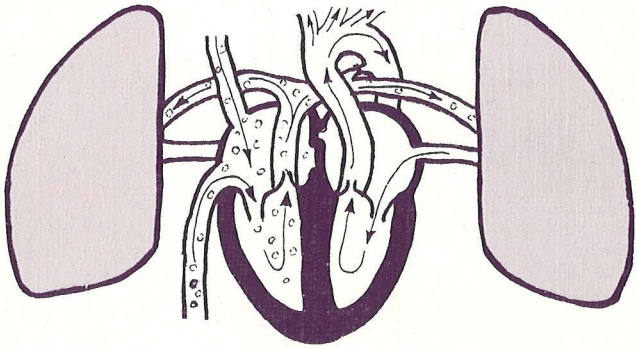
Anne Vik

VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS

Hemodynamic Effects and Detection of Gas Emboli by Transesophageal Echocardiography



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TAPIR
1993

Publication from Department of Biomedical Engineering
Faculty of Medicine
University of Trondheim
N-7005 Trondheim, Norway

ISBN 82-519-1459-0

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I. Vik, A., A. O. Brubakk, T. R. Hennessy, B. M. Jenssen, M. Ekker, and S. A. Slørdahl. Venous air embolism in swine: transport of gas bubbles through the pulmonary circulation.
J. Appl. Physiol. 69: 237-244, 1990.

II. Vik, A., B. M. Jenssen, and A. O. Brubakk. Effect of aminophylline on transpulmonary passage of venous air emboli in pigs.
J. Appl. Physiol. 71: 1780-1786, 1991.

III. Vik, A., B. M. Jenssen, and A. O. Brubakk. Paradoxical air embolism in pigs with a patent foramen ovale.
Undersea Biomed. Res. 19: 361-374, 1992.

IV. Vik, A., B. M. Jenssen, O. Eftedal, and A. O. Brubakk.
Relationship between venous bubbles and hemodynamic responses after decompression in pigs.
Undersea & Hyperbaric Med. 20: 233-248, 1993.

V. Vik, A., B. M. Jenssen, and A. O. Brubakk.
Arterial gas bubbles after decompression in pigs with patent foramen ovale.
Undersea & Hyperbaric Med. 20: 121-132, 1993.

VI. Vik, A., B. M. Jenssen, and A. O. Brubakk. Comparison of haemodynamic effects during venous air infusion and after decompression in pigs.
Eur. J. Appl. Physiol. (in press).

ABBREVIATIONS

VGE: venous gas embolism

PGE: paradoxical gas embolism

DCS: decompression sickness

PFO: patent foramen ovale

PAP: mean pulmonary artery pressure

MAP: mean arterial pressure

PVR: pulmonary vascular resistance

$\dot{Q}$: cardiac output

Pao_2: oxygen tension in arterial blood

RVSP: right ventricular systolic pressure

TEE-transducer: transesophageal echocardiographic transducer

Original manuscripts included in this thesis are referred to by their roman numeral.

ACKNOWLEDGEMENTS

I wish to express my gratitude to colleagues and collaborators at the Department of Biomedical Engineering in Trondheim. In particular I wish to thank:

* Alf Brubakk, who has been my supervisor during the entire period. I admire his continuous enthusiasm, creativity and encouragement, and his marvelous ability to be engaged in a hundred projects at the same time. I wish to thank him for letting me feel like a "real scientist" from the first day.
* Bjørn Munro Jenssen, my coworker during all the work, both during the experimental part of the study and during the preparation of the manuscripts. I appreciate his critical scrutiny especially when preparing my first manuscripts.
* Olav Sande Eftedal, who developed the software for the postprossessing of bubble counts in the ultrasound images, and who was always ready to answer questions about ultrasound and bubble detection.
* Arnfinn Sira, for his ingenious way of solving all the practical problems concerning equipment to the chamber. Without his work, the chamber dive experiments could not have been performed.
* Stig Slørdahl, my friend and colleague through almost ten years, who actually was the one that persuaded me to initiate this work.
* Bjørn Angelsen for suggesting the use of the transesophageal echocardiographic transducer, and Steinar Ommedal for technical support.
* Olaf Normann, for teaching me how to handle a Macintosh computer, and for always being available to help with the software.
* Anne Lise Ustad, for help to punch data into the computer during the last experiments.
* Mari Thune, who shared my office during the first years of this work, with whom I had many inspiring discussions on statistics and science as well as on non-scientific issues.

In addition, I am indebted to the following persons:

* Arvid Påsche and the staff at the Section for Extreme Work Environment, Sintef Unimed, for letting me finish my work on this thesis while being employed at their department.
* Petter Mowinckel, MedStat Research, Strømmen, and Harald Johnsen, Department of Clinical Chemistry, Regional Hospital, Trondheim, for

teaching me statistics and allowing me to discuss statistical problems with them.

* Valerie Flook, Department of Biomedical Sciences, University of Aberdeen, Scotland, for reviewing the final version of this thesis.
* Johan Vandenbogaerde, who introduced me to the use of transesophageal echocardiography at the Department of Cardiology, University Hospital, Gent, Belgium.
* Hilde Kvithyll, Ingolf Hansen and Sissel Holm Olsen, at the Department of Laboratory Animals, Regional and University Hospital, Trondheim, for help with the pigs.

I also wish to thank my husband, Frank, and our three children, Andrea, Torarin and Vera, for their love.

The present work was carried out during the years 1988-1992, and the main financial support has come from Phillips Petroleum Company Norway (the HADES-project). Without this support and the encouragement of the company's chief medical officer, Dr. Tor Nome, this study would not have been possible. Further support has been given by the FUDT-project (Statoil, Hydro, Saga), the Norwegian Space Center and Sør-Trøndelag County Administration.

Trondheim 15. 03. 93

Anne Vik

In the final version of this thesis, two figures of the experimental setup have been included. Stig Koteng is acknowledged for drawing the figures on the computer.

Trondheim 28. 10. 93

1. INTRODUCTION

1.1 VENOUS GAS EMBOLISM (VGE)

VGE is an important issue of concern both in the accomplishment of several medical procedures, and in activities involving decompression. This thesis describes effects of VGE during experimental gas infusion and after experimental decompression. It is therefore suitable to start the introduction by a short presentation of the literature describing VGE during medical procedures, followed by a review of studies on experimental gas infusion, and finally discuss VGE in relation to decompression related problems.

1.1.1 VGE during medical procedures

VGE was a much feared complication during the nineteenth century in the spontaneously ventilated patient, with many surgical procedures carried out in the sitting or semisitting position. Thus, already in 1839, Amussat published a book on VGE (5), and a second long dissertation appeared in 1885 by Senn (165). Since then, VGE during medical procedures has been further explored, and attention has been focused on the prevention of serious episodes of VGE. However, a considerable number of cases of VGE is still reported every year (148).

Venous air embolism, the most frequent form of VGE, occurs when there is open access to the venous circulation above the level of the heart, creating a pressure gradient leading to the right atrium. Thus, especially neurosurgery in the sitting position (41, 78, 84, 120, 122, 131) and some of the gynecological surgery (101, 133, 194), seem to predispose for VGE. In addition, VGE may appear in patients with a central venous catheter (98, 138), during the insertion of an epidural catheter (139), during orthopedic surgery (63, 130), during laparoscopy (74, 195), and during liver transplantation (107). Fatal cases of venous air emboli during sexual intercourse during pregnancy have also been reported (112).

VGE is variable in its clinical expression, but the signs and symptoms of massive VGE, that were already described in 1885 by Senn, are: a millwheel murmur, gasping respiration, cyanosis, and cardiovascular collapse (165). If the patient is mechanically ventilated, he occasionally tries to institute vigorous spontaneous breathing. Since the effects of VGE may be so serious that the patient dies, early detection and treatment are crucial factors during air embolism.

During the last decades, many methods for detection of VGE during surgery have been suggested. The esophageal stethoscope was introduced by Smith in 1954 (171), whereas Lewis and Rees (1964) suggested that electrocardiogram Lead VI was optimal for detection of air (111). Brechner and Bethune (1971) introduced the use of end-tidal CO_2 monitoring for the detection of air emboli (22), and Munson and colleagues (1975) claimed that a rise in pulmonary artery pressure (PAP) was an early sign of VGE (137). Monitoring of transcutaneous O_2 (73), exhaled nitrogen (119, 123) and airway pressure (170) has also been introduced as detection methods of VGE.

Already in 1968, ultrasonic Doppler was introduced as a method for the detection of VGE during medical procedures (119), and it has proven to be superior to all above-mentioned methods. The ultrasonic device permits the detection of very small volumes of gas (26, 71). During the last decade, the transesophageal Doppler and echocardiographic transducer has been introduced in the monitoring of patients at risk of developing VGE during different kinds of surgery (66, 121). Two-dimensional imaging is even more sensible to small amounts of gas than Doppler. Transesophageal echocardiographic (TEE) transducers make it possible to monitor the right and the left atrium simultaneously, and thereby also allow the detection of gas bubbles that have passed from the right side of the heart to the left side of the heart (3, 66). The occurrence of arterial gas bubbles is discussed further on in a separate section in this introduction.

The principle behind treatment of air embolism consists of closure of the point of air access, removal of air from the circulatory system and maintenance of cardiorespiratory stability (162). Aspiration of air through a right atrial catheter (132), Durant's maneuver, i.e. placing the patient in the left lateral decubitus position (52) and closed chest cardiac massage are simple and noninvasive techniques (148). If episodes of hypotension occur, vasopressors are indicated. In procedures involving nitrous oxide, the use of nitrous oxide should be discontinued following the influx of large quantities of air, and ventilation with 100 % oxygen should be commenced immediately (136, 148, 162). After the initial emergency procedures, the treatment of choice is hyperbaric oxygen (126, 138, 148). Thus, transport of the patient to a hyperbaric chamber and immediate treatment may reduce any neurological complications of gas bubbles in the cerebral arteries secondary to the VGE.

1.1.2 VGE during experimental gas infusion

Experimental studies using different species have been performed to study responses of VGE and elucidate pathophysiological mechanisms. Early experiments were mainly aimed at determining the lethal dose of venous injection of various gases in different animals (85, 192). After the Second World War, measurements of several circulatory and respiratory variables were made during bolus injection of gas (70, 96, 118). During the last two decades, most of the studies have used continuous air infusion to produce VGE (1, 30, 33, 37, 94, 166, 180-183). It has been argued that conclusions from the studies using bolus injections might not necessarily be relevant to clinical situations where air enters an open vein at a low rate until it suddenly becomes clinically significant (1, 41). Other gases than air, such as helium, nitrogen, carbon dioxide and oxygen have also been used, and the effects on hemodynamic variables and on blood gases seem partly to depend on the physical properties of the gases within the bubbles (94, 96, 166, 180-183).

The reported effects of experimental VGE seem to vary, depending both on the animal model, e.g. species, anesthesia, ventilation, oxygenation, the overall preparation, and on the method of producing VGE. Thus, the injection of bolus doses of gas and the continuous infusion of gas may give different results (1, 180). Furthermore, the dose of gas (30, 180), the type of gas or gas mixture (180), and the site of injection, peripherally or centrally (96), will have an influence on the effects.

However, there seems to be some widely accepted effects of VGE , such as an initial rise in the pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), and a decrease in arterial oxygen tension (Pao_2) (1, 37, 94, 118, 180). The central venous pressure usually increases, and left atrial pressure may increase or decrease (96, 118, 127). Both arterial hypertension and hypotension as well as changes in cardiac output ($\dot{Q}$) and systemic vascular resistance in both directions have been reported (1, 37, 47, 78, 94, 96, 118, 180). Large doses of VGE are, however, always followed by a decrease in $\dot{Q}$, arterial hypotension and death as the endpoint (96, 159). Death may be caused by gas in the outflow tract of the right ventricle, that acts as a mechanical obstruction and prevents blood to flow into the pulmonary circulation, or the right ventricle may fail as a result of the increased PVR, arterial hypoxia and hypercarbia. The studies that use spontaneously breathing animals may give different results from the studies using mechanically ventilated animals (181), since the former animals may increase their ventilation after initial gasps and thereby e.g. are able to prevent an increase of carbon dioxide in the arterial blood.

The PAP and PVR start to increase appreciably only after approximately 50 % of the pulmonary vascular bed has been embolized (117). There are two reasons why it is necessary to obstruct more than half of the pulmonary vasculature to induce an increase in resistance; Firstly, the arteries and veins of the lungs are compliant and can accommodate two-to threefold increases in blood volume with only a 1-2 mmHg increase in pressure. Secondly, the recruitment of additional pulmonary vessels minimizes the pressure changes in lung vasculature after vascular obstruction (117, 146). However, the gas emboli induce an increase in PAP and PVR both by obstructing the vessels mechanically and by inducing vasoconstriction of the vessels. Several studies (44, 70, 100, rev in 117) have been performed to find evidence for vasoconstriction, which seems to be limited to smaller arteries and arterioles < 100-200 μm. However, Shirai *et al.* claimed that emboli ≤ 500 μm also induce vasoconstriction (168). Thus, larger-sized gas bubbles induce an increase in PAP only by their mechanical obstruction of the vessels.

There seems to be some disagreement about involvement of sympathetic mechanisms in mediating the increased PVR seen after microembolization (rev in 117). However, there are many studies indicating that humoral factors are responsible for vasoconstriction, and the most likely humoral mediators of the pulmonary vasoconstrictor response after microembolization are; thromboxane A_2, histamine and serotonin (117). The mediators are released from platelets after aggregation, from mast cells, intrapulmonary macrophages and leukocytes (117, 146). It is also likely that mediator release or reflex mechanisms, following microembolization, can influence variables of the systemic circulation.

The most important cause of arterial hypoxemia that occurs immediately after pulmonary microembolization, is an imbalance in regional ventilation and perfusion (94, 117). The embolization induces a redistribution of blood flow, so that regions having a low ventilation-perfusion ratio appear.

In addition to the above-mentioned effects, microvascular permeability in the lungs may increase during gas embolization, and may result in pulmonary edema (147). Gas bubbles have been shown to induce platelet aggregation *in vitro* (177), while no such effects on the platelets were found in sheep (2). The complement system seems to be activated *in vitro* by gas bubbles (11).

The gas bubbles are excreted to the alveoli from the arterioles (156) and possibly also from capillaries, and some gas may be dissolved in the blood. This fact makes gas embolization different from the embolization of thrombi and solid particles (12). Some of the gas bubbles may escape filtration in the pulmonary circulation and enter the pulmonary veins and thereby reach the arterial circulation. It has been shown that although physiological variables have returned to baseline

values after VGE, there may be gas bubbles left in the pulmonary circulation for a long period (33).

1.1.3 VGE during and after decompression

a) VGE and decompression sickness

More than three centuries ago, Boyle observed a discrete bubble in the viper's eye, and he set forth a thoroughly modern interpretation of the condition which we now refer to as "bends" or decompression sickness (DCS) (21). During the nineteenth century, several studies were reported on the condition which developed in caisson workers when they were permitted to return too rapidly to normal atmospheric pressure after exposure to pressure of several atmospheres. A similar condition came to be recognized in divers. In 1878, Bert demonstrated in a most conclusive manner that DCS is primarily the result of inert gas bubbles in tissues and blood (13).

Since then, it has been widely accepted that DCS is caused by formation of inert gas bubbles within the intravascular or extravascular spaces. The bubbles that form in tissue or blood produce local damage and intravascular blockage and give rise to a variety of symptoms and signs. The relationship between endogenous bubble formation and symptoms of the disease is not clearly understood (45, 53), and there seems to be some controversy about the relationship between VGE and DCS. DCS has actually occurred in divers, in whom few bubbles were detected by Doppler in the pulmonary artery (9). However, it is mostly considered that high loading of venous gas bubbles as detected by e.g Doppler, predisposes for the development of DCS (54, 58, 67, 142, 172).

DCS is normally divided into type I (mild) and type II (serious) (54). The type I or "pain only" includes limb or joint pain, itching, skin rash and/or localized swelling. The type II includes any symptoms from the central nervous system, inner ear affection, cardiopulmonary symptoms, and also any type I symptoms which develop under pressure, and other organ manifestations. It has been assumed that the type II DCS involves the spinal cord more often than the brain. In the 1070 cases of DCS in the central nervous system that Francis and coworkers reviewed (60), cerebrum was stated to be involved in approximately 35 %.

In addition, a type III DCS has been postulated as another, more serious manifestation when the intravascular bubbles from pulmonary barotrauma seed the circulation and tissues, which are loaded with inert gas from previous dive

exposures (54, 140). The pressure gradient from the supersaturated tissues causes inert gas to diffuse into the bubbles.

However, during the last years, a descriptive clinical classification of the decompression illnesses has been suggested as an alternative to the conventional etiological and mechanistic categories (77). It has been argued that the distinction between mild and serious DCS is artificial, and has little justification in clinical practice (57). The evolution and presentation of symptoms, time of onset, the gas burden and any evidence of barotrauma, are suggested as the categories of core information in such a new clinical classification (77).

DCS is treated by the use of 100 % oxygen and recompression. Other conventional first aid management must also be considered, and parenteral fluids should be given to reverse the often accompanying hemoconcentration. On the other hand, intravenous steroids, lidocaine infusion and the use of perfluorocarbon emulsions are controversial treatment modalities (76).

b) Long-term effects

The concept "silent bubbles" was introduced by Behnke in 1951 (10). He claimed that venous gas bubbles arise during many decompressions, without inducing any symptoms of DCS. When Doppler monitoring was introduced into diving medicine (72, 173), this hypothesis was verified, since many divers developed no DCS in spite of having gas bubbles in the pulmonary artery (9, 53, 58, 142, 172).

The evaluation of decompression tables has normally used DCS as an endpoint. However, long-term sequelae of silent gas bubbles have been an issue of concern both nationally and internationally during the last decade (8, 56). Todnem and colleagues claimed to have shown such long-term effects of the central nervous system in deep divers (179), and Segadal and coworkers asked for follow-up studies for the evaluation of any long-term manifestations in the lung in professional divers (164). However, several etiological factors may be involved, including increased oxygen tensions in the breathing gas, high pressure factors, and decompression factors.

c) The formation of inert gas bubbles and physiological effects

Since venous gas bubbles are involved in DCS and such gas bubbles may even induce long-term effects, both mechanisms of bubble formation and any physiological effects need to be further elucidated. The physiology of gas uptake and elimination, and related problems of decompression, have been studied for more than 100 years, but are still not completely understood. However, what is known is

that gas bubbles probably will form when the partial pressure of dissolved gas exceeds the environmental pressure. This condition is termed supersaturation.

Many different species have been exposed to pressure and decompressed to study bubble formation. Small-sized animals as guinea pigs, cats, rats, mice, hamsters, frogs and crabs have been used in experimental studies (17, 20, 87, 116, 125). Boycott *et al.* argued that larger animals as e.g. goats were preferable as models for humans, since both the uptake and elimination of gas, and therefore bubble formation, would be dependent on the relative circulation of the animal (20).

In most of the earlier experimental studies, bubble formation was studied directly during the experiment after free preparation of veins and arteries, or at autopsy by looking for intra- and extravascular bubbles. After the introduction of Doppler, this ultrasonic device was also applied in decompression experiments, using different animal models (7, 19, 46, 72, 143, 173).

Until the study of Bove *et al.* in dogs in 1974 (19), the measurements of physiological effects of VGE after decompression had been limited. Since then, effects of VGE on the pulmonary and the systemic circulations and on gas exchange in sheep (7, 143), dogs (34-36) and goats (46) have been reported after decompression.

The hemodynamic effects of decompression seem to be dependent on both the animal preparation and the dive profile. However, following rapid decompressions, and therefore bubble formation, an increase in PAP and PVR as well as a decrease in Pao_2 are observed (7, 19, 34). After a rapid decompression in sheep, no change in Pao_2 was observed, which could be due to a small amount of gas bubbles in the pulmonary circulation (143). The changes in mean arterial pressure (MAP) and $\dot{Q}$ seem to be less predictable: A decrease in MAP has been observed in most studies (7, 34-36), whereas an increase was observed in dogs (19). A decrease in $\dot{Q}$ was observed in sheep (143), but an increase seemed to occur in goats (46). Thus, the effects of VGE after decompression seem, to some extent, to be comparable to those observed during gas infusion. This observation may indicate that the gas infusion could serve as a model for decompression studies, and it has been suggested that both air injection and air infusion could be used as such models (7, 12).

d) Detection and quantification of gas bubbles

One of the major problems in research concerning decompression, is the fact that the amount of gas that is liberated is unknown. When venous gas infusion or gas injection has been used to study effects of VGE, the infused volume of gas is known, although the size of the bubbles that enter the pulmonary circulation, is

unknown. After decompression, there is great inter- and intra-individual variability in bubble formation (53, 172). There may be individuals who develop no bubbles and others who develop a lot of venous gas bubbles after they have been exposed to the same dive profile. Moreover, in the same individual using the same dive profile, the degree of bubble formation may vary from one exposure to another.

Since the physiological effects of VGE after decompression are dependent on the degree of venous gas loading, it is of importance to try to quantify the amount of gas. The ideal model to study mechanisms of bubble formation as well as to study physiological effects of the bubbles and pathophysiological mechanisms, must include a method to measure or estimate the amount of gas that appears as gas bubbles. Gas bubbles may be either extra- or intravascular and VGE may, in fact, be late manifestations of bubble formation in tissues (54). However, the amount of gas bubbles in the pulmonary artery, the usual place for Doppler monitoring of gas bubbles, most likely reflects the total endogenous gas phase, since the vessel receives venous flow from the whole body (53).

Spencer and Oyama asked as long ago as in 1971 for "techniques of determining the numbers and sizes of bubbles, as well as for computing the volume of gas passing through a given vascular channel" (174). Powell and coworkers tried to make an estimation of the amount of gas that appeared as bubbles after decompression by comparing the increase in right ventricular systolic pressure (RVSP) with the increase in RVSP observed during venous air infusion at different rates (154). From this comparison they suggested the dose of gas after decompression at which the different Doppler grades occurred (Spencer's 0-4 scale). Such a grading system as the Spencer code, and also the Kisman-Masurel Doppler code, is nonlinear and somewhat subjective (163).

Ultrasound imaging seems to be even more sensitive to gas bubbles than Doppler, but Powell *et al.* suggested that, using two-dimensional imaging, quantification of the number of the bubbles or the gas volume released during decompression, would be as difficult as with Doppler techniques (154). More recently, it has been argued that ultrasound imaging may have several advantages in the detection and quantification of intravascular bubbles (23, 24, 97). The conventional B-scan may be used for such purpose, as well as the M-mode method, that gives a display in which the x-axis is the time parameter.

In addition, the advantage of detecting gas bubbles also on the left side of the heart should be considered by the use of ultrasound imaging. Thus, the TEE-transducer could be an exiting modality for the assessment of postdecompression gas emboli in animal experiments. Such a transducer has actually been developed at our department and was available just in time for our experiments (6).

1.2 ARTERIAL GAS EMBOLISM

In addition to inducing the above-mentioned physiological effects, VGE may result in arterial gas emboli. Firstly, venous gas bubbles may travel through the pulmonary circulation and enter the pulmonary veins and the left atrium, although the pulmonary circulation is usually considered to be a good filter for gas bubbles as well as for other emboli.

Secondly, venous gas bubbles may pass through a patent foramen ovale (PFO) or other extraordinary connections in the heart to reach the left side of the heart. In as much as 20-34 % of humans, dependent on age, the foramen ovale is patent after fetal life (82). Normally, however, it is functionally closed, since the pressure in the left atrium is higher than the pressure in the right atrium and the *septum primum* functions as a valve. The term paradoxical gas embolism (PGE) is used to describe arterial gas embolism after passage of venous gas bubbles either through the pulmonary circulation or via a PFO.

In addition, arterial gas bubbles may occur independently of VGE, e.g. after direct injection of gas bubbles into the arterial circulation. Finally, during decompression, gas bubbles may, at least theoretically, arise by *de novo* formation. All four mechanisms for the occurrence of arterial gas bubbles are commented on in the following sections.

1.2.1 Arterial gas embolism during medical procedures

PGE has been observed during many different medical procedures. Although it occurs infrequently, the potential for PGE exists, and it is associated with morbidity and mortality. Any procedures that introduce gas bubbles into the venous circulation, may actually predispose for PGE. Some patients are, however, at a higher risk of developing PGE, as e.g. patients that undergo surgery in the sitting position, or patients that are mechanically ventilated using positive end-expiratory pressure, since those conditions may reverse the pressure gradient between the atria, and thereby result in passage of gas bubbles through a PFO (150, 151). Furthermore, patients with livercirrhosis may develop intrapulmonary shunts that favor transpulmonary passage of gas bubbles (175).

Normally, the PGE is diagnosed since the patients suffer from neurological deficits after an episode of VGE (133, 135, 194). Arterial gas bubbles may also be observed during neurosurgery by watching the gas bubbles in the arteries (79, 86), or gas bubbles in the cerebral circulation may be visible on CT scans (135). After

fatal cases, autopsy has revealed gas bubbles in the cerebral or coronary circulations (79, 113), and/or multifocal infarctions in the brain assumed to be due to gas embolism (120, 175). After the introduction of intraoperative monitoring by echocardiography, gas bubbles have been observed in the left atrium or ventricle also in patients who do not show any obvious symptoms after the operation (65).

In most reported cases (41, 98, 126, 135, 138, 175, 194), it is not known if the gas bubbles have entered the arterial circulation after passage through a PFO or after transpulmonary passage. In a few cases, transpulmonary passage has been indicated after a postmortem investigation has failed to show a PFO or other intracardial connections (14, 86, 120). Furthermore, a PFO has been diagnosed in some of the patients who have suffered from VGE and arterial gas embolism, using contrast echocardiography and the Valsalva maneuver, or at autopsy (79, 113, 129, 133). Thus, the relative contribution of transpulmonary passage or passage of gas bubbles through a PFO to the cases of arterial gas embolism, has not been elucidated. If a PFO is a high risk factor for the occurrence of arterial gas emboli during VGE, patients may be investigated for the presence of a PFO before surgical procedures in which the incidence of VGE is high. It should be mentioned, however, that contrast echocardiography may induce cerebral symptoms in a few of the patients with a right-to-left shunt in the heart (18, 109).

In medical procedures, gas bubbles may also enter the arterial circulation by direct introduction of gas bubbles into the arteries. This may happen during arterial catheterization (138) or after rupture of an arterial gas baloon (64). After cardiopulmonary bypass operations, gas bubbles are ejected into the aorta after the heart has been refilled with blood. Furthermore, use of extracorporeal circulation may introduce microbubbles into the circulation, and there is still particular concern about brain damage observed after coronary bypass operations (90).

1.2.2 Arterial gas embolism during experimental gas infusion

Paradoxical gas embolism has been studied experimentally by infusing air through a catheter into the venous circulation in dogs (28-32, 78, 96, 102, 118, 193) and sheep (47, 174), and the appearance of gas bubbles in the systemic arterial circulation has been monitored. The experimental work has usually aimed at studying transpulmonary passage of gas bubbles. Thus, animals found to have an atrial septal defect have been excluded, at least in some of the studies. We may assume that animals with a PFO have also been excluded in those studies, although

Spencer and Oyama in their paper by a postmortem investigation "excluded the existence of *obvious* right-to-left shunts in all animals" (174).

The above-mentioned studies show that bubbles emerge into the arterial circulation if the animals receive gas at sufficiently high rate during continuous infusion or at a sufficiently high dose during bolus injection. It therefore seems to be possible to overload the filtering capacity of the lungs. Studies in dogs anesthetized with pentobarbital (30-32), showed that this capacity was exceeded if the air infusion rate was 0.30 ml kg^{-1} min^{-1} or higher, whereas arterial gas bubbles were detected already at the dose of 0.15 ml nitrogen kg^{-1} min^{-1} in sheep (174). These results could indicate species-differences.

Furthermore, it has been possible to reduce the threshold value for transpulmonary passage in dogs by changing anesthesia from pentobarbital to halothane (193). This latter anesthetic may act as a vasodilator of the pulmonary circulation (51). Similarly, aminophylline, another dilator of the pulmonary circulation, reduced the filtering capacity of calibrated air bubbles in dogs. Butler and Hills detected bubbles in the femoral arteries in all four aminophylline pretreated dogs after injection of bubbles $\leq$ 130 μm (28). Also, the effects of arterial gas bubbles seemed to be dramatic, resulting in arterial hypotension in the dogs pretreated. Finally, pretreatment with hyperbaric oxygen seemed to permit 60 μm bubbles to escape pulmonary filtration in dogs, and the authors speculated about the possibility of increases in the concentration of surfactant molecules in the pulmonary blood after pretreatment with oxygen (29).

Thus, the size of the bubbles may be important for any transpulmonary spillover to occur. Gas bubbles that are smaller than the capillaries have the possibility of traversing the capillary bed and enter the pulmonary veins. It has been observed that microspheres $\leq$ 8 μm, readily passed through the pulmonary circuit in dogs, whereas only a few of those larger than this size passed into the arterial circulation (160). However, it has been argued that microbubbles of 8 μm size, used e.g. as ultrasonic contrast, will totally dissolve in a shorter time than the pulmonary capillary to left atrial circulation time, due to surface tension effects (128).

A cut-off diameter of 20-30 μm for transpulmonary passage of gas bubbles has been suggested (28, 38). However, arteriovenous shunts or anastomosis in the pulmonary circulation may permit larger gas bubbles to escape filtration during certain conditions. The existence of such channels is still controversial (146). Some authors have suggested arteriovenous anastomosis 390-500 μm in diameter (144, 157, 178), whereas others have argued that channels of such a size do not exist in normal lungs (39, 75, 104).

Although it is known that gas bubbles pass through a naturally occurring PFO or other intracardial connections, e.g. during contrast echocardiography, such passage of venous gas bubbles into the left side of the heart seems to be almost unexplored experimentally. Deal and colleagues collected 30 ml air in the bubble trap placed across the arch of the aorta in one sheep that had a PFO, whereas little and no gas was collected in the other sheep without a PFO (47). Furthermore, Black and coworkers created an atrial septal defect surgically in pigs, and studied the occurrence of arterial gas bubbles during different ventilation (15). The relationship between the dose of gas in the pulmonary vasculature and passage of gas bubbles through a PFO has therefore not been elucidated. Neither have the hemodynamic changes necessary to induce a right-to-left shunt, and thereby any PGE, been studied.

In these earlier studies, the occurrence of arterial gas bubbles has been monitored directly by inspection of the pulmonary veins, by collection of any gas in a bubble trap connected to the aorta, or by the use of Doppler probes. Such Doppler probes have often been located peripherally. However, the TEE-transducer is probably, as already mentioned, a better tool to study the occurrence of arterial bubbles. This statement is based on the fact that it provides an image of the left atrium, and possibly also of the pulmonary veins, close to the lungs. In addition, passage of gas bubbles through a PFO may be monitored. In the study of Gottdiener *et al.*, precordial echocardiography was used (78), and transesophageal echocardiography has also been used to detect gas bubbles in the left atrium or in the ascending aorta in a few experimental studies (15, 193).

1.2.3 Arterial gas embolism during and after decompression

Traditionally, damage to the central nervous system caused by decompression has been attributed to occlusion of the systemic arterial circulation by gas emboli (13, 20, 92). However, the role of arterial gas bubbles in the development of symptoms from the central nervous system is still controversial. Hallenbeck and coworkers proposed an alternative mechanism for spinal cord DCS, which was based on the obstruction of the epidural vertebral venous plexus by bubbles (83). Recently, it was suggested that intravascular bubbles are involved in cerebral DCS, and only in the cases of spinal DCS in which the onset is late. Otherwise, spinal DCS is assumed to be due to bubble formation within the tissue (61, 62).

One reason for suggesting different mechanisms behind cerebral and spinal DCS, is the assumption that the brain is damaged less frequently than the spinal

cord (60). The brain constitutes 97-98 % of the central nervous system. Moreover, it receives some 75-85 times more blood flow than the spinal cord (103), and should therefore receive proportionately more arterial emboli. In addition, the effects of buoyancy will favor the appearance of arterial gas bubbles in the brain. In clinical disorders involving known systemic embolization, such as fat embolism, the presence of a thrombus in the left atrium, or subacute bacterial endocarditis, the brain is the major target organ (69). Finally, the spinal cord lesions are primarily found in the white matter, whereas the grey matter is affected during ischemic events (61).

