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Reduction of vascular bubbles: methods to prevent the adverse effects of decompression

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Reduksjon av gassbobler i blodbanen: metoder for å forebygge ugunstige effekter av dekompresjon.

Når en dykker returnerer til overflaten etter dykking, kan det dannes gassbobler i kroppen som følge av overmetning av gasser. Slike gassbobler kan igjen føre til trykkfallsyke, men det gjenstår fremdeles å finne alle mekanismene bak denne sammenhengen. Gassbobler er derimot gode indikatorer på risiko for trykkfallsyke, og den gjennomgående arbeidshypotesen i denne avhandlingen har vært at gassbobler i blodbanen er den bakenforliggende årsaken til alvorlig trykkfallsyke. Det å redusere mengden gassbobler vil dermed øke sikkerheten for dykkeren.

Avhandlingen består av tre studier som på forskjellige måter forsøker å redusere boblemengden ved trykkreduksjon. Alle arbeidene er gjennomført med bruk av gris som forsøksdyr, og alle dykkene er simulert i trykk-kammer spesielt laget for slike studier. For å måle gassbobler har vi benyttet ultralydavbildning, samt at vi har tatt ut kar for å måle eventuelle funksjonelle endringer i disse i etterkant av dykkene.

Den første studien demonstrer en ny metode for å redusere gassbobledannelsen ved dekompresjon. Ved kortvarig å øke trykket under pågående trykkreduksjon kan boblemengden signifikant reduseres, resultatene viser at en modell som tar hensyn til bobledannelse beskriver resultatene bedre enn en tradisjonell modell som bare tar hensyn til overmetningen. I den andre studien har vi for første gang vist at gassbobler i blodbanen kan påvirkes medikamentelt også hos store dyr under dekompresjon fra metning. Ved å gi nitrater umiddelbart før dekompresjonen startet, ble mengden gassbobler signifikant redusert sammenlignet med kontrollene som ikke fikk tilført nitrater. Studien åpner veien for videre studier av biokjemiske prosesser involvert i både dannelsen av og effektene av gassbobler. I den siste studien undersøkte vi om en behandlingsprosedyre for trykkfallsyke til bruk når et trykk-kammer ikke er tilgjengelig ville være effektiv om behandlingstrykket ble redusert fra 190 kPa til 160 kPa med pusting av ren oksygen. Vi viste her at trykket var tilstrekkelig for å fjerne boblene etter dykket, men vi forhindret ikke skader på blodkarene.

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CONTENTS

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Trondheim, October 2007

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LIST OF PAPERS

I. Møllerløkken A, Gutvik C, Berge VJ, Jørgensen A, Løset A, Brubakk AO. Recompression during decompression and effects on bubble formation in the pig. *Aviat Space Environ Med* 78(6): 557 - 560, 2007.

II. Møllerløkken A, Berge VJ, Jørgensen A, Wisløff U and Brubakk AO. Effect of a short-acting NO donor on bubble formation from a saturation dive in pigs. *J Appl Physiol* 101: 1541-1545, 2006.

III. Møllerløkken A, Nossum V, Hovin W, Gennser M, Brubakk AO. Recompression with oxygen to160 kPa eliminates vascular gas bubbles, but does not prevent endothelial damage. *Europ J Underwater Hyperbaric* Med 8(1&2): 11 – 16, 2007.

ABBREVIATIONS AND DEFINITIONS

ACh Acetylcholine
ATA Atmosphere absolute
BK Bradykinine
CNS Central nervous system
DCS Decompression sickness
IWR In-water recompression
kPa Kilopascal
NO Nitric oxide
SNP Sodium nitroprusside
TEE Transesophaegal echocardiography

Caisson work: Work in hyperbaric air atmosphere.

Critical gradient: The largest difference in the surrounding pressure and internal pressure without formation of bubbles.

Decompression: Refers to the process undertaken when moving from surroundings with higher pressures to surroundings with lower pressures.

Saturation: In diving, this refers to the state where the body is at equilibrium where no more nitrogen can be absorbed, unless the partial pressure of the nitrogen in the breathing gas is increased. This form of diving is usually preferred when diving deeper than 50 meters of seawater.

Supersaturation: In diving, this refers to a situation where the nitrogen pressure in the tissues exceeds the ambient pressure.

Tissue tension: The level of any gas in a specific tissue.

INTRODUCTION

Aims of the study

The purpose of all decompression procedures is to prevent injury to the diver, and it is generally agreed that these injuries are caused by the formation of gas bubbles in the body. As gas bubbles are formed in nearly all decompressions, and the risk of developing decompression sickness (DCS) increases with the number of gas bubbles, the underlying hypothesis throughout this work has been that vascular gas bubbles are the main initiator of serious DCS. Hence, reducing the amount of gas bubbles will consequently increase the safety of the diver. The main objective was to:

- Study the effect of changing decompression profiles on the amount of vascular gas bubbles
- Study the effect of nitric oxide on bubble reduction in saturation decompression
- Study the preventive effects of removing gas bubbles after a strenuous decompression by simulating in-water recompression with oxygen on functional changes caused by gas bubbles

The activity of diving

Diving is not only a worldwide popular leisure time activity, but also a professional activity both in several industries and in the military. Diving has distinct risks to health owing to its physical characteristics. Most health hazards in diving are the consequence of changes in gas volume and formation of gas bubbles due to reduction of ambient pressure during a diver's ascent. Knowledge of the behaviour of any mixture of breathable gases under increased ambient pressure is crucial for safe diving and the understanding of the pathophysiology of compression or decompression related disorders.

