The relationship between venous gas bubbles and adverse effects of decompression after air dives.

O.S. EFTEDAL[1], S. LYDERSEN[2] AND A.O. BRUBAKK[1]

[1]Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; [2]Unit for Applied Clinical Research, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway.

Eftedal OS, Lydersen S, Brubakk AO. The relationship between venous gas bubbles and adverse effects of decompression after air dives. Undersea Hyperb Med 2007; 34(2):99-105.The presence of gas bubbles in the vascular system is often considered a sign of decompression stress and several studies in the existing literature have addressed the relationship between the amount of bubbles detected by ultrasound Doppler systems and the incidence of decompression sickness. The use of ultrasound imaging has some important advantages to Doppler systems, and here we have looked at the relationship between the amount of intravascular gas bubbles detected by ultrasound echocardiography and the incidence of signs and symptoms of decompression stress after 203 air dives. The results show that venous gas bubbles detected by ultrasound imaging is a highly sensitive, although not specific, predictor of such adverse effects of decompression. Our results agree with the published concordance between Doppler detected bubbles and decompression sickness. We conclude that bubble detection by ultrasonic scanning of the heart can be used as a tool to assess the safety of decompression procedures for air dives.

INTRODUCTION

Endogenous gas bubbles due to supersaturation, primarily by inert gases (1), cause decompression sickness (DCS). Although never formally "scientifically proven", this has been generally agreed since Paul Bert published the first systematic study in 1878 demonstrating the presence of gas bubbles in blood and tissue after decompression (2). Still, the pathophysiological mechanisms are not fully clear. It is now generally recognised that DCS is a systemic illness with a complex pathogenesis. There is evidence that some manifestations of DCS are caused by autochthonous bubbles, but it has also been shown that circulating vascular gas bubbles induce endothelial damage and haematological and immunological responses that are probably central in the development of the DCS syndrome (3).

Gas bubbles in liquids are strong reflectors of sound, and various modes of ultrasound are well suited for detection of circulating vascular gas bubbles. Doppler systems are most commonly used, and there are several studies published on the correspondence between venous gas emboli (VGE) and the risk of developing DCS for various modes of decompression (4-11). The results of the studies differ, but in general they show that a diver can have a large quantity of bubbles without any symptoms of decompression sickness. As a consequence, the presence of gas bubbles alone is of no diagnostic value in individual cases. On the other hand, most of the studies

also show that absence of detectable bubbles is a good predictor of decompression safety. Thus, if an association between gas bubbles and DCS risk could be established with some degree of accuracy, bubble detection could be used as a tool for validation of the safety of decompression procedures.

Today, although the initial design of decompression tables is performed with mathematical models aimed at keeping the amount of undissolved gas at a minimum, the parameter of success in the subsequent testing of the tables is usually the incidence of decompression sickness (12). Two important problems with this mode of validation are the vast number of dives required to prove the safety of a procedure and the possible long term effect of "silent bubbles", i.e. bubbles that do not cause overt DCS. Limiting the number of detectable gas bubbles rather than the incidence of clinical DCS symptoms in deciding the threshold of acceptable decompression stress would greatly reduce the number of dives required for evaluation of new tables (7,9,13,14). Also, the risk of inflicting damage to the health of test divers is reduced; i.e. you do not have to induce decompression sickness to conclude that the tested table has an unacceptable DCS risk. Finally, possible long-term damage from "silent bubbles" would be limited (15).

Interpretation of ultrasound Doppler signals for bubble detection is time consuming, requires highly trained observers and extreme concentration. We have previously proposed the use of a dedicated scoring code for quantification of intravascular gas bubbles in scan images (16). We demonstrated that the method enables even untrained individuals to score bubbles in the pulmonary artery accurately. We have also shown that there is close agreement between the proposed grading system for imaging and the Spencer code for quantification of gas bubbles in Doppler signals (17). In the current study we have looked at the correspondence between intravascular bubbles as quantified by the image scoring system and decompression related signs and symptoms in simulated compressed air dives with increased oxygen decompression.

METHODS

The study was carried out on 204 simulated compressed air dives. All dives were sub-saturation dives, diving depths were between 80 and 150 feet of seawater (245 - 460 kPa(g)), and both dry and wet dives were performed. Ninety-six of the decompressions were staged using heliox or trimix (both mixes with 50 % O_2) and 100% O_2. The other 108 were surface decompressions using 100% O_2, thus increased O_2-levels were used in all decompressions in the study.