However, since the spinal cord weighs only 40 g and the white matter 25 g, the target organ is a very sensitive reflector of both subtle and major changes. It is possible that minor changes in the brain, that weighs 1400 g, do not induce symptoms as readily as in the spinal cord (176). Also, some of the symptoms assumed to be due to lesions in the spinal cord, could actually be due to lesions in the brain (149).

Recent studies by Moon and colleagues and Wilmshurst and coworkers suggested an increased risk of some forms of decompression sickness in divers with a PFO compared to those without such an opening between the two atria (134, 191). Since a PFO may permit venous gas bubbles to escape filtration in the lungs by emerging directly into the left atrium from the right atrium, these latter studies support the view that arterial gas embolism is involved in some forms of DCS.

Arterial gas bubbles have been detected in divers during decompression (25) and at autopsy after fatal accidents (89). Such gas bubbles have also been observed in both small and large animals during and after decompression (19, 20, 110, 116, 173, 184). Thus, there is no doubt that arterial gas bubbles occur during or after some decompressions.

As mentioned previously, these arterial gas bubbles may appear as a result of transpulmonary passage or passage through a PFO. Furthermore, if the lung has been overinflated during a rapid ascent, gas may escape direct into the pulmonary veins after alveolar rupture (76, 92). It has been widely accepted that gas bubbles may occur in the cerebral circulation after such a barotrauma. Actually, the diagnosis of arterial gas embolism, seems until recently to have been confined to such cases (141, 149). However, evidence of lung injury is seldom found during clinical or radiological investigation after arterial gas embolism (76).

Finally, arterial gas bubbles may be the result of *de novo* formation of gas bubbles if exposure to hyperbaric pressure is sufficiently short (< 5 min) and the decompression rate sufficiently fast > 0.3-1 fsw/sec, (92, 106). All gas nuclei in the blood will not be destroyed and supersaturation of the arterial blood may occur

during the rapid decompression. However, an experimental study using goats did not succeed in demonstrating such bubbles in the arterial circulation after a short hyperbaric exposure and a rapid decompression (155).

Although both small and large animals have been used to study PGE after hyperbaric exposure, a distinction between animals with and without a PFO does not seem to have been made in any of the studies. Thus, neither transpulmonary passage nor passage of gas bubbles through a PFO has been studied separately or systematically in animals during and after decompression. It is not obvious that the results from the gas infusion studies testing the filtering capacity of the lungs, can be extrapolated to explain what may happen during and after decompression. For instance, it is likely that the gas bubbles that occur after decompression are smaller (40, 93) than those that occur during a continuous air infusion using a catheter ≥ 0.5 mm I.D. (2), which may influence the transpulmonary passage.

1.3 CHOICE OF EXPERIMENTAL ANIMAL

The dog has been the most used experimental animal in all kinds of VGE studies, both in experiments using gas infusion or gas injection and in decompression experiments (1, 19, 28-36, 78, 94, 96, 102, 118, 166, 180-183, 193). VGE studies have also been performed using sheep (2, 7, 47, 143, 174), goats (46), and in smaller animals as hamsters (116), rabbits (192), guinea pigs (20) and rats (152).

Differences in effects of VGE on hemodynamics and gas exchange and on the filtering capacity of the lung, suggest that species differences may exist (30, 174, 192). Extrapolation of the results to humans may therefore be questioned. The dog is for instance considered to be an athletic animal, whereas the human is grouped together with the sedentary animals. This latter fact implies species-differences in lung structure and function (27, 187).

The last two decades, the pig has gradually gained more acceptance as a good experimental model for cardiopulmonary research, and it has been argued that there are similarities of the pulmonary and cardiovascular systems between the pig and the human (49, 50, 88, 158, 161). Fife and colleagues claimed that the pig was a good model for decompression studies, and the pig seems to have been used in a few previous decompression studies (59, 153). However, when I started the work on this thesis, neither physiological effects of VGE nor the filtering capacity of the lungs, had been tested previously in pigs.

2. PURPOSE AND DEVELOPMENT OF THE STUDY

The initial attention of the study was to test the filtering capacity of the pulmonary vasculature for venous gas bubbles, and find out if it was possible to reduce this capacity by means of different factors (Papers I and II). Since the pig did not seem to have been used as an experimental animal for VGE studies, it was also valuable to describe the hemodynamic effects of VGE in this species.

Our initial experiments on VGE, suggested a PFO to be an important pathway for venous gas bubbles to enter the arterial circulation in pigs (Paper III). At approximately the same time as that became evident for us, the work that concluded with increased incidence of some forms of DCS in divers with a PFO (134, 191), was reported. Thus, those reports encouraged us to go on and study the occurrence of arterial gas bubbles during and after decompressions.

We started the study using a simple pig model (Paper I). The animals were mechanically ventilated, and in addition to monitoring arterial gas bubbles, only a few physiological variables were measured (Fig. 1). During the following experiments, the model was extended and partly changed, using spontaneously breathing pigs, to study the occurrence of venous and arterial gas bubbles during and after decompression (Papers IV and V) (Fig. 2).

Since both air infusion experiments and decompression experiments were performed to study effects of VGE and the occurrence of arterial gas bubbles, a comparison of the two models for VGE was performed (Paper VI).

The main questions that we addressed in the present study were:

1. Is it possible for venous air bubbles to escape pulmonary filtration and emerge into the pulmonary veins and the left atrium in pigs?

2. Does aminophylline, an assumed pulmonary vasodilator, reduce the filtering capacity of the pulmonary circulation in pigs as observed to occur in a previous study in dogs?

3. Are venous gas bubbles more likely to enter the left side of the heart after passage through a patent foramen ovale than after transpulmonary passage during continuous air infusion and after decompression?

4. Is it possible to develop an animal model to study venous bubble formation after decompression? Furthermore, can a relationship be shown between number of gas bubbles in a two-dimensional ultrasound image of the pulmonary artery and changes in variables of the pulmonary circulation?

5. Do the two models of VGE; VGE during air infusion and VGE formed after decompression, induce the same hemodynamic effects?

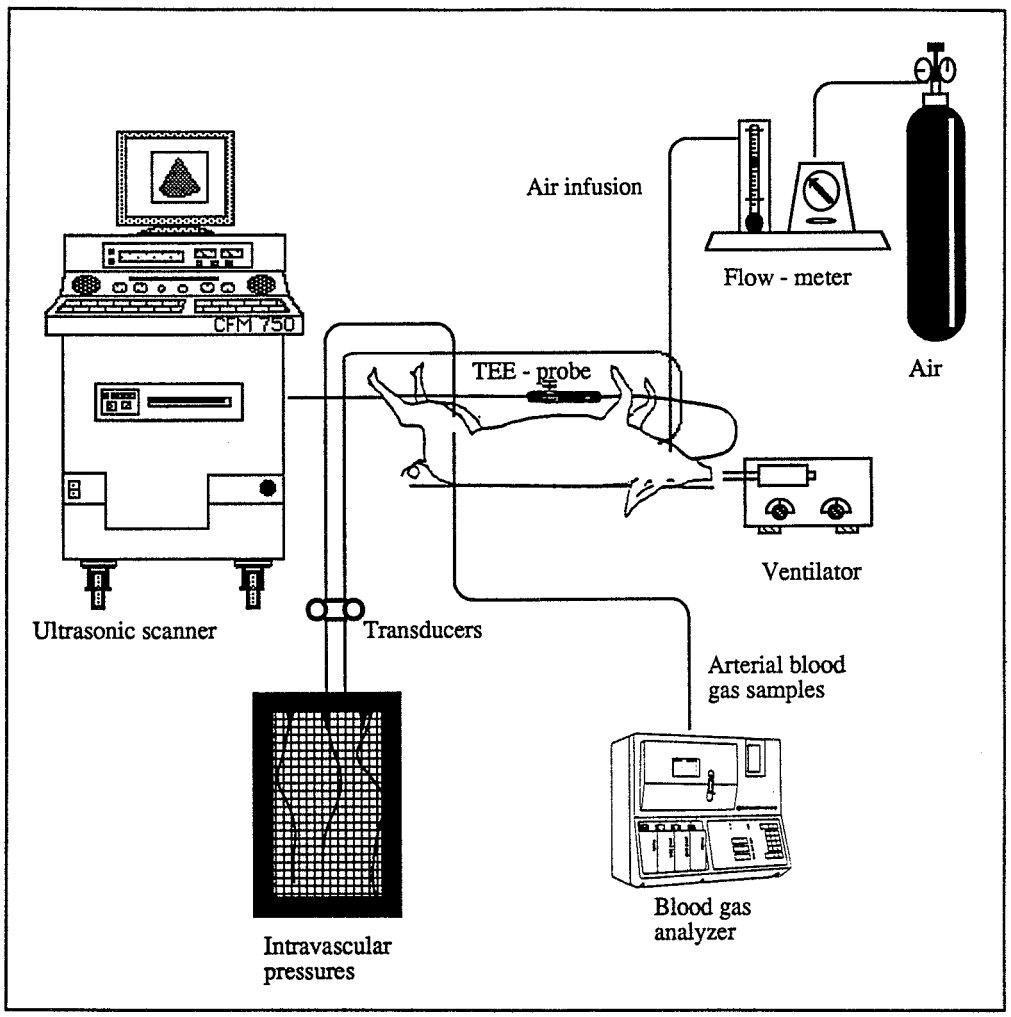

Fig. 1. Experimental setup during the first air infusion experiments.

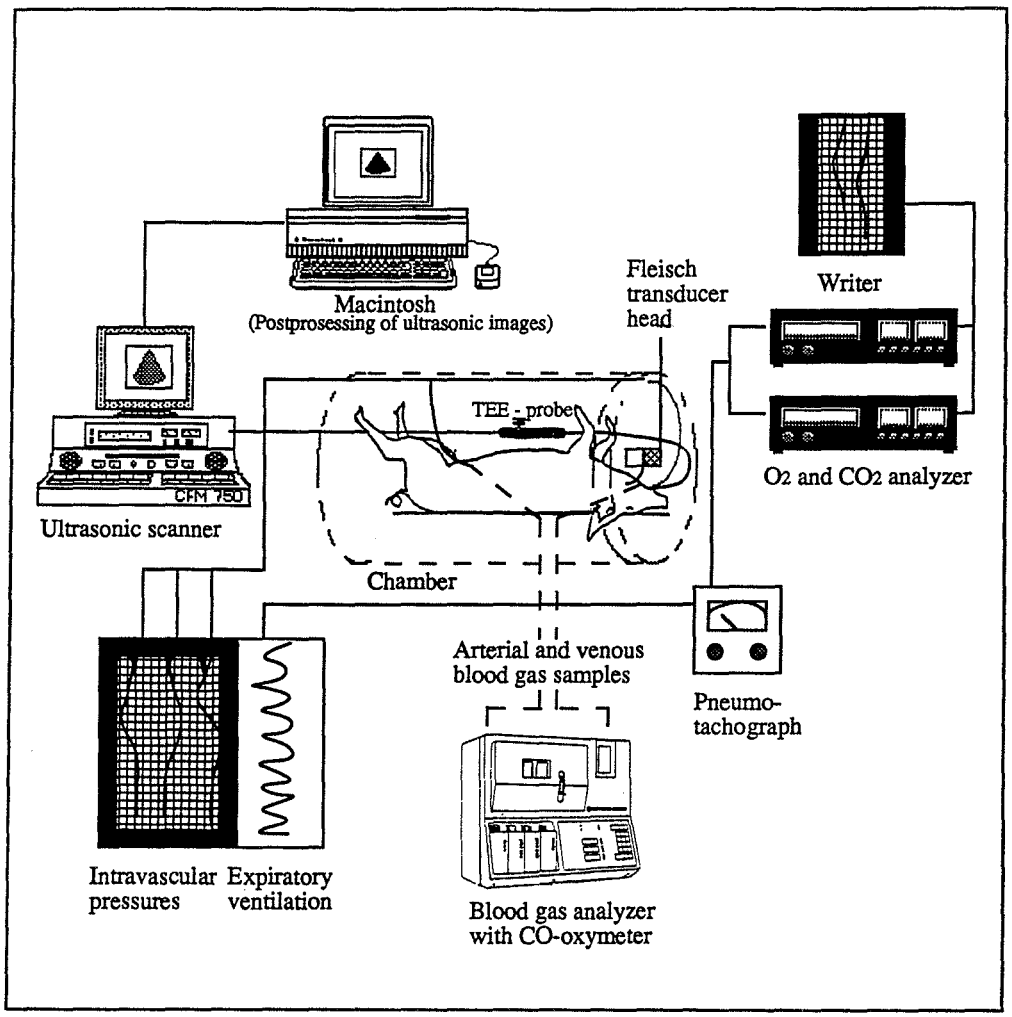

Fig. 2. Experimental setup during the decompression experiments.

3. SUMMARY OF RESULTS

Paper I describes the effects of VGE during continuous air infusion into the right ventricle in mechanically ventilated pigs at three different infusion rates. The effects on the hemodynamic variables and the blood gases seemed to be dependent on infusion rate. A cardiovascular collapse was observed in some of the pigs during the infusion of 0.10 ml kg^{-1} min^{-1} and in all pigs during the infusion of 0.20 ml kg^{-1} min^{-1}, since a dramatic drop in MAP was observed and the PAP also decreased after the initial increase. A threshold value (0.10 ml kg^{-1} min^{-1}) for the appearance of arterial gas bubbles was established, below which all VGE seemed to be filtered in the lungs. Before arterial gas bubbles were observed, the MAP had decreased to values < 40 mmHg and the PAP had returned to almost baseline values after a peak value. Never were arterial gas bubbles observed at MAP values > 40 mmHg and at high PAP values.

Paper II describes the effects of pretreatment with aminophylline, a presumed pulmonary vasodilator, on the filtering capacity of the lungs. In addition to using continuous air infusion at different rates, calibrated gas bubbles of different sizes were injected into the right ventricle. We did not find any difference between pigs that received pretreatment with aminophylline and control pigs, neither with regard to transpulmonary passage nor with regard to hemodynamic effects. Injection of microbubbles ≤ 50 μm resulted in arterial gas bubbles in two of eight cases. Despite the fact that only 0.5 ml air was used during a period of < 2.5 min, injection of small-sized bubbles (≤ 50 μm) induced significant effects on PAP.

Paper III describes a study, in which the passage of gas bubbles through a PFO is compared with the passage of gas bubbles through the pulmonary circulation during continuous air infusion at different rates. It was sometimes possible to watch the PFO in the atrial septum during the experiment, but the final diagnosis of a PFO could only be done after the experiments by a postmortem investigation. The controls, i.e. pigs that did not have a PFO, were mostly those from the previous studies that were initiated to investigate filtering capacity of the lungs (papers I and II). Similarly, most of the pigs with a PFO were those excluded from the same studies. The results showed that the pigs with a PFO had a higher incidence of arterial gas bubbles than those without a PFO. The passage of gas bubbles through a PFO seemed to be dependent on infusion rate, and both the PAP and the MAP had changed significantly from baseline values when the first arterial gas bubbles were detected in the pigs with a PFO.

Paper IV describes a model for studying venous bubble formation and physiological responses after decompression. The model consisted of anesthetized pigs that were breathing spontaneously, and a relative estimation of venous gas bubbles in the pulmonary artery was performed by the use of bubble counts in the ultrasound image provided by a TEE-transducer. The bubbles were counted automatically after the experiments, by a software program developed at our institute. The results showed individual variation in bubble formation and a close association between bubble count and changes in variables of the pulmonary circulation. The immediate increase in MAP after surfacing, which was followed by a decrease, did not relate to bubble count.

Paper V describes the occurrence of arterial gas bubbles in pigs with and without PFO after a rapid decompression. The pigs were divided into two groups after the experiments by a positive or negative postmortem finding of a PFO. Since the venous bubble count was known in the pigs in both groups, the relative number of gas bubbles could be compared and excluded as a reason for any difference between the two groups. The results showed that all six pigs with a PFO had arterial gas bubbles, whereas such gas bubbles were detected in only two of the eight pigs without a PFO. The incidence of arterial gas bubbles was therefore significantly higher in pigs with a PFO than in control pigs. However, in most PFO pigs, the number of gas bubbles had to be sufficiently high to induce an increase in PAP, before any gas bubbles occurred in the ascending aorta.

Paper VI presents a comparison of the two models of producing VGE; the air infusion model and the decompression model. The same anesthetic regimen was used to allow the pigs to breathe spontaneously. The results showed that the changes in the variables of the pulmonary circulation were qualitatively the same during the initial 30 min after the rapid decompression or during air infusion (0.05 ml kg^{-1} min^{-1}). However, the variation in the variables was much greater in the pigs after decompression than in the pigs during air infusion. Similarly, during the following 30 min of the experiment, the variables returned toward baseline values in the decompression group, whereas only a slight decrease or increase towards baseline values was observed in the air infusion group. Finally, the rapid increase in MAP followed by a decrease, that appeared after decompression, was not observed during air infusion. None of the pigs had arterial gas bubbles during air infusion, and two pigs had arterial bubbles after decompression, and the results were therefore inconclusive with regard to transpulmonary passage.

4. DISCUSSION

4.1 EFFECTS OF VGE

It was surprising to find that the infusion rates of 0.10 and 0.20 ml kg^{-1} min^{-1} induced a cardiovascular collapse in most of the pigs (Paper I and II). These doses had been used in dog experiments, and even 0.30-0.35 ml kg^{-1} min^{-1} did not seem to induce such large hemodynamic effects in dogs (30, 32, 102). It is difficult to compare the results from different experimental animals, using different experimental preparations in different laboratories. However, our results suggest a larger hemodynamic response to the same volume of gas in the pulmonary circulation in pigs than in dogs.

In paper I, we suggested that the discrepancy between our findings and those of others could be explained by the fact that the alveolar and capillary surface area was smaller in the sedentary pig than in the athletic dog, according to the principle of symmorphosis (27, 187, 188). This may reduce the capacity for eliminating intravascular gas bubbles from the blood to the alveoli. Also, Wolffe and Robertson concluded that the amount of air necessary to produce death in rabbits and dogs when injected intravenously, seemed to be directly proportional to the size of the pulmonary artery and its branches (192).

In addition, the pigs and other animals such as sheep, goats, cows and cats have intrapulmonary macrophages in the pulmonary circulation. These cells may release thromboxane A_2, a potent vasoconstrictor, when exposed to particles of different kinds in the pulmonary circulation (186). This fact could also contribute to the difference in response between dogs and pigs, since no intrapulmonary macrophages have been found in dogs. Such cells have been observed in humans, although it appears that their number is relatively small in the normal lung (48).

After decompression, none of the pigs seemed to be overloaded with gas bubbles in the same way as during air infusion so that a severe systemic hypotension occurred (Paper IV). There were considerable differences in response, since some pigs had few bubbles, whereas others developed a lot of bubbles. Thus, it was possible to study the effects of both high and low bubble count on the pulmonary and systemic circulations.

A comparison of the profiles of the changes in PAP during air infusion (0.05 ml kg^{-1} min^{-1}) and after decompression, revealed that the PAP increases observed in the latter pigs were of both higher and lower magnitude than the increases observed in the pigs that received air infusion. Since many smaller-sized bubbles probably occur after decompression (40, 93), the bubbles may induce

vasoconstriction in the pulmonary vasculature, that will influence the PAP response (44). Moreover, after decompression the bubble count will increase to maximum values, and thereafter decrease, a time course that does not occur during continuous air infusion at a constant rate (Paper VI). Caution should therefore be exercised if the amount of gas in the pulmonary circulation is estimated from the PAP increase. However, Powell and coworkers did not pay attention to these possible differences between the air infusion model and the decompression model, when they tried to estimate the dose of gas that entered the pulmonary artery after decompression in sheep (154).

The results after decompression were predictable in the way that VGE induced increases in PAP and PVR and a decrease in Pao_2, which are qualitatively the same results as observed during air infusion. The results were also in accordance with the results from other animal studies after rapid decompression (7, 19, 34). However, the immediate increase in MAP observed in 13 of 14 pigs after decompression (Paper IV and V), was different from the change in MAP observed during air infusion, both in mechanically ventilated pigs and in spontaneously-breathing pigs (Paper I and VI). In the latter pigs we did not find any obvious tendency for the MAP change. An increase in MAP has been observed in other studies in dogs both during air infusion (180) and after decompression in dogs (19).

We can only speculate on the reason why there seemed to be a different response in MAP after decompression than during air infusion. The peaking of MAP could solely have been an effect of the rapid decompression that followed the compression. Furthermore, smaller-sized gas bubbles that arise after decompression and enter the pulmonary circulation, may induce reflex-mechanisms or release humoral mediators. Finally, bubbles that are located in the peripheral circulation and tissues, may induce an increase in SVR and MAP as suggested by Bove *et al.* (19).

4.2 THE OCCURRENCE OF ARTERIAL GAS EMBOLI

4.2.1 Transpulmonary passage

The pulmonary circulation in pigs seemed to be very resistant to transpulmonary passage of gas bubbles during continuous air infusion. This statement is based on the fact that only during circulatory collapse did the gas bubbles escape filtration in the lungs (Paper I). The results contradict most of the results from other studies on transpulmonary passage in dogs and sheep, since in

those studies, gas bubbles have been detected in the arterial circulation at high PAP values and without having a great decrease in MAP (30, 31, 78, 102, 174). It has been suggested that a high driving pressure is necessary to force the gas bubbles through narrow capillaries or arteriovenous anastomosis, since the force of the surface tension will prevent any passage through the channels (29, 31, 38). However, arterial gas bubbles have occurred in dogs during gas injection also at normal PAP values (193).

Aminophylline did not seem to reduce the filtering capacity for gas bubbles in pigs. Since vasodilators as aminophylline and halothane reduced the filtering capacity of the lungs in dogs (28, 193), it has been suggested that this could be due to opening of arteriovenous shunts (193). It has also been argued that a high PAP can open such shunts e.g. during overloading of gas (71, 144). We have not been able to find any literature that shows arteriovenous anastomosis in the pulmonary circulation of the pig.

During a continuous air infusion, the size of the gas bubbles will be dependent on the internal diameter of the infusion catheter, on the flow at the infusion site and on the mixing in the ventricle that may fracture gas bubbles into smaller ones (91). The exact diameter of the infusion catheter has not always been reported, but usually it has been between 0.5-1.6 mm (2, 30, 36). Since the infusion catheter used in our experiments had an I.D of 0.76 mm, it is therefore unlikely that the difference between the results from our studies and those of others on transpulmonary passage, can be explained by a discrepancy in the size distribution of the gas bubbles.

The size distribution may, however, be of importance, since during the infusion of gas bubbles $\leq$ 50 μm (Paper II), we detected gas bubbles in the left atrium during two out of eight injections, without having a cardiovascular collapse. Since bubbles as small as 5 μm were injected, the bubbles that appeared in the left side of the heart could have been small-sized bubbles, i.e. bubbles that had a diameter < 20 μm. These gas bubbles could therefore have passed through the capillaries, since their size was below the assumed cut off-diameter for transcapillary passage (28, 38).

After decompression, bubbles were detected in the ascending aorta in two out of eight pigs without a PFO (Paper V). In contrast to the situation during air infusion (Paper I), the transpulmonary passage appeared when the MAP was within the normal range and the PAP was $\geq$ 30 mmHg. The gas bubbles that were observed in the ascending aorta had a very low intensity in the ultrasound image, an observation that indicates transpulmonary passage of small-sized bubbles (114,

145). This assumption accords with the finding of many small venous gas bubbles (4 μm) after decompression in dogs (40).

4.2.2 Passage through a PFO

Both the results from the first study and that using aminophylline (Paper I and II), suggested that the lung filter was very effective in pigs. During the same experiments, it seemed obvious that gas bubbles in the left atrium were more likely to appear in pigs with a PFO than in those without such an opening between the atria (Paper III). The results after decompression supported the conclusion from the air infusion study, since gas bubbles entered the arterial circulation more often through a PFO than through the pulmonary circulation. After decompression the size distribution of the gas bubbles is assumed to be different from that occurring during air infusion (Paper V).

Lately, the importance of a PFO in medical procedures and diseases as a way for passage of both thrombi and gas bubbles to the arterial circulation, has been considered in several studies (15, 16, 43, 80, 99, 105, 108, 115, 169). Our results, from the first published experimental study on PGE through a PFO, support the view that PFO should be considered a risk factor for PGE during medical procedures.

Although, a PFO has been mentioned as a pathway for arterialization of venous gas bubbles also in divers (89, 167), it seems partly to have been neglected as a factor predisposing for arterial gas bubbles during or after decompression (19, 116, 173). The studies about the relationship between the occurrence of some forms of decompression sickness and the incidence of PFO in divers (134, 191), showed that the existence of a PFO should be an issue of concern also in diving medicine. Actually, Wilmshurst focused on the problem already in 1986, when he reported a case of arterial gas embolism and transient neurological deficits in a scuba diver that had an atrial septal defect (189). During the last years, the importance of a PFO as a selection criterion for divers, has been debated (190).

Our results may help to understand the findings in the above-mentioned studies in divers with a PFO. Thus, it is likely that the existence of a PFO is a risk factor for arterialization of gas bubbles, and hence for serious DCS. However, a recent study shows that many divers may not experience any DCS, despite having a PFO (42). Those results may not contradict the results from the above-mentioned studies, but may only suggest that there is a complex pattern of factors involved in the development of DCS and that the gas bubbles probably only initiate the process.

4.3 THE MODEL FOR DECOMPRESSION STUDIES

In paper IV and V, we present the results from a decompression model using spontaneously breathing pigs. Such a pig model has not been presented before, and the advantages of this model are; Firstly, the possibility to detect venous gas bubbles and actually do a relative estimation of the venous gas that enter the pulmonary artery and thereby the pulmonary vasculature as bubbles. Furthermore, physiological effects can be measured and related to the number of venous gas bubbles. In addition, the use of a TEE-transducer, provides the opportunity to study the occurrence of arterial gas bubbles in the left atrium or the ascending aorta during or after decompression. Since 30-40 % of our pigs have a PFO, the occurrence of arterial gas bubbles after passage through a PFO can also be studied.

No previous decompression model has incorporated all these potentials in one model. Some other models using larger-sized animals have been presented to study hemodynamic effects as we did (7, 19, 34, 35, 143). However, the possibility to estimate the amount of gas bubbles noninvasively and study transpulmonary passage of gas bubbles as well as passage of gas bubbles through a PFO, is unique.

A rapid decompression was chosen to generate gas bubbles. However, it may be difficult to relate physiological effects to the number of gas bubbles in the two-dimensional image in pigs that are exposed to only moderate decompression stress. If the decompression profile produces few gas bubbles, the M-mode method may therefore be more suitable for quantifying the echoes from microbubbles, since the x-axis in the display is the time parameter (23, 97).

Although, similarities between the air infusion and the decompression model exist, the results revealed both qualitative and quantitative differences in the hemodynamic variables measured or estimated (Paper VI). After decompression, there was individual variation in bubble formation, and the number of bubbles was time dependent. In contrast, the same volume rate was used during the entire infusion period in all pigs that received air infusion. There was little inter-individual variation in the number of bubbles in the latter pigs, as evaluated by the bubble count in the image of the pulmonary artery. Furthermore, as mentioned previously, there are probably more smaller-sized bubbles after decompression, than during air infusion using catheters ≥ 0.5 mm I.D., which may influence the pulmonary vascular response. Finally, the compression followed by the rapid decompression may itself induce changes in the pulmonary and the systemic circulations. The use of small-sized catheters and infusion of air at a gradually increasing infusion rate, followed by a gradually decreasing rate, could eliminate some of the differences between the two models.

4.4 METHODOLOGICAL CONSIDERATIONS

4.4.1 Experimental procedure

Although a pig model for cardiovascular research had already been established at our department when we started the work, the model had not been developed to do VGE studies. In addition, the pig was unexplored as a an experimental animal for VGE studies. These facts may have influenced the design of the first studies (Paper II and III). It was especially surprising to find such a high incidence of PFOs in the pigs, that may be almost 40 % in a large population of pigs at that age. The occurrence of a PFO seemed to be genetic, since one farmer delivered pigs that had a PFO in 70-80 % of the pigs.

Our study was initiated using a simple pig model (Paper I). After the first studies, measurements were introduced to calculate cardiac output ($\dot{Q}$) using the Fick principle (Paper VI and VI). It has often been argued that use of the direct Fick method for measuring $\dot{Q}$ requires the existence of stable conditions during the last 1-5 min before sampling (146). However, if an oxygen analyzer is used that measure oxygen consumption continuously, 30-45 sec may be sufficient for stabilization after circulatory and respiratory changes (81). The main source of error during an unsteady state is changes in pulmonary volume (81). An increase in this volume during the initial 15 min after decompression may actually have resulted in an underestimation of both the decrease in $\dot{Q}$ and the increase in SVR at maximum MAP increase. The thermodilution method was not chosen, since it includes the introduction of microbubbles that can influence the results. However, it is possible that this is a minor problem, and the method should be considered. Since gas bubbles interfere with the Doppler flow spectrum of the pulmonary artery, the transesophageal transducer could not be used to measure flow during our experiments.

It was initially planned to study decompression effects by the use of the same pig model as that used in the air infusion studies. However, the chamber was too small to allow the ventilator to be placed into it. Since no stable preparation was achieved using spontaneously breathing pigs anesthetized with pentobarbital, a change in anesthesia was also necessary. Thus, a new and better pig model was introduced for our research (Paper IV).

An objection could be raised to the results from the two studies on the occurrence of arterial gas bubbles in pigs with a PFO, since the results of the experiments were already known when the diagnosis of a PFO was made (Papers III and V). Thus, an autopsy was not performed "blind" as regards the results, a fact

that could have influenced the finding of a PFO. Some of the narrow PFOs were difficult to detect, and at least during the initial experiments it can not be excluded that we could have missed a few of them. However, this weakness of the method is unlikely to change the conclusion, since normally the diagnosis was simple to make. Furthermore, the conclusion is supported by the results from experiments done later on in our laboratory, when the diagnosis of a PFO has been done "blind" as regards the results (unpublished observations).

4.4.2 Detection of gas bubbles by ultrasound

The use of the TEE-probe was the main method during the whole study. Both the venous gas bubbles in the pulmonary artery and the arterial gas bubbles, in either the left atrium or the ascending aorta, were detected by this tool. In addition, it provided an image of the atrial septum, so that a PFO could sometimes be observed as a channel, normally during gas loading when the VGE in the pulmonary circulation seemed to change the pressure gradient between the atria and thereby induce a right-to-left shunt.

During the initial experiments (Paper I-III), we wished to detect arterial gas bubbles as close to the lungs as possible, to be sure that the transpulmonary passage was studied. Since the TEE-probe provided a view of both the right pulmonary artery and the left atrium including the entrance of one of the right pulmonary veins, this view was considered to be perfect for such a study (Fig. 1, paper I). Mostly, it was easy to position the probe to get a high quality image of these cardiac structures. However, in some pigs, an image of the ascending aorta/aortic arch and the main pulmonary artery was preferable, since echoes from the lungs disturbed the first image (Fig. 2, paper I).

During and after decompression, this latter view was normally used (Papers IV-VI). The estimation of gas loading was performed using the image of the main pulmonary artery, since this vessel transports all the gas bubbles to the lungs. After the dive, the transducer could always be moved 1-2 cm further down to provide the image of the atrial septum, that sometimes allowed direct monitoring of the passage of gas bubbles through a PFO.

Although ultrasound imaging seems to have a lower threshold for detection of gas bubbles than the Doppler method (154), only a two-dimensional slice of the pulmonary artery or the aorta is available for detection and quantification of gas bubbles. This, of course, limits the method at present. In addition, it is not verified exactly how small the gas bubbles can be, and still be detected. The detection

threshold is both dependent on the frequency of the transducer, and the depth from the probe at which bubbles are to be detected (23). Gas bubbles, 5-50 μm, injected as foam, were clearly detected in the pulmonary artery, and were also observed as single bubbles in the left atrium (Paper II). After a bolus injection of Albunex, which includes air bubbles coated with albumin (≈ 5 μm) to be used as ultrasound contrast, high intensity spots were clearly observed in the pulmonary artery using the present equipment (Paper I).

It should be noted that also solid particles may appear as high intensity spots in the blood, e.g. thrombi. However, the size of an erythrocyte aggregate has to be considerable greater (120 μm) to have approximately the same back-scattered intensity as a gas bubble with a diameter of 18 μm (23). It could be proposed that the high intensity spots observed after the circulatory collapse (Papers I and II) were thrombi arising secondary to the slow circulation. However, the autopsy revealed gas bubbles in the left heart or coronary circulation of the pigs.