When diving, the ambient pressure increases with increasing depth underwater and the uptake of gas increases both with increasing depth and time at depth. Thus, to keep the lungs from collapsing, breathing gas must be supplied under high pressure. A diver breathing air is exposed to three different gases; nitrogen (N_2), oxygen (O_2) and carbon dioxide (CO_2). Air

contains roughly 21% O_2 and 79% N_2. While O_2 is being metabolized, N_2 is metabolically inert and is therefore not consumed. Any inert gas which is inspired under pressure will be absorbed, but each gas has different properties of solubility and diffusivity which will affect the uptake. The present thesis has focused on N_2 as the inert gas. The exchange of dissolved inert gas between blood and tissue is controlled by blood flow and diffusion. Because of its inert nature, N_2 remains dissolved until the N_2 pressure in the lungs decreases, at which N_2 is removed by the reverse respiratory process, a process which may take several hours [1]. Decompression procedures have been developed to prevent gas coming out of solution forming a gas phase, thus protecting the diver from developing gas bubbles upon surfacing.

Decompression and bubbles

Paul Bert demonstrated in 1887 that bubbles often were associated with symptoms of DCS [2]. The pathophysiology of DCS was studied throughout the latter part of the nineteenth century, but little work was done on how to prevent injury. Berts hypothesis that bubbles caused DCS was later central to Haldanes theory, and he argued that if bubbles could be avoided no DCS would occur [3]. Haldane observed caisson workers and discovered that they did not experience any symptoms of DCS after being decompressed from 2 ata (absolute atmosphere) to 1 ata. Based on his observation Haldane proposed that decompressions would be bubble free as long as the difference between the dissolved N_2 tension in tissue and the absolute pressure, the supersaturation, did not exceed a critical value. We now know that bubble formation during decompression is not simply the consequence of inert gas supersaturation, as numerous experiments indicate that bubbles originate as pre-existing gas nuclei [4].

A systematic study of the phenomena accompanying decompression is complex and difficult, as practical measurement methods to monitor the processes taking place in body tissue are lacking. Various mathematical models used to describe the decompression process reflect only a small part of the total phenomena [5]. However, the introduction of ultrasound, both Doppler and imaging, to detect vascular gas bubbles generated during and after a decompression, have made it possible to compare different decompression situations and models without the binominal endpoint DCS or no DCS. Bubbles detected in the vasculature do not necessarily lead to DCS, but their presence may be indicative of bubbles elsewhere in the body [6]. Gas bubbles, in the absence of clinical manifestations of DCS, have been

introduced as “silent bubbles”. However, incidents of DCS are generally accompanied by bubbles; hence, the risk of DCS appears to be increased [7] .

Gas bubble formation

If no dissolved gas is present, pure water will not form bubbles until the local pressure is reduced to about -1400 atm. This is known as *de novo* formation of bubbles and represents the tensile strength of water [8]. In a decompression situation, such pressure reduction is unrealistic, and in stead of *de novo* formation of bubbles one believes that the bubbles grow from some small, ever-existing nuclei containing gas [9].

A bubble in a solution will grow or shrink by gas diffusion according to whether the solution is supersaturated or undersaturated. The internal pressure of a spherical gas bubble in a liquid depends on the bubble radius, the surface tension of the liquid and the external gas pressure as described by LaPlace’s law.

$$P_{bubble} - p_{amb} = 2\gamma/R + \delta$$

where P_{bubble} is the gas tension inside the bubble, p_{amb} is the gas tension in the fluid surrounding the bubble, γ is the surface tension in the liquid-gas interface, R is the bubble radius and δ is additional deformation pressure opposing bubble expansion.

It follows from the LaPlace equation that the pressure inside the bubbles is always greater than the surrounding pressure. The pressure difference, ΔP, results in an outward diffusion of gas, and the bubble will therefore shrink and finally dissolve. Surfactants in the liquid migrate to the bubble surface and reduce both γ and ΔP; thus stabilizing the bubble. The smaller the bubbles, the grater are their inner pressure. Thus, small bubbles dissolve more quickly then large bubbles.

Gas embolism

Intravascular gas bubbles occur in the venous system during most decompressions [10] [11], and are also known as vascular air embolism. Air embolisms are of great concern not only in activities involving decompression, but also in the operating room or other patient care

situations [12]. In the operation room, vascular air embolism is the entrainment of air (or exogenously delivered gas) from the operative field or other communication with the environment into the venous or arterial vasculature. There are two main categories of gas embolism, venous gas embolism (VGE) and arterial gas embolism (AGE). VGE and AGE are distinguished by different mechanism of gas entry and site where the emboli ultimately may lodge.

Venous gas embolism

Venous air embolism is the most frequent form of VGE, and may occur when gas enters the venous system [13]. The gas, if not trapped, will be transported along the venous system and enter the pulmonary arteries. The first microvessels encountered by venous bubbles are the pulmonary capillaries, and it has been demonstrated *in vivo* that bubbles, generated by decompression or being directly infused to the venous circulation, become trapped here [14]. Venous gas bubbles may also develop following laproscopy, by accidental injection or in cardiopulmonary bypass surgery [15] [16] [17]. Also, neurosurgery in the sitting position seem to predispose for VGE [18].

Arterial gas embolism

There are several possible pathways by which gas bubbles can enter the arterial circulation. The lung is considered to be a good filter for gas bubbles, but the lung may be damaged, resulting in bubbles travelling through the pulmonary vein and the left atrium. Gas bubbles may break through the lung filter if the lung is overloaded with gas [19] and enter the arterial circulation. In addition, venous gas bubbles may pass through a patent foramen ovale (PFO) or other extraordinary connections in the heart to reach the arterial circulation. The Foramen Ovale is functionally closed in the majority of the population, but it has been shown to be patent after foetal life in approximately 30% of humans [20]. The lung can also become overinflated during a rapid ascent, and in this case gas may escape directly into the pulmonary veins after alveolar rupture [21]. Arterial gas bubbles have been detected in divers after excursions [10], during decompression from saturation dives [22] and at autopsy after fatal accidents [23]. Arterial gas bubbles have also been observed in large animals during and after decompression [19] [24], and arterial shunting has been shown during exercise [25].