The test subjects were male professional divers with valid offshore medical certificates. The dives were performed at the National Hyperbaric Centre in Aberdeen, Scotland. The local committee for human experimentation had approved all protocols and procedures.

An ultrasound scanner, CFM 750 Color Flow Scanner from Vingmed Sound a/s, Horten, Norway, was used to obtain ultrasound images for detection of intravascular gas bubbles. Ultrasound frequency used was 2.35 MHz.

Ultrasound scanning was performed on each diver at 15 or 20 minute intervals for at least 2 hours after completion of the dive, except when recompression treatment was commenced in the two-hour bubble detection period. During scanning, the diver was lying horizontally on his left side and the ultrasonic transducer was placed over the precordium in the 5th intercostal space. All scores in this study were done with the diver at rest, which from our experience yields lower scores than when the diver is moving. When present, venous gas bubbles could be seen in the images as bright

spots in the right ventricle and pulmonary trunk. We used a previously published grading system (16) shown in Table 1 for semi-quantitative estimation of the number of venous gas bubbles present.

Table 1. Definition of the image grading code

Grade	Definition
0	No observable bubbles
1	Occasional bubbles
2	At least 1 bubble every 4 heart cycles
3	At least 1 bubble every heart cycle
4	At least 1 bubble per cm^2 in every image
5	"White-out", single bubbles cannot be discriminated

The endpoint of the study was all signs and symptoms observed or reported that may be related to the decompression. We have used the term "adverse effects of decompression" (AED). This includes, but is not limited to, cases of overt decompression sickness.

In the analysis, the observed amount of gas bubbles is represented by maximum bubble grade. This is in accordance with most studies on Doppler detected bubbles and DCS incidence. All dives are grouped according to this maximum bubble grade. The AED incidence for each group is calculated, and 95% confidence intervals are given by the Agresti and Coull method (18). The association between bubble grade and AED is analyzed by logistic regression. The observed VGE/AED relationship in our data set is compared to a previously published data set on Doppler detected bubbles (19) by fitting a logistic regression model with bubble grade and data set as independent variables. Possible nonlinear effects of bubble grade as well as interactions in the logistic regression models were checked and found non-significant. P-values less than 0.05 were considered significant.

RESULTS

A total of 204 dives were performed with 16 cases of AED. One diver had grade 3 venous bubbles shortly after surfacing, rapidly increasing to grade 4 accompanied by arterial bubbles. This diver was given prophylactic recompression treatment as the risk of severe complications was considered high. He had no signs or symptoms of decompression stress and we have excluded him from the statistical analysis. Maximum observed bubble grade and AED incidence for the remaining 203 dives are shown in Table 2; the AED risk estimate is the percentage of observed AED cases relative to the total number of dives for each grade. All cases of AED are described in Table 3, see page 96.

The logistic regression analysis showed a highly significant association between bubble grade and AED: Odds ratio 2.7 per bubble grade, 95% confidence interval 1.5 to 5.0, $p<0.001$.

Table 2. Results from the experimental dives

Bubble grade	Number of dives	Cases of AED	AED risk, %	
			Estimate	95% confidence interval
0	66	0	0	0.0 to 6.8
1	35	2	6	0.7 to 19.8
2	30	2	7	0.9 to 22.6
3	65	9	14	7.3 to 24.6
4	7	3	43	16.0 to 74.9
5	-	-	-	-

DISCUSSION

In a presentation of US Navy experience on decompression table validation, Thalmann states: "Minor symptoms such as fatigue or transient niggles must be considered as they probably indicate a higher level of decompression stress than completely asymptomatic dives..." (12). The major practical application of a

Table 3. Description of cases of AED

Case	Max grade	Treatment	Response	Manifestation	Time of onset (rel. to surfacing)
1	3	USN 6	Resolution	Pain, shoulder	> 120 min.
2	2	USN 6	Resolution	Pain, right shoulder	> 120 min.
3	4	USN 6	Resolution	Pain, left elbow	60 min.
4	3	USN 6	Resolution	Pain, left elbow	25 min.
5	3	USN 6	Resolution	Skin rash on legs and itching	100 min.
6	4	USN 6	Resolution	Partial loss of vision and rash on shoulders	40 min.
7	3	USN 6	Resolution	Skin rash on legs	60 min.
8	1	USN 6	Resolution	Skin rash	< 20min.
9	1	USN 6	Resolution	Skin rash	< 20min.
10	3	USN 6	Resolution	Skin rash	< 20min.
11	4	USN 6	Resolution	Skin rash on abdomen	?
12	2	-	-	Tingling sensation in hands and feet	0 min.
13	3	-	-	Transient pain in elbow and knee	0 min.
14	3	-	-	Transient pain in right ankle	25 min.
15	3	-	-	Pain in left shoulder	?
16	3	-	-	Itching chest and legs	120 min.

correspondence between detected VGE and decompression outcome will most likely be in table validation, thus in our opinion the same principle should be applied here. In our study we had cases of minor decompression-related signs and symptoms that would not qualify for the DCS diagnosis in an operational setting and we have therefore used the term AED. We believe that the use of AED rather than DCS enables discrimination between decompression procedures that would be found of equal risk if only overt DCS was considered.