The occurrence of arterial gas bubbles was monitored by at least two different observers during all experiments. Since the images were videotaped during the entire experimental period, the tape was viewed afterwards. The detection of the first bubbles in the left atrium or in the aorta was always followed by the occurrence of several bubbles within the following 10-15 sec, so that there was no uncertainty with regard to the time point of detection of arterial gas bubbles.

4.4.3 Statistics

The variables have been treated as having a normal distribution throughout the study. Thus, the data have been presented by means, and standard deviations to show individual variability (descriptive statistics) (Papers II, III and V). Furthermore, parametric hypothesis tests (analysis of variance, Student's *t* test) have been used. However, the non-parametric Spearman's rank correlation has been used in papers III and IV, since any non-linear association also can be tested by the method.

Confidence intervals present a range of values, on the basis of the sample data, in which the population value may lie (68). Since there has been a major shift in policy by many leading medical journals towards encouraging or even requiring authors to use confidence intervals when presenting their main results (4, 68), 95 % confidence intervals have been estimated for the variables in Papers IV and VI.

There are several ways of analyzing serial measurements (124, 185), Matthews *et al.* (124) and Altman (4) have recommended to use summary measures instead of e.g. repeated measures analysis of variance. Analysis of summary measures is easy to perform and interpret for nonstatisticians. When the variables show a peaked time course, such measures could be e.g. the maximum value and the time to reach maximum value (Papers VI-VI). In addition, it is informative to present the time course by graphical display of individual variables (4, 124).

The above-mentioned procedures avoid the problems of dependent values, missing observations and multiple comparisons. Since multiple significance testing gives a high probability of finding a significant difference just by chance, methods to deal with this problem have to be used when many hypothesis tests are performed. Thus, we have applied the Bonferroni method in the earliest papers (papers II-III). The problem of multiple comparisons had also to be considered when many variables were tested in paper IV.

4.5 FUTURE PERSPECTIVES

During the last one and a half year, the decompression model has been modified to some extent. Studies have been done to estimate bubble formation and physiological effects during different dive profiles using different breathing gases. A method to measure nitrogen in blood has been developed (95), and by the use of the pig model, it is now possible to estimate nitrogen uptake and elimination and e.g. study the relationship to the number of venous gas bubbles. This might be a step towards the elucidation of the mechanisms of bubble formation.

The method of gas quantification by the use of bubble counts in an ultrasound image, will be improved if the method also includes the estimation of bubbles size (55). In addition, three-dimensional imaging may allow counting in two perpendicular planes of the pulmonary artery.

This thesis points out another pathway for future research, since the pig model could be excellent for studying effects of the arterial gas bubbles on the brain after decompression. Firstly, to establish the methods to monitor brain damage, it is preferable to infuse gas bubbles at known size and volume rate directly into the carotid arteries or the aorta. Thereafter, the rapid decompression presented in this work (Papers IV-VI), could be used to produce VGE in the pigs, followed by an estimation of the number of venous gas bubbles. Three experimental groups of pigs will then appear; One group is supposed to have only VGE and no arterial gas bubbles, a second group may have arterial gas bubbles

after transpulmonary passage, and therefore possibly small-sized gas bubbles, and a third group of pigs will have a PFO, and therefore probably larger-sized arterial bubbles than those occurring in the second group. A fourth group may actually also appear, since some pigs may have no detectable VGE, and no arterial gas bubbles, but probably still have endogenous gas generation. By monitoring the carotid arteries by ultrasound, the passage of gas bubbles to the cerebrum can be partly estimated. Such an animal model for investigating brain damage after decompression has not been presented before, and might have the potential of elucidating some of the pathophysiological mechanisms of DCS as well as of any long-term effects on the brain.

5. CONCLUSIONS

1. Normally the pig lung is very effective as a filter of gas bubbles. Aminophylline does not seem to reduce the filtering capacity of the pulmonary circulation in pigs. Our results indicate that the transpulmonary passage is dependent on bubble size.

2. Venous gas bubbles are more likely to enter the left side of the heart through a PFO than by transpulmonary passage, both during air infusion in mechanically ventilated pigs and after decompression in spontaneously breathing pigs.

3. A pig model has been developed to study bubble formation and physiological effects during and after decompression. A clear association between number of bubbles in a two-dimensional image of the pulmonary artery and changes in the variables of the pulmonary circulation was observed. This model has great potentials for future research on decompression related problems, since it also includes the detection of arterial gas bubbles in pigs with and without a PFO.

4. Air infusion in pigs induces changes in the variables of the pulmonary circulation that are qualitatively the same as after a rapid decompression. The rapid increase in MAP observed after decompression did not appear during air infusion. The discrepancies between the two models should be considered before choosing the air infusion model to study effects of VGE that occur after decompression.

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Paper I

Paper I

Venous air embolism in swine: transport of gas bubbles through the pulmonary circulation

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VIK, A., A. O. BRUBAKK, T. R. HENNESSY, B. M. JENSSEN, M. EKKER, AND S. A. SLØRDAHL. *Venous air embolism in swine: transport of gas bubbles through the pulmonary circulation.* J. Appl. Physiol. 69(1): 237–244, 1990.—The assumption that the lung is an effective filter for gas bubbles is of importance for certain occupations (e.g., divers, astronauts) as well as in the accomplishment of several medical procedures. The filtering capacity was tested in pigs by use of continuous air infusion into the right ventricle and a transesophageal echocardiographic transducer for detection of air in the left atrium. Twenty pigs, anesthetized with pentobarbital sodium and mechanically ventilated, were divided into groups that received air at infusion rates of 0.05 (*group 1a, n* = 7), 0.10 (*group 2, n* = 6), and 0.20 (*group 3, n* = 5) $ml \cdot kg^{-1} \cdot min^{-1}$. Two pigs served as controls. The breakthrough incidence was 0, 67, and 100%, respectively. *Group 1a* received a second infusion of 0.10 $ml \cdot kg^{-1} \cdot min^{-1}$ (*group 1b, n* = 7), and spillover of bubbles occurred in only 14% of these pigs. Infusion of gas caused a maximum increase in mean pulmonary arterial pressure (PAP) of 129 ± 9% to 39.2 ± 1.3 (SE) mmHg, with no significant difference between the groups. Breakthrough was observed only in animals with a dramatic reduction in mean arterial pressure and a PAP that returned to almost-normal values at spillover time. Our results suggest that the threshold value for breakthrough of air bubbles in pigs is reduced compared with that in dogs. The hemodynamic consequences at a given infusion rate are, however, greatly enhanced.

breakthrough; spillover; transesophageal echocardiographic transducer; decompression sickness; arterial bubbles; repeated embolizations

EVEN THOUGH serious gas embolism is a rare event in clinical medicine, it still occurs, either as an accidental massive air injection into the venous system or as the result of different therapeutic maneuvers. Gas in large volumes is used to insufflate the abdominal cavity for laparoscopy, and fatal incidents have occurred (14). During neurosurgical procedures in the sitting position, ~30–40% of the patients are reported to show signs of intravascular air (25).

In some occupations, as with cassion work, diving, or extravehicular activity in space, the worker is subjected to decompressions that in many if not all cases lead to venous gas bubbles. These bubbles have been called "silent bubbles" because they are regarded as having no pathological effects on the organism (3).

The lung has been assumed to be an excellent filter for gas bubbles, and arterial gas embolism is considered to be a rare event in the absence of intracardiac shunts. However, if gas enters the arterial side, it can have serious consequences, especially in the cerebral circulation (16, 24). The Trendelenburg position does not seem to prevent arterial gas bubbles ejected from the heart into the aorta from reaching the brain (7).

Several studies on dogs (5, 6, 35) and sheep (30) have demonstrated that gas bubbles will break through the lung filter if the lung is overloaded. We chose to develop a pig model to test the effect of gas embolism. The anatomic and physiological similarity of the cardiovascular, respiratory, and hematological systems between the pig and the human has been pointed out (11, 12). More specifically, the young pig (>2 mo) has a lung circulation morphologically similar to that of adult humans (27). The pig also seems to respond to exercise in the same way that humans do with regard to oxygen consumption and cardiac output (17, 28).

We studied the effect of venous air embolism on the lung circulation and the possibility of air bubbles breaking through to the systemic circulation in pigs. An ultrasonic system that included a transesophageal echocardiographic transducer (TEE) permitted the detection of microbubbles as they emerged into the left atrium from the pulmonary veins (2).

MATERIALS AND METHODS

Surgical procedures. Twenty domestic farm swine of both sexes (age ~3 mo, body wt 23.5 ± 0.3 kg) were used in this study. They were anesthetized with pentobarbital sodium (25–35 mg/kg) via an ear vein, and anesthesia was maintained by a 5- to 15-$mg \cdot kg^{-1} \cdot h^{-1}$ continuous intravenous infusion of pentobarbital sodium. The pigs were tracheotomized and ventilated in the supine position with a volume-regulated ventilator (model 613, Harvard Apparatus, South Natick, MA) with a tidal volume of 7–8 ml/kg, a frequency of 10–12 breaths/min, and an oxygen content of the air mixture of 25–30%. The ventilator was adjusted to maintain arterial P_{O_2} (Pa_{O_2}) between 105 and 135 mmHg and arterial P_{CO_2} (Pa_{CO_2}) <40 mmHg. The urinary bladder was drained through a cystostomy, and body temperature was recorded by a rectal thermometer (Exacon MC 8700) and kept at normal

levels (37.5–38.5°C) by a heating pad and wrappings.

A saline-filled polyvinyl catheter (7 Fr) was introduced into the right femoral artery to record the pressure in the aorta and obtain samples for blood gas analysis. The catheter was connected to a pressure transducer (Statham P23 ID) that was calibrated against a mercury manometer with zero pressure referred to the left ventricular midlevel. Arterial blood gases were measured on an IL-1306 pH/blood gas analyzer (Instrumentation Laboratories). Samples were obtained at 1, 2, 3, and 5 min after the start of gas infusion, and later every 5th min. The right femoral vein was cannulated with a similar catheter to provide venous access for fluid infusion, and 0.9% NaCl was infused continuously during the experiment at a rate of ~18 $ml \cdot kg^{-1} \cdot h^{-1}$.

Both jugular veins were dissected free to allow introduction of a thin polyethylene catheter (0.76 mm ID). The catheter to be used for air infusion was placed in the right ventricle, and the location was verified by connection to a pressure transducer. The second catheter was placed in the pulmonary artery to continuously record pressure. After placement of all catheters and the electrodes for electrocardiogram registrations in a position giving a high R peak of the QRS complex, ≥30 min were allowed to elapse for stabilization, and base-line data were collected during the next 30 min.

Blood flow was not measured in these animals because we wanted to keep intervention to a minimum. Even dilution techniques may introduce microbubbles to the pulmonary circulation and interfere with the flow pattern of the air bubbles.

Bubble detection. A TEE probe (7.5 MHz, CFM 700, Vingmed, Horten, Norway) was inserted 30–40 cm into the esophagus and positioned to provide a simultaneous two-dimensional image of the right pulmonary artery and the left atrium (Fig. 1). By withdrawing the transducer 1–2 cm, we were also able to obtain a view of the aorta and the main pulmonary artery in a second image. The air bubbles were seen as high-intensity spots in the blood (Fig. 2), and, because there is a proportionality between the intensity of the reflected signal and the

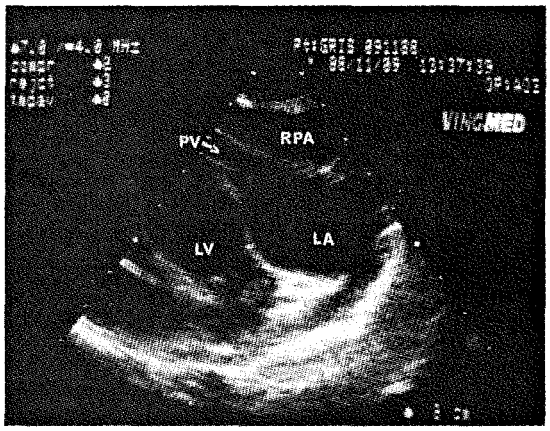

FIG. 1. Ultrasonic image of right pulmonary artery (RPA) and right pulmonary vein (PV) entering left atrium (LA). LV, left ventricle.

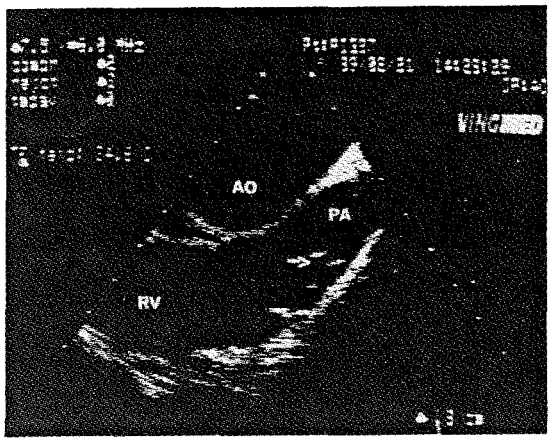

FIG. 2. Air bubbles can be seen as high intensity spots (arrow) in pulmonary artery (PA). AO, aorta; RV, right ventricle.

radius of the bubble (22), it was possible to get an impression of bubble size. We monitored the left atrium to detect the microbubbles as they emerged into the left side of the heart from the pulmonary veins, and the ultrasound image was continuously videotaped during the experiments.

Air infusion. Air was infused continuously into the right ventricle by a specially constructed infusion system that consisted of a syringe that injected gas through a catheter (0.76 mm ID). The infusion was controlled by use of high-pressure air and a calibrated flowmeter. The size of the gas bubbles at the tip of the catheter varied between 2 and 2.5 mm diam when infused into stationary water, as verified by a photographic technique. Bubble size did, however, depend on flow at the infusion site, and it is likely that the bubbles fractured into microbubbles in the turbulent flow of the ventricle (18).

Two pigs served as controls and received no air during 3–4 h of the experiment. The others were divided into three groups, with infusion rates of 0.05 (*group 1a, n* = 7), 0.10 (*group 2, n* = 6), and 0.20 (*group 3, n* = 5) $ml \cdot kg^{-1} \cdot min^{-1}$. With regard to *groups 2* and *3*, the infusion was continued until the pig died, but no longer than 150 min. None of these animals received a second infusion. In *group 1a*, the infusion was stopped after 90 min, and during a recovery period of 30 min the mean pulmonary arterial pressure (PAP) and the mean arterial pressure (MAP) returned to control values. Although Pa_{O_2} and Pa_{CO_2} did not reach preembolization values, they returned to values which were within the normal range for pigs. The pigs then received a second infusion of air at a rate of 0.10 $ml \cdot kg^{-1} \cdot min^{-1}$ for 35 min (*group 1b, n* = 7). The occurrence of microbubbles in the left atrium was determined by several observers during the experiment and later verified by repeated viewings of the tapes.

The mean pressures were calculated from the pressure curves according to the formula MAP or mean PAP = 1/3 pulse pressure + diastolic pressure.

Postmortem, the hearts of the pigs were investigated for septal defects. None of the animals in this study had

any openings of the atrial septum, but four additional animals were excluded because of this.

Statistics. The data were analyzed by one-way and two-way analysis of variance and Student's *t* test (paired and unpaired). $P < 0.05$ was defined significant. All values are given as means ± SE.

RESULTS

Controls. In both pigs we observed an increase in MAP of 7 mmHg during the 1st h, followed by a slight decrease that led to values 2 and 10 mmHg below base line at the end of the experimental period 2 h later. The changes in PAP and Pa_{O_2} never exceeded ±3 and 14 mmHg, respectively, from control values. The variations of the three parameters at any time during a period of 30 min were minimal.

Breakthrough of gas bubbles. It was usually possible to obtain high-quality images of the right pulmonary artery and left atrium. By slightly moving the transducer, we were able to see pulmonary veins on both the left and the right side, and the bubbles were usually observed as they emerged into the left atrium from the right pulmonary vein. After breakthrough of the first microbubble, the number of bubbles seen in the left atrium increased steadily during the next 3–5 minutes.

The results can be seen in Table 1. The mean transit time of *group 2* (measured from start of infusion to bubble breakthrough) was 15.4 ± 1.9 (SE) min ($n = 4$), and infused volume was 1.5 ± 0.2 ml/kg. In *group 3*, breakthrough occurred after 17.2 ± 9.2 min ($n = 5$), and a volume of gas of 3.4 ± 1.8 ml/kg was infused at breakthrough time. The transit time was not significantly different between *group 2* and *group 3*.

In contrast to *group 2*, breakthrough of bubbles was observed in only one *group 1b* pig that received its second infusion. The breakthrough time was almost doubled to 29 min, which indicated an infused volume of 2.9 ml/kg.

PAP response. An immediate rise in PAP was observed after the air infusion began (Fig. 3, Table 2). There was a close relationship between the time to reach maximum PAP and infusion rate, whereas the maximum pressure attained was constant. Although there was no significant difference ($P = 0.068$) in PAP maximum time between *group 1b* and *group 2*, there was a tendency to a slower PAP response of the pig receiving its second infusion.

TABLE 1. *TEE detection of arterial bubbles after venous air infusion*

Group No.	*n*	Infusion Rate, $ml \cdot kg^{-1} \cdot min^{-1}$	Breakthrough			
			n	%	Pig no.	Time, min
1a	7	0.05	0	0		
1b	7	0.10	1	14	*38*	29
2	6	0.10	4	67	*16*	11.5
					17	16.5
					18	13.5
					20	20
3	5	0.20	5	100	*23*	9
					24	8
					26	7
					28	8
					32	54

n, No. of pigs. The 4 groups included 18 pigs and 25 infusions. *Group 1b* values are for the 2nd infusion.

The lowest infusion rate led to a plateau at a PAP level ~5 mmHg below maximum pressure, but although the three other groups received air at different infusion rates, two kinds of PAP reactions were observed: *1)* In 12 pigs the PAP decreased constantly after the peak was reached, and in nine of these (75%) spillover of bubbles occurred. *2)* In six pigs the PAP stabilized at a high level during the first 35 min, and no breakthrough of bubbles was observed during this period (0%). The PAP of *pig 32* (*group 3*), however, started to decrease after 40 min of infusion, and bubbles were detected 14 min later in the left atrium.

PAP at the time of bubble breakthrough was 23.0 ± 8.9 mmHg ($n = 10$), and there was no significant difference between *groups 2* and *3*.

MAP response. MAP decreased in all animals (Fig. 4 and Table 2), and when 0.05 $ml \cdot kg^{-1} \cdot min^{-1}$ were infused, MAP fell slowing during the first 15–20 min and was then stabilized ~15–20 mmHg below the starting point. We observed two different types of MAP reactions when the two largest infusion rates were used: a slower and smaller pressure decrease in six pigs, comparable to that of *group 1a*, and a sudden and more dramatic pressure response that usually led to death in 15–30 min if the infusion was continued in 12 pigs. These reactions were compatible with the two different PAP reactions observed, and the pigs with a stable MAP therefore stabilized at a high PAP as well. The MAP of *pig 32* (*group 3*) started to decrease dramatically after 40 min of infusion, and breakthrough occurred 14 min later. At spillover time, the MAP was only 27.5 ± 11.7 mmHg ($n = 10$), and there was no significant difference between *group 2* and *group 3*.

Blood gas response. The Pa_{O_2} decreased significantly after air infusion in all groups (Fig. 5). Pa_{O_2} tended to decrease relative to infusion rate during the first part of the infusion. After 10 min, however, there was no significant difference between the groups. The Pa_{O_2} responses of *group 1b* and *group 2*, which both received 0.10 $ml \cdot kg^{-1} \cdot min^{-1}$, were not the same during the first 5 min, and after 5 min of infusion the difference in the change in Pa_{O_2} between the two groups was significant ($P = 0.007$). *Group 1b*, however, received another infusion first, and Pa_{O_2} at zero point was significantly lower than the control values of the other three groups. The Pa_{CO_2} increase was similar in the four groups, and the control values of *group 1b* were significantly different from those of *group 1a* and *group 3*.

DISCUSSION

This study demonstrated that the lung is a very good filter for gas bubbles. However, if the volume rate of gas infusion is large enough, microbubbles will appear in the left atrium. The infusion rate required for breakthrough to occur was only 0.10 $ml \cdot kg^{-1} \cdot min^{-1}$. If the dose was increased further, microbubbles emerged into the left heart in all instances.

Earlier studies in dogs and sheep did not reveal the same large pressure drop on the systemic side or the

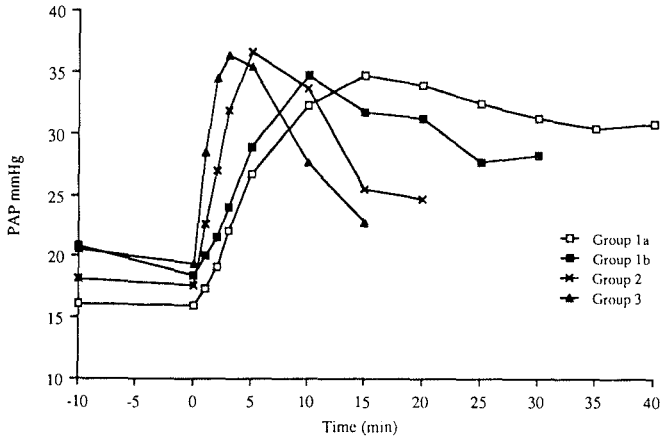

FIG. 3. Mean PAP during the first 40 min of infusion. Pressure curves are terminated when the first pig in each group died, except for *group 1a*, in which all pigs survived.

TABLE 2. *Mean PAP and MAP during first 40 min of infusion*

	PAP, mmHg					MAP, mmHg				
Time, min	Controls (*n* = 2)	*Group 1a* (*n* = 7)	*Group 1b* (*n* = 7)	*Group 2* (*n* = 6)	*Group 3* (*n* = 5)	Controls (*n* = 2)	*Group 1a* (*n* = 7)	*Group 1b* (*n* = 7)	*Group 2* (*n* = 6)	*Group 3* (*n* = 5)
0	16.5±1.5	16.0±1.1	18.4±0.6	17.6±1.0	19.4±2.0	108±7.5	105±7.0	101±7.6	96±6.5	112±8.7
1	16.5±1.5	17.3±1.3*	20.0±0.7*	22.6±1.6*	28.4±2.7	108±7.5	106±6.5	100±8.4	93±6.9	102±8.6
2	16.5±1.5	19.1±1.6*	21.6±0.7*	27.0±1.8*	34.4±2.9*	108±7.5	104±7.3	97±8.2	89±7.8	84±12.1
3	16.5±1.5	22.1±2.4*	24.0±1.2*	31.8±1.7*	36.4±4.1*	108±7.5	103±7.2	93±9.5*	81±9.7*	63±16.1*
5	16.8±1.8	26.7±3.1*	28.9±1.7*	36.7±2.5*	35.4±3.5*	108±7.0	99±7.2*	81±12.1*	67±9.7*	58±15.7*
10	17.0±1.0	32.3±2.9*	34.7±3.2*	33.7±4.3*	27.6±4.5	109±9.2	89±6.6*	71±12.3*	50±13.1*	45±13.5*
15	17.0±1.0	34.7±3.0*	31.7±3.5*	25.5±4.6	22.8±4.6	110±7.0	84±8.0*	65±13.8*	38±12.7*	42±14.6*
20	17.0±1.0	33.9±2.9*	31.1±3.4*	24.7±3.9		111±7.5	87±9.0*	69±15.5*	36±11.9*	
25	17.3±0.8	32.4±2.0*	27.7±4.2			111±7.5	86±9.0*	65±14.8*		
30	17.5±0.5	31.1±1.9*	28.1±4.2			112±7.5	87±9.0*	58±14.5*		
35	17.3±0.3	30.3±1.8*				112±8.3	90±10.2*			
40	17.0±0.0	30.7±1.4*				113±9.0	87±9.6*			

Values are means ± SE; *n*, no. of pigs. * $P < 0.05$ compared with control values.

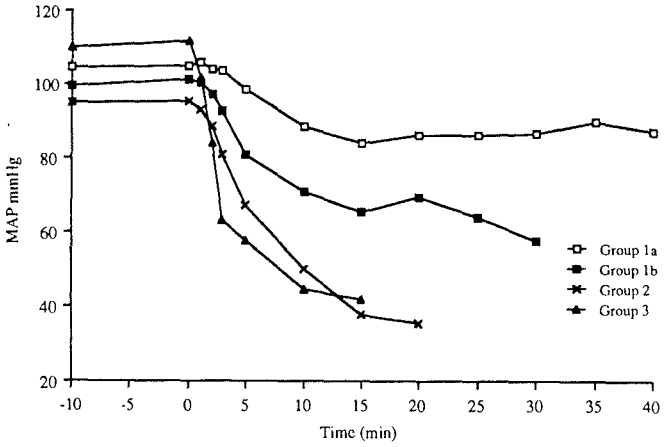

FIG. 4. MAP during the first 40 min of infusion is demonstrated for each group. Curves are terminated when the first pig in each group died, except for *group 1a*, in which all pigs survived.

subsequent decrease after a rapid rise in the mean PAP in the period before breakthrough (5, 6, 30, 35). However, the infusion rates used in our experiments are far below the rate of 0.30 ml·kg^{-1}·min^{-1} used in dogs to obtain spillover of air (5). In unanesthetized sheep that received a nitrogen infusion, breakthrough occurred at 0.15 ml·kg^{-1}·min^{-1} (30).

Interspecies differences in lung structure and function, and thereby in the ability to eliminate intravascular gas bubbles, might explain some of the discrepancies between our findings and those of others concerning breakthrough and hemodynamic reactions. The maximal oxygen consumption is more than twofold greater in the athletic dog than in the sedentary pig (17). According to the

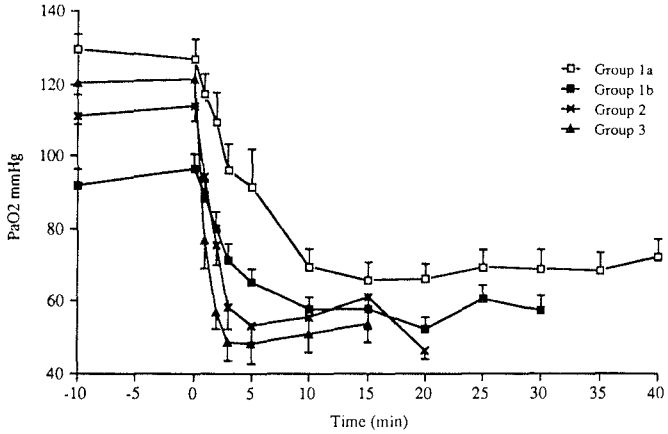

FIG. 5. Pa_{O_2} response during the first 40 min of infusion. Curves are terminated when the first pig in each group died, except for *group 1a*, in which all pigs survived. Error bars, SE.

principle of symmorphosis (34), both the alveolar and the pulmonary capillary surface, and thus also the mass-specific pulmonary diffusion capacity, are larger in athletic mammals than in sedentary mammals (4, 33). Thus the capacity for eliminating intravascular gas bubbles from the blood to the alveoli is probably increased in athletic mammals such as the dog.

Detection. When the role of the lung as a bubble filter is evaluated and different studies are compared, the site of detection for gas bubbles and the detection threshold for ultrasonic equipment have to be considered. We do not know the exact gas-detection threshold of the 7.5-MHz TEE probe used in this study. However, albumin-coated gas bubbles (Albunex, Nycomed) of ~5-μm size could be detected in the pulmonary artery when injected as a bolus (unpublished observations). Small numbers of air bubbles of a mean size of 20–50 μm could be clearly seen as single hyperintense spots. The system used in this study is certainly more sensitive than Doppler systems to detect spillover of air bubbles (13), especially if the Doppler probes are placed on peripheral arteries.

As mentioned earlier, it was usually possible to obtain high-quality images of the right pulmonary artery and the left atrium. When the highest infusion rate of 0.20 $ml \cdot kg^{-1} \cdot min^{-1}$ was used, the bubbles in the pulmonary artery sometimes reflected most of the ultrasound, which prohibited further propagation and caused unsatisfactory signals past the bubbles; it was difficult to observe breakthrough of bubbles into the left atrium. By moving the transducer back and forth, providing the two different images (Figs. 1 and 2), it was also possible to observe bubbles if they emerged into the aorta. In almost all cases, however, bubbles were detected in the left atrium before they were seen in the aorta.

Hemodynamic changes and blood gas tensions. PAP started to rise immediately after injection of gas. The rate of increase in pressure was closely related to the rate of infusion, as had also been observed in dogs (31), whereas the maximal pressure attained was constant and independent of the infusion rate. Continuing the infusion therefore did not produce any additional pressure increase, and a threshold appeared to have been reached above which PAP did not increase any further (1).

In the animals infused at the lowest infusion rate, and in some of the animals that received the higher doses, the PAP reached its maximum value and remained at a plateau. This effect has been seen in other studies (1, 5, 9, 29, 31) and is considered to be an indication that a balance between the rate of gas infusion and the rate of gas elimination into the alveolar space has been reached (32). Implicit to this view have been the assumptions that all microbubbles continued to dissolve rapidly within the pulmonary capillaries and that no gas phase actually existed within the capillary bed. However, this last assumption may be invalid, because Butler et al. (8) recently demonstrated that microbubbles could still be detected in the lung for 30–40 min after an infusion was stopped.

At the higher infusion rates, PAP in most cases fell quite rapidly after reaching its maximal value, which may have been caused partly by a failure of the right ventricle (31) in the face of an increased resistance and low Pa_{O_2} values as the infusion rate greatly exceeded the gas elimination. Differences in lung vascularization between species (4, 33) may explain the reduced recruitment capacity of normally closed capillaries in pigs during air infusion. The PAP response will be enhanced compared with that of dogs (29), when the vascular bed is occluded by gas bubbles at a given infusion rate. Furthermore, the right ventricle has to work against a high resistance and may fail to sustain its work capacity. This reduced contractility of the heart could be observed when the two-dimensional image was watched as the infusion went on.

We observed breakthrough of bubbles only in those animals that also suffered from a large drop in MAP. The pressure decrease on the arterial side usually happened immediately after air bubbles were introduced, which indicates that a release of vasoactive substances or a reflex mechanism could be responsible. A decrease in pulmonary bloodflow, which happens when $\geq$65% of the pulmonary vascular bed has to be obstructed (23), must not, however, be discounted as an explanation. By watching the ultrasonic image of the heart movement

and size of the left atrium, it was possible to exclude heart failure as the reason for the immediate pressure drop in these pigs.

The very low MAP values at breakthrough time were suggestive of a preterminal condition. To test if the situation was at all reversible, the infusion of 0.10 ml·kg^{-1}·min^{-1} was stopped 2–3 min after the breakthrough became apparent in two pigs. Although MAP at this point was as low as ~25 mmHg, both pigs survived, and their MAPs recovered to almost base-line values in 10–20 min without any air aspiration or further resuscitation. A few minutes after the infusion was stopped, the microbubbles ceased to emerge into the left atrium. Thus, by detecting arterial gas breakthrough at a sufficiently early stage, we were able to arrest and reverse what appeared to be imminent collapse. The arterial bubbles did not seem to be the cause of death in the pigs not surviving the infusion, because three pigs demonstrated the same course of progress without any breakthrough of microbubbles. Electrocardiogram registrations revealed arrhythmia, and the ultrasonic image showed a greatly reduced contractility, which indicated a low cardiac output during the last 5–10 min before the pigs died.

When air bubbles enter the lung vasculature, they tend to move into the upper regions of the lung (9, 10). Thus there will be a diversion of flow to the lower parts of the lung that leads to a ventilation-perfusion mismatch, which is probably the main reason for the decrease in Pa_{O_2} (23). An increased physiological dead space will increase Pa_{CO_2} (20, 29).

Breakthrough related to PAP, MAP, and gas elimination. We were not able to detect air bubbles in any pig while the PAP stabilized at a high level, and the MAP decrease was only 15–20 mmHg. Therefore, it seems that for breakthrough to occur in our pigs without an atrial septal defect, the MAP has to be very low and/or the PAP must return to almost-normal values after the rapid rise. These conditions might be necessary, although not sufficient, as we were not able to detect bubbles in the left atrium in three pigs that also demonstrated this pressure response. The infusion rate of 0.10 ml·kg^{-1}·min^{-1} was probably too low for breakthrough to occur in these pigs. All the pigs that received 0.2 ml·kg^{-1}·min^{-1} demonstrated this pressure response, except for *pig 32*, in which breakthrough was not detected before the pressures decreased after >40 min of air infusion.