The pathophysiology of gas bubbles

The sympthomatology of DCS is heterogeneous and not entirely explained by a mechanically mechanism. Distal symptoms are frequently seen, but several central organ systems, including the central nervous system (CNS) and the respiratory system, may be affected as well. It is quite possible that the pathogenesis of DCS, at least in part, may be of an inflammatory origin as there is a great interindividual susceptibility to decompression trauma and furthermore, repetitive dives have resulted in greater tolerance to DCS due to acclimatization [26] [27] [28] [29]. Bubbles may further evoke a tissue response with activation of platelets, the coagulation cascade [30] [31] [32], and complement [27].

The pathological effects of bubbles may cause a mechanical disruption of the tissue concerned, for example the endothelium [33], with compression of non-compliant tissue or blood vessels and lymphatics, or from simply obstructing blood vessels.
Signs and symptoms of DCS differ with the pressure profile and the breathing gas. Neurological symptoms are most common after short deep dives or altitude exposures with little or no preoxygenation. It is generally assumed that localized gas bubbles are responsible for all DCS incidents in the CNS. However, Wilmshurst and Bryson [34] showed that a large PFO can be found in about 50% of divers having central nervous symptoms. They have also observed that large shunts correlate well with spinal cord DCS. Wilmshurst [35] demonstrated further that there is a relationship between right-to-left shunts and cutaneous DCS, which often is associated with more serious DCS involving the CNS and the lung [36] [37]. Gas bubbles can cause changes in barrier permeability even in the absence of clinical manifestations of DCS. Breakdown of the blood-brain-barrier (BBB) and blood-lung-barrier (BLB) may allow proteins and leukocytes to move into the extra vascular brain tissue, with subsequent formation of oedema [38] [39] [40]. Leukocytes have been implicated in the progressive fall in cerebral blood flow and decreased cerebral function in animal models of gas embolism [41] [42]. Various plasma proteins including the coagulation system, complement and kinins are also activated by bubbles [43] [44].

While bubbles in the venous system can explain pulmonary symptoms of DCS, there are other manifestations of DCS that can only be explained by bubble formation within the tissue themselves [45]. Extravascular bubbles may form in tissue that is aqueous or lipid, and except for extreme decompression, bubbles are seldom observed in heart, liver and skeletal muscle

[46]. Daniels [47] reported that the earliest bubbles detected were intravascular, but that substantial accumulation of stationary bubbles would occur before any signs of DCS. In the periphery of the body, small intravascular bubbles may grow into sufficient size to occlude small vessels and as such give rise to stationary intravascular bubbles. Blocking of the microcirculation causes not only tissue ischemia but also retards the elimination of dissolved gas and so produces local areas with gas tensions higher than the surrounding tissue [48]. Once formed, extravascular bubbles persist for long periods of time. Evidence of persistent gas bubbles up to two days after the original decompression has been shown [48].

Endothelium

The endothelium plays a key role in the short- and long-term regulation of the cardiovascular system and is the source of many factors that influence blood flow, blood coagulation as well as angiogenesis [49]. The vascular endothelium consists of a monolayer of cells lining the luminal surface of all blood vessels in the body (figure 1). The endothelium functions by sensing various physiologic stimuli and triggering release of multiple vasoactive substances, including nitric oxide (NO). Such physiologic stimuli can be both substances present in the blood or the shear stress associated with the blood flow. A large number of vasoactive substances are produced and secreted from endothelial cells to act on the underlying vascular smooth muscle cells. The balance between dilating and contracting factors is critical for maintaining vascular homeostasis [50].

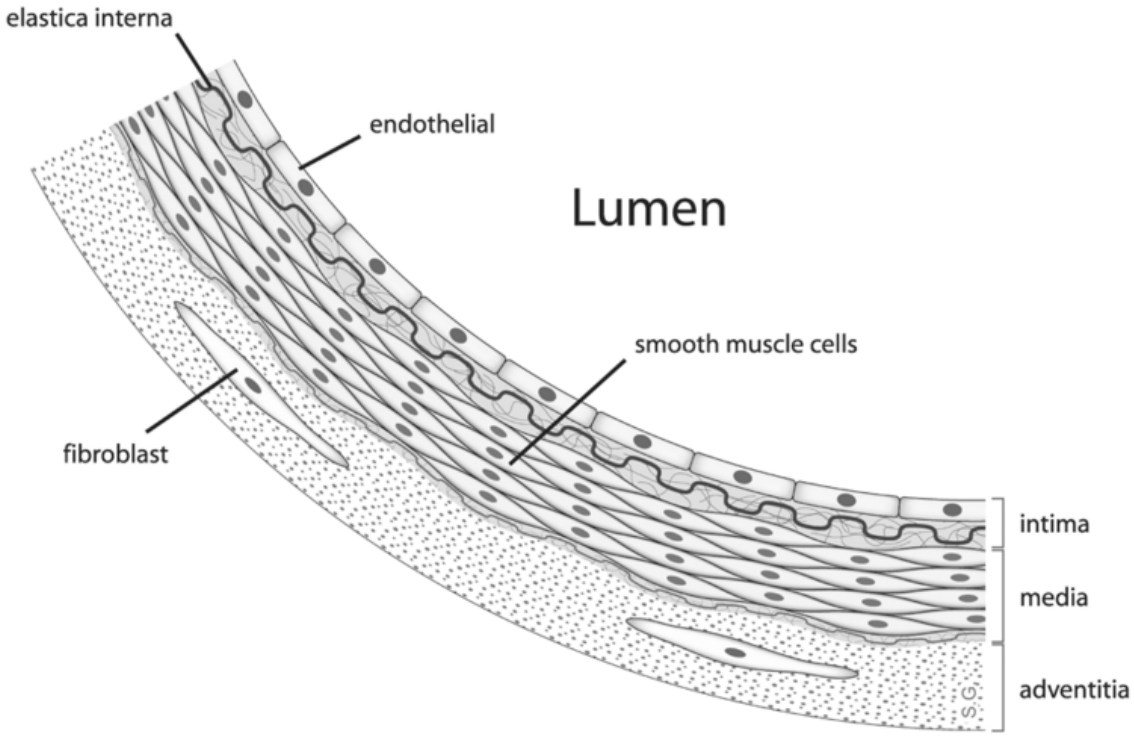

Figure 1. The structure of the blood vessel wall with the three layers intima, media and adventitia. The figure is reproduced in agreement to conditions given by Stijn A. I. Ghesquiere, http://creativecommons.org/licenses/by-sa/2.5/.