All measurements in the study were done with the diver at rest, lying on his left side. We observed that movement in many cases produced transient showers of bubbles, probably caused by detachment of bubbles from vessel walls and valves in the venous system. The same observation has been made in studies using ultrasound Doppler and with the diver standing (7,8,19). These studies indicate that bubble scoring after movement gives the same trend as scoring during rest, but is more sensitive in detecting bubbles. The scoring system used in this study was not designed for scoring after movement, thus transient peaks in bubble signals after movement have not been considered.

Sawatzky suggested that inclusion of scores from the subclavian vein increases the sensitivity of Doppler bubble detection because of the greater ease with which bubbles can be detected in peripheral veins compared to the precordium, where moving structures in the heart and turbulent blood flow causes background noises that may mask bubble signals (19). We believe that this is less of a problem in ultrasound imaging, where spatial resolution enhances discrimination between gas bubbles and tissue structures.

We did not at any time observe grade 5 bubbles, and for the statistical analysis of the data we have regarded the grading scale as a 5-level system (grades 0 to 4). Based on animal experiments, where we have observed a near 100% mortality for grade 5 bubbles (unpublished observations), we think that this amount of bubbles would be associated with a very high incidence of AED, and probably also a high mortality rate.

All cases of AED are described in Table 3. Cases 1-6 were in our opinion clear-cut cases of decompression sickness. Most of the other cases would probably not be considered DCS in operational diving. It is worth noting that 8 of the 16 cases of AED involved cutaneous manifestations. This is far more than would be expected based on prevalence studies of various manifestations of decompression illness from

Divers Alert Network (3.5%) and Institute of Naval Medicine (9.7%) (20). The reason for this difference is not clear, but relation to decompression is supported by the immediate resolution upon recompression in the 7 cases that were treated.

Decision to treat was made by the responsible doctor alone. The responsible doctor was informed of the divers' bubble grades and in one case prophylactic treatment was administered due to high and rapidly increasing venous bubble numbers accompanied by arterial bubbles (Figure 1). This case illustrates one important advantage of ultrasound imaging for bubble detection; the ability to monitor the arterial and venous circulations simultaneously. This diver was later shown, by colour flow Doppler, to have a patent foramen ovale. As mentioned previously he was excluded from the statistical analysis.

A total of 11 divers with AED were treated using USN Treatment Table 6, all of them responded with complete resolution of symptoms after a single treatment. The remaining 5 cases resolved spontaneously before treatment was commenced. The divers were not blinded with respect to observed bubble grade, thus a possible "nocebo effect" of the presence of detectable bubbles can not be excluded.

Post-dive scanning of the divers was performed at 15 or 20 minutes intervals. Each scan lasted for a period of 2-4 minutes, typically. This means that bubble peaks of short duration may have been missed. In cases where treatment was given, it also means that we do not necessarily know the bubble grade at the time of onset of symptoms, and certainly not whether higher bubble grades would have been reached if treatment had not been given. These limitations, which are common for all intermittent bubble monitoring procedures, will cause an overestimation of the AED risk for low bubble grades and possibly an underestimation for higher grades. Cases 8 and 9 illustrate this problem. In both cases the first scan showed grade 1 bubbles, but before the second scan could be started, both divers developed widespread skin rashes and were therefore immediately recompressed. The reason for the prompt recompression was the early time of onset of the rashes, and the fact