Our study suggests that, when gas infusion exceeds gas elimination, breakthrough will eventually occur. Factors reducing the elimination into the alveolar space will therefore increase the likelihood of breakthrough at an otherwise subcritical volume rate of gas. It has been shown in dogs that embolization with air will nearly double the retention of nitrogen (20), and Verstappen (32) showed in his study on dogs that gas elimination was proportional to the PAP level. This is in agreement with our experiments, in which breakthrough was observed only in the pigs with a considerable decrease in PAP after the peak pressure was reached. The PAP decrease would result in reduced bubble pressure and reduced gas elimination, but the pressure gradient would still be sufficiently high to force the air through the pulmonary circulation. In Butler and Katz's study in dogs (6), the driving pressure at the time of spillover was considerably elevated from the base-line values. These data are not in accordance with our own observations in pigs, because we found only a slight pressure increase at the time of breakthrough. In dogs the use of halothane, which acts as a dilator on the pulmonary circulation, has demonstrated that breakthrough is greatly enhanced without increasing the pressure gradient compared with the control values (35).

There might be a possibility for air bubbles to bypass the capillaries and reach the systemic circulation via arteriovenous anastomoses (e.g., through the Sperr arteries), which should be kept in mind when the relationship between breakthrough and the MAP response is discussed. Considerable attention has been given to the existence of such vessels (21), and the low arterial pressure observed in our study at breakthrough time may provide triggering mechanisms for the opening of these vessels if they really exist. Thus an imbalance between gas infusion and gas elimination could indirectly be responsible for spillover through such channels. Because the TEE probe detected bubbles very close to the lung vasculature as they emerged from the pulmonary veins and were tracked into the left atrium, it appears that some of these extraordinary pathways may be discounted.

The usual concept is that the lung functions as a sponge-type filter through which microbubbles below a certain diameter will pass, whereas larger bubbles are trapped and dissolved in the lung. The effect of microbubbles on the lung might better be viewed as generating a continuous gas phase in the vascular system, where factors that influence gas elimination will be of great importance for breakthrough. The data of Butler et al. (6) and the theoretical analysis by Chang et al. (10) suggest that if the lung does act as a filter, then it should filter microbubbles larger than ~20–30 μm. Clearly the length of the vessel, and by implication is overall volume, is of considerable importance for entrapment of bubbles. Gorman et al. (15) showed that if bubbles of >200 μm were injected into the cerebral circulation, they became trapped in vessels of similar size. However, they could be seen to enter vessels as long emboli and not as discrete bubbles. If these emboli were longer than 5,000 μm, they were always trapped, but if their length was <500 μm, they were never trapped.

It is interesting to note that the microbubbles monitored in the left atrium seemed to be much smaller than the infused bubbles that entered the pulmonary artery, which indicated breakthrough via vessels of small diameter based on the fact that there is a porportionality between the intensity of the reflected signal and bubble size (22). Based on our results, however, we are not able to conclude whether gas bubbles are breaking through the capillary bed, shunts, or arteriovenous anastomoses.

Repeated embolizations. One of the surprising observations made in this study was the tendency to a different response to 0.10 ml·kg^{-1}·min^{-1} of *group 2* and *group 1b*. The latter group had previously received an infusion of 0.05 ml·kg^{-1}·min^{-1}, and apparently the first (smaller)

infusion rate appeared to act as a "pretreatment" because the response to higher rate was less marked than that without this pretreatment. When *groups 1b* and 2 were compared, the first group behaved as if the pigs were infused at a rate between 0.05 and 0.10 $ml \cdot kg^{-1} \cdot min^{-1}$ of air. During the first 10 min, the PAP response as well as the falling Pa_{O_2} profile resembled *group 1a* more than *group 2*, and the MAP graph lay between that of *group 1a* and *group 2*. Breakthrough that approached the spillover incidence of *group 1a*, occurred in only one pig and breakthrough time was doubled.

The base-line values of *group 1b* were not significantly different from those of *group 2*, except for Pa_{O_2}. However, it is difficult to explain the observed tendency by just the lowered Pa_{O_2} of *group 1b*. One explanation for the pretreated group's reaction as if the pigs received air at a lower rate could be enhancement of gas elimination. Any recruitment of surface-active molecules within the blood to the air-blood interface (19) may alter the surface tension of the bubbles and thereby affect the rate of resorption. Perry et al. (26) showed an attenuation of the cardiovascular response to air infusion after direct injection of a surface-active substance. However, their dogs also received an air infusion pretreatment, and the reduced response could also have been an example of the same tendency of repeated infusions observed in our study.

Conclusion. This study is in agreement with previous studies that showed that the lung is an excellent filter for gas, although the threshold value for breakthrough in pigs seems to be below that of dogs as far as these studies are comparable. The hemodynamic consequences of air infusion at a given rate were, however, greater, and breakthrough was only observed in pigs that suffered from a dramatic pressure drop on the arterial side of the circulation. At breakthrough time, PAP of those pigs had returned to almost-normal values, because the rapid rise in PAP was followed by a subsequent decrease.

The skilled help of the staff at the Department of Animals at the University of Trondheim is appreciated.

This study was supported by Statoil, Vingmed Sound A/S, and the Norwegian Space Center.

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Received 23 August 1989; accepted in final form 16 March 1990.

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Paper II

Paper II

Effect of aminophylline on transpulmonary passage of venous air emboli in pigs

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VIK, A., B. M. JENSSEN, AND A. O. BRUBAKK. *Effect of aminophylline on transpulmonary passage of venous air emboli in pigs.* J. Appl. Physiol. 71(5): 1780–1786, 1991.—Aminophylline has been shown to dramatically reduce the filtering capacity of the lung in dogs during venous air embolism. Similarities have been pointed out between the cardiovascular and respiratory systems of the pig and of humans. We therefore wanted to find out whether aminophylline also modifies the transpulmonary spillover of microbubbles to the arterial circulation of the pig. Twenty-eight pigs were anesthetized with pentobarbital sodium and mechanically ventilated. Aminophylline was injected intravenously into 10 of the pigs before the introduction of air bubbles into the right ventricle, while the other 18 pigs served as controls. A transesophageal echocardiographic probe was used to detect eventual air bubbles in the left atrium or in the aorta. Pigs received either air infusion, at rates varying from 0.05 to 0.20 ml · kg^{-1} · min^{-1}, or calibrated microbubbles, 5–300 μm diam. We found that aminophylline-treated pigs did not show any change in spillover incidence compared with controls. Furthermore, in both groups the spillover during continuous air infusion seemed to be a preterminal event, because the pigs had very low arterial pressure when arterial bubbles were observed. Finally, there was an increase in mean pulmonary arterial pressure from 18 ± 3.4 to 26 ± 2.2 (SD) mmHg (n = 4, P < 0.01) in aminophylline-treated pigs after a bolus injection of microbubbles (≤50 μm, total volume <0.5 ml). Our results suggest that aminophylline does not modify the transpulmonary passage of microbubbles in this porcine model. In addition, it would seem that the pulmonary circulation of the pig is sensitive to very small volumes of air, when injected as microbubbles.

decompression sickness; spillover; transesophageal echocardiographic transducer; pulmonary circulation

THE EFFECTS of venous air embolism (VAE) have been studied for more than a century (29) and remain an important issue. The pulmonary circulation is usually an effective filter for gas bubbles, and arterial embolism after VAE is a rare event. However, during various surgical procedures, microbubbles in the arterial circulation may sometimes occur (13, 20, 22). Likewise, some of the neurological symptoms of decompression sickness are probably caused by gas bubbles in the cerebral arteries, assumed to arise in the venous circulation (23). Although venous bubbles may emerge into the left atrium via a patent foramen ovale (22), transpulmonary passage of venous bubbles has also been observed (13, 20).

When the lung becomes overloaded with gas, it has been possible to observe a transpulmonary spillover of bubbles into the systemic circulation in pigs (32), sheep (30), and dogs (3, 5, 35). Furthermore, the filtering capacity of the pulmonary circulation can be reduced after the use of different anesthetics (35) and drugs (3) and after hyperoxia (4). Butler and Hills (3), for example, showed that aminophylline treatment of four dogs was followed by a transpulmonary passage of bubbles after the injection of microbubbles (≤130 μm). The hemodynamic effects of spillover were also quite dramatic.

Aminophylline, which reduced the filtering capacity in dogs (3), is a xanthine that stimulates cardiac muscle and relaxes smooth muscle. It is therefore considered to act as a vasodilator of both the systemic and the pulmonary vessels (25). The drug is commonly used in human medicine, and if it has the property of reducing the filtering capacity of the lung also in humans, this would have serious clinical implications (10).

We decided to use the pig to study the aminophylline effects on VAE, because certain anatomic and physiological similarities are known to exist between the cardiovascular and respiratory systems of the pig and of humans (8, 9, 26). In addition, the O_2 consumption and cardiac output of the pig during exercise resemble those of humans (14, 28). Finally, the results of a recent study of pigs (32) indicate that the effects of VAE on the hemodynamics and spillover of bubbles into the arterial circulation may differ from those observed in dogs (5).

Thus, the present study was made to test whether aminophylline modifies the transpulmonary passage of VAE in pigs as it does in dogs (3). We assessed this ability by comparing the incidence of spillover and the hemodynamic changes in aminophylline-treated and untreated control pigs. VAE included both continuous air infusion and the injection of calibrated microbubbles.

MATERIALS AND METHODS

Surgical procedures. The experiments were made on 28 domestic farmyard pigs of both sexes (age ~3 mo, body wt 20–28 kg). The pigs were fasted for 16 h with free access to water. Fifteen to 20 min before induction of anesthesia the pigs received premedication; 7–9 mg/kg azaperone (Sedaperone, Janssen) were injected intramuscularly. Pentobarbital sodium was then given intravenously (25–35 mg/kg) via an ear vein, and anesthesia was maintained by a continuous intravenous infusion of pentobarbital (5–15 mg · kg^{-1} · h^{-1}). A tracheotomy was performed, and the animals were ventilated in the supine position with a volume-regulated respirator (model 613,

Harvard Apparatus, South Natick, MA) with a tidal volume of 7–11 ml/kg, a frequency of 10–14 breaths/min, and an oxygen content of the air mixture of 25–30%. The urinary bladder was drained through a cystostomy. Body temperature was monitored by a rectal probe (Exacon MC 8700) and maintained at 37.5–38.5°C by use of a heating pad.

The right ventricle and the pulmonary artery were catheterized via the jugular veins with polyethylene tubing (0.76 mm ID). The catheter in the right ventricle functioned as an air infusion catheter, and the other measured the pulmonary arterial pressure. In three pigs that received microbubbles as foam, a 7F polyvinyl catheter substituted for the infusion catheter. Another 7F polyvinyl catheter was inserted into the right femoral artery and advanced into the abdominal aorta for continuous monitoring of arterial pressure. For four of the pigs, the treatment was extended to include measurement of central venous pressure by introducing a catheter (0.76 mm ID) into the right atrium through one of the jugular veins. All pressures were recorded using Statham P23 ID transducers, which were calibrated against a mercury manometer, with zero pressure referred to the left ventricular midlevel. The right femoral vein was cannulated with a 7F polyvinyl catheter to provide venous access for fluid infusion and aminophylline injection. Arterial blood was sampled from the aortic catheter, and gas tensions were analyzed with a pH/blood gas analyzer (model 1306, Instrumentation Laboratories). After surgery was finished, ≥30 min were allowed to elapse for stabilization. During the initial part of this period, the respirator frequency and tidal volume were adjusted to keep the arterial P_{O_2} (Pa_{O_2}) between 105 and 135 Torr and the arterial P_{CO_2} (Pa_{CO_2}) <42 Torr. Baseline data were recorded during the following 0.5-h period.

Aminophylline injection. During the last part of the stabilization period, 15 mg/kg aminophylline (Theofyllamin, Hydro Pharma) were injected intravenously into 10 pigs (*group A*). To minimize the hemodynamic effects, the injections were given over a 10-min period. One pig (*10 A*) received aminophylline after first having served as a control pig. Two pigs (*1 A* and *2 A*) received only 7.5 mg/kg before the first air infusion but an additional dose of 7.5 mg/kg was injected before the second infusion. In experiments that continued for >1 h, a maintenance dose of 0.8–0.9 $mg \cdot kg^{-1} \cdot h^{-1}$ was established. After 30 min for stabilization, baseline measurements of hemodynamic variables and blood gases were made. Arterial blood was sampled for analysis of serum aminophylline concentration just before the first air bubbles were introduced. The pigs received the large loading dose to ensure that therapeutic serum levels were achieved (55–110 μmol/l for humans). This dosage was within the range used in other experimental studies intended to investigate the effects of aminophylline on humans, pigs, and dogs (11, 21).

Detection of arterial bubbles. Arterial gas bubbles were observed as they emerged into the left atrium or the aortic arch by use of a transesophageal echocardiographic transducer (TEE probe, 7.5 MHz, CFM 700, Vingmed, Horten, Norway) (1). The TEE probe was inserted 30–40 cm into the esophagus and provided a two-dimensional image of the heart from behind. Usually it was positioned

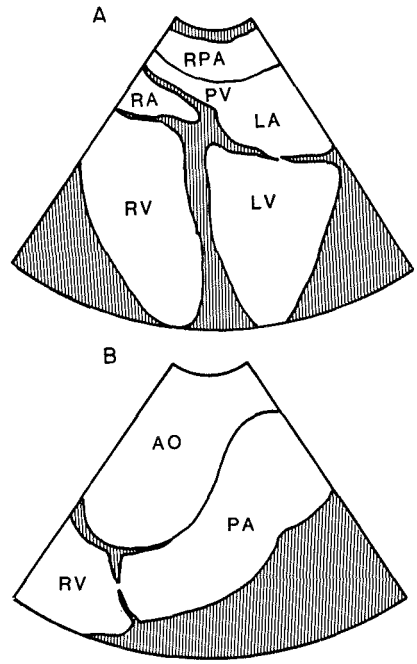

FIG. 1. Ultrasound images including both left and right sides of the heart. RPA, right pulmonary artery; PV, pulmonary vein; LA, left atrium; LV, left ventricle; RV, right ventricle; RA, right atrium; AO, aorta; PA, pulmonary artery.

at a level from which the right pulmonary artery and the left atrium could be visualized simultaneously (Fig. 1*A*). By withdrawing the transducer by 1–2 cm, it was also possible to obtain a view of the aorta and the main pulmonary artery in a second image (Fig. 1*B*). The air bubbles were visible as high-intensity spots in the blood. During the experiments, the ultrasonic images were recorded on videotape so that at least two observers could verify any spillover.

Microbubble production. Air was infused continuously through the right ventricular catheter (0.76 mm ID), and the infusion was controlled by a calibrated flowmeter. These bubbles had a diameter of ~2 mm when infused into stationary water. However, it was not possible to determine the size of the bubbles when they entered the pulmonary circulation, because both the rate of flow at the infusion site and any mixing in the ventricle would have influenced the size distribution (15).

Five pigs received a slow infusion of calibrated microbubbles, which ranged from 110 to 300 μm diam. These bubbles were produced by forcing compressed air through a cannula (needle) made of vitreous silica capillary tubings (25 μm ID, Scientific Glass Engineering, Ringwood, Victoria, Australia) and into a slowly flowing infusion fluid (50–100 ml/h, Macrodex with NaCl, Pharmacia) containing 1% of a surfactant (Tween 20, Riedel-de Haën, D-3016 Seeizel, Germany). After their production, the bubbles in the infusion fluid passed through a bubble-counting size-determining device and then into

TABLE 1. *Procedure for continuous air and calibrated microbubble infusion in control pigs*

Pig No.	Infusion Rate, ml·kg^{-1}·min^{-1}	Infusion Period, min	Pause, min	Total Infusion	n
1–7 C	0.05	90	30	0.05	7
	0.10	35		0.10	7
8–13 C	0.20	>15*		0.20	6
14 C	120	30			
15 C	300	30			
16 C	200	20			
17 C	110	30		CMB†	4
18 C	5–50	<2.5	30		
	5–50	<2.5			
10 A	5–50	<2.5	30		
	5–50	<2.5		CMB‡	4

C, control; A, aminophylline treated (later); CMB, calibrated microbubbles; *n*, no. of infusions. * One pig died after 15 min of infusion; infusion lasted 20 min in others except one pig in this group that received 60 min of infusion. † Slow infusion; ‡ bolus infusion.

TABLE 2. *Procedure for continuous air and calibrated microbubble infusion in aminophylline-treated pigs*

Pig No.	Serum Aminophylline, μmol/l	Infusion Rate, ml·kg^{-1}·min^{-1}	Infusion Period, min	Pause, min	Total Infusion	n
1 A	36	0.05	60	30		
	60	110	20			
2 A	39	0.05	30	30		
	48	0.10	30			
3 A	85	0.05	30	30		
	75	0.10	30			
4 A	62	0.05	30	30		
	54	0.10	30			
5 A	76	0.05	30	30	0.05	5
	71	0.10	30		0.10	4
6 A	53	0.20	20			
7 A	106	0.20	20		0.20	2
8 A	73	5–50	10		CMB*	2
9 A	52	5–50	<2.5	30		
	55	5–50	<2.5			
10 A	85	5–50	<2.5	30		
	77	5–50	<2.5		CMB†	4

n, No. of infusions. * Slow infusion; † bolus infusion.

the animal's right ventricle via the infusion catheter (0.76 mm ID) (16).

Three pigs received injections of a bolus of foam consisting of microbubbles that were 5–50 μm diam. The foam, which was injected through a 7F polyvinyl catheter for a period of 1–2.5 min, consisted of a mixture of 2.67 ml X-ray contrast agent (76% Urografin, 370 mg J/ml, Schering, Berlin, Bergkamen, Germany) and 1.33 ml surfactant (Tween 20). The solution was mixed by use of a syringe connected via a three-way stopcock to another syringe containing 0.5 ml of gas. The bubbles were made by moving the solution backward and forward at least 30 times. The size of the bubbles had already been determined in a previous study by examining foam samples under a light microscope (16).

Experimental protocol. The pigs were divided into two main groups: a control group (*group C*, $n = 19$) and an aminophylline-treated group (*group A*, $n = 10$). One pig (*10 A*) was included in both groups because it had served as a control before aminophylline treatment. Some of the pigs in *group C* had been included in a previous study (32). However, the anesthetic regimen and the surgical preparations were identical to the present ones. Furthermore, the baseline mean values of all the measured variables were not statistically different from those of the other pigs. An exception, however, was Pa_{O_2} values for one of the control groups that were significantly decreased compared with those for the corresponding aminophylline-treated group (see RESULTS). The air infusion rates and the different sizes of the calibrated microbubbles used in the present experiments are given in Tables 1 and 2. The infusions of 0.05 ml·kg^{-1}·min^{-1} lasted for 90 min in *group C* and 30 min in *group A*. After a recovery period of 30 min, the pigs infused with 0.05 ml·kg^{-1}·min^{-1} received a second infusion of air at a rate of 0.1 ml·kg^{-1}·min^{-1}. Both the mean pulmonary arterial pressure (PAP) and the mean arterial pressure (MAP) had by then returned to control values. Although the Pa_{O_2} and Pa_{CO_2} did not reach preembolization values, they returned to values that were within the normal range for pigs (12). The largest infusion rate used was 0.2 ml·kg^{-1}·min^{-1}.

TABLE 3. *Spillover of microbubbles to arterial circulation in control and aminophylline-treated pigs*

Infusion Rate, ml·kg^{-1}·min^{-1}	Control Group				Aminophylline-Treated Group			
		Spillover				Spillover		
	n	*n*	%	Time, min	*n*	*n*	%	Time, min
0.05	7	0	0		5	0	0	
0.10*	7	1	14	29	4	0	0	
0.20	6	6	100	16.8±18.4	2	2	100	8.8±6.0
5–300†	4	0	0		2	0	0	
5–50‡	4	1	25	<1	4	1	25	<1

Time values are means ± SD; *n*, no. of infusions. * 0.10 ml·kg^{-1}·min^{-1} was 2nd infusion in these pigs. † Slow infusion; ‡ bolus infusion.

The hearts of the pigs were investigated for septal defects, both before the experiments by means of the TEE probe and at autopsy, for eventual exclusion of any pigs found to have a patent foramen ovale or other heart defects.

Statistics. The group data were analyzed by analysis of variance and subsequently by paired and unpaired Student's *t* tests with Bonferroni correction for multiple comparisons. The incidences of spillover in subgroups of *groups C* and *A* were compared using Fisher's exact test. $P < 0.05$ was defined as significant. Data are shown as means ± SD.

RESULTS

Spillover. The incidence of spillover for the aminophylline group did not differ from that of the control group (Table 3). No arterial spillover of VAE was observed in animals of either group that had received the lowest infusion rate (0.05 ml·kg^{-1}·min^{-1}). Microbubbles appeared in the left atrium of all animals that had received air at the highest infusion rate (0.20 ml·kg^{-1}·min^{-1}). Mean spillover time during the latter rate of infusion was 8.8 ± 6.0 (SD) min ($n = 2$) for *group A*, compared with 16.8 ±

TABLE 4. *Hemodynamic changes during continuous air infusion in control and aminophylline-treated pigs*

Infusion Rate, ml·kg^{-1}·min^{-1}	Group	n	PAP, mmHg			MAP, mmHg			Pa_{O_2}, Torr			Pa_{CO_2}, Torr		
			Baseline	5 min	10 min	Baseline	5 min	10 min	Baseline	5 min	10 min	Baseline	5 min	10 min
0.05	C	7	16±3.0	27±8.1	32±7.7	105±18	99±19	89±18	127±16	91±28	69±13	38±4	42±3	48±5
0.05	A	5	17±3.6	30±4.0	36±1.3	105±16	104±15	95±20	123±11	74±9	64±4	39±3	47±5	52±4
0.10	C	7	18±1.7	29±4.4	35±8.6	101±20	81±32	71±33	97±11	65±9	58±9	46±4	52±7	55±6
0.10	A	4	19±4.0	33±3.9	36±7.3	100±12	90±16	63±15	115±8*	67±9	59±9	44±3	51±3	54±3
0.20	C	6	19±4.3	33±8.9	26±9.9	110±18	51±35	41±28	122±15	50±12	53±11	39±4	46±2	50±2
0.20	A	2	16±2.1	27±6.4	23±5.7	94±1	29±5	31±16	119±13	52±16	56±21	36±2	49±12	52±2

Values are means ± SD. C, control group; A, aminophylline-treated group. PAP, mean pulmonary arterial pressure; MAP, mean arterial pressure; Pa_{O_2} and Pa_{CO_2}, arterial Po_2 and Pco_2, respectively. * Significantly different from C, $P < 0.05$.

18.4 min (n = 6) for *group C*. Because *group C* included one pig that had spillover after infusion for 54 min, however, the spillover times of *group A* resembled those of the other pigs of *group C*. We were not able to detect any air bubbles in the left atrium or the aorta in any of the pigs that had received calibrated microbubbles as a slow infusion. After bolus injections of microbubbles ≤50 μm, spillover appeared in one of the four injections made in both groups. The bubbles were few and were detectable only in the left atrium and not in the aorta. The low intensity of the reflected echo signal indicated that these microbubbles were small (19).

Hemodynamic changes. There were no significant differences in the hemodynamics of the control and the aminophylline-treated groups at any of the infusion rates used (Table 4). Pigs that received an air infusion of 0.05 ml·kg^{-1}·min^{-1} showed an increase in PAP and a decrease in MAP. These pressures became stabilized in both groups after 10–15 min of infusion. The hemodynamic responses were greater in the pigs that had received air at the highest infusion rate (0.20 ml·kg^{-1}·min^{-1}): an immediate increase in PAP was followed by a rapid decrease after just a few minutes, and a rapid decrease in MAP was observed as well. However, in one of the pigs in the control group, the decreases in MAP and PAP did not appear until 40 min of infusion time. We observed individual variations in the pressure profiles for the pigs that received air infusion of 0.10 ml·kg^{-1}·min^{-1}. In some, the hemodynamic reactions resembled those found after an infusion of 0.05 ml·kg^{-1}·min^{-1}, whereas others showed a secondary fall in PAP, as was observed in general after the infusion of 0.02 ml·kg^{-1}·min^{-1}. At spillover time, MAP was 28.0 ± 14.4 mmHg (n = 2) in *group A* and 27.0 ± 9.9 mmHg (n = 7) in *group C*. Furthermore, PAP was 23.5 ± 10.6 mmHg in *group A* and 21.1 ± 11.5 mmHg in *group C* at the time of detection of arterial bubbles.

No effects on PAP and MAP were found in the aminophylline-treated pigs that had received calibrated microbubbles at a slow rate. In three of the four control pigs also, no changes in PAP or MAP were observed after the slow infusion of calibrated microbubbles. In the fourth pig, which received an infusion of 200-μm bubbles, an increase in PAP of 60% and a decrease in MAP of 28% were observed during the first 4 min. However, 5 min later the pressures had returned to baseline values.

Injection of microbubbles as a bolus was followed by a decrease in PAP, MAP, and central venous pressure (CVP) during the first minute after injection. MAP then returned to the baseline value during the following minute, whereas the PAP and CVP (NS) values increased above the baseline ones (Table 5). The increases in PAP, caused by the injection of foam, reached their maximum values 3–5 min after the injection had started. The aminophylline-treated group showed a significant increase in mean PAP of 45% (from 18 ± 3.4 to 26 ± 2.2 mmHg, n = 4, $P < 0.01$), and a mean increase of 44% (from 16 ± 1.9 to 22 ± 6.9 mmHg, n = 4, NS) was observed in the control group. The hemodynamic reactions of *group A* were not different from those of *group C*. Likewise, no differences in pressure profiles were noted when the values for the pigs that had had arterial bubbles were compared with those of pigs in which no bubbles were observed. The pressure response during the initial minute after the bolus injection was probably caused by the Tween 20 in the foam. In a pilot study the same amount of Tween 20 that was present in the foam was injected to test for its hemodynamic effects and resulted in a pressure response comparable with the decrease in the three pressures observed during the initial minute after the foam injection. Furthermore, PAP, MAP, and CVP then returned to their baseline values, and no further increases in PAP and CVP were followed.

Blood gases. An immediate decrease in Pa_{O_2} and an increase in Pa_{CO_2} were observed after continuous air infusion (Table 4). No difference was observed between the control and the aminophylline-treated groups of pigs that had received infusions of 0.05 and 0.20 ml·kg^{-1}·min^{-1}. At the infusion rate of 0.10 ml·kg^{-1}·min^{-1}, the decrease in Pa_{O_2} 5 and 10 min after the infusion started was greater for *group A* than for *group C*. However, one should note that the baseline Pa_{O_2} values for these same two groups differed significantly.

DISCUSSION

Aminophylline, which is considered to be a vasodilator of the lung circulation (25), did not seem to modify the transpulmonary passage of microbubbles in the pig, nor did it have any influence on the hemodynamic reactions during venous air embolism. Spillover was an almost preterminal event, except when bubbles of ≤50 μm were injected as a bolus. Thus the lung filter mechanism of the pig seems to be very resistant to transpulmonary passage of air bubbles when the pig has been anesthetized with pentobarbital and is mechanically ventilated. The venous bubbles included both continuous air infusion and calibrated microbubbles of different sizes.

TABLE 5. *Hemodynamic changes during bolus injection of calibrated 5- to 50-μm-diam microbubbles*

		PAP, mmHg				MAP, mmHg				CVP, mmHg			
Group	*n*	Baseline	3 min	5 min	10 min	Baseline	3 min	5 min	10 min	Baseline	3 min	5 min	10 min
C	4	16±1.9	21±7.3	21±4.9	17±3.4	101±4	102±7	102±8	103±8	2.0±1.0	2.3±0.4	2.3±0.4	1.7±0.8
A	4	18±3.4	26±1.7	24±2.4	20±0.9	104±10	104±12	105±7	104±8	2.0±2.0	2.7±1.4	2.9±1.2	2.3±1.4

Values are means ± SD. CVP, central venous pressure. There were no significant differences between *C* and *A* values.

During continuous air infusion at different rates, aminophylline treatment did not lead to an increase in the incidence of spillover. We observed bubbles in the left atrium or the aortic arch of all the pigs that received an infusion of 0.2 $ml \cdot kg^{-1} \cdot min^{-1}$ and in one of the control pigs that received 0.10 $ml \cdot kg^{-1} \cdot min^{-1}$ as a second infusion. Although some of the groups were small, which makes it difficult to use appropriate statistical methods, the same tendency was observed in both the control and the aminophylline-treated groups of pigs. At spillover time also, both groups of pigs had very low MAP values, an indication of a preterminal event. This dramatic decrease in MAP, which was observed during the infusion of air at the highest rates, may have been the result of a failing heart in the face of a high pulmonary vascular resistance, combined with hypoxia and hypercapnia during barbiturate anesthesia (32). Thus the injection of a presumed pulmonary vasodilator did not seem to cause any change in the mechanism for the transpulmonary passage of microbubbles when the pigs received continuous air infusions at the above rates.

The use of calibrated microbubbles was included in this study to evaluate the effect of small microbubbles of known size on the pulmonary circulation and lung-filtering capacity. Spillover to the left atrium was observed after one of the bolus injections of microbubbles of ≤50 μm diam in both *group A* and *group C*. The microbubbles were detected only in the left atrium and not in the aorta, which might indicate that they were dissolved and destroyed in the left ventricle (15). The arterial bubbles were few in number, and their intensity in the two-dimensional ultrasonic image was low. The latter fact suggests that the bubbles were small (19).

The above observations may indicate passage of <10-μm-diam bubbles through the pulmonary capillaries after a bolus injection of microbubbles. This assumption is based on the fact that 18% of the injected foam used in our study probably included bubbles <10 μm diam. (16). Furthermore, other experimental work has demonstrated that, in dogs, most microspheres <8 μm diam are able to pass through the pulmonary circulation (27). No hemodynamic consequences of the transpulmonary spillover in our pigs were observed, which could suggest that small bubbles as well as a minor total volume of air had reached the arteries. Finally, there was no difference between the control and aminophylline treated-groups.

An objection that could be raised to the present study is the use of a surfactant (Tween 20) as the carrier solution of the calibrated microbubbles. The surfactant could have favored spillover by reducing the forces that prevent the forward movement of an air embolus through the pulmonary capillaries, as has been suggested by other workers (4). However, few bubbles were observed breaking through in only 25% of the bolus injections. There is therefore little evidence that Tween 20 had any impact on spillover.

One limitation of our study is the fact that the infusion of 0.05 $ml \cdot kg^{-1} \cdot min^{-1}$ lasted for 30 min in the aminophylline-treated groups of pigs compared with 90 min for the control pigs. The groups that received an infusion of 0.10 $ml \cdot kg^{-1} \cdot min^{-1}$ are not therefore exactly comparable, because the Pa_{O_2} of *group C* was significantly lower than that of *group A* before the infusion started. Although the baseline PAP values were the same in the two groups, the ventilation-to-perfusion ratio might have been different, thereby introducing a second independent variable. We have suggested a protective effect of an earlier infusion on a subsequent one in a previous study (32). If such an effect occurs, it follows that *group A* should be less protected against spillover than *group C*, because the initial infusion lasted for less time in *group A*. However, we did not observe any tendency for spillover incidence to be increased in this group compared with the control group. Altogether, the results of the infusions of 0.10 $ml \cdot kg^{-1} \cdot min^{-1}$ therefore support the other results, which demonstrated that no obvious increase in the transpulmonary passage of gas bubbles took place in the aminophylline-treated pigs.

Similarly, the observation periods during the continuous air infusion were not exactly the same for all groups. However, spillover was observed before 30 min of infusion in all pigs with arterial bubbles in both control and aminophylline-treated groups. The only exception was one pig in the control group that showed spillover after 54 min of infusion, and this pig had by then low arterial pressure. Thus this pig demonstrated the same tendency for spillover to occur as a preterminal event as the rest of the pigs in both groups.

The results from the present study therefore contrast with the observations of Butler and Hills (3). After an infusion of microbubbles (≤130 in diam, total air <0.5 ml) as a bolus, they detected bubbles in one of the femoral arteries after a few minutes in all four of the dogs treated with aminophylline. Also, the hemodynamic consequences of spillover were dramatic, with a marked fall in pressure on the systemic side of the circulation and a decrease in right ventricular pressure. These pressure decreases are stated to have occurred after bubbles were detected in the arteries. One difference between our study and theirs is the fact that their dogs were breathing spontaneously, whereas our pigs were ventilated with a respirator by use of intermittent positive pressure. The distributions of the inspired gas may therefore have been different, as well as the intra-alveolar pressures during inspiration and expiration (24). These differences could

have influenced the pulmonary blood flow and, thereby, the results of the two studies.