The essential role of the endothelium in vasodilatation was found by coincidence by Furchgott and Zawadzki [51]. They discovered when rubbing the intimal surface of a rabbit aorta the vasodilating effect of Acetylcholine (ACh) decreased compared to unrubbed strips of aorta. But, the rubbing had no effect on the vasoconstricting agents, and rubbing of the adventitial surface of the strip had no effect on the response to ACh, suggesting the response observed was selectively endotheliumderived involving vasodilation of vascular smooth muscle cells.

During resting conditions, the endothelial cells lining the blood vessels is a relatively inert surface that regulates and secures unhindered flow of cellular elements through the capillary beds. In response to an inflammatory signal initiated by bubbles, endothelial cells may be converted from an inactivated to an activated state resulting in cellular functional changes. These changes may in turn “un-stabilise” pre-existing nuclei and make them grow into bubbles. Activation of the endothelium generates endothelial microparticles (EMP), which are

fragments of activated endothelial cells. These may in turn reduce the endothelial function, possibly by increasing expression of the endothelial adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1) and E-selectin, and by influencing NO production [52] [53]. Following a decompression, this activation could be caused by endothelial damage from gas bubbles. The pathway is not exclusive for decompression-related bubbles, as endothelial activation has been observed in a number of cardiovascular diseases and from using heart-lung-machines [54]. In endothelial dysfunction, ACh fails to induce normal relaxation, and may in fact induce a paradoxical vasoconstriction by binding of cholinergic receptors on the smooth muscle cell surface. Thus, endothelial function is linked to cardiovascular health.

Nitric oxide

When stimulated by substances present in the blood, or by shear stress associated with blood-flow, endothelial cells can release both constricting and dilating substances. NO is the most important vasodilator released by endothelial cells [55]. The function of the endothelium has been a major research area in the modern understanding of the circulatory system ever since the identification of endothelium-derived relaxing factor, which is a key mediator of vasodilation, was identified as NO. NO is a small uncharged radical compound produced by oxidation of the terminal guanidino nitrogen of the amino acid L-arginine (figure 2). The process is catalyzed by the constitutive endothelial isoform of NO synthase (eNOS), after stimulation by ACh binding to muscarinic receptors. Then, NO enters the smooth muscle cells and initiates the signal cascade that ultimately decreases Ca^{2+} and induces vasorelaxation. Besides ACh, shear stress, bradykinin (BK), adenosine tri-phosphate (ATP), ischemia and a large number of extra-and intracellular factors may also mediate NO production [56]**.** Inorganic nitrates, such as sodium nitroprusside (SNP), can activate the same effector pathway by providing an inorganic source of NO. Their activity is thus not dependent on the functional integrity of the vascular endothelium.

