurance that DCS will not occur again.

Statement 6

The options outlined in statement 5 require careful consideration of the risks and benefits and the clinical setting that led to screening (IV).

Statement 7

Following closure of a PFO and before returning to diving, the diver requires a repeat bubble contrast echocardiogram demonstrating shunt closure, a minimum of three months after the closure (III).[15,17-19]

Statement 8

Diving should not be resumed until satisfactory closure of the PFO is confirmed, and the diver has ceased potent antiplatelet medication (aspirin is acceptable) (III).[15,17-19]

Statement 9

Venous bubbles can also enter the systemic circulation through Intrapulmonary shunts, although the role of this pathway in the pathogenesis of decompression sickness is not as well established as PFO. These shunts are normally closed at rest. They tend to open with exercise, hypoxia and beta adrenergic stimulation, and close with hyperoxia. It is therefore plausible that exercise, hypoxia and adrenergic stimulation after a dive could precipitate decompression sickness when it might not otherwise have occurred, while supplemental oxygen is likely to minimize this effect.

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