A comparison of the results of the two studies also raises the question of interspecies differences in the pharmacological effects of aminophylline. However, a dose-response study (11) has demonstrated the same effects of aminophylline on the pulmonary circulation of dogs and pigs. In that study, and also in the study by Butler and Hills (3), the dosages used were the same as in our experiments, and in all cases the animals were pentobarbital anesthetized and mechanically ventilated. In both species, the drug had a profound effect on already constricted vessels, e.g., during hypoxia. Only a slight pulmonary vasodilation was observed under normal conditions, i.e., when the muscle tone was not already enhanced. Likewise, a decrease in pulmonary vascular resistance has been observed in humans suffering from chronic obstructive pulmonary disease after aminophylline administration (21).

The study made by Yahagi et al. (35) supports the results of Butler and Hills (3), that vasodilators lower the threshold for spillover in dogs, whereas the results of our experiments do not show that this happens in pigs. Although it is difficult to compare the two studies because of a divergence in experimental design, we would suggest that interspecies differences exist in the pulmonary circulation (34) and, thereby, variances in the effects of venous air embolism. For both species capillary width is considered to be the same, although the capillary surface areas may differ (34). The results of other studies have suggested the existence of arteriovenous anastomoses in dogs (2) and in humans (31), whereas other experiments have not demonstrated the existence of such vessels in the same two species (18, 33). We do not know if such arteriovenous connections exist in pigs. Opening of shunts by vasodilators might be suggested to explain the spillover of gas (35); our results would then indicate that few or none of these vessels exist in pigs.

Interestingly enough, significant changes in PAP were observed after the introduction of foam (0.5 ml or <0.025 ml/kg of air) in our pigs. This dose was only 10% of what was needed to induce an increase in PAP in dogs (6). Larger bubbles were probably used in the latter study than in our experiments, because a bolus of air was injected via a catheter and not as calibrated microbubbles. This would in fact be in agreement with the observation that infusion of small (30-μm) particles will lead to a relatively larger increase in pulmonary arterial pressure than larger particles (>170 μm) (7). However, our results could also suggest that the threshold required for the vasoconstriction of pulmonary vessels is lower in pigs than in dogs (17). The results of our pilot study showed that use of Tween 20 on its own induced a decrease in PAP rather than an increase. Thus, it is unlikely that the carrier solution could explain the PAP reaction.

The introduction of calibrated bubbles 110–300 μm in diam was not followed by any hemodynamic changes. An exception was one pig, in which we observed a decrease in MAP and an increase in PAP during the first few minutes of the experiment. The decrease in MAP could have been an effect of the Tween 20, although the increase in PAP was not compatible with a Tween 20 reaction. Also, the Tween 20 concentration in the slow infusions was very low. An infusion of 1,500–4,000 bubbles per minute corresponds to an air infusion of <0.001 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}. It is difficult to suggest any explanation for this reaction because it was recorded in only one pig. However, it could lend support to the other results that indicate that the lung circulation of the pig exhibits a high sensitivity for microbubbles.

In conclusion, aminophylline, a pulmonary vasodilator, does not seem to increase the transpulmonary passage of venous gas bubbles in this porcine model. Furthermore, the hemodynamic response found during air embolism was not significantly different from that shown by the control group. In both groups the spillover was a preterminal event during continuous air infusion. Finally, our results may indicate that the pulmonary circulation of the pig is sensitive to very small volumes of air when injected as microbubbles.

The authors thank H. Kvithyll and S. Holm Olsen at the Animal Laboratory of the Trondheim Regional and University Hospital for their help and M. Thune for valuable discussions on the draft manuscript.

This work was supported by the Sør-Trøndelag County Administration, Statoil, and the Norwegian Space Center. A. Vik is a research fellow of Sør-Trøndelag County.

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Received 28 June 1990; accepted in final form 14 June 1991.

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Paper III

Paper III

Undersea Biomedical Research, Vol. 19, No. 5, 1992

Paradoxical air embolism in pigs with a patent foramen ovale

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Vik A, Jenssen BM, Brubakk AO. Paradoxical air embolism in pigs with a patent foramen ovale. Undersea Biomed Res 1992; 19(5):361–374.—Recent studies have indicated that divers with a patent foramen ovale (PFO) are at risk of developing some forms of decompression sickness. Thus, the objective of the present study was to investigate if the occurrence of paradoxical air embolism (PAE) was enhanced in pigs with a PFO compared to the occurrence in pigs without such a defect. Out of 54 pigs, 18 had a PFO (group PFO), and the other 36 composed the controls (group C). The pigs were anesthetized, mechanically ventilated, and received venous air infusion at four different rates (0.050, 0.075, 0.100, and 0.200 ml · kg^{-1} · min^{-1}). PAE was monitored by use of a transesophageal echocardiographic probe to detect if any arterial air bubbles were present in the left atrium or the aorta. We found that PAE appeared at a lower infusion rate in group PFO than in group C. When PAE occurred, the mean pulmonary arterial pressure and the mean arterial pressure were significantly higher in pigs with a PFO than in the control pigs. Finally, the infused air volume per kilogram of body weight in group PFO was significantly lower than that observed in group C. The results demonstrated that the risk of PAE occurring in mechanically ventilated pigs with a PFO was greater compared to the risk observed in pigs without a PFO.

swine
air embolism
paradoxical air embolism
congenital heart defect
patent foramen ovale
decompression sickness

Arterial gas embolism may be the result of either direct injection of gas bubbles into the arteries during the course of various medical investigations or treatments (1), or the result of venous gas bubbles reaching the arterial side of the circulation. The latter case is termed paradoxical air embolism (PAE), and observations during various therapeutic procedures (2, 3), as well as during experimental studies (4–9), have demonstrated the possibility of venous gas bubbles becoming arterialized. PAE occurs if gas bubbles pass through the pulmonary circulation (5–9) or if they pass via connections within the heart (2, 4, 10, 11), usually a patent foramen ovale (PFO).

Barotrauma of the lungs of divers, during their ascent to the surface, may permit gas bubbles to escape into the pulmonary veins and thence into the arterial circulation (12). Otherwise, arterial bubbles observed in divers (11, 13) have generally been

assumed to be due to PAE resulting from inert gas bubbles being liberated from the peripheral tissues and venous blood during decompression. The importance of intravascular bubbles, and thereby of PAE, in decompression sickness has still not been elucidated. However, recent studies (14, 15) have suggested an increased risk of some forms of decompression sickness occurring in divers with a PFO.

In previous studies (8, 9) we demonstrated that the lung circulation in the pig is an excellent filter for gas. In those studies we had to exclude more than 30% of the pigs after the experiments because a PFO was diagnosed at autopsy. However, the experiments suggested that a PFO was an important mechanism for PAE occurrence. The aim of the present study was therefore to compare the incidence of PAE, during venous air embolism, in pigs with a PFO with the incidence in control pigs. Furthermore, we wished to compare the hemodynamic changes as well as the infused volumes of air at the time of arterial bubble detection in the two pig populations.

MATERIALS AND METHODS

Surgical procedure

Fifty-four domestic farmyard pigs (2–3 mo. of age, body weight 18–32 kg, 23 ± 3.0 kg, SD) were used as experimental animals in this study. The pigs were fasted for 16 h, with free access to water. Fifteen to 20 min before induction of anesthesia, the pigs received premedication: 7–9 mg/kg azaperonum (Sedaperone, Janssen) intramuscularly. Pentobarbital sodium was thereafter given intravenously (25–35 mg · kg^{-1}) via an ear vein, and the induced anesthesia was maintained by a continuous i.v. infusion (5–15 mg · kg^{-1} · h^{-1}). A tracheotomy was performed, and the animals were ventilated in the supine position using a volume-regulated respirator (model no. 613, Harvard Apparatus, South Natick, MA). A tidal volume of 7–11 ml · kg^{-1}, a frequency of 10–16 breaths · min^{-1}, and an oxygen content of the air mixture of 25–35% were used. The urinary bladder was drained through a cystostomy. Body temperature was monitored by a rectal probe (Exacon, MC 8700) and maintained at 37.5°–38.5°C using a heating pad.

The right ventricle and the pulmonary artery were catheterized via the jugular veins, using polyethylene tubing (0.76 mm i.d.). The former functioned as an air infusion catheter, whereas the latter measured pulmonary arterial pressure. In 7 of the pigs with a PFO, the infusion catheter was positioned in the right atrium after withdrawal from the right ventricle. The placement was verified by pressure measurement, and the catheter was withdrawn another 1–2 cm to ensure optimal positioning in the atrium. In 30 pigs an additional polyethylene catheter (0.76 mm i.d.) was introduced into the right atrium for measurement of right atrial pressure. A polyvinyl catheter (7F) was inserted into the right femoral artery and advanced into the abdominal aorta for continuous monitoring of arterial pressure. All pressures were recorded using Statham P231D transducers, which were calibrated against a mercury manometer, with zero pressure referred to the left ventricular mid-level. The right femoral vein was cannulated with a polyvinyl catheter (7F) to provide venous access for fluid infusion (0.9 % NaCl, 12–18 ml · kg^{-1} · h^{-1}). Arterial blood was sampled from the aortic catheter, and gas tensions were analyzed using an IL 1306 pH/blood gas analyzer (Instrumentation Laboratories, MA). At least 30 min were allowed to elapse

for stabilization after the surgery had been completed. During the initial part of this period, the respirator frequency and tidal volume were adjusted to keep the arterial P_{O_2} (Pa_{O_2}) between 105 and 135 mmHg and the arterial P_{O_2} (Pa_{CO_2}) below 42 mmHg. Baseline data were recorded during the following half-hour period.

Bubble detection

A transesophageal echocardiographic probe (TEE 7.5 MHz) interfaced with a CFM 700 color flow scanner (Vingmed A/S, Horten, Norway) was inserted and positioned to obtain a simultaneous, two-dimensional view of the right pulmonary artery and the left atrium (Fig. 1*A*) or of the pulmonary artery and the aorta (8). This ultrasound image made it possible to detect the bubbles when they emerged into the left side of the heart either from the pulmonary veins or from the right atrium (Fig. 1*B*), indicating

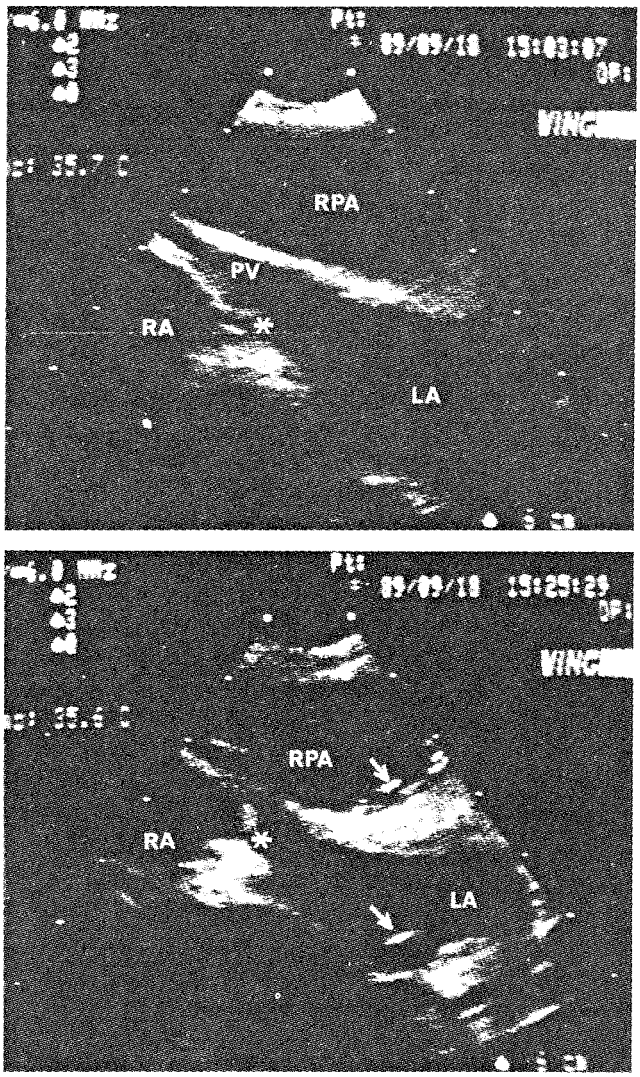

Fig. 1. *Top*, ultrasound image of the left atrium (*LA*) with PFO constituting a channel (*asterisk*) in the atrial septum. PFO diameter 1.5 mm. *RA*, right atrium; *PV*, pulmonary vein; *RPA*, right pulmonary artery. *Bottom*, same ultrasound image after air infusion started. High intensity spots (*arrows*) indicate the presence of several air bubbles in the right pulmonary artery and in the left atrium of one bubble that has emerged through the PFO. Right atrium can be seen to bulge into the left atrium, and the diameter of the pulmonary vein is reduced.

the onset of PAE. The ultrasound images were stored on videotape during all infusion periods.

Air infusion

Air was infused continuously through the right ventricular catheter or right atrial catheter (0.76 mm i.d.), and the infusion was controlled by a calibrated flowmeter. Infusion rates of 0.050, 0.075, 0.100, and 0.200 ml · kg^{-1} · min^{-1} were used. The bubbles had a diameter of approximately 2 mm when infused into stationary water. However, it was not possible to determine the size of the bubbles when they entered the pulmonary circulation because both the rate of flow at the infusion site and any mixing in the ventricle will have influenced the size distribution (16).

Experimental procedure

During experiments to study the transpulmonary passage of gas in the pig (8, 9), we observed a high incidence of PFO. The hearts of all pigs were investigated at autopsy after the experiments. When a PFO was diagnosed either during the infusions or always at autopsy, the pig was excluded from the previous studies and was included in this report to form group PFO. Consequently, the animals without a PFO from these earlier studies serve as controls in the present study. In addition, another 22 pigs are included, of which 15 received a surfactant, Pluronic (Fluka Chemie AG, Buchs, Switzerland), for other unrelated studies. This drug did not seem to alter hemodynamic variables measured in this study or the incidence of PAE after transpulmonary passage (unpublished observations). The protocol was the same during all experiments, except for the positioning of the infusion catheter: Seven of the pigs with a PFO had a right atrial catheter, whereas the remainder of the pigs with a PFO and all the control pigs had a right ventricular infusion catheter.

Eighteen pigs with a PFO (group PFO) received air at a rate of 0.050, 0.075, 0.100, and 0.200 ml · kg^{-1} · min^{-1}. Eleven pigs received only one infusion. In the remaining 7, the infusion was terminated as soon as bubbles were detected in the left atrium, because the bubbles could be observed when they emerged through a PFO. The PFO then constituted a "channel" in the atrial septum of the ultrasound image (Fig. 1). The infusion catheter was thereafter withdrawn from the right ventricle to reach the right atrium, as verified by pressure measurement, to study PAE during atrial infusions. The animals were allowed to recover for a minimum of 20 min. The intravascular pressures and blood gases had by then either returned to the baseline values or had remained unchanged for at least 5 min. We then proceeded with the next study condition, which included infusion of air at the lowest infusion rate (0.050 ml · kg^{-1} · min^{-1}) if this rate was not the one that had already been used. The infusion was terminated when PAE was observed, or, if no arterial bubbles were detected, the air infusion was terminated after the pressures became stabilized, but always $\leq$ 30 min. At least 20 min were again allowed to elapse for a return to baseline values or for stabilization of intravascular pressures and blood gases, whereafter the pigs received air at successive higher infusion rates. The same procedure with respect to termination of continuous air infusion and stabilization, between each infusion as described above was used. Because the mean arterial pressure (MAP) often did not return to the baseline values during the recovery periods, no infusion was started unless

MAP reached at least 70 mmHg. Thus, most of the 7 pigs that received repeated embolizations received only 3 infusions. A total of 32 infusions were given to the 18 pigs with a PFO, 18 of these were right atrial infusions (group PFO_{RA}), and 14 were right ventricular infusions (group PFO_{RV}).

Thirty-six pigs without a PFO acted as controls (group C) in the experiments. Air was infused at rates of 0.050 (22 pigs), 0.100 (5 pigs), and 0.200 ml · kg^{-1} · min^{-1} (9 pigs) into the right ventricle. The air infusions lasted 30 min and these animals received only a single infusion.

The hearts of all pigs of both group PFO and group C were investigated at autopsy, and the diameter of any opening in the atrial septum was measured in millimeters. The presence of a PFO in this study was therefore based on the findings at autopsy.

Statistics

Fisher's exact test (one-tailed) was used to compare incidence of PAE in group PFO and group C. To test if there were any significant changes in intravascular pressures when arterial bubbles appeared, analysis of variance and subsequent Student's *t* test with Bonferroni correction for multiple comparisons were used. Furthermore, differences in intravascular pressures and infused volume of air between groups were tested by the same procedure. Spearman's rank correlation (r_s) was used to test any significance of correlation between PAE time and infusion rate. $P < 0.05$ was defined significant. Values are presented as means ± SD.

RESULTS

Incidence of paradoxical air embolism

The incidence of PAE tended to be higher in group PFO than in group C during all infusion rates (Table 1). During the infusion at the lowest rate (0.050 ml · kg^{-1} · min^{-1}) the difference was significant for both group PFO_{RA} and group PFO_{RV} when they were compared with group C ($P = 0.010$ and $P = 0.019$, respectively). Furthermore,

TABLE 1
INCIDENCE OF PAE IN PIGS WITH A PFO (GROUP PFO_{RA} AND GROUP PFO_{RV}) AND IN CONTROLS (GROUP C)[a]

Infusion Rate, ml · kg^{-1} · min^{-1}	Group PFO_{RA}	Group PFO_{RV}	Group C
0.050	3/7[b] (43%)	2/4[b] (50%)	0/22 (0%)
0.075	4/5 (80%)	[c]	[c]
0.100	4/5 (80%)	1/1	3/5 (60%)
0.200	1/1	9/9 (100%)	6/9 (67%)
Total infusions	18	14	36

[a]The infusion catheter was positioned in the right atrium in group PFO_{RA} and in the right ventricle in group PFO_{RV} and group C. [b]$P < 0.02$ compared to control group. [c]No animals were tested at this infusion rate.

the incidence tended to decrease with decreasing infusion rate in pigs with a PFO. However, a threshold value did not appear in this group, although such a threshold value (0.100 ml · kg^{-1} · min^{-1}) was observed in group C.

The bubbles emerging into the left atrium through a PFO (Fig. 1) demonstrated a higher intensity in the ultrasonic image than the air bubbles detected in the pigs without a PFO. This observation could indicate that the arterial bubbles were larger in the pigs with a PFO than in the control pigs (17). Furthermore, the number of bubbles that reached the systemic circulation seemed to be increased in group PFO compared to group C.

Paradoxical air embolism in relation to hemodynamic changes

The hemodynamic changes observed in control pigs after the infusion rates of 0.050, 0.100, and 0.200 ml · kg^{-1} · min^{-1} have been extensively described in previous papers (8, 9). The pigs of group PFO seemed to follow the same pressure profiles as those of group C. Thus, the air infusions were followed by an increase in mean pulmonary arterial pressure (PAP) and in mean right atrial pressure (RAP) and by a decrease in MAP. The three intravascular pressures stabilized after 5–20 min during all infusions at the two lowest rates, 0.050 and 0.075 ml · kg^{-1} · min^{-1} (Fig. 2*A*). In

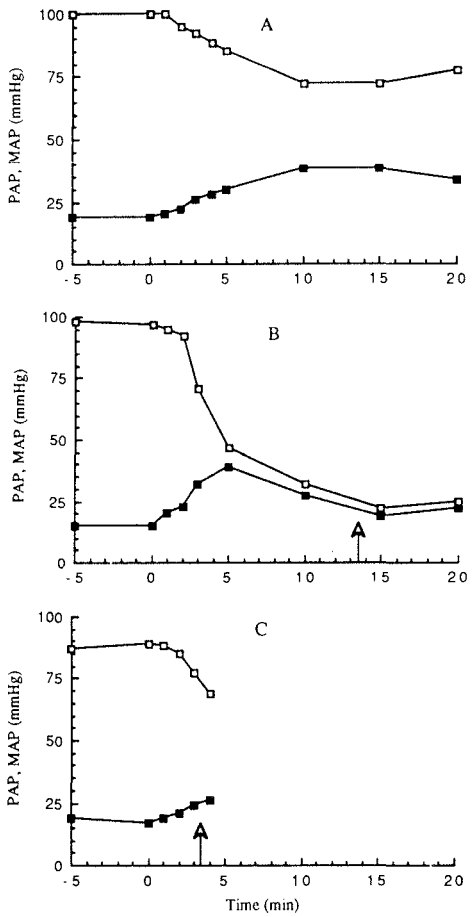

Fig. 2. Course in time of PAP (*solid squares*) and MAP (*open squares*) response in 3 pigs. Zero time is the start point of the air infusion. *A*, pig that received 0.05 ml · kg^{-1} · min^{-1} without any PAE; *B*, pig from group C that received 0.100 ml · kg^{-1} · min^{-1}, with PAE; *C*, pig with a PFO that received 0.100 ml · kg^{-1} · min^{-1}, with PAE. *Arrows* indicate the different points at which PAE occurred in the two latter pigs.

contrast, the infusion rates of 0.100 and 0.200 were usually followed by a subsequent decrease after the immediate rise in PAP (Fig. 2*B*). A steadily increasing RAP and a decreasing MAP were observed as well. Some of the pigs that received air at the two highest rates died before the 30-min infusion was finished, associated with a large decrease in their MAP to values below 20 mmHg.

At PAE time, PAP and RAP were significantly increased in both group PFO_{RA} ($P < 0.001$ and $P = 0.008$, respectively) and group PFO_{RV} ($P < 0.001$ and $P = 0.008$, respectively) (Table 2), and MAP was significantly reduced compared to baseline values ($P < 0.001$ for both groups).

Thus, in pigs with a PFO, arterial bubbles were detected during the period when the PAP increased. Furthermore, MAP, although significantly reduced from baseline, was still 76% (group PFO_{RA}) and 67% (group PFO_{RV}) of the mean baseline value (Fig. 2*C*). In contrast, control pigs showed arterial bubbles when PAP had returned to baseline values after the immediate increase, and MAP was only 28% of mean baseline value (Fig. 2*B*). PAP and MAP in the two PFO subgroups were therefore significantly higher than the corresponding intravascular pressures in group C (Table 2). One should note, however, that the mean baseline MAP for group PFO_{RA} was significantly lower than that for group C ($P = 0.011$).

Infused air volume

There was a negative correlation between infusion rate and time of detection of arterial bubbles for group PFO_{RA}, group PFO_{RV}, and group C (Fig. 3). However, this correlation was nonsignificant for the first group. Furthermore, the infused volume for group PFO_{RA} (0.62 ± 0.34 ml · kg^{-1}, SD) and for group PFO_{RV} (0.73 ± 0.28 ml · kg^{-1}) was significantly lower than that for group C (1.83 ± 0.64 ml · kg^{-1}, $P < 0.001$) (Fig. 4). No significant difference was observed between the two PFO subgroups ($P > 0.3$).

Paradoxical air embolism in relation to size of the patent foramen ovale

The size of the PFOs as determined at autopsy was 4.5 ± 3.1 mm in diameter, range 1.0–12.5 mm (Fig. 5, $n = 17$, one of the PFOs was not measured). The size of the PFO was not related to the occurrence of PAE; there was no correlation between

TABLE 2
INTRAVASCULAR PRESSURES WHEN PAE OCCURRED IN PIGS WITH A PFO AND IN CONTROL PIGS[a]

		PAP, mmHg		MAP, mmHg		RAP, mmHg	
Group	*n*	Baseline	At PAE Time	Baseline	At PAE Time	Baseline	At PAE Time
PFO_{RA}	12	18 ± 4.0	31 ± 5.3^b	83 ± 9^b	63 ± 13^b	3.7 ± 1.6	4.6 ± 1.5
PFO_{RV}	12	16 ± 3.9	34 ± 4.8^c	94 ± 15	60 ± 18^b	3.3 ± 1.4^d	5.2 ± 1.9^d
C	9	18 ± 4.0	23 ± 8.0	101 ± 15	27 ± 6	—	—

[a]Values are means ± SD. [b]$P < 0.05$; [c]$P < 0.01$; compared to group C. *n*, no. of infusions with PAE. [d]$n = 9$.

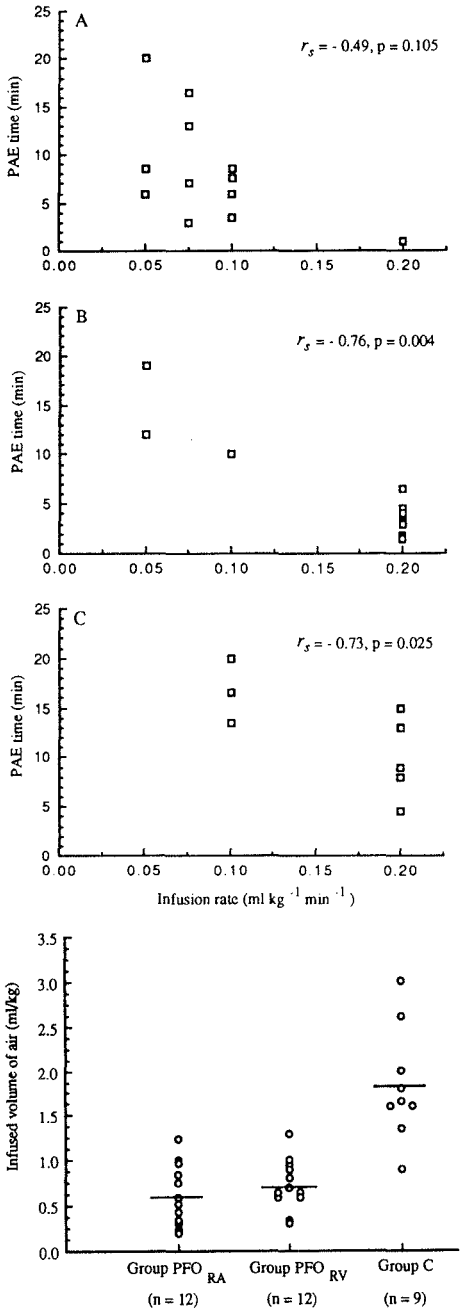

Fig. 3. Relationship between infusion rate and time of onset of PAE. r_s, Correlation coefficient (using Spearman's rank correlation). *A*, group PFO_{RA} (n = 12 infusions with PAE); *B*, group PFO_{RV} (n = 12 infusions with PAE); *C*, group C (n = 9 infusions with PAE).

Fig. 4. Infused air volumes at time of the PAE (i.e., the time at which PAE was observed) is demonstrated for group PFO_{RA}, for group PFO_{RV}, and for group C. *Straight lines* indicate mean values. $P < 0.001$ for both PFO groups when compared to the control group.

injected air volume and size. Furthermore, no correlation was found between size of the PFO and either the increase in RAP or PAP or the decrease in MAP. Thus, in spite of possessing PFOs of 11 and 12.5 mm diameter, 3 of the pigs given right atrial infusions at the lowest rate, 0.050 ml · kg^{-1} · min^{-1}, did not develop arterial bubbles.

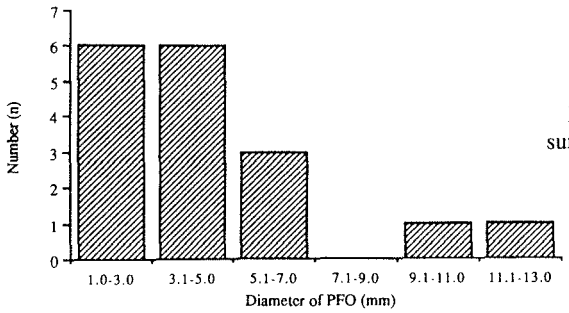

Fig. 5. Size distribution of the PFO measured in 17 pigs.

However, bubbles did appear in the left atrium of some of those pigs with a foramen of 1.0 mm diameter at the same infusion rate.

DISCUSSION

The present study has demonstrated that venous air bubbles were more likely to emerge into the left atrium through a PFO than via the pulmonary circulation in mechanically ventilated pigs. When arterial bubbles were detected, the hemodynamic changes were less dramatic in the pigs with a PFO than in the control pigs. Finally, a lesser volume of air was infused before arterial bubbles appeared in the former group compared to the latter. Previous studies have tried to investigate the phenomenon of PAE in dogs (5, 6), in sheep (7), and in pigs (4, 8, 9) either by studying the passage of gas bubbles through a surgically created, atrial septal defect (4) or through the pulmonary circulation (5–9). A comparison of animals with a naturally occurring atrial septal defect, namely a PFO, with animals without such a connection has to our knowledge not been reported previously.

Incidence of paradoxical air embolism and hemodynamic changes

The incidence of PAE seemed to be related to the air infusion rate in both group PFO and group C. In control pigs, no PAE occurred during infusion at the lowest rate, suggesting a threshold value for PAE appearance (8). We do not know if a threshold value also would appear in pigs with a PFO if infusion rates below 0.050 $ml \cdot kg^{-1} \cdot min^{-1}$ were used. The hemodynamic effects during air infusion at lower rates might not be large enough to induce a shunt from the right to the left atrium. However, in 5% of humans, a right-to-left shunt exists during spontaneous breathing, without the use of a Valsalva maneuver to change the pressure gradient between the atria (18, 19). It is therefore possible that such a shunt can occur also in the pigs before air bubbles enter the pulmonary circulation and change the hemodynamics.

If no right-to-left shunt is present at baseline levels, there certainly have to be hemodynamic alterations during venous air embolism for air bubbles to emerge into the left atrium through a PFO. Our study revealed significant changes in PAP, MAP, and RAP at PAE time. Gas loading in the pulmonary circulation at these doses (≥ 0.050 $ml \cdot kg^{-1} \cdot min^{-1}$) will increase the PAP in pigs (8). Furthermore, increased PAP may induce a backward pressure resulting in an increased RAP. Finally, the

MAP decrease might be explained by a reduced blood flow or a reduced vascular resistance or both (20), variables that were not measured or calculated in our pigs.

Other experimental studies have tried to relate the occurrence of PAE to the gradient existing between the mean pressures in the atria, but Black et al. (4) did not succeed in demonstrating a positive gradient between the right and the left atrium when the mean pressures were compared at the time that arterial bubbles were detected. However, they did find that the RAP exceeded the left atrial pressure (LAP) during some stages of the heart cycle. In the present study, the RAP was significantly increased at PAE time, but LAP was not measured.

In another study of 6 pigs, we measured LAP during a 15-min infusion of 0.050 $ml \cdot kg^{-1} \cdot min^{-1}$ (21). A left conventional thoracotomy was performed, with a catheter inserted directly into the left atrium. A decrease of 1–2 mmHg was observed in these pigs after 5 and 10 min infusions, followed by a stabilization during the final 5 min. In 1 pig a more dramatic MAP decrease was observed than in the other pigs, and the LAP fall was then even larger. Although the pigs in the present study had their chests closed during the experiments, we would not expect the direction of the change in LAP to be different from the change in LAP observed in pigs with open chests.

Our results show that PAE time tended to correlate inversely with the infusion rate. This can be explained by the fact that the rate of change in PAP and in MAP during air infusion is related to the rate of infusion (8), and that a change in PAP and MAP was necessary for a right-to-left shunt to occur in the pigs.

Size of the patent foramen ovale

In this study, 33% of the pigs had a PFO. Since the pigs were selected from several other studies, this incidence will only be approximate. The opening was usually valvelike, which is difficult to mimic when surgically creating an atrial septal defect (4). PFO has been demonstrated at autopsy in 20–34% of humans with no history of cardiac disease (22). Furthermore, the size of the opening in the pigs (mean: 4.5 mm, range 1.0–12.5 mm) did not differ much from those measured in humans [mean: 4.9 mm, range 1–19 mm (22)]. It has been suggested (18) that the size of the PFO may be important for the occurrence of PAE. However, we were not able to demonstrate any relationship between the size of the PFO and the incidence of PAE or the infused air volume. Nor did we find any relationship between the hemodynamic changes at PAE time and the size of the PFO. However, it is likely that a large opening in the atrial septum will permit more blood to reach the left atrium from the right atrium if a right-to-left shunt is present. Thus, more bubbles may reach the left side of the heart through a large opening than through a very narrow PFO, and the bubbles could thereby induce more serious symptoms in the arterial circulation in the former case than in the latter.