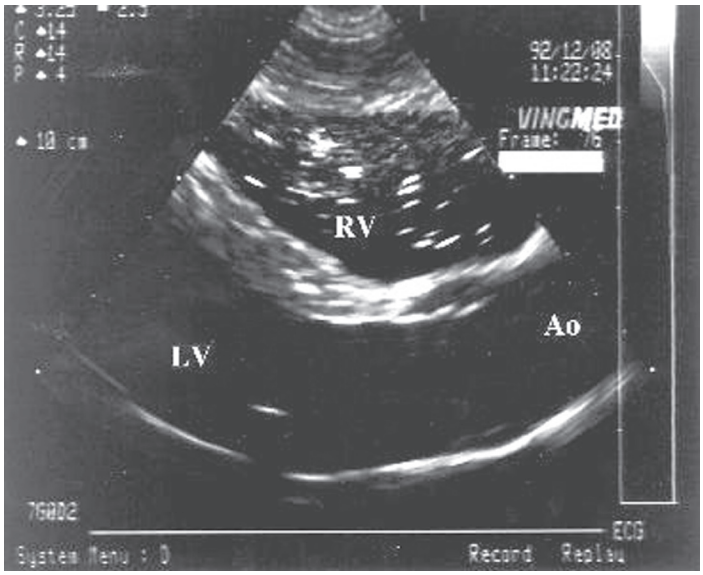

Fig. 1. Ultrasound image showing multiple gas bubbles in the right ventricle (RV) and one gas bubble in the left ventricle (LV). Ao – Aorta. The diver was later shown to have a patent foramen ovale.

that skin rashes in some cases are associated with severe forms of DCS (20). We suspect that these two divers had higher bubble grades at the onset of symptoms than during the first scan.

In this study the amount of intravascular gas bubbles is represented by the single highest observed bubble score. Calculating the time integral of bubbles during the whole post-dive observation period would give an estimate of the total volume of intravascular gas. Due to the categorical nature of the data with non-uniform intervals this would require for some sort of linearization, e.g. the Kisman integrated severity score (21). However, it has been shown that endothelial damage caused by intravascular gas bubbles is related to the maximum number of bubbles rather than duration of bubble exposure (22), thus it may be that maximum observed bubble grade is in fact a better measure for decompression stress than a time integral of the total number of bubbles.

It has been shown in saturation diving (11) that the correspondence of DCS with VGE is different from what is seen in bounce diving, with a higher proportion of DCS cases not accompanied by detectable bubbles. This may be due to involvement of slower tissues with respect to gas uptake and elimination. Also, the symptomatology of DCS manifestations differs, with a higher proportion of musculoskeletal DCS for saturation diving (23), particularly from the lower limbs (24), supporting the hypothesis that other tissues are involved.

It has also been claimed that the breathing gas has implications for the VGE/DCS correspondence. Powell and Johanson found that higher arterial oxygen tensions increased the tolerance to VGE (25). However, their observations were limited to 32 exposures, and the difference was not statistically significant. In an analysis of 1,726 nitrox and 1,508 heliox dives performed at the Defence and Civil Institute of Environmental Medicine (DCIEM) in Toronto, Canada, Sawatzky found no difference in VGE/DCS correspondence when using highest observed Kisman-Masurel (KM) score (7), irrespective of rest/movement or location (precordial or subclavian veins) (19). As DCS is caused by gas bubbles primarily consisting of inert gas, which have no physiological effects per se, the breathing gas composition intuitively should not influence on the VGE/DCS correspondence. This is supported by the findings of Thorsen et al. (26) who found no difference in platelet aggregation for bubbles containing different inert gases.

We have previously shown (17) close agreement between the image grading system and the Spencer code for Doppler signals (7). The Spencer code is in practice virtually identical to the KM grading system, but is designed for precordial measurements at rest. Thus, our observation of VGE/AED correspondence should be comparable to observations using either Spencer code or KM code under similar conditions (precordial measurements at rest). To our knowledge, the DCIEM data presented by Sawatzky (19) is the most extensive data set published. As previously mentioned, these data include 1726 nitrox dives. DCS diagnoses in this study were based on criteria established at a workshop in Bethesda, Maryland in 1988 (27). These criteria are more liberal than what is generally used in clinical practice and applying the criteria to our cases of AED, all except case 16 would have been classified as DCS. A combined logistic regression analysis of our data and the Sawatzky data showed no effect of data set ($p=0.69$ for interaction and $p=0.46$ for linear effect).

Our results show that there is a definite positive association between intravascular gas bubbles detected precordially by ultrasound scanning and AED incidence in sub saturation air dives. There is no statistical difference between the VGE/AED association we have observed and previously published VGE/DCS observations under the same conditions

using Doppler detection of bubbles. The data indicate that in spite of low specificity, the high sensitivity of VGE with respect to AED makes bubble detection a valuable tool for evaluation of the safety of sub saturation decompression tables. The established VGE/AED relationship should be used to evaluate decompression stress in validation of decompression tables, reducing number of test dives required and reducing the risk of inflicting decompression injury to test divers.