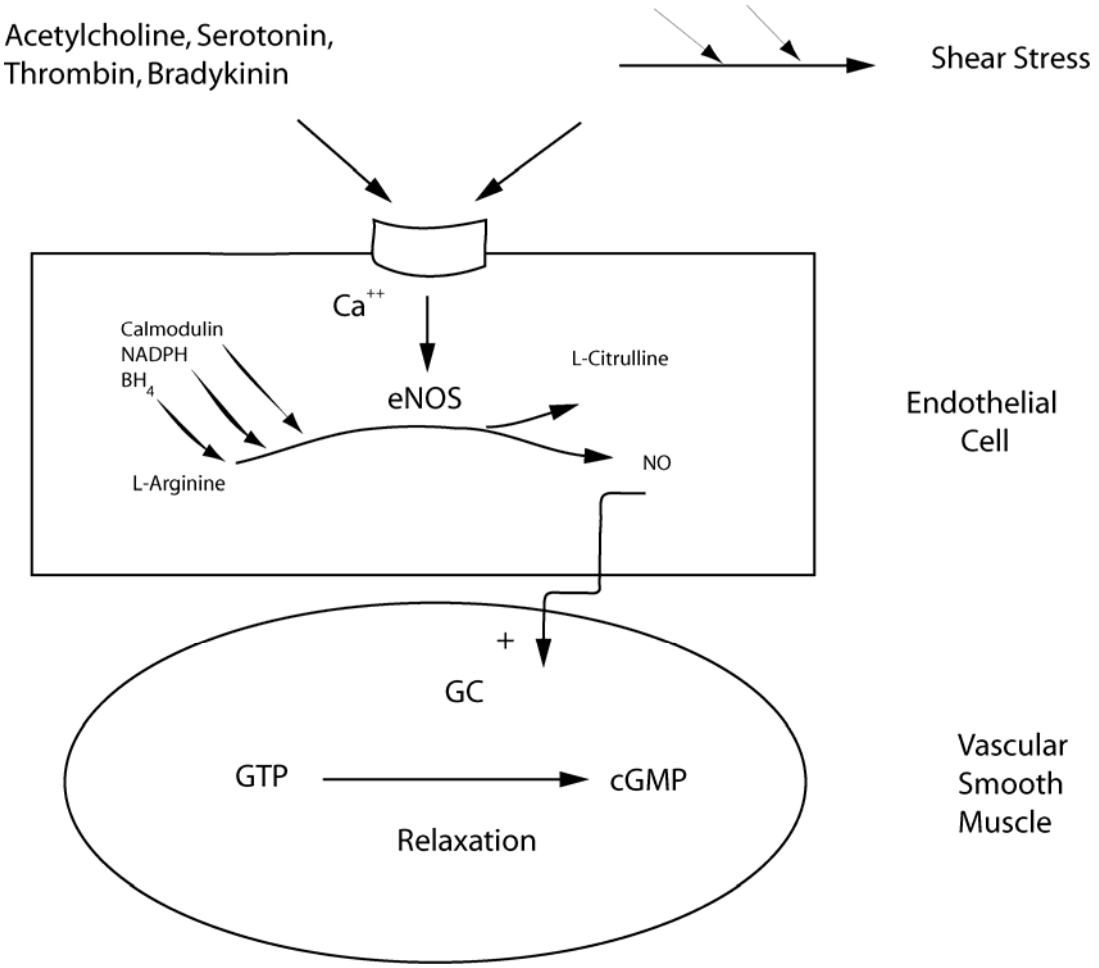

Figure 2. The nitric oxide signalling pathway. BH_4 = tetrahydrobiopterin; Ca^{++} = calcium ion; cGMP = cyclic guanosine monophosphate; eNOS = endothelial nitric oxide synthase; GC = guanylate cyclise; GTP = guanosine triphosphate; NADPH = reduced nicotinamide-adenine dinucleotide phosphate; NO = nitric oxide. Figure modified from [57].

Once released from the endothelium, NO diffuses through the vascular wall and into the smooth muscle cells, where it activates the cytosolic enzyme guanyl cyclase. This enzyme activation increases levels of cellular cyclic GMP, which causes relaxation of the vessel wall. NO is quite reactive and is broken down within few seconds; thus it has a strictly local effect. Higher levels of NO in the smooth muscle cell induce relaxation and are an important cause of improved endothelial function after exercise training [58]. Decreased bioavailability of NO is characteristic for endothelial dysfunction, and contribute to hypertension, atherogenesis, and the progression of cardiovascular disease.

Prevention of decompression injury

To protect the diver from a critical level of supersaturation, different decompression tables have been evolved. The first decompression table was developed by Haldane in 1908, and all common decompression schedules in use since have been based on the model that the body could tolerate a two-to-one reduction in ambient pressure without symptoms [59]. In animals, a fast decompression rate has been demonstrated to be a determining factor for DCS [60] [61].

Other methods to prevent injury to the diver, besides the development of decompression tables, have involved O_2 before exposure [62], exercise before exposure [63] [64] [65] [66], medication in fluid balance and surface tension [67] [68] and use of drugs before exposure [69] [70]. After a single bout of high-intensity aerobic exercise 20 h before a dive bubble formation was suppressed preventing death in rats. The beneficial effect was explained by the possibility that there was an increase in vascular endothelial NO bioavailability after the exercise. However, it has been shown that bubble production is increased by NO blockage in sedentary but not in exercised rats, indicating that the exercise effect may be mediated by other factors than NO [69]. Our laboratory have previously shown that even low bubble loads lead to endothelial dysfunction [14], and have shown the relationship between exercise and endothelial function [58]. Exercise is also one of the treatments recommended for chronic endothelial dysfunction, which indicates further the importance of physically fitness in diving. As younger, slimmer, or aerobically fitter divers has been shown to produce less bubbles compared with older, fatter, or poorly physically fit divers [71], the idea of personalization of decompression tables and computers has evolved. As Moon et al.[72] wrote: “the probabilistic models on which tables and computers are based should reflect the individual reality of the divers, to enable them to conduct their dives in accordance with their individual characteristics”.

Heat shock proteins (HSP) is present in most cells, and play a key role in normal cellular homeostasis and cell protection from damage in response to stress-stimuli. Endurance exercise is an example of a stressor which increases the expression of HSP70 [73]. Increased expression of HSP70 and following protection of rats from air embolism-induced lung injury has been found with heat shock pre-treatment before diving [74]. Thus, exercise-induced HSP70 production seems to affect the bubble formation after diving with a different mechanism than the NO pathway [63].

Biochemical agents are also of interest with regards to reactive oxygen and nitrogen species (ROS and NOS). Oxidative stress in the vessel wall is associated with the generation of ROS/NOS by several oxidases. ROS reduces the local NO by hyperoxic vasoconstriction and impairment of NO dependent vasodilatation [75]. A variety of antioxidants have proved to be protective on the pulmonary endothelial function after a cardiopulmonary bypass [76] and on acute endothelial dysfunction after diving [77] .

Another attractive candidate has been the use of fluorocarbons. These compounds are characterized by a high gas dissolving capacity (O_2, CO_2, inert gas), low viscosity and chemical and biological inertness [78]. The O_2 solubility of fluorocarbons is 20 to 25 times greater than that of blood plasma [79]. Thus, intravenous administration of these agents may increase tissue O_2 delivery. Also, because of higher diffusion gradients, the effect of the fluorocarbons upon bubbles would be a reduction in bubble size. Reduced mortality in gas embolism [80] reduced brain infarct size [81] and improved cardiovascular function after air embolization [82] have been found in animals, but the efficiency of perfluorocarbons in humans is still to be proved [83].

Treatment of DCS in remote areas

The first described treatment of decompression sickness was by Pol and Wattelle in 1841. They observed that caisson workers were relieved by symptoms if they were re-enterd into the high-pressure environment. But it was not until 1924 in the US Navy Diving Manual that recompression treatment was recommended for divers [83]. Several years later the use of O_2 under pressure became recognized. Today, there are different treatment tables depending on the severity of the decompression accident, ranging from tables to use when one suspects/diagnose arterial gas embolism, to treatment-tables for saturation accidents. All these treatments require a hyperbaric chamber. But, in situations where several hours will elapse before the diver(s) can be brought to a recompression facility, treatment of DCS still remains a significant problem. A large number of the divers treated have significant sequelae with signs and symptoms from the CNS [84] [45].