Limitations of the study

In clinical situations, venous bubbles usually reach the right atrium via the two caval veins. Thus, one objection to the results of our study may be the inclusion of results based on air infusions through a right ventricular catheter. The direction of blood flow in relation to the localization of the atrial septal defect has been suggested as one of the reasons why the gradient between the two mean atrial pressures is

insufficient to be critical for occurrence of PAE (4). However, in the present study the results obtained during right ventricular infusions were not significantly different from those obtained during atrial infusions. When arterial bubbles were detected there was a tendency for the hemodynamic changes to be larger in group PFO_{RV} than in group PFO_{RA}. This could be explained by the fact that a retrograde flow from the right ventricle into the right atrium was required before the air bubbles could reach the left atrium. In all pigs the increase in PAP during embolization probably increased this retrograde flow backward through the tricuspid valve and thereby also increased the RAP.

The rate of air bubbles delivered to the right atrium was much higher during atrial infusions than during ventricular infusions because most of the bubbles entered the pulmonary artery during the ventricular infusions. This study shows that the rate of this delivery to the right atrium probably was not very important because there was no significant difference between the 2 groups when infused volume was compared. It was the gas bubbles that entered the pulmonary circulation and induced an increase in PAP that probably determined the RAP/LAP gradient and thereby any PAE.

Furthermore, pigs in the control group all had a right ventricular catheter because the study was initially designed to investigate transpulmonary passage. It is unlikely that the positioning of the catheter could have influenced either the incidence or the time of PAE appearance in these pigs. This is because the time it takes for bubbles infused into the right atrium to reach the right ventricle is negligible, and eventually it is the gas loading in the pulmonary circulation that determines any transpulmonary passage in control pigs.

Another limitation to the study is the use of pigs that received Pluronic. The surfactant did not seem to alter transpulmonary passage of bubbles or the hemodynamic variables measured in the present study. Also, the diameter of the PFOs will be larger than the diameter of most of the bubbles. It is therefore unlikely that Pluronic would influence the shunt or the transport of bubbles between the two atria.

Finally, one should note that MAP at the baseline level was significantly lower in group PFO_{RA} than in group C. This could be because some of the former pigs had received several infusions and the recovery time ($\geq$ 20 min) was inadequate, whereas the pigs in group C only received one infusion. Since the results of group PFO_{RA} did not differ from those of group PFO_{RV}, this difference in experimental protocol did not seem to be of importance for the conclusion in this study.

Clinical implications

As we have also demonstrated in previous studies, it was difficult to break down the lung filter of mechanically ventilated pigs by either overloading (8) or by use of a pulmonary vasodilator (9). The spillover of bubbles into the arterial circulation seemed to be an almost preterminal event, in contrast to what was observed in pigs with a PFO. This difference was also reflected in the larger volume of air infused in the control pigs at PAE time, compared to the volume infused in the PFO pigs. Thus, if the pigs without a PFO were able to maintain a MAP above 40–50 mmHg, no arterial bubbles could be detected. Other studies have shown that this is not the case with dogs (5, 6) or sheep (7). Although caution is required when extrapolating experimental findings, if our model provides a reasonable prediction for humans, the

20–34% of the population who have a PFO will be at greater risk of developing PAE when venous air bubbles are present.

In surgical procedures in which the incidence of venous air embolism is high, e.g., neurosurgery in the sitting position (3), some patients have lately been investigated before treatment, using preoperative echocardiography to detect any PFO, after contrast injection and Valsalva maneuver. Black et al. (23), however, concluded that the advantage of this at present was not worth the added expense because the incidence of false-negative results from such examinations was too high. Intraoperative transesophageal echocardiography was suggested as being a better choice because it can be used to detect a PFO, venous air embolism, or bubbles in the left heart during the operation (24, 25).

The studies of Moon et al. (14) and Wilmshurst et al. (15) in divers with a history of decompression sickness have focused on the importance of PFO as the pathway for venous bubbles into the arterial circulation, and eventually into the cerebral circulation. Our results could lend support to their conclusions that the existence of a PFO enhances the risk of PAE. However, it is important to emphasize that our pigs were ventilated with a respirator, using intermittent positive pressure ventilation (IPPV). This condition will not be directly comparable to the divers' situation because they are breathing spontaneously during decompression. IPPV can alter hemodynamics such as the right atrial pressure and the pulmonary blood flow (26). Likewise, the two highest infusion rates used in our study are probably considerably higher than those experienced by divers. Finally, it was not possible to estimate the size of the venous bubbles introduced, because this depends on the flow rate at the infusion site as well as on mixing in the right ventricle (16). The measured size of the venous bubbles in dogs after decompression was 19–700 μm (27). It is likely that the size of the present bubbles in our infusions lay in the upper part of this range, and some may have been even larger.

Our results showed a delay before PAE occurred, which indicates that no right-to-left shunt was present at baseline. However, as mentioned previously in this discussion, in about 5% of human control subjects a shunt has been revealed by spontaneous breathing without increasing the intrathoracic pressure by a Valsalva maneuver (18, 19). In these individuals, bubbles emerge into the left atrium immediately after appearance in the right atrium because there is already a right-to-left shunt, at least during some stages of the heart cycle. Both the study by Moon et al. (14) and that by Wilmshurst et al. (15) demonstrated that divers with such a shunt show an even greater susceptibility to developing some form of decompression sickness. It is possible that we could have detected a right-to-left shunt at baseline in some pigs if we had increased the number of pigs with a PFO. It is likely that such a shunt could be detected only during right atrial infusions, because the right ventricular infusions probably were dependent on a small increase in the PAP for bubbles to flow retrograde to the right atrium. Finally, the pressure gradient between the atria in mechanically ventilated pigs may differ from that in spontaneously breathing pigs, and the two pig models may therefore give different results.

Thus, we conclude that, in mechanically ventilated pigs, venous air bubbles are more likely to emerge into the left atrium through a PFO than via the pulmonary circulation. When arterial bubbles were detected, the PAP, MAP, and RAP were significantly changed from baseline values. The hemodynamic changes were, however, less dramatic in the pigs with a PFO than in the control pigs. Finally, the volume of air infused before PAE occurred was less in the former pigs compared to the latter.

The skilled help of the staff at the Laboratory Department of Animals at the University of Trondheim is much appreciated.

This study has been supported financially be the Norwegian companies Statoil, Hydro and Saga (the FUDT program), by the Norwegian Space Center, and by the Sør-Trøndelag County Administration.—*Manuscript received July 1991; accepted March 1992.*

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Paper IV

Paper IV

Undersea & Hyperbaric Medicine, Vol. 20, No. 3, 1993

Relationship between venous bubbles and hemodynamic responses after decompression in pigs

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Vik A, Jenssen BM, Eftedal O, Brubakk AO. Relationship between venous bubbles and hemodynamic responses after decompression in pigs. Undersea & Hyperbaric Med 1993; 20(3):233–248.—We present a new pig model for studying relationships between venous gas bubbles and physiologic effects during and after decompression. Sixteen pigs were anesthetized to allow spontaneous breathing. Eight of them underwent a 30-min exposure to 5 bar (500 kPa) followed by a rapid decompression to 1 bar (2 bar/min); the remaining eight served as controls. The pigs were monitored for intravascular bubbles using a transesophageal echocardiographic transducer, and bubble count in the two-dimensional ultrasound image of the pulmonary artery was used as a measure of the number of venous gas bubbles. Effects on physiologic variables of the pulmonary and the systemic circulations were either measured or estimated. We detected venous bubbles in all pigs after decompression, but the interindividual variation was large. The time course of changes in the mean pulmonary artery pressure, in the pulmonary vascular resistance, in the arterial oxygen tension, and in the pulmonary shunt fraction followed the time course of the bubble count. In contrast, such a relationship to the number of venous gas bubbles was not found for the immediate increase in mean arterial pressure and for the changes in the other variables of the systemic circulation. We conclude that the number of venous gas bubbles, as evaluated by the bubble count in the ultrasound image of the pulmonary artery, is clearly related to changes in the variables of the pulmonary circulation in this pig model.

swine, decompression sickness, air embolism, pulmonary circulation, echocardiography

Venous gas bubbles are known to be formed in divers during or after many decompressions (1–3). Such bubbles may be "silent" and induce no acute symptoms (3), or they may induce symptoms of DCS. However, it is also possible that silent bubbles can induce minor damage in tissues and result in long-term effects in divers (4). Regarding DCS, the precise cause of the disease is unknown, but it is clear that the pathogenesis proceeds via the formation of an endogenous gas phase. Thus, to elucidate the importance of venous gas bubbles in the pathogenesis of DCS as well as in the development of any long-term effects in divers, the relationship between the amount of gas that appears as bubbles in the venous circulation and physiologic responses is an important issue.

Many decompression experiments using different animal models have been performed during the last century, but monitoring of the hemodynamic effects in larger-sized animals has only been done in a limited number of studies (1, 5–11). Symptoms of DCS such as paresis, "chokes," or death have been used as an endpoint, and usually the amount of venous gas emboli in the pulmonary circulation has been unknown.

To study the relationship between intravascular gas bubbles formed during decompression and their physiologic responses, reliable systems for determining the presence and quantities of intravascular gas bubbles are required. Doppler instruments are by far the most common application of ultrasound for bubble detection (1, 12). However, it has been argued that ultrasound imaging may have several advantages in the detection (1) and possibly in the quantification of intravascular gas bubbles (12, 13).

In this study, we present a pig model for investigating the occurrence of venous gas bubbles and the physiologic responses of decompression stress. This species was chosen because certain cardiopulmonary similarities between the pig and the human have been pointed out (14, 15). The young pig (>2 mo.) has a lung circulation morphologically similar to that of adult humans (16), and the pig seems to respond to exercise in the same way that humans do with regard to oxygen consumption and cardiac output (17, 18). We have developed a method for estimating relative quantities of gas bubbles in the venous circulation of the pig by counting bubbles in the ultrasound image of the pulmonary artery (19). These bubble counts were related to changes in physiologic variables, something that has not been reported previously.

MATERIALS AND METHODS

Surgical procedure

Sixteen domestic farm swine (2–3 mo. old, body weight 19.5–29 kg) were used as experimental animals. The pigs were fasted for 16 h with free access to water. Fifteen to twenty minutes before induction of anesthesia, the pigs received premedication; 7–9 mg/kg azaperonum (Stresnils, Janssen) were injected intramuscularly. Atropinsulfat (1 mg, Atropin, Hydro Pharma) was thereafter given intravenously via an ear vein, and anesthesia was induced by thiopental sodium (5 mg/kg, Thiopenton Natrium, Nycomed Pharma) and ketamine (20 mg/kg, Ketalar, Parke Davis) maintained by a continuous i.v. infusion of ketamine in 0.9% NaCl (30 $mg \cdot kg^{-1} \cdot h^{-1}$). A tracheotomy was performed, whereafter the pigs were in the supine position, breathing spontaneously through an endotracheal tube. Body temperature was monitored by a rectal probe and maintained at 37.5°–38.5°C using a heating pad during surgery. During the dive the temperature inside the chamber was regulated (29.5°–30.5°C). Since a superficial, irregular respiratory pattern was observed approximately 30 min after anesthesia was induced, a bolus dose of α-chloralose in 0.9% NaCl (10–15 mg/kg, 0.25% solution, Sigma, St. Louis, MO) was injected intravenously. One or two supplemental doses were usually injected during the following 30 min to achieve a more regular respiratory rate. It was necessary, however, to restrict the dose to avoid CO_2 tensions above 6 kPa in the arterial blood (20). During the rest of the experimental period, no supplemental doses of α-chloralose were

injected because the anesthetic is known to have a longlasting effect (21). After the injection of the α-chloralose solution, the ketamine infusion provided the pigs with i.v. fluid at a rate of approximately 3–4 ml · kg^{-1} · h^{-1}.

Two polyethylene catheters (0.76 mm i.d.) were introduced into the left jugular vein and moved into the pulmonary artery to measure pulmonary arterial pressure and to obtain mixed venous blood for gas analysis. A third catheter was positioned in the right atrium via the right jugular vein for measurement of central venous pressure. Two polyethylene catheters (1.14 and 0.76 mm i.d.) were inserted into the right femoral artery and advanced into the abdominal aorta for continuous monitoring of arterial pressure and to obtain samples for analysis of blood gas composition.

Measurements and calculations

All intravascular pressures were recorded on a Grass polygraph (model 7D, Grass Instrument Co, Quincy, MA) using transducers (Sorensen Transpac II, Abbott Laboratories), which were calibrated against a mercury manometer, with zero pressure referred to the left ventricular mid-level. Calculations of mean pulmonary arterial pressure (PAP), mean arterial pressure (MAP), and mean central venous pressure (CVP) in millimeters of mercury, and calculation of heart rate (HR, beats/min) were made after the experiments.

Arterial and mixed venous blood were analyzed for P_{O_2} and P_{CO_2} using an IL 1306 pH/blood gas analyzer (Instrumentation Laboratories), and the blood gases were corrected for changes in rectal temperature using standard methods. Further, hemoglobin (Hb, g/100 ml), $\%O_2Hb$ (% of oxyhemoglobin), and %COHb (% of carboxyhemoglobin, *see Eq.6*) for calculating content of oxygen were measured using an IL 482 CO-Oxymeter (Instrumentation Laboratories). Oxygen content in arterial (Ca_{O_2}, ml/100 ml) and mixed venous (Cv_{O_2}) blood was calculated according to the equation:

$$Ca_{O_2} \text{ (or } Cv_{O_2}) = (1.53 \cdot Hb \cdot \frac{\%O_2Hb}{100}) + (P_{O_2} \cdot 0.003) \qquad (1)$$

where 1.53 (ml/g) is the oxygen transport capacity of 1 g of pig hemoglobin [calculated from data given by Hannon et al. (22)]; and (P_{O_2} · 0.003) is the amount of oxygen (ml/100 ml) physically dissolved in the plasma.

Estimates of pulmonary blood flow ($\dot{Q}$, ml · kg^{-1} · min^{-1}) were made using the direct Fick method:

$$\dot{Q} = \frac{\dot{V}_{O_2}}{Ca_{O_2} - Cv_{O_2}} \qquad (2)$$

where $\dot{V}_{O_2}$ is the oxygen consumption (ml · kg^{-1} · min^{-1}) calculated according to the equation (23):

$$\dot{V}_{O_2} = \dot{V}_E \cdot \frac{F_{I_{O_2}} - F_{E_{O_2}}}{[(1 - F_{I_{O_2}}) + RQ \cdot (F_{I_{O_2}} - F_{E_{O_2}})] \cdot BW} \qquad (3)$$

$\dot{V}_E$ (ml · min^{-1}, converted to standard conditions after the experiment, STPD) is the expiratory flow; $F_{I_{O_2}}$ and $F_{E_{O_2}}$ are the O_2 fractions of the inspiratory and expiratory air, respectively; RQ is the respiratory quotient, assumed to be 0.90; and BW is the body weight of the pig. The $\dot{V}_E$ was measured by a flow transducer head (Fleisch

no. 2) connected to a two-way valve located at the proximal end of the endotracheal tube. By means of thin-gauge polyethylene tubing, the alternating differential pressure was fed to a pneumotachograph (Gould Godart), and $\dot{V}E$ was recorded continuously on the Grass polygraph (except during the chamber dive). The pigs breathed room air during the experiment, and the FI_{O_2} was analyzed before the experiment by sampling a fraction of room air, drying it using Silica gel, removing CO_2 by the use of a CO_2 absorbent (Ascarite), and passing it into an oxygen analyzer (S3A, Applied Electrochemistry). FE_{O_2} was measured continuously during the experiment (except during the chamber dive) by sampling a fraction of the respiratory gas from the expiratory tubing. The values were recorded on a chart writer (Watanabe Servocorder, SR 6310).

The total pulmonary shunt fraction was calculated using the equation:

$$\dot{Q}_s/\dot{Q}_t = \frac{Cc_{O_2} - Ca_{O_2}}{Cc_{O_2} - Cv_{O_2}} \quad (4)$$

where $\dot{Q}_s$ = shunt flow and $\dot{Q}_t$ = flow through the pulmonary system. Cc_{O_2} (end-capillary oxygen content, ml/100 ml) was calculated according to the equation:

$$Cc_{O_2} = (1.53 \cdot Hb \cdot K) + (0.0031 \cdot PA_{O_2}) \quad (5)$$

where

$$K = (1 - \frac{\%COHb}{100}) - 0.02 \quad (6)$$

for $PA_{O_2} < 125$ mmHg. PA_{O_2} (alveolar tension of O_2, mmHg) was estimated as:

$$PA_{O_2} = [FI_{O_2} \cdot BP] - [Pa_{CO_2} \cdot (FI_{O_2} + \frac{1 - FI_{O_2}}{RQ})] \quad (7)$$

where BP is the barometric dry pressure.

In estimating pulmonary vascular resistance (PVR, mmHg · ml^{-1} · kg · min), left atrial pressure was assumed to be zero.

$$PVR = PAP/\dot{Q} \quad (8)$$

Systemic vascular resistance (SVR, mmHg · ml^{-1} · kg · min) was estimated as:

$$SVR = (MAP - CVP)/\dot{Q} \quad (9)$$

Bubble detection

A transesophageal echocardiographic (TEE) probe (6.5 MHz) interfaced with a CFM 750 color flow scanner (Vingmed, Horten, Norway) was inserted and positioned to obtain a simultaneous two-dimensional view of the pulmonary artery and the aorta (24). The ultrasound images were stored on videotape during the compression and decompression periods, as well as during the following 90 min. Digitized images were transmitted at regular intervals from the CFM scanner to a Macintosh II computer. These images were subsequently processed using a software program for

automatic quantification of the number of gas bubbles (19) (Fig. 1). Thus, a relative estimate of the amount of venous gas bubbles in the pulmonary artery was obtained.

The minimum size of a bubble that could be automatically detected and counted was not limited by the software program, but by the ultrasound equipment, because no information was lost in the process of digitizing and transferring the images to the computer. Small-sized gas bubbles ($\leq$50 μm) have been injected into a hydromechanical simulator of the cardiovascular system and detected and counted after transmission of digitized images (19). We do not know exactly the detection threshold of the TEE probe used in this study, but most likely it detects gas bubbles far below 50 μm (24, 25). We had technical problems with the penetrator in the chamber in one of the first experiments in this study, allowing no accurate counting of the bubbles in the ultrasound image. However, the TEE probe has provided a high-quality image of the pulmonary artery in >97% of our subsequent pig experiments.

Experimental procedure

After surgery, the pigs were placed inside a chamber (300 liter) specially constructed to fit pigs of this size. At least 30 min were needed for stabilization, and predive data were collected at 20 min and at 3–5 min before compression started.

Eight pigs [decompression group, BW 22.8 kg (SD 2.0)] underwent a 30-min exposure to 5 bar (500 kPa) (compression rate 2 bar/min), followed by a rapid decompression to 1 bar (2 bar/min). Bottom time was calculated from the beginning of compression to the beginning of decompression. The pigs were breathing chamber air during the experimental dive, and soda lime was placed inside the chamber to prevent an increase of CO_2 in the chamber atmosphere. Continuous monitoring of gas bubbles in the pulmonary artery and of intravascular pressures was carried out during the dive, using special chamber connectors. Data were collected immediately after surfacing, and then every 5th min during the initial 30 min after decompression. Thereafter measurements were made at 15-min intervals, with the final measurement made after 90 min. The first values for $\dot{Q}_s/\dot{Q}_t$, $\dot{Q}$, PVR, and SVR were calculated 5 min after surfacing. After the experiments, the hearts of all the pigs were investigated at autopsy; none of the animals had a patent foramen ovale.

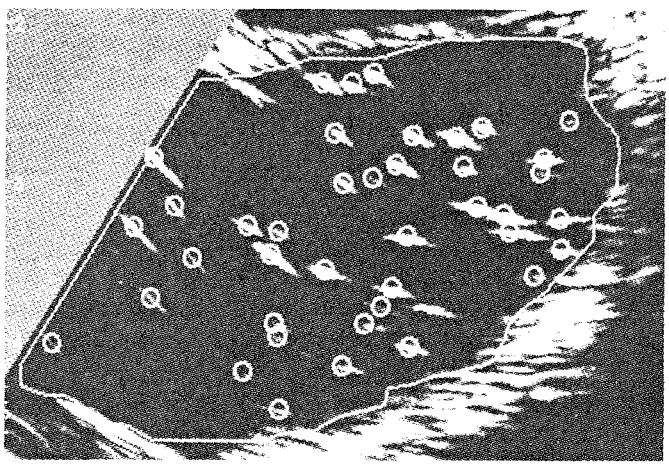

FIG. 1—Ultrasound image of the pulmonary artery in one pig after decompression. Gas bubbles have been detected (*circles*) and counted automatically after transmission to a Macintosh II computer.

Eight additional pigs served as controls [control group, BW 23.6 kg (SD 2.9)]. They were subjected to a procedure identical to that of the decompression group, except that they underwent no compression. Data measurements were obtained at the same intervals as those for the pigs exposed to pressure. The observation period was 110 min, which corresponds to the period from −50 to 60 min postdecompression for the decompression group.

Statistics

Data were analyzed on a Macintosh computer (Stat Works version 1.2, Cricket Software Inc., Philadelphia, PA). Maximum and minimum values of each variable were compared with the base-line values for any significant effects, using paired Student's t test. Furthermore, the times taken to reach maximum change from base line were calculated (26). In the control group, base-line values were compared with the corresponding values at the end of the observation period using paired Student's t test. Spearman's rank correlation was used for analysis of correlation. Because many variables were tested, $P < 0.01$ was defined as the level of significance; $0.01 < P < 0.05$ indicated a tendency, although no significant effect could be shown. Values are presented as means (95% confidence interval, CI) in the text, in the tables, and in figure 4.

RESULTS

Formation of gas bubbles

Gas bubbles appeared in the pulmonary artery in all pigs. We usually detected the first bubbles during the last 10–15 s of the decompression (at approximately 1.5 bar) or immediately after "surface" was reached. The relative bubble count increased rapidly during the ensuing period, to reach a maximum at 21 min (95% CI 13 to 29) (Fig. 2). Thereafter the bubbles decreased in number, but it was still possible to observe venous gas bubbles 90 min after decompression in all pigs. The time to reach maximum value of the bubble count was chosen so that no increase >10% occurred during the following period. As can be seen from Fig. 2, five of the pigs had many bubbles in the pulmonary artery, whereas the two remaining pigs (no. 29 and 31) generated considerably fewer bubbles (range of maximum bubble count: 58–338 bubbles $\cdot s^{-1} \cdot cm^{-2}$).

Hemodynamic responses

Pulmonary arterial pressure increased rapidly after decompression (Table 1). Ninety minutes after decompression, PAP had returned to predive values or was lower than predive values. The time course of the PAP changes was related to changes in relative bubble counts, as demonstrated in Fig. 2. A correlation between time to reach maximum PAP and time to reach maximum bubbles was observed, although it was not significant ($r_s = 0.80$, $P = 0.033$, $n = 7$). However, in most pigs, the highest PAP values appeared before the highest number of bubbles was counted. An increase in PAP of ≤1 mmHg was accepted as a normal variation when

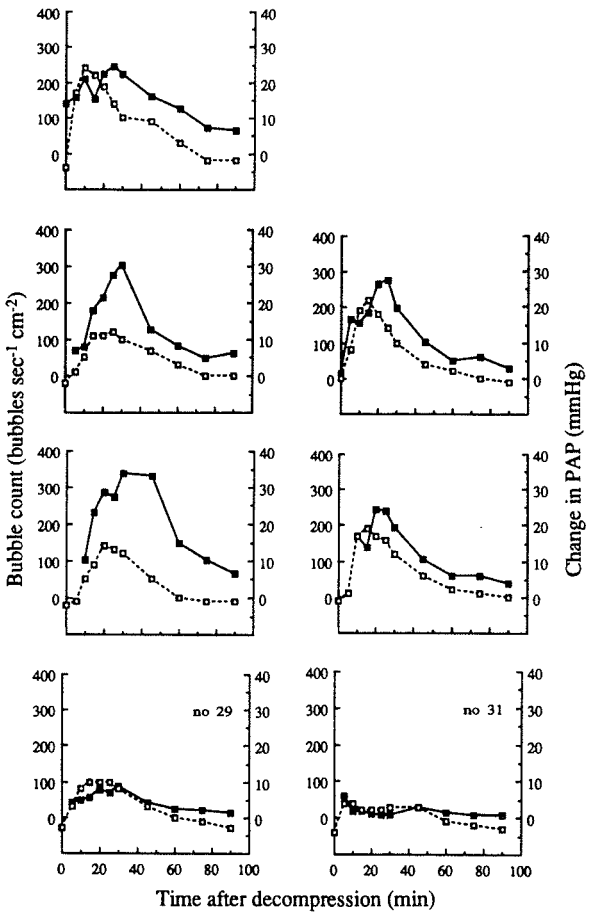

FIG. 2—Bubble formation after decompression as evaluated by bubble counts in a two-dimensional image of the pulmonary artery in seven pigs. Time course of bubble count (*solid squares*) is plotted together with the corresponding changes in the PAP (*open squares*) in each pig, i.e., changes from the predive values.

choosing the maximum value of PAP. Although there seemed to be a relationship between the maximum bubble count and the corresponding change in PAP, as demonstrated in Fig. 2, no significant correlation was observed ($r = 0.43$, $P = 0.34$, $n = 7$), which could be due partly to small sample size.

The other variables of the pulmonary circulation, $\dot{Q}_s/\dot{Q}_t$ and Pa_{O_2} (Fig. 3) and PVR, also showed a time-dependent response similar to that observed for the bubble count. It should be noted that the Pa_{O_2} values were very high and showed wide variations immediately after the chamber dive (13.9–23.6 kPa) due to the high P_{O_2} tension in the chamber and probably to differences in the ventilatory pattern during the last period of the hyperbaric exposure.

Central venous pressure increased rapidly to reach peak values (Table 2), followed by a decrease below predive values. Similarly, MAP increased in all pigs to reach maximum values (Fig. 4). A decrease below predive values was thereafter observed. In contrast, $\dot{Q}$ values tended to be reduced compared to the predive values when MAP reached its maximum. SVR was therefore significantly higher than it was before the dive. SVR thereafter decreased and stabilized at a level between the peak and the predive values, whereas $\dot{Q}$ remained low throughout the experiment. No changes in HR could be detected.

Table 1: Hemodynamic variables of the pulmonary circulation in eight pigs before and after decompression[a]

Point of Time	PAP, mmHg	Time, min	PVR,[b] $mmHg \cdot ml^{-1} \cdot kg^{-1} \cdot min^{-1}$	Time, min	$\dot{Q}s/\dot{Q}t$[c]	Time, min	Pa_{o_2}, kPa	Time, min
Baseline	15.5		0.07		0.11		12.6	
(95% CI)	(12.4–18.6)		(0.05–0.09)		(0.08–0.14)		(11.6–13.6)	
Max. response	32.0	14	0.18	16	0.39	18	7.9	20
(95% CI)	(25.3–38.7)	(10–18)	(0.14–0.22)	(10–22)	(0.22–0.56)	(15–21)	(5.9–9.9)	(17–23)
P	0.001		0.003		0.006		<0.001	

[a]Values are means and 95% confidence interval. [b]$n = 6$. Time, time in minutes to reach maximum response; [c]$n = 7$.

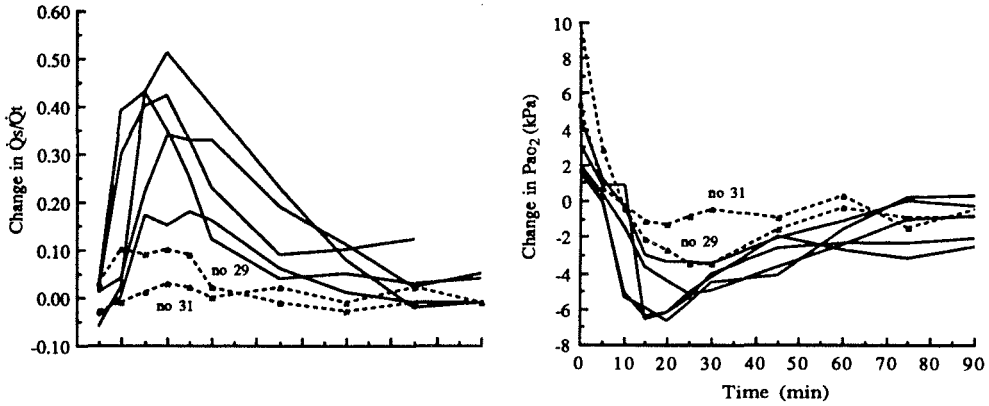

FIG. 3—Change in shunt fraction ($\dot{Q}_s/\dot{Q}_t$) and in arterial O_2 tension (Pa_{O_2}) (i.e., from predive values) after decompression in seven pigs in which bubbles were counted. Few bubbles were counted in pigs 29 and 31.

Control group

The measured and calculated physiologic variables in the control group remained stable throughout the 110-min observation period (Table 3). However, the $\dot{Q}_s/\dot{Q}_t$ demonstrated a tendency to decrease, and the SVR tended to increase slowly.

DISCUSSION

We have presented a pig model that allowed us to do a relative estimation of the number of gas bubbles that entered the pulmonary circulation after decompression. Furthermore, this estimate of venous gas bubbles could be related to physiologic effects. If we assume there is a relationship between the occurrence of DCS and the total gas loading in the body, and possibly the amount of gas that enters the pulmonary artery as gas bubbles (27), this model can be of great value in further research on decompression-related problems.

Responses to gas bubbles in the pulmonary circulation

We expected the pigs to generate venous gas bubbles because a severe decompression profile had been chosen in this experiment. However, in two of the pigs, very few bubbles were detected. Thus, the great variation in the degree of bubble formation observed in our eight pigs accords with the individual variability in endogenous gas generation found in humans (3).

The results clearly demonstrated relationships between the time course of the bubble count and the time course of the changes in PAP. During air infusion, a relationship has been shown to exist between the infusion rate and the rate of increase in PAP (24, 28). Furthermore, maximum PAP values have been shown to be dose-related up to a threshold above which PAP does not increase any further (29, 30). Since the number of gas bubbles that enters the pulmonary circulation after decompression is time-dependent, it is difficult to extrapolate the results from studies on continuous air infusion to explain effects caused by decompression. It is likely,

Table 2: Hemodynamic variables of the systemic circulation in eight pigs before and after decompression[a]

Point of Time	CVP, mmHg	Time, min	MAP, mmHg	Time, min	$\dot{Q}$,[b] $ml \cdot kg^{-1} \cdot min^{-1}$	SVR,[b] $mmHg \cdot ml^{-1} \cdot kg^{-1} \cdot min^{-1}$	HR, beats/min
Baseline	1.8		85		204	0.37	130
(95% CI)	(0.9–2.7)		(75–95)		(166–242)	(0.27–0.47)	(104–156)
Max. response	2.9	9	101	11	177	0.53	131
(95% CI)	(0.9–4.9)	(7–11)	(88–114)	(8–14)	(141–213)	(0.41–0.65)	(107–155)
P	0.058		0.011		0.033	0.009	0.911

[a]Values are means and 95% CI. Time, time to reach maximum response. Values for $\dot{Q}$, SVR, and HR are those measured or calculated at time of maximal MAP response. [b]$n = 6$.

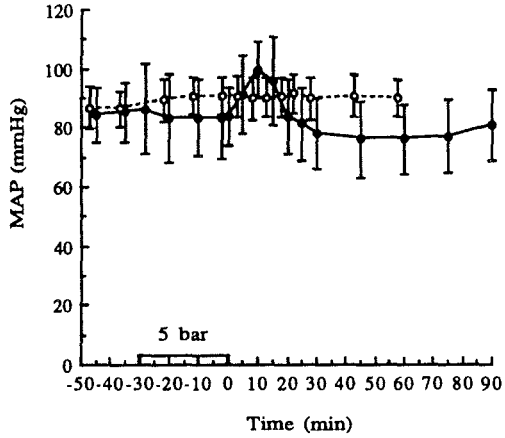

Fig. 4—Effects of rapid decompression on MAP for the eight pigs in the decompression group (*solid circles*). Control group underwent no compression (*open circles*, $n = 8$). For clarity, the values presented in the figures for the control group are 2 min later than those actually recorded at the times shown. *Error bars* = 95% CI.

however, that a relationship exists between the number of venous gas emboli and PAP changes after decompression. The rate of increase in PAP, the maximum PAP value, and the rate of decrease in PAP are therefore probably related to the amount of gas that appears as bubbles in the pulmonary circulation.

In the two pigs in which few bubbles were detected, we observed a small increase in PAP, whereas a larger increase in PAP was observed in the pigs that had many bubbles in the pulmonary artery. These findings suggest that the bubble count in the ultrasound image can be used as an indication of the amount of gas that appears as venous bubbles in different individuals. One should note, however, that a considerable range of individual PAP changes occur during continuous air infusion, in spite of using the same infusion rate (24, 30). The correlation between the dose of venous gas bubbles and PAP changes in a single individual is therefore not sufficiently close to allow accurate prediction, even when the amount of gas that enters the pulmonary circulation as bubbles is known. In addition to low sample size, this latter fact could explain why we did not find a significant correlation between maximum bubble count and the corresponding PAP changes.

Interestingly, maximum values of PAP were reached before maximum bubble count in most of the pigs. In several pigs, the PAP had started to decrease when the number of gas bubbles seemed to be at its highest. We suggest that vasoconstriction in the pulmonary vasculature contributed to the rapid increase in PAP during the initial 20 min after decompression. In most of the pigs, a small decrease in all three intravascular pressures was observed during compression. A high Pa_{O_2} during compression may induce a relative vasodilation in the pulmonary vasculature and thereby reduce the PAP (31). Vasoconstriction in the pulmonary circulation after decompression could be secondary to this "hyperoxic vasodilation." However, the relationship between bubble count and PAP changes (Fig. 2), as well as the correlation between time to reach maximum bubble count and time to reach maximum PAP, suggests that gas bubbles in the pulmonary circulation contributed to the major increase in the PAP.

It is well documented that gas emboli, in addition to obstructing the pulmonary vasculature mechanically, induce vasoconstriction either by the release of mediators or by activating reflex mechanisms (32). Small-sized bubbles (<170 μm) are more likely to induce vasoconstriction than larger-sized bubbles (33). In dogs, it was found

Table 3: Hemodynamic variables of eight control pigs at base line and at the end of the observation period (110 min)[a]

Point of Time	PAP, mmHg	PVR,[b] $mmHg \cdot ml^{-1} \cdot kg^{-1} \cdot min^{-1}$	$\dot{Q}s/\dot{Q}t$[b]	Pa_{o_2}, kPA	CVP, mmHg	MAP, mmHg	$\dot{Q}$,[b] $ml \cdot kg^{-1} \cdot min^{-1}$	SVR,[b] $mmHg \cdot ml^{-1} \cdot kg^{-1} \cdot min^{-1}$	HR, beats/min
Baseline	16.0	0.07	0.20	12.0	1.6	87	233	0.37	126
(95% CI)	(15.0–17.0)	(0.06–0.08)	(0.12–0.28)	(10.2–13.8)	(0.5–2.7)	(80–94)	(180–286)	(0.30–0.44)	(102–150)
110 min	15.5	0.08	0.16	12.3	1.7	90	215	0.44	117
(95% CI)	(13.1–17.9)	(0.06–0.10)	(0.08–0.24)	(10.8–13.8)	(0.8–2.6)	(83–97)	(142–288)	(0.34–0.54)	(104–130)
P	0.598	0.220	0.021	0.431	0.785	0.288	0.079	0.026	0.316

[a]Values are means and 95% CI. [b]$n = 7$.

that the inert gas bubbles increased in size during the initial 25-min period after decompression (34). We suggest that the rapid increase in PAP in our pigs, that occurred immediately after surfacing, was caused by small-sized bubbles that induced vasoconstriction. During the following period, larger-sized bubbles probably induced less vasoconstriction, and the PAP could actually decrease despite an increasing number of bubbles.

Changes in the other three variables of the pulmonary vasculature, PVR, Pa_{O_2}, and $\dot{Q}_s/\dot{Q}_t$, were also related to bubble count. The $\dot{Q}_s/\dot{Q}_t$ ratio, or shunt fraction, describes the fraction of blood that is passing through unventilated areas from the right to the left of the heart, and the $\dot{Q}_s/\dot{Q}_t$ and Pa_{O_2} values are usually related (31). During pulmonary microembolization, collapsed lung units probably induce an increase in $\dot{Q}_s/\dot{Q}_t$ (32). Inasmuch as none of the pigs had a patent foramen ovale, this can be excluded as a factor contributing to the increase in $\dot{Q}_s/\dot{Q}_t$ (32). The course of these three variables supports the finding of a relationship between the number of gas bubbles after decompression, as evaluated by bubble count in the ultrasound image, and effects on the pulmonary circulation.

Responses in the systemic circulation

Central venous pressure and MAP values increased after decompression and returned to base line when the bubble count reached maximum. SVR and $\dot{Q}$ did not show the same relationship to the bubble count as the four variables of the pulmonary circulation did. An activation of the sympathetic nervous system or a release of vasoactive substances could explain the sudden increases in MAP and SVR values and the decrease in $\dot{Q}$ values. Bove et al. (6) speculated that the rise in systemic resistance observed in their dogs could be due to obstruction of peripheral vascular beds by local bubble formation or bubble emboli. We know that only two of our pigs had arterial gas bubbles that had escaped pulmonary filtration (35), but the increases in MAP and SVR were observed in all eight pigs. A rapid increase in plasma catecholamines has been observed after decompression in dogs (8), and no increase in MAP was reported, but data were not presented for the period when MAP and SVR peaked in the present study. Since the changes in MAP, SVR, and $\dot{Q}$ observed in our study are compatible with the effects of norepinephrine on the systemic circulation (36), we could speculate that a release of catecholamine may contribute to the effects we report.

During air infusion in mechanically ventilated pigs, we demonstrated a decrease in MAP, and a small decrease was observed in the present pigs after the MAP had reached peak values and returned to base-line values (Fig. 4). The secondary decrease in MAP was therefore most likely an effect of venous gas emboli, whereas the immediate increase could be an effect of both the decompression and the gas bubbles.

In the control pigs we observed that both the measured and the calculated values of most monitored variables remained very stable throughout the 110-min observation. When anesthetized, spontaneously breathing animals are used in experimental studies, atelectasis of the lungs and thereby reduced alveolar ventilation and increased $\dot{Q}_s/\dot{Q}_t$ ratio may be a complication (31). The opposite situation was observed in our pigs, namely a tendency for the $\dot{Q}_s/\dot{Q}_t$ to decrease, which indicates a satisfactory ventilation in the pig model. Although there was a tendency for SVR to increase

slowly in the control pigs, this cannot explain the rapid change in SVR in the decompression group, where the SVR curves peaked 5–15 min after decompression.

It has often been argued that use of the direct Fick method for measuring $\dot{Q}$ requires the existence of stable conditions during the last 3 min before sampling (31). However, if an oxygen analyzer is used to measure oxygen consumption continuously, 30–45 s may be sufficient for stabilization after circulatory and respiratory changes (37). The main source of error during an unsteady state is changes in pulmonary ventilation (37). Unpublished data show a small increase in ventilation during the initial 15 min after decompression in our pigs, which may have resulted in an overestimation of $\dot{V}O_2$ and $\dot{Q}$. Thus, both the decrease in $\dot{Q}$ and the increase in SVR calculated at maximum MAP may have been underestimated.

Studies on sheep (1, 5, 11), dogs (6–9), and goats (10) have also been performed to elucidate physiologic effects after rapid decompressions. In these studies, different animal models and different dive profiles were used, so it is difficult to directly compare the observed effects. The study by Bove et al. (6) on anesthetized, spontaneously breathing dogs exposed to 8 bar (40–60 min) followed by rapid decompression seemed to demonstrate qualitatively the same hemodynamic effects as observed in our pigs. Right ventricular pressure, PVR, CVP, MAP, and SVR all increased, whereas $\dot{Q}$ and Pa_{O_2} decreased. An exception was the HR, which increased in their dogs but not in our pigs.

Method of detection and quantification of gas bubbles

In most of the above-mentioned studies in other animal species (1, 5, 6, 10, 11), ultrasound Doppler was used to detect bubbles. Powell et al. (1) tried to estimate the amount of gas that appeared as bubbles after decompression by comparing the increase in right ventricular systolic pressure (RVSP) with the increase in RVSP observed during venous air infusion at different rates. From this comparison they suggested the dose of gas after decompression at which the different Doppler grades occurred (Spencer's 0–4 scale). Atkins et al. (5) also presented Doppler results, using Spencer's code and mean effects of the physiologic variables, whereas D'Aoust et al. (10) indicated a relationship between the increase in bubble count as measured by Doppler and the decrease in mixed venous N_2 content.

The use of two-dimensional imaging and a software program for automatic counting of bubbles in the pulmonary artery introduces new possibilities for quantification of the venous bubbles arising during and after decompression (19). One major advantage over Doppler grading methods is that the two-dimensional imaging requires little previous training, whereas training is required for the use of Doppler grade analysis (38). Better spatial resolution suggests that the scanning method is more sensitive than the Doppler method (Fig. 1). Finally, the ultrasound imaging method gives an objective, continuous, and linear scale of the number of intravascular gas bubbles detected. The Doppler gradings are somewhat subjective, and the relationship between the grades and the number of gas bubbles is non-linear. Furthermore, the grading scale is not continuous. Using two-dimensional imaging, the occurrence of arterial gas bubbles can also be monitored simultaneously (1, 24, 35)

The disadvantage of the two-dimensional imaging system is that the equipment is more expensive and complicated and less portable than the Doppler system. It should be noted that two-dimensional imaging only permits approximate quantification of

the amount of gas that enters the pulmonary vasculature as gas bubbles, because the images do not cover the whole pulmonary artery and no attempts have been made to estimate the size of the detected bubbles. Despite these limitations, a TEE transducer is a valuable tool for detection and semiquantification of gas bubbles when anesthetized animals are used in decompression-related research.

We thank A. Sira for development of chamber instrumentation and H. Kvithyll and I. Hansen at the Animal Laboratory of the Trondheim Regional and the University Hospital for their help.

This study has been supported financially by Statoil and Phillips Petroleum, Norway. Some of these results were presented at the XVIIth Annual Meeting of EUBS on Diving and Hyperbaric Medicine, Crete, Greece, 29 September to 3 October 1991, and published in the proceedings.—*Manuscript received September 1992; accepted March 1993.*

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Paper V

Paper V

Undersea & Hyperbaric Medicine, Vol. 20, No. 2, 1993

Arterial gas bubbles after decompression in pigs with patent foramen ovale

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Vik A, Jenssen BM, Brubakk A.-O. Arterial gas bubbles after decompression in pigs with patent foramen ovale. Undersea & Hyperbaric Med 1993; 20(2):121–132.—With patent foramen ovale (PFO), thought to be a risk factor for some forms of DCS, venous bubbles may pass through the patent opening to become arterial bubbles. We exposed 14 anesthetized, spontaneously breathing pigs to air at 5 bar (500 kPa, absolute pressure) for 30 min and then rapidly decompressed at 2 bar/min to 1 bar. We measured intravascular pressures, blood gases, and, with transesophageal echocardiology, bubbles in the pulmonary artery and ascending aorta. Autopsy showed that six of the pigs had a PFO. Arterial bubbles occurred more frequently in the PFO group (in six out of six) than in the non-PFO group (in two out of eight, $P < 0.01$). When arterial bubbles were detected, the venous bubble count and the pulmonary artery pressure tended to be lower in pigs with PFO than in pigs without a PFO. We conclude that a PFO increases the risk of arterial bubbles after decompression.

decompression sickness, right-to-left shunt, air embolism, spillover, congenital heart defect, patent foramen ovale

Arterial gas bubbles have been detected in divers after decompression (1), and they may be involved in DCS (2). Except during barotrauma of the lungs (3), these arterial gas bubbles are assumed to arise on the venous side of the circulation (4). Venous gas bubbles may enter the arterial circulation as a result of either transpulmonary passage (5, 6) or passage through a patent foramen ovale (PFO) (7, 8). Such arterial bubbles are termed paradoxical gas emboli.

Recent studies have indicated that the risk of some forms of DCS is increased in divers with a PFO (9, 10), and it is therefore possible that venous gas bubbles that arise during and after decompression are more likely to traverse a PFO than to travel through the pulmonary vasculature into the arterial circulation. This assumption is supported by the results of an experimental study in pigs; during air infusion we found an increased incidence of arterial gas bubbles in pigs with a PFO compared to pigs without a PFO (11). To our knowledge, no decompression study has investigated passage of venous gas bubbles through a PFO into the arterial circulation.

The aim of the present study was to test the hypothesis that after rapid decompression, pigs with a PFO are more likely to have arterial bubbles than pigs without a PFO. Since we have developed a pig model that allows estimation of relative quantities of gas bubbles in the venous circulation after decompression, using two-dimensional imaging of the pulmonary artery, the occurrence of arterial gas bubbles could be related to the degree of venous gas loading.

MATERIALS AND METHODS

Surgical procedures

Fourteen domestic farm swine (2–3 mo. old, body weight 19.5–29.0 kg) were used as experimental animals. The pigs were fasted for 16 h with free access to water. Fifteen to twenty minutes before induction of anesthesia, the pigs received premedication: 7–9 mg/kg azaperonum (Stresnils, Janssen) was injected intramuscularly; atropinsulfate (1 mg, Atropin, Hydro Pharma) was thereafter given intravenously via an ear vein. Anesthesia was induced by thiopental sodium (5 mg/kg, Thiopenton Natrium, Nycomed Pharma) and ketamine (20 mg/kg, Ketalar, Parke Davis) and maintained by a continuous i.v. infusion of ketamine in 0.9% NaCl (30 $mg \cdot kg^{-1} \cdot h^{-1}$). A tracheotomy was performed, after which the pigs were breathing spontaneously through an endotracheal tube, in the supine position. During surgery, body temperature was monitored by a rectal probe and maintained at 37.5°–38.5°C using a heating pad. During the dive, the temperature inside the chamber was also regulated (29.5°–30.5°C). Because a superficial, irregular respiratory pattern was observed approximately 30 min after anesthesia was induced, a bolus dose of α-chloralose in 0.9% NaCl (10–15 mg/kg, 0.25% solution, Sigma, St. Louis, MO) was injected i.v. One or two supplemental doses were usually injected during the following 30 min to achieve a more regular respiratory rate. After injection of the α-chloralose solution, the ketamine infusion provided the pigs with i.v. fluid at a rate of approximately 3–4 $ml \cdot kg^{-1} \cdot h^{-1}$.

Two polyethylene catheters (0.76 mm i.d.) were introduced into the left jugular vein and moved into the pulmonary artery to measure pulmonary arterial pressure and to obtain mixed venous blood samples for gas analysis. The third catheter was positioned in the right atrium via the right jugular vein for measurement of right atrial pressure. Two polyethylene catheters (1.14 and 0.76 mm i.d.) were inserted into the right femoral artery and advanced into the abdominal aorta for continuous monitoring of arterial pressure and to obtain samples for analysis of blood-gas composition. All intravascular pressures were recorded on a Grass polygraph (model 7D, Grass Instrument Co., Quincy, MA) using transducers (Sorensen Transpac II, Abbott Laboratories) that were calibrated against a mercury manometer, with zero pressure referred to the left ventricular mid-level. Calculations of mean pulmonary atrial pressure (PAP), mean right arterial pressure (RAP), and mean arterial pressure (MAP) in millimeters of mercury were made after the experiments. Arterial blood gases (Pa_{O_2} and Pa_{CO_2}) in kilopascals were measured on an IL-1306 pH–blood gas analyzer (Instrumentation Laboratories).

Bubble detection

A transesophageal echocardiographic (TEE) transducer (6.5 MHz), interfaced with a color-flow ultrasonic scanner (CFM 750, Vingmed A/S, Horten, Norway), was inserted and positioned to obtain a simultaneous two-dimensional view of the pulmonary artery and the aorta. If arterial bubbles occurred, it was possible to change the position of the transducer to provide an image of the pulmonary artery, the right atrium, and the left atrium. Ultrasound images were stored on videotape during compression and decompression periods, as well as during the following 90 min. Venous and arterial gas bubbles could be counted automatically after transmission of digitized images from the CFM scanner to a Macintosh computer, or the bubbles could be counted manually from the stored images (12).

Experimental procedure

After surgery was finished, the pigs were placed inside a chamber (300 liter), specially constructed to fit pigs of this size. At least 30 min were needed for stabilization, and the predive data used in the present study were collected 3–5 min before compression started.

Fourteen pigs underwent a 30-min exposure to 5 bar (500 kPa, absolute pressure; compression rate 2 bar/min) followed by a rapid decompression to 1 bar (2 bar/min). Bottom time was calculated from the beginning of compression to the beginning of decompression. The pigs were breathing chamber air during the dive, and soda lime was placed inside the chamber to prevent an increase of CO_2 in the chamber atmosphere. Monitoring of bubble formation and intravascular pressures was done during the dive using special chamber connectors, and after decompression monitoring continued, with the final measurement made after 90 min.

After the dive experiments, the hearts of all the pigs were investigated at autopsy; six pigs were found to have a patent foramen ovale (1.8–5.0 mm diameter) and made up the PFO group [body weight 23.6 kg (SD 2.9)], whereas the other eight had no PFO and served as controls [the non-PFO group, body weight 22.8 kg (SD 2.0)]. The results concerning venous bubble formation and relationship to hemodynamic responses in the non-PFO group will be published separately.

Statistics

Fisher's exact test (one-tailed) was used to test whether the incidence of arterial gas bubbles was higher in the PFO group than in the non-PFO group. Maximum values of venous bubble count were tested for any difference between the groups by the unpaired Student's *t* test. Predive values and the maximum or minimum values of intravascular pressures and blood gases in the two groups were compared using a two-way analysis of variance and the Student's *t* test, with Bonferroni correction for multiple comparisons. For the PFO group, paired Student's *t* test was used to test if each variable had changed significantly from the predive values when the first

arterial gas bubbles were detected. Most values are cited as means (SD), although individual observational values are presented separately for the non-PFO group.

RESULTS

Venous gas bubbles

We observed gas bubbles in the pulmonary artery in all pigs in both the PFO and non-PFO groups. Venous bubbles appeared immediately after the surface was reached or even 10–15 s before (at approximately 1.5 bar) and they increased in number to reach a maximum between 5 and 30 min afterward. The maximum bubble count in the PFO group [200 bubbles · s^{-1} · cm^{-2} (SD 152)] did not differ significantly from that of the non-PFO group [221 bubbles · s^{-1} · cm^{-2} (SD 107), $P = 0.77$] (Fig. 1). Ninety minutes after the decompression, bubbles were still present in the pulmonary artery in all pigs (one pig in the PFO group died 35 min after decompression).

Arterial gas bubbles

Arterial gas bubbles appeared in all six of the pigs with a PFO and in only two of eight pigs that had no PFO (Fig. 2 and Table 1). The difference between the groups was significant, $P = 0.009$). The bubbles were detected in both groups in the ascending aorta during the initial 15 min after surfacing. In one PFO pig we detected arterial bubbles 4 min after decompression. Due to technical problems we do not know if this pig had arterial bubbles immediately on reaching the surface. In both groups the number of arterial bubbles increased until a peak was reached between 15 and 30 min after decompression, whereafter the bubble count decreased again. For both groups the count of arterial bubbles seemed to follow the same time course as the count of venous gas bubbles (Fig. 3). When arterial bubbles were detected, the venous bubble count seemed to be lower in the PFO group than in the non-PFO group (Table 2). Sixty minutes after decompression, solitary arterial bubbles were observed occasionally in the PFO group; none was observed in any pig without a PFO.

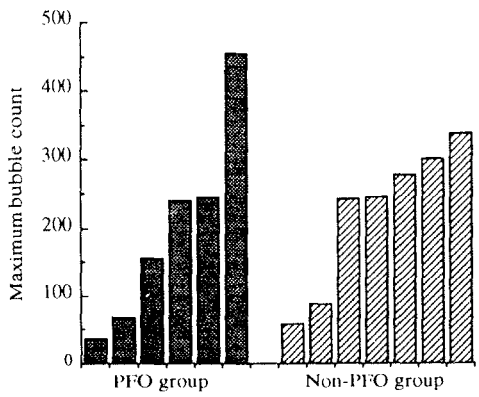

FIG. 1—Maximum bubble count (bubbles · s^{-1} · cm^{-2}) of six pigs in the PFO group and seven pigs in the non-PFO group. (In the eighth pig in the non-PFO group, the quality of the ultrasound image was reduced and permitted no accurate counting to be done.)

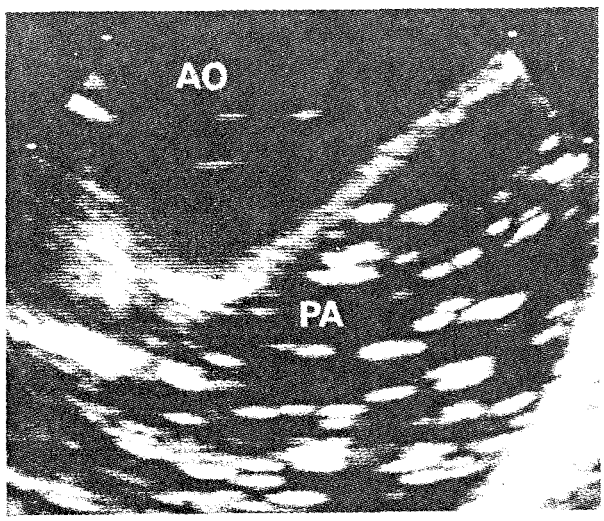

FIG. 2—Ultrasound image of the pulmonary artery (*PA*), with many air bubbles, and the aorta (*AO*), in which three bubbles can be observed.

Table 1: Incidence and Time of Detection of Arterial Gas Bubbles in Pigs with PFO and in Pigs Without a PFO

		Arterial Gas Bubbles	
Group	*n*	Incidence	Time,[a] min
PFO	6	6/6[b] (100 %)	<4[c], 7, 8, 10, 13, 15
Non-PFO	8	2/8 (25 %)	10, 12

[a]Minutes after decompression; [b]$P = 0.009$ compared to the incidence in the non-PFO group; [c]exact time for the occurrence of arterial gas bubbles is not available (*see* text).

Hemodynamic changes

The PAP, RAP, and MAP values for both groups formed a peaked curve after surfacing (Fig. 4). When arterial gas bubbles were detected in the PFO group, both PAP and MAP values had increased significantly from the predive values (Table 2). In the two pigs without a PFO that had arterial gas bubbles, the same variables had also increased at time of detection of arterial bubbles. At that time, the increase in PAP seemed to be much greater in the non-PFO group than in the PFO group.

When the predive and maximum values of PAP, RAP, and MAP from PFO pigs were compared with data from pigs without a PFO, there were no significant differences (Table 3). Similarly, there was no difference between predive values or minimum values of the Pa_{O_2}, or between predive Pa_{CO_2} values for PFO pigs and pigs without PFO. No change in the Pa_{CO_2} was observed after decompression in any of the groups.

One pig in the PFO group died 35 min after decompression. No increase in MAP was observed in this pig after surfacing, in direct contrast to the increase observed in all the other pigs in both groups.

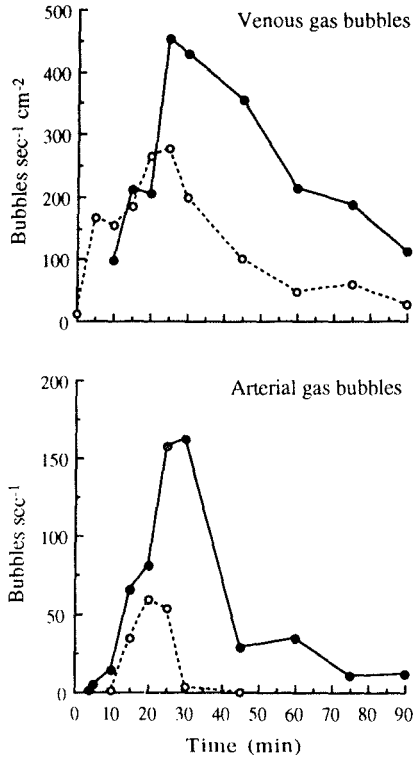

FIG. 3—Time course of development of venous and arterial gas bubbles in one of the pigs in the PFO group (*closed circles, solid line*) and in one of the pigs in the non-PFO group (*open circles, dotted line*). (Venous bubble count is given as bubbles per second per square centimeter, whereas the arterial bubble count is bubbles per second in the aorta.)

Table 2: Venous Bubble Count and Hemodynamic Variables at the Time When Arterial Gas Bubbles Were Detected

Group	*n*	Point of Time	Venous Bubble Count, bubbles · s^{-1} · cm^{-2}	PAP, mmHg	RAP, mmHg	MAP, mmHg
PFO	5	predive		15 (1)	2.4 (1.5)	83 (12)
		arterial bubbles[a]	45 (41)	20 (3)	2.7 (1.2)	90 (15)
		P values		0.005	0.242	0.010
	#6[b]	predive		20	1.5	78
		arterial bubbles[a]		≤ 21	1.5	≤ 81
Non-PFO	2	predive		11, 13	1.5, 3.0	80, 88
		arterial bubbles[a]	155, 170	30, 32	2.0, 4.0	94, 104

[a]Data obtained at the time when arterial gas bubbles were first detected. [b]The sixth pig is not included in the statistical evaluation (*see* text), and venous bubble count was not available at time of detection of arterial bubbles. *P* values are for the comparison of hemodynamic variables before the dive and when arterial gas bubbles were detected. Values are means (SD) in the PFO group; values for individual observations are shown for the non-PFO group.

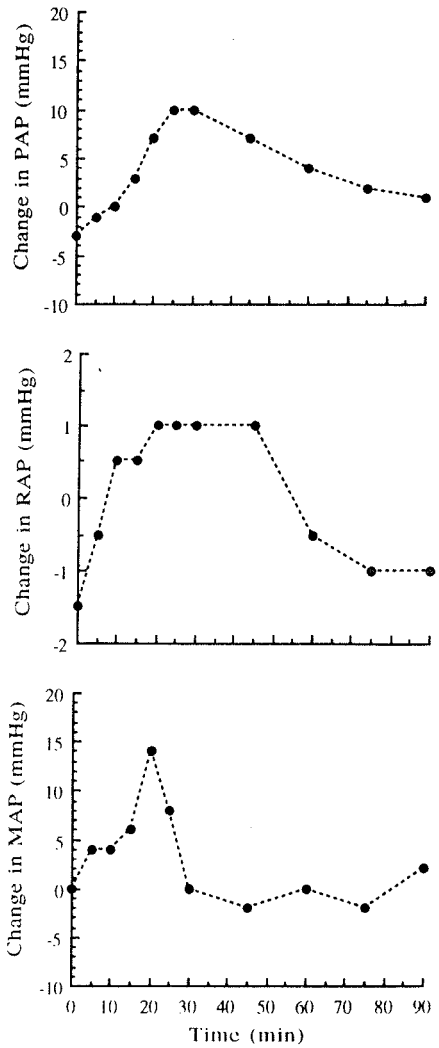

FIG. 4—Time course of changes from predive values in the PAP, RAP, and MAP after decompression, demonstrated by the profiles of one pig in the PFO group that had a maximum venous bubble count near the mean values in both groups (246 bubbles · s^{-1} · cm^{-2}).

DISCUSSION

The present study in pigs shows that after decompression, gas bubbles in the arterial circulation were more likely to have passed through a PFO than to have followed a transpulmonary route. This statement in based on the finding of a higher incidence of arterial gas bubbles in pigs with a PFO than in pigs without a PFO. Furthermore, the results suggest a tendency for arterial gas bubbles to occur at lower venous bubble count and lower PAP values in the PFO group than in the non-PFO group. These findings indicate that arterial bubbles appeared at a lower loading of venous gas bubbles in the PFO pigs than in the pigs without a PFO (13–15). It should be mentioned, however, that only two pigs in the non-PFO group were found to show arterial bubbles.

Table 3: Maximum or Minimum Values of Hemodynamic Variables and Blood Gases After Decompression[a]

		PAP, mmHg		RAP, mmHg		MAP, mmHg		Pa_{O_2}, kPa		Pa_{CO_2},[b] kPa
Group	*n*	Predive	Max	Predive	Max	Predive	Max	Predive	Min	Predive
PFO	6	16 (2)	33 (8)	2.3 (1.4)	3.3 (1.4)	82 (11)	93 (13)	11.7 (0.77)	7.6 (2.1)	5.7 (0.6)
Non-PFO	8	16 (4)	32 (8)	1.8 (1.2)	2.9 (1.0)	85 (12)	101 (16)	12.6 (1.20)	7.9 (5.5)	5.5 (0.2)

[a]No significant difference was observed between the two groups. Values are means (SD). [b]No change was observed for the Pa_{CO_2}.

Inasmuch as there was no difference between maximum values of venous bubble count in the two groups, we can assume that a similar amount of gas appeared as venous bubbles in the PFO group and the non-PFO group. This assumption is supported by the fact that the maximum change in intravascular pressures and blood gases did not differ between the groups (13–15). Thus, our results cannot be explained by a higher venous gas loading or a different ventilation in the PFO pigs compared to that of the pigs without a PFO.

The occurrence of arterial gas bubbles has been investigated in decompression studies on other animal species (16–19). In three of these four studies, venous gas bubbles seemed to arise before any gas bubbles were detected in the arterial circulation (17–19). However, conclusions about transpulmonary passage were drawn without any account being taken of the fact that bubbles might have emerged through a PFO.

We detected arterial gas bubbles in all pigs with a PFO, and we therefore assume that the gas bubbles had passed through the PFO. Since the occurrence of arterial gas bubbles seemed to follow the same time course as the venous bubble count, it is unlikely that arterial gas bubbles appeared as a result of barotrauma of the lung during rapid decompression. Immediately after surfacing we detected venous gas bubbles but no arterial bubbles in five of the pigs in the PFO group. This finding indicates that no right-to-left shunt was present when the surface was reached (20). Inasmuch as the PAP values had changed significantly from predive values when arterial bubbles were detected, an increase in PAP was probably necessary before a right-to-left shunt could occur (21). This suggestion accords with our results from a previous study (11) using air infusion in mechanically ventilated pigs with a PFO, where we also observed an increase in PAP at the time arterial bubbles were detected.

The sixth pig in the PFO group had arterial bubbles <4 min after surfacing, and almost no changes in PAP and MAP and no change in RAP were observed. We can only speculate on the possibility that this pig had a right-to-left shunt before any gas emboli entered the pulmonary circulation. Such a shunt, that is not dependent on a Valsalva maneuver or other factors to change the pressure gradient between the atria, does appear in 5–6% of humans (22, 23).

Another pig in the PFO group died 35 min after surfacing; in contrast, all pigs in the control group survived. We do not know whether arterial gas bubbles were the cause of this death, although an increased mortality was observed in decompressed hamsters that had gas bubbles in the arterial circulation (19). Arterial hypotension was observed only a few minutes after the first bubbles were detected in the ascending aorta, but the number of arterial bubbles recorded in this pig did not seem to be higher than the number in the other five pigs. It is possible that lower MAP values predive (74 mmHg before compression), compared to those observed in most of the other pigs, contributed to the cardiopulmonary collapse.

Gas bubbles in the ascending aorta were also detected in two of the eight pigs without a PFO. Although formation of gas bubbles in the arterial circulation by de novo nucleation is theoretically possible, it is generally accepted that, except during barotrauma, arterial gas bubbles arise on the venous side of the circulation (4). Thus, the arterial bubbles most likely followed a transpulmonary route. The bubbles were first observed in the aorta when the count of venous gas bubbles was high (Table 2) and the PAP values had increased approximately 100% compared to the baseline values. During air infusion in mechanically ventilated pigs without a PFO (15), we

also detected arterial bubbles when the gas loading was high. However, arterial bubbles only appeared after a circulatory collapse, which indicated a very resistant lung filter. During and after decompression, the venous gas bubbles are probably smaller (4–700 μm) (24, 25) than during air infusion (26). We therefore suggest that it was some of the smaller-sized bubbles that escaped pulmonary filtration after decompression in two of the pigs without a PFO (27).