REFERENCES

1. Weathersby PK, Hart BL, Flynn ET, Walker WF. Role of oxygen in the production of human decompression sickness. *J Appl Physiol* 1987 December;63(6):2380-7.
2. Bert P. Barometric pressure. Researches in experimental physiology. Translated by Hitchcock MA and Hitchcock FA, Colombus, Ohio, College Book Company; 1943. Republished by Undersea Medical Society, Inc. Bethesda, Maryland; 1978.
3. Francis TJR, Mitchell SJ. Pathophysiology of decompression sickness. In: Brubakk AO, Neuman TS, eds. Bennett and Elliott's Physiology and Medicine of Diving, 5th edition. London, Saunders; 2003:530-56.
4. Gotoh Y, Nashimoto I. Decompression bubbles in caisson workers. *Japanese Journal of Hygiene* 1977 October;32(4):529-33.
5. Conkin J, Powell MR, Foster PP, Waligora JM. Information about venous gas emboli improves prediction of hypobaric decompression sickness. *Aviat Space Environ Med* 1998 January;69(1):8-16.
6. Bayne CG, Hunt WS, Johanson DC, Flynn ET, Weathersby PK. Doppler bubble detection and decompression sickness: a prospective clinical trial. *Undersea Biomed Res* 1985 September;12(3):327-32.
7. Nishi RY. Doppler evaluation of decompression tables. In: Lin YC, Shida KK, eds. Man in the Sea, vol. 1. San Pedro, California: Best Publishing Company 1990:297-316.
8. Gardette B, Lemaire C, Lamy D, Le Chuiton J. Heliox bounce dive decompressions (180 msw). In: 5th annual meeting of the European Undersea Biomedical Society. Bergen: EUBS 1979:120-6.
9. Eatock BC. Correspondence between intravascular bubbles and symptoms of decompression sickness. *Undersea Biomed Res* 1984;11:326-9.
10. Balldin UI, Pilmanis AA, Webb JT. Central nervous system decompression sickness and venous gas emboli in hypobaric conditions. *Aviat Space Environ Med* 2004 November;75(11):969-72.
11. Gardette B. Correlation between decompression sickness and circulating bubbles in 232 divers. *Undersea Biomed Res* 1979 March;6(1):99-107.
12. Thalmann ED. USN experience on decompression table validation. In: Schreiner HR, Hamilton RW, eds. Validation of decompression tables. The 37th Undersea and Hyperbaric Medical Society Workshop, Bethesda, Maryland: UHMS 1989:33-42.
13. Vann RD, Dick AP, Barry PD. Doppler bubble measurements and decompression sickness. *Undersea Biomed Res* 1982;9(suppl):24.
14. Vann RD. Mechanisms and risks of decompression. In: Bove AA, Davis JC, eds. Diving Medicine. 2nd ed. Philadelphia, Pennsylvania: W.B. Saunders Company 1990: 29-49.
15. Eckenhoff RG. The role of monitoring venous gas emboli after decompression. Letter to the editor. *Undersea Biomed Res* 1985 December;12(4):485-6.
16. Eftedal O, Brubakk AO. Agreement between trained and untrained observers in grading intravascular bubble signals in ultrasonic images. *Undersea Hyperb Med* 1997;24(4):293-9.
17. Brubakk AO, Eftedal O. Comparison of three different ultrasonic methods for quantification of intravascular gas bubbles. *Undersea Hyperb Med* 2001;28(3):131-6.
18. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportion. *The American Statistician* 1998;52(2):119-26.
19. Sawatzky KD. The relationship between intravascular Doppler-detected gas bubbles and decompression sickness after bounce diving in humans. MSc thesis, York University, Toronto 1991.
20. Francis TJR, Mitchell SJ. Manifestations of decompression disorders. In: Brubakk AO, Neuman TS, eds. Bennett and Elliott's Physiology and Medicine of Diving, 5th edition. London, Saunders; 2003:578-99.
21. Jankowski LW, Nishi RY, Eaton DJ, Griffin AP. Exercise during decompression reduces the amount of venous gas emboli. *Undersea Hyperb Med* 1997 June;24(2):59-65.
22. Nossum V, Koteng S, Brubakk AO. Endothelial damage by bubbles in the pulmonary artery of the pig. *Undersea Hyperb Med* 1999;26(1):1-8.
23. Berghage TE. Decompression sickness during saturation dives. *Undersea Biomed Res* 1976 December;3(4):387-98.