Today much recreational diving takes place at remote locations where transportation of an injured diver to a recompression chamber might take several hours. Although there are arguments whether the time to treatment is of importance or not [85] [86] [87] [88], it appears

that with longer delays (6 h or more), further delay does not affect the outcome of the treatment significantly [86]. Thus, to achieve the best possible outcome the diver should be treated promptly, and longer delay than a few hours should in any case not be allowed. In view of this development there has been renewed interest regarding in-water recompression treatments.

METHODS

Animal research guidelines

All experimental procedures conformed to the *European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes*, and all protocols were approved by the Norwegian Council for Animal Research.

The animals

In the present studies, pigs (*Sus scrofa*) were used as experimental animals. The choice of animal model was based on the experimental expertise in the Baromedical and Environmetal Physiology group, which have established and used this model in several previous studies [89], [33], [61], [19], [90], [91].

In paper II male pigs of the strain Norwegian Landrace (*Sus scrofa domestica*) were used. In paper I and III both sexes of a more common bred pig called hybrid were the choice of experimental animal. All pigs weighed between 18 and 22 kg when arriving at the housing facilities at St Olavs Hospital in Trondheim, and were 8–12 weeks old. The pigs were acclimatized for one week before start of any of the experiments and were under the supervision of a veterinarian. They received a pellet diet once a day and had free access to water.

Surgery

Before the experiments in all of the three papers, the animals were fasted for 16 h with free access to water. On the day of the experiment, they received premedication with 10 ml Stresnil (Azaperon, Janssen-Cilag Pharma, Wien) and 2 ml Stesolid (Diazepam 5 mg · kg^{-1}, Dumex-Alpharma AS, Copenhagen) i.m. After 20 min, atropinesulfate (Atropin, 1 mg i.v.; Nycomed Pharma) was given via an ear vein. Anaesthesia was induced by thiopental sodium (5 mg · kg^{-1} Pentothal Natrium, Abbott Scandinavia) and ketamine (20 mg · kg^{-1} Ketalar; Pfizer). The anaesthesia was maintained by a continuous i.v. infusion of ketamine in 0.9% NaCl (30 mg · kg^{-1} · h^{-1}) together with bolus doses of α-chloralose in 0.9% NaCl (10-15 mg ·

kg^{-1} injected i.v.; 0.25% solution). A tracheotomy was performed to allow the pigs to breathe spontaneously through an endotracheal tube. Throughout the experiments, the pigs were in a supine position. The depth of anaesthesia was maintained at an even level, as judged by clinical observation and the various measured physiological variables as outlined in each of the papers.

In all three papers, polyethylene catheters were introduced both in the left jugular vein and in the abdominal aorta through the right femoral artery for obtaining blood samples and blood gas measurements. One of the catheters in the abdominal aorta was dedicated for arterial blood pressure measurements. Catheters were also positioned in the right atrium via the right jugular vein for measurements of central venous pressure (all three papers) and administration of NO or saline (paper II)

Deep body temperature was measured continuously throughout the experiments by a rectal thermometer in all three papers, and was adjusted through regulation of the chamber temperature by a coil of circulating warm water. Body temperature was kept between 38 and 39 ^{o}C.

The animals were then treated as thoroughly outlined in each of the papers.

Hyperbaric chamber

A dry hyperbaric chamber was used in each of the three studies to simulate the different dives and decompressions being performed. The hyperbaric chamber and its instrumentation is shown in figure 3. The chamber has a volume of 300 L, and is pressurized with air. Inside the chamber the pig breaths spontaneously using a closed system isolated from the air used to increase the pressure. The different pressure profiles and breathing gases are described in more detail in the papers.

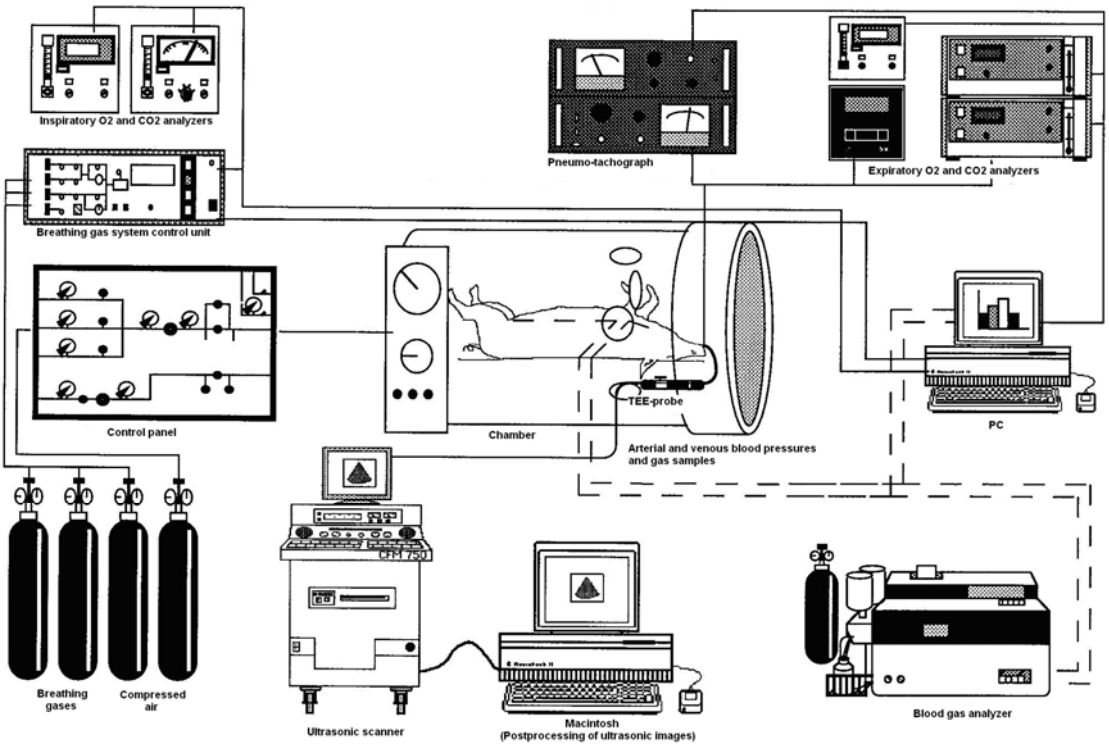

Figure 3. Schematic figure of the pressure chamber and its subsystems. TEE-probe, transesophaegal echocardiographic probe.