We obtained our results from an animal model involving severe decompression stress on anesthetized pigs; furthermore, the number of pigs used in the study was low. Caution is therefore called for when extrapolating the results to humans. However, it has been suggested that arterial gas bubbles are involved in DCS (2), and our results may help to understand the increased risk of DCS observed in divers with a PFO (9, 10). It is, however, important to be aware of a recent study by Cross et al. (28) in which a PFO was detected in 31% of divers who never experienced DCS. This incidence is close to that found at autopsy in humans (29). Their results show that in divers, the presence of a PFO alone is insufficient to induce symptoms of the disease. It is important to keep in mind that the passage of gas bubbles through a PFO is always dependent on the venous gas loading and thereby on the decompression profile. Thus, in five of our six pigs with a PFO, we observed arterial gas bubbles when the amount of gas that appeared as bubbles in the pulmonary circulation was sufficiently high to have induced an increase in the PAP. Furthermore, in a previous study on pigs that received an air infusion (11), we observed that the risk of arterial gas bubbles seemed to decrease with a decrease in the infusion rate.

It is often assumed that arterial gas emboli that appear in divers during the initial 5–15 min after decompression occur as a result of barotrauma of the lung (3). In such cases, clinical and radiologic evidence of lung pathology is rare (3). We therefore speculate on the possibility that venous gas bubbles have entered the arterial circulation through a PFO in some of those cases of arterial gas embolism.

In conclusion, this study has demonstrated that after a rapid decompression in pigs, the pigs with a PFO were more likely to have arterial gas bubbles than pigs without a PFO. The results may explain some of the mechanisms behind the findings of an increased risk of DCS in divers with a PFO.

We appreciate the skilled help of the staff at the Animal Laboratory of the Trondheim Regional and University Hospital.

This study was supported by Phillips Petroleum Company, Norway, and by the Norwegian Space Center.

Some of the results were presented at the XVIIth Annual Meeting of EUBS on Diving and Hyperbaric Medicine, Crete, Greece, 29 September to 3 October 1991, and were included in the proceedings of that meeting.—*Manuscript received October 1992; accepted January 1993.*

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Paper VI

Paper VI

Comparison of haemodynamic effects during venous air infusion and after decompression in pigs.

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Abbreviated title: VGE during air infusion and after decompression.

Eur. J. Appl. Physiol. (in press)

Summary: We have compared haemodynamic effects of venous gas emboli (VGE) during continuous air infusion and after rapid decompression in pigs. Eight anaesthetized and spontaneously breathing pigs received continuous air infusion at a rate of either 0.05 ml kg^{-1} min^{-1} (6 pigs, air infusion group) or 0.10 ml kg^{-1} min^{-1} (2 pigs). Another eight pigs (decompression group) underwent a 30 min compression to 5 bar (500 kPa, absolute pressure), followed by a rapid decompression (2 bar/min). Haemodynamic variables were measured or calculated, and bubbles in the pulmonary artery were monitored using transesophageal echocardiography. The results showed less variation in the maximum increase in mean pulmonary arterial pressure (PAP) during air infusion (0.05 ml kg^{-1} min^{-1}) than after decompression, although the mean maximum increase did not differ between the two groups (28.0 mmHg, 95 % CI 23.5 to 32.5, vs. 32.0 mmHg, 95 % CI 25.3 to 38.7, $p = 0.3$). The PAP stabilized or decreased very slowly after peak values were reached in the air infusion group, whereas the PAP decreased rapidly during the same period in the decompression group. No significant changes in mean arterial pressure were observed during air infusion (0.05 ml kg^{-1} min^{-1}), in contrast to the rapid increase and the subsequent decrease, that appeared after decompression. Finally, the maximum bubble count was much lower in the air infusion group than in most of the pigs in the decompression group. The two pigs that received 0.10 ml kg^{-1} min^{-1} stopped breathing after 5 min infusion, developed arterial hypotension and died.

Key words: decompression sickness, air embolism, pulmonary circulation, swine, arterial gas bubbles.

Introduction

Venous gas embolism (VGE), a common finding after decompression, is associated with decompression sickness (Edmonds et al. 1992), and it is also a feared complication during many medical procedures (Matjasko et al. 1985; McGrath et al. 1989; Orebaugh 1992). Numerous experimental studies have therefore described effects of gas emboli on the pulmonary and the systemic circulations (Berglund and Josephson 1970; Spencer and Oyama 1971; Bove et al. 1974; Verstappen et al. 1977; Adornato et al. 1978; Butler and Hills 1979; Butler and Hills 1985; Catron et al. 1987a; Vik et al. 1990)

The effects of VGE have been studied using different procedures. One or several bolus dosis of gas, usually air, have been injected into the venous circulation through a catheter (Mandelbaum and King 1963; Verstappen et al. 1977), or gas has been introduced as a continuous infusion (Adornato et al. 1978; Sergysels et al. 1978; Butler and Hills 1985; Vik et al. 1990). Moreover, calibrated gas bubbles have been introduced as an injection of varying duration (Butler and Hills 1979; Butler and Hills 1981; Vik et al. 1991). Effects of VGE have also been studied by exposing the experimental animal to pressure followed by a decompression severe enough to generate gas bubbles in the venous circulation or by exposing the animal to subatmospheric pressure (Bove et al. 1974; Neuman et al. 1980; Catron et al. 1987a; Atkins et al. 1988). During the two last decades, the studies have focused on the physiological effects of continuous air infusion, and it has been argued that venous air embolism during medical procedures usually resembles VGE that appears during a continuous gas infusion (Adornato et al. 1978). However, this experimental procedure of VGE may represent neither the sequence of events, nor the patho-physiological processes, that occur during and after decompression. It is therefore not obvious that the knowledge gained during experiments on continuous air infusion, can be extrapolated to the situation that occurs after decompression.

In the present study, we wanted to evaluate the air infusion model as a model for VGE after rapid decompressions. We compared haemodynamic effects in pigs during air infusion with the corresponding effects in pigs after decompression (Vik et al. 1993), and factors contributing to different results are discussed. We chose two infusion rates likely to induce PAP increases of the same magnitude as the PAP increases observed after decompression in pilot experiments.

Materials and methods

Surgical procedures. Sixteen domestic farm swine (2-3 months of age, body weight 19.5-29 kg) were used as experimental animals. The pigs were fasted for 16 hrs with free access to water. Fifteen to 20 minutes before induction of anaesthesia, the pigs received premedication; 7-9 mg/kg azaperonum (Stresnils ®, Janssen) were injected intramuscularly. Atropinsulfat (1mg, Atropin ®, Hydro Pharma) was thereafter given intravenously via an ear vein, and anaesthesia was induced by thiopental sodium (5 mg/kg, Thiopenton Natrium ®, Nycomed Pharma) and ketamine (20 mg/kg, Ketalar ®, Parke Davis), maintained by a continuous intravenous infusion of ketamine in 0.9 % NaCl (30 mg kg^{-1} h^{-1}). A tracheotomy was performed, whereafter the pigs were breathing spontaneously in the supine position through an endotracheal tube. Body temperature was monitored by a rectal probe and maintained at 37.5-38.5°C using a heating pad during surgery. During the chamber dive, the temperature inside the chamber was regulated (29.5-30.5 °C). Since a superficial, irregular, respiratory pattern was observed approximately 30 min after anaesthesia was induced, a bolus dose of α-chloralose in 0.9 % NaCl (10-15mg/kg, 0.25 % solution, Sigma, St. Louis, NO., USA,) was injected intravenously. One or two supplemental doses were usually injected during the following 30 min period to achieve a more regular respiratory rate. The pigs that received air infusion, first served as control pigs in a previous study over a period of maximum 110 min (Vik et al. 1993). A small bolus dose of α-chloralose (5-10 mg/kg) was therefore injected 15 min before the air infusion started to ensure sufficient depth of anaesthesia. After the α-chloralose solution had been injected, the ketamine infusion provided the pigs with i.v. fluid at a rate of approximately 3-4 ml kg^{-1} h^{-1}.

Two polyethylene catheters (0.76 mm ID) were introduced into the left jugular vein and moved into the pulmonary artery to measure pulmonary arterial pressure and to obtain mixed venous blood for gas analysis. In eight pigs that received air infusion, measurements of pressure and sampling of mixed venous blood were performed through the same catheter, and the second catether was therefore positioned close to the entrance of the superior caval vein to allow infusion of air into the right atrium. A third catheter was positioned in the right atrium via the right jugular vein for measurement of central venous pressure. Two polyethylene catheters (1.14 mm and 0.76mm ID) were inserted into the right femoral artery and advanced into the abdominal aorta for continuous monitoring of arterial pressure and to obtain samples for analysis of blood-gas composition.

Measurements and calculations. All intravascular pressures were recorded on a Grass polygraph (model 7D, Grass Instrument CO. Quincy. Mass. USA) using

transducers (Sorensen Transpac II Abbott Lab.), which were calibrated against a mercury manometer, with zero pressure referred to the left ventricular mid-level. Calculations of mean pulmonary arterial pressure (PAP), mean arterial pressure (MAP) and mean central venous pressure (CVP) in mmHg were made after the experiments.

Arterial and mixed venous blood were analysed for pO_2 and pCO_2 (kPa) using an IL 1306 pH/ Blood Gas Analyser (Instrumentation Laboratories), and the blood gases were corrected for changes in rectal temperature using standard methods. Furthermore, Hb (hemoglobin, g/100 ml) and $\%O_2Hb$ (% of oxyhemoglobin) for calculating content of oxygen (Vik et al. 1993), were measured using an IL 482 CO-Oxymeter (Instrumentation Laboratories).

Estimates of pulmonary blood flow ($\dot{Q}$, ml kg^{-1} min^{-1}) were made using the direct Fick method: $\dot{Q} = \dot{V}O_2 / (CaO_2 - CvO_2)$

where CaO_2 and CvO_2 are arterial and venous oxygen content, respectively, and $\dot{V}O_2$ is the oxygen consumption (ml kg^{-1} min^{-1}). The $\dot{V}O_2$ was calculated after measurements of $\dot{V}E$ (expiratory flow, ml/min) by a pneumotachograph (Gould Godart), using a flow transducer head (Fleisch no 2) connected to a two-way valve located at the proximal end of the endotracheal tube, and after measurements of O_2-fractions of the inspiratory and expiratory air by means of an oxygen analyser (S3A, Applied Electrochemistry) (Vik et al. 1993).

Pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR, in mmHg ml^{-1} kg min) were estimated as:

$$PVR = PAP / \dot{Q} \text{ and } SVR = (MAP - CVP) / \dot{Q}$$

After surgery was finished, the pigs were allowed at least 30 min for stabilization.

Bubble detection. A transesophageal echocardiographic probe (6.5 MHz) interfaced with a CFM 750 Color Flow Scanner (Vingmed, Horten, Norway), was inserted and positioned to obtain a simultaneous two-dimensional view of the pulmonary artery and the aorta (Vik et al. 1990). The ultrasound images were stored on videotape during the continuous air infusion. Similarly, the images were videotaped during the compression and decompression periods, as well as during the following 60 min. In addition, digitized images were transmitted from the CFM scanner to a Macintosh II computer at regular intervals during air infusion (0.05 ml kg^{-1} min^{-1}, two pigs) and after decompression (seven pigs). These images were subsequently prosessed using a software programme for automatic quantification of the number of gas bubbles (Eftedal and Brubakk 1993). Bubbles could also be counted manually from the video images.

Experimental procedure. Eight pigs received a 60 min air infusion at a rate of 0.05 ml kg^{-1} min^{-1} (six pigs, air infusion group, body wt 24.0 kg (SD 3.4)) or at a

rate of 0.10 ml kg^{-1} min^{-1} (two pigs, 22 and 23 kg). The air was infused into the right atrium through a polyethylene catheter (ID. 0.76 mm) and was controlled by a calibrated flowmeter. The remaining eight pigs (decompression group, body wt 22.8 kg (SD 2.0)) underwent a 30 min exposure to 5 bar (500 kPa, absolute pressure) (compression rate 2 bar/min), followed by a rapid decompression to 1 bar (2 bar/min). In both the air infusion group and the decompression group, data were collected every fifth minute during the initial 30 min during infusion or after decompression. Thereafter measurements were made at 15 min intervals, with the final measurement to use in the present study made after 60 min. All hearts were investigated after the experiments for the existence of any patent foramen ovale.

Statistics. Data were analysed on a Macintosh computer (Stat WorksTM version 1.2, Cricket Software Inc., Philadelphia, PA). The two groups were compared by presenting individual profiles of changes in the different variables (Matthews et al. 1990). If these profiles suggested any difference, the maximum change from baseline in the two groups were compared by a Student's t test. Values are means and 95 % confidence interval (95 % CI). Fisher's exact test (one-sided) was used to test if the incidence of arterial gas bubbles was reduced in the air infusion group compared to the decompression group. $P < 0.05$ was defined significant.

Results

Venous gas bubbles. The venous bubble count in the air infusion group (0.05 ml kg^{-1} min^{-1}) is presented in fig.1 by the count in two of the pigs, as estimated by automatic counting. The count of the remainder was estimated by manually counting from the videotaped images, and all had less than 100 bubbles sec^{-1} cm^{-2}. In all pigs, except two, in the decompression group, the maximum bubble count was considerably higher than the bubble count observed in the pigs throughout the 60 min infusion of air. The bubbles were not counted in the two pigs that received 0.10 ml kg^{-1} min^{-1}, since they stopped breathing after 5 min infusion, developed arterial hypotension and died.

Haemodynamic changes. Before air infusion and compression started, there was no difference between the corresponding variables in the two groups, as can be seen from tables 1 and 2. The PAP increased during the initial period of gas loading to reach a maximum value at approximately the same time in both groups (Fig. 2). There was little variation in the maximum values of the air infusion group, whereas the variation was large in the decompression group. In the pigs in the air infusion group, the PAP stabilized or decreased very slowly during the rest of the 60 min infusion period, in contrast to the PAP in the decompression group that decreased after the peak value and almost reached baseline values after 60 min. The same tendency was observed for the PVR, although the same smooth and peaked profiles as those observed for the PAP could not be observed (Fig. 3). This could reflect that the accuracy of variables dependent on the direct Fick method was lower than the accuracy of the other variables, especially during the initial 30 min of the observation period (Guyton et al. 1973; Vik et al. 1993)

The Pao_2 decreased in both groups, and the minimum value was reached at approximately the same time. The variation in the decrease was, however, less in the air infusion group than in the decompression group (Fig. 4). Furthermore, the Pao_2 remained low after 60 min air infusion, whereas the Pao_2 tended to return towards baseline values 60 min after decompression.

During the initial 20 min of air infusion, MAP increased in three pigs, decreased in two pigs and showed no obvious tendency in the sixth pig (Fig. 5). In contrast, the MAP increased in all pigs after decompression, whereafter a decrease to values below predive was observed. The maximum change from baseline during the initial 20 min period of gas loading, was significantly less in the air infusion group than in the decompression group (0 mmHg, 95 % CI ÷ 8 to 8, vs. 19 mmHg, 95 % CI 6 to 32, p = 0.004).

$\dot{Q}$ did not show any obvious tendency to change during the air infusion, whereas $\dot{Q}$ decreased in all pigs after decompression and remained reduced

throughout the observation period. However, when MAP reached its minimum or maximum values, the change in $\dot{Q}$ was not significantly different between the two groups, which could be due to low sample size (÷ 18 ml kg^{-1} min^{-1}, 95 % CI ÷ 74 to 38, vs. ÷ 27 ml kg^{-1} min^{-1}, 95 % CI ÷ 50 to ÷ 4, $p > 0.6$). Changes in SVR in both directions were observed in the air infusion group, in contrast to the peaking in SVR that was observed after decompression in all pigs. There was a tendency for the change in SVR to be different between the groups (0.03 mmHg ml kg^{-1} min^{-1}, 95 % CI÷ 0.10 to 0.26, vs. 0.16 mmHg ml kg^{-1} min^{-1}, 95 % CI 0.06 to 0.26, $p = 0.063$).

Arterial gas bubbles. The incidence of gas bubbles detected in the ascending aorta in the air infusion group (0/6) was not significantly different from the incidence in the decompression group (2/8, $p > 0.3$).

Discussion

In the present study, the haemodynamic effects of continuous air infusion (0.05 ml kg^{-1} min^{-1}) were compared with the corresponding effects of a rapid decompression severe enough to generate gas bubbles in all pigs. The highest infusion rate (0.10 ml kg^{-1} min^{-1}) seemed to be too large for the pulmonary circulation to deal with in spontaneously breathing pigs. This observation is in agreement with the results from previous studies in mechanically ventilated pigs, since a cardiovascular collapse also occurred in some of those pigs during infusion at this rate (Vik et al. 1990).

We observed less variation in PAP response in the air infusion group than in the decompression group. This accords with the fact that the volume of gas that entered the pulmonary circulation, was the same in all pigs during air infusion, whereas large interindividual variation in the number of gas bubbles occurred in the pigs after decompression, and therefore probably also in the total amount of gas deliberated (Fig. 1). Previous air infusion studies have shown that relationships exist between the infusion rate and the rate of increase in PAP (Verstappen et al. 1977; Vik et al. 1990), and maximum PAP values have been shown to be dose-related up to a threshold, above which PAP does not increase any further (Adornato et al. 1978; Butler and Hills 1985). After decompression, the PAP changes are also assumed to relate to the amount of gas that appears as emboli in the pulmonary vasculature (Powell et al. 1982; Vik et al. 1993).

It could therefore be interesting to try to estimate the amount of gas that appeared as bubbles in the pulmonary vasculature after decompression, by e.g. comparing the PAP profiles of the decompression group with those of the air infusion group. Thus, the curves of the PAP increase (Fig. 2) could suggest both higher and lower gas loading in the decompression group than in the air infusion group (0.05 ml kg^{-1} min^{-1}).

However, since the size distribution may influence the PAP response, caution should be exercised if the amount of gas emboli in the pulmonary circulation after decompression is estimated from PAP increase. It has been shown that small-sized emboli (30 μm diam.) induce a disproportionately larger response in the PAP than larger-sized emboli (≥ 170 μm diam.), due to vasoconstriction (Dalen et al. 1967; Malik 1983). We demonstrated in a previous study that a very small dose of air (< 0.5 ml) infused as bubbles ≤ 50 μm increased the PAP significantly in pigs (Vik et al., 1991). However, a recent study in cats, demonstrated that also 500 μm beads induced vasoconstriction of the pulmonary vessels (Shirai et al. 1988).

Similarly, the effects of the mechanical obstruction on the PAP are dependent on the size of the gas bubbles, which determines the site at which the

gas emboli lodge in the pulmonary vasculature (Dalen et al. 1967). Thus, the PAP increase may be difficult to predict accurately during VGE, since the size distribution will be of importance both for any vasoconstriction and any mechanical obstruction that contribute to the increase in PAP.

An important difference between the two models of VGE could therefore be that the size distribution of the gas emboli differ during the two conditions. This statement is based on the assumption that gas bubbles that appear during continuous air infusion are larger-sized compared to those that arise spontaneously after decompression. During air infusion, the bubble size is dependent on the internal diameter of the infusion catheter, which seems to vary between 0.4-1.6 mm in air infusion studies (Hlastala et al. 1979; Albertine et al. 1984; Butler and Hills 1985; Catron et al. 1987a). Also, the bubble size depends on the flow at the infusion site and on any mixing in the ventricle (Hills 1974). Albertine et al. (1984) infused gas bubbles through a catheter with an internal diameter of 0.58 mm, and found by histological examination that the air emboli were restricted to pulmonary vessels having a diameter of 100-1000 μm. In contrast, gas bubbles have been estimated to have a diameter of 19-700 μm after decompression (Hills and Butler 1981), and even large numbers of 4 μm microbubbles have been detected (Christman et al. 1986).

The number of gas bubbles counted in the pulmonary artery from the two-dimensional image in the air infusion group, was far below the maximum number of bubbles counted in most of the pigs after decompression. This fact supports the assumption of larger-sized bubbles during air infusion than after decompression, since doubling of the infusion rate (0.10 ml kg^{-1} min^{-1}) resulted in a cardiovascular collapse. It also follows that it is impossible to compare the dose of gas by comparing the bubble counts during the two different conditions.

Any comparison of PAP profiles during continuous air infusion and after decompression for the estimation of gas loading, must also consider any influence on the immediate increase in PAP of vasoactive mediators or reflexmechanisms secondary to the previous compression and decompression (Catron et al. 1987b). In contrast, such a contribution to the increase in PAP can be eliminated in the pigs that received an air infusion.

The changes in Pao_2 and PVR were related to changes in PAP. Similarly, there was less variation in changes of the variables in the air infusion group than in the decompression group. These results therefore support the conclusion made, based on the findings of PAP changes. During the last 30 min of the experimental period, almost no changes in PAP, Pao_2 and PVR were observed in the air infusion group, whereas the corresponding variables in the decompression group returned

towards baseline values. This difference is in agreement with the fact that the dose of gas was the same throughout the infusion period, and a steady state situation was achieved (Verstappen et al. 1977), whereas the bubble count decreased in the decompressed pigs during the last 30 min.

The increase in MAP that appeared in the decompression group, was not observed in the air infusion group. Neither was the following decrease. Moreover, the SVR increase and the decrease in $\dot{Q}$ in the decompression group could not be observed in the air infusion group. We have suggested in a previous study (Vik et al. 1993) that the rapid decompression could activate the sympathetic nervous system or induce a release of vasoactive substances. This could explain the immediate increase in MAP in the decompression group. Also, bubble formation peripherally in other body tissues may influence the MAP and the SVR (Bove et al. 1974). Finally, small-sized bubbles in the pulmonary circulation may induce reflex mechanisms or release humorale mediators that also act on the systemic circulation (Malik 1983). Thus, these factors could all explain why the change in MAP that appeared in the decompression group, was not observed in the air infusion group.

Since we did not detect any gas bubbles in the ascending aorta in the air infusion group, it is likely that this dose of gas did not exceed the filtering capacity of the lung. This is in agreement with previous studies in mechanically ventilated pigs (Vik et al. 1990; Vik et al. 1991). Two pigs in the decompression group had arterial gas bubbles, and no patent foramen ovale was found at autopsy. Since the venous gas bubbles are assumed to be smaller after decompression than during continuous air infusion, we could speculate that small-sized gas bubbles bypassed the lungfilter in these pigs (Butler and Hills 1979).

The air infusion model has not been evaluated previously as a model for decompression studies. However, it is obvious that many gas infusion studies have been initiated to gain insight into the effects and pathophysiological mechanisms of VGE after decompression. A few research groups have presented the results from both air infusion and decompression experiments in the same study: Bove et al. (1974) studied effects on the cardiovascular system in dogs both after a rapid decompression and after multiple injections of air at varying doses in five dogs. However, no comparison of the haemodynamic results during the two conditions was done. Catron et al. (1987a) studied effects of He-O_2 breathing after decompression and during air infusion, and observed a greater increase in PAP and PVR during He-O_2 breathing in the three pigs that received an air infusion. They concluded that the air infusion model was not a complete model of decompression-induced VGE, and suggested differences in the size of the obstructing bubbles to be a major factor contributing to different results. Powell et al. (1982) tried to

estimate the amount of gas that appeared as venous bubbles after decompression in sheep, by comparing the maximum increase in right ventricular systolic pressure (RVSP) with the increase in RVSP observed during venous air infusion at different rates. However, they did not seem to pay any attention to the possible difference in size distribution during air infusion compared to after decompression.

In conclusion: Similarities between the air infusion model and the decompression model exist, but several factors may contribute to a difference between the models. A similar PAP response may appear during the initial period of an air infusion and after decompression. However, caution should be exercised if the amount of gas deliberated as bubbles after decompression is estimated from a comparison of the PAP changes observed during the two conditions. This is based on the assumption of larger-sized bubbles during air infusion compared to smaller-sized bubbles after decompression. We suggest that introduction of smaller gas bubbles, e.g. by the use of small-sized catheters, and infusion of air bubbles at a gradually increasing infusion rate, followed by a gradually decreasing rate, could eliminate some of the differences between the two VGE models.

Acknowledgements

This study has been supported financially by Statoil and Phillips Petroleum Company Norway. We thank O. Eftedal for performing the bubble counting, A. Sira for development of chamber instrumentation and H. Kvithyll and I. Hansen at the Animal Laboratory of the Trondheim Regional and the University Hospital for their help.

Some of the results have been presented at the XVIIth Annual Meeting of EUBS on Diving and Hyperbaric Medicine, Crete, Greece, September 29 - October 3, 1991, and published in the proceedings.

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TABLE 1. Haemodynamic variables of the pulmonary circulation and Pao_2 at maximum response during air infusion (0.05 ml kg^{-1} min^{-1}) and after decompression.

Group	n	PAP (mmHg)			PVR (mmHg ml^{-1}kg min)		Pao_2 (kPa)		
		Baseline	Max	Time min	Baseline	Max	Baseline	Max	Time min
Air infusion	6	15.5	28.0	14	0.08	0.17	12.2	8.0	22
(95 % CI)		(12.5 - 18.5)	(23.5 - 32.5)	(9 - 19)	(0.07 - 0.09)	(0.15 - 0.19)	(10.3 - 14.2)	(6.1 - 9.9)	(17 - 27)
Decompression	8	15.5	32.0	14	0.07	0.18	12.6	7.9	20
(95 % CI)		(12.4 - 18.6)	(25.3 - 38.7)	(10 - 18)	(0.05 - 0.09)	(0.14 - 0.22)	(11.6 - 13.6)	(5.9 - 9.9)	(17 - 23)

Values are means and 95 % confidence interval. Max: maximum response during the initial 30 min period. When the maximum values were chosen, a normal variation of 1 mmHg for PAP and 0.15 kPa for Pao_2, was accepted. Time to reach maximum values for PVR is not presented, since the PVR curves were not typically peaked.

TABLE 2. Haemodynamic variables of the systemic circulation at maximum response of MAP during air infusion (0.05 ml kg^{-1} min^{-1}) and after decompression.

Group	n	MAP (mmHg)			Q† ($ml\ kg^{-1} min^{-1}$)		SVR† ($mmHg\ ml^{-1} kg\ min$)	
		Baseline	Max	Time min	Baseline	At max MAP	Baseline	At max MAP
Air infusion	6	90	91	14	202	171	0.45	0.49
(95 % CI)		(83 - 97)	(80 - 102)	(10 - 18)	(174 - 230)	(144 - 198)	(0.40 - 0.50)	(0.43 - 0.55)
Decompression	8	85	101	11	204	177	0.37	0.53
(95 % CI)		(75 - 95)	(88 - 114)	(8 - 14)	(166- 242)	(141 - 213)	(0.27 - 0.47)	(0.41 - 0.65)

Values are means and 95 % confidence interval. Max: maximum response during the initial 30 min period. † n = 5 for the air infusion group, n = 6 for the decompression group. When the maximum values for MAP were chosen, a normal variation of 1.5 mmHg was accepted.

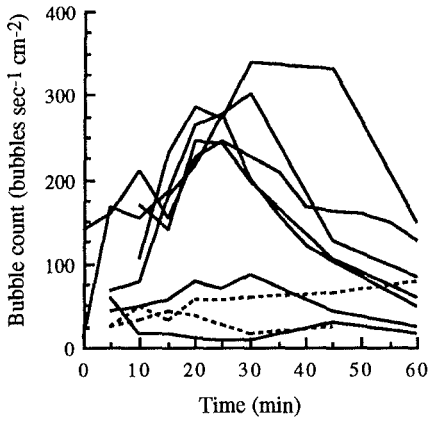

FIG. 1. Bubble counts in a two-dimensional ultrasound image of the pulmonary artery during air infusion (0.05 ml kg^{-1} min^{-1}) in two pig (dotted lines) and after decompression in seven pigs (solid lines).

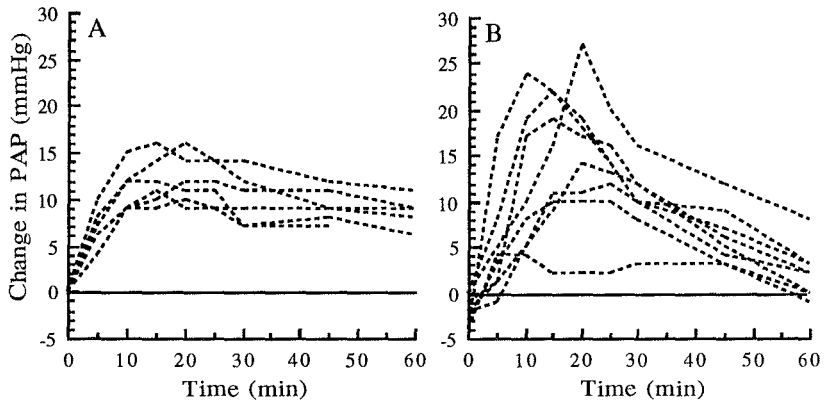

FIG. 2. Changes in PAP during air infusion in six pigs (0.05 ml kg^{-1} min^{-1}) (A) and after decompression in eight pigs (B). Individual profiles are presented. The solid horisontal line shows the zero level. (Predive values are used as baseline values for the decompression group).

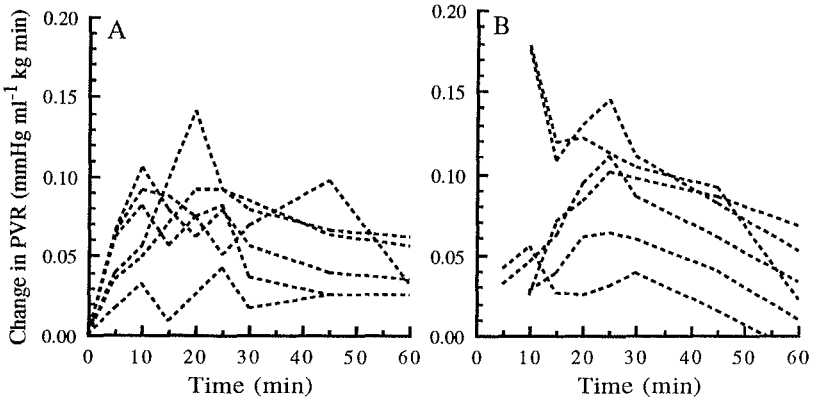

FIG. 3. Changes in PVR during air infusion (A) and after decompression (B) (six pigs).

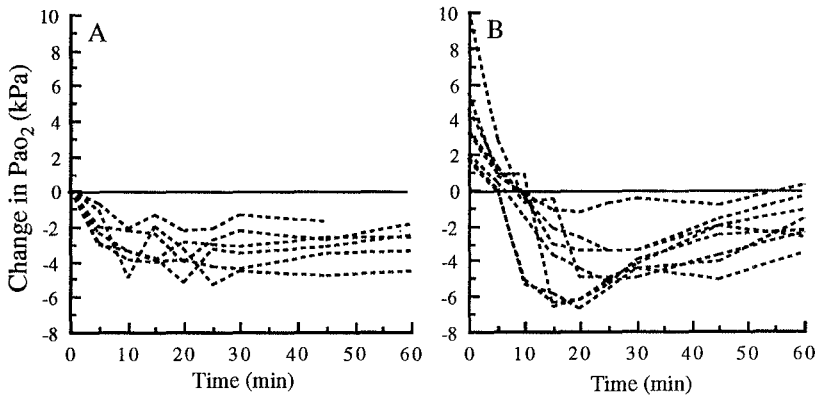

FIG. 4. Changes in Pao_2 during air infusion (A) and after decompression (B). It should be noted that the Pao_2 was high in the decompression group after surfacing because of high pO_2 tension in the chamber during pressure exposure.

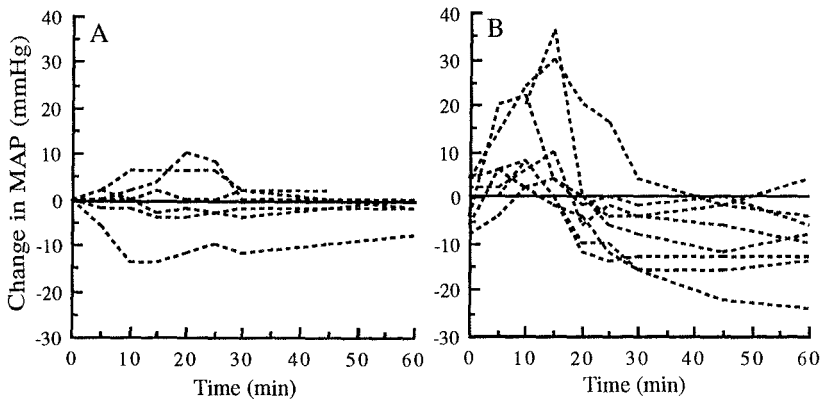

FIG. 5. Changes in MAP during air infusion (A) and after decompression (B).

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