Bubble detection

A 5.0 MHz transesophageal echocardiographic transducer was inserted in the esophagus and positioned to obtain a simultaneous two-dimensional view of the pulmonary artery and the aorta. The transducer was connected to an ultrasonic scanner (CFM 750; Vingmed Sound, Horten, Norway), and data was continuously transferred to a Macintosh computer which analysed the amount of bubbles detected in the pulmonary artery. From the images, the amount of bubbles in the right ventricular outflow tract is given as number of bubbles per square centimetre (bubbles · cm^{-2}) as described by Eftedal & Brubakk [92]. Simultaneous to the automatic counting system by the computer, the amount of bubbles seen in the pulmonary artery was graded on a scale between 0 and 5 according to a grading scale given the following definition: 0 = no bubbles; 1 = an occational bubble; 2 = at least one bubble every 4^{th} heartcycle; 3 = at least 1 bubble in each heart cycle; 4 = continous bubbling, at least one bubble/cm^2 in all frames; 5 = bubbles causing frequent distortion of image ("white-out") [93].

Blood gas measurements

Both arterial and venous blood was sampled during each experiment. In paper I and II the blood samples were analyzed on an ABL 330 blood gas analyzer (Radiometer, Copenhagen, Denmark). In paper III the blood samples were analysed on an ABL 700 blood gas analyzer (Bergman Diagnostika, Lillestrøm, Norway).

Endothelial tension measurements

An isolated organ bath model was used to study the local pharmacological mechanisms and signalling pathways in isolated vessels and allows the exclusion of any influence from higher regulatory systems. The equipment for the tension measurements were identical to the system previously developed and described [94]. Two Vessel Tension Measuring Instruments, each containing four channels with four separate buffer containers, were connected in series. A total of eight vessel segments could therefore be tested at the same time.

The pulmonary artery from the right lung and the right carotid artery were carefully dissected and stored in oxygenated (5% CO_2; 95% O_2) sodium-Krebs buffer solution for a maximum of 24 h. The vessels were cut into cylindrical segments and mounted in the isolated organ bath. The contractile capacity of each vessel segment was examined by exposure to a potassium-rich K-krebs buffer solution.

Norepinephrine in cumulative doses was used to precontract the segments until they had reached a stable level. The relaxation response was tested with cumulative doses of ACh (10^{-9} – 10^{-4}M) and BK (10^{-11}- 10^{-6} M) and the response was depending on the degree of damage to the endothelial layer. The relaxation response I_{MAX} is defined as the maximal dilatory response induced by an agonist expressed as a percentage of the precontraction induced by a precontracting agent. T_{MAX} is defined as the maximum level of stabilised relaxation response. In addition, -pED_{50} is defined as the concentration of the agonist that leads to 50% of the relaxation response (I_{MAX} or T_{MAX}). The functionality of the vascular smooth muscle cells was tested with SNP, which are endothelial independent. The vessels that did not respond had a functional failure in the vascular smooth muscle cells, and these segments were rejected.

Tension measurements were performed in paper III, and are described in further detail there.

Statistics

All statistical analyses were performed using SPSS 13.0. In paper I, II and III a student t-test for independent samples was used to compare the number of bubbles during the observation period. In paper II Mann-Whitney U test was used to evaluate differences in the blood-gases, and in paper III the Mann-Whitney U test was used to evaluate the tension data. The choice of a non-parametric test was based on the low number of experimental animals.

All data in the three papers have been presented as mean with standard deviation as outlined in each of the three papers. The level of significance was set to $P<0.05$.

SUMMARY OF PAPERS

Paper I

Møllerløkken A, Gutvik C, Berge VJ, Jørgensen A, Løset A, Brubakk AO. Recompression during decompression and effects on bubble formation in the pig. *Aviat Space Environ Med* 78(6): 557-560, 2007.

A modified USN standard air dive profile and a dive profile which had a 5 min recompression of 50 kPa at the end of each of the three last decompression stops before ascending to the next stop depth was compared with regard to bubble formation during and after decompression. Bubbles were detected with an ultrasonic transducer, and counted by an automated programme. All animals which underwent the modified USN standard air dive profile developed bubbles, whereas only one animal in the recompressed group had detectable bubbles. The results can not be explained by any traditional supersaturation based model of decompression, since they would have predicted the opposite result. In stead, we suggest that a gas-phase model of decompression would be more suitable for describing our findings.

Paper II

Møllerløkken A, Berge VJ, Jørgensen A, Wisløff U and Brubakk AO. Effect of a short-acting NO donor on bubble formation from a saturation dive in pigs. *J Appl Physiol* 101: 1541-1545, 2006.

Our laboratory has previously shown that NO is involved in the protection against vascular gas bubble formation. In this paper we investigated the effect of a short acting NO donor given immediately before start of decompression from saturation on vascular gas bubble formation in pigs. This study was the first to use large animals to demonstrate the protective effects of nitrates with regard to decompression effects. The bubbles were detected by the means of ultrasound, and counted continuously by an automated computer programme. Significant decrease in the amount of vascular gas bubbles were found in the pigs receiving NO immediately before decompression started compared with a control group. No significant differences were found in blood pressure, although a higher heart rate was observed in the

experimental group. The study clearly demonstrates that NO is exceptionally effective in reducing bubble formation also from saturation.

Paper III

Møllerløkken A, Nossum V, Hovin W, Gennser M, Brubakk AO. Recompression with oxygen to160 kPa eliminates vascular gas bubbles, but does not prevent endothelial damage. *Europ J Underwater Hyperbaric* Med 8(1&2): 11–16, 2007.

The effect on bubble formation of recompression to 160 kPa with oxygen 60 min after a strenuous dive was investigated in this study. The study was initiated in order to use our knowledge of bubble-detection and investigate the possibilities for remote diving sites to perform simple first aid if the proper treatment facilities are too far away, and to do so with as little risk for oxygen seizures as possible. 60 min after the dive, the experimental group were recompressed to 160 kPa breathing oxygen for additional 60 min, while the control group remained at the surface breathing air. The recompression did remove the vascular gas bubbles, but did not prevent an impaired endothelial response. We speculate that the 60 min before initiating treatment is too long to avoid bubble induced damage to the endothelium.

RESULTS AND DISCUSSION

Reduction of vascular bubbles was achieved by short recompressions at the end of the standard decompression stops from an air dive in pigs, indicating that a gas phase model describes most accurately the decompression process (Paper I). Further, injection of a short acting NO donor 30 min before start of decompression from a sub-saturation dive was found to give a significant reduction of vascular gas bubbles detected in the right ventricular outflow tract in pigs (Paper II). In paper III the effectiveness of a simulated in-water recompression to 160 kPa with oxygen showed rapid removal of vascular gas bubbles detected after the dive, but did not prevent an impaired endothelial response.

Gas bubbles and validation of decompression procedures

One of the main problems related to the development of new and improved decompression procedures and the validation of decompression profiles, is the large variability between individuals, both in DCS incidence and bubble formation. Even in animal experiments, where physiological variables are tightly controlled, there is a considerable and significant difference in response between individuals. The same dive can produce few or many bubbles, and the response to bubbles differ as well. Further, studies have shown that numerous professional divers have suffered DCS in spite of using accepted procedures. These studies concluded that there probably is a considerable underreporting of clinical symptoms related to decompression [95] [96].

A workshop in 1989 at Undersea and Hyperbaric Medicine Society (UHMS)[97] addressed the validation of decompression procedures. They concluded that procedures should be validated primarily by extensive, dedicated laboratory testing before putting into the field for "operational evaluation". Based on the assumption that procedures that give no symptoms of DCS will have no effect upon the health of the individual, and that if mild DCS can be prevented, than more serious changes will not be found [93]. The endpoint for testing has been the occurrence of DCS or not.

Modern decompression procedures have a low incidence of clinical DCS; around 0,3-1%. Proving the safety of the dives using DCS as an endpoint with a reasonable degree of

confidence will require many more dives than are normally feasible. With the binominal distribution more than 300 exposures on the same procedure with no incidents are needed to confirm a DCS risk below 1% with a 95% confidence interval. For recreational diving, the incidence should be considerably lower than this, requiring even more testing before the procedure can be put into practical use. Also, the diagnosis of DCS can be quite subjective. Using circulating gas bubbles as an indicator for the safety of the dive provides more information than DCS itself in assisting the severity of a dive profile. Hence, the main reason for detecting vascular gas bubbles is to obtain comparative information, post-dive, to assist in determining whether or not a table or profile is safe or hazardous by determining the quantity and duration of bubbles resulting from that profile [6]. Recent work by Eftedal *et al*.[98] combines the information obtained from the detection of vascular gas bubbles with previous knowledge and assumptions, and points the way for validating decompression procedures by using smaller sample sizes then one have been obliged to do historically.

The influence of gas bubbles on decompression models

Different decompression models all seek to give the best control of bubble growth, but present decompression theory appears seriously deficient in its treatment of gas exchange and bubble growth. Hence, decompression models that incorporate even the most advanced of these treatments remain incomplete. When used to prescribe decompression procedures, they all allow some degree of bubble formation in order to reach an acceptable balance between productive bottom time, decompression obligation and risk of DCS. But they inevitably focus on the control of gas supersaturation and bubble formation per se, and fail to consider the effect of bubbles after they have diminished or resolved.

Haldane put up a ratio of supersaturation which could be tolerated without bubble formation after ascent to the surface or the next decompression stop, and divided the body into five different tissues with distinct properties for gas elimination [2]. Being multi-tissue-models, Haldane models rely on inert gas remaining dissolved in the blood and the body tissues during decompression. The typical staged decompression profile produced by a Haldanian model utilizes relatively shallow stops in order to maximize the off-gassing gradient for the presumably dissolved inert gas, and do not take into account any free phase of gas; that is, do not account for the effect of bubbles. It has been shown that elimination of nitrogen from a bubble is slower than the elimination of nitrogen dissolved in the tissue [99] [2].

Bubble models are designed to cater for free-phase gas as well as dissolved gas. In stead of maximum tensions that Haldanian models use, bubble models use critical gradients to minimize the bubble growth by keeping the tension of inert gas within the bubbles equal to, or higher than, the tissue tension. In this way, inert gas will diffuse out from, rather than into, the bubbles. The bubble size will hence be reduced. The most efficient elimination of free-phase gas is at greater ambient pressures as this is where the internal pressures of the bubbles are highest and, hence, the driving force of gas from the bubble is greatest. By utilizing slow ascent rates and deeper decompression stops, bubble models aim to eliminate or minimize any differences in ambient pressure and total tissue tension (supersaturation) and thereby control the volume of free-phase gas within the body.

There are two mechanisms which affects the exchange of inert and metabolic gas between tissue and blood, and that is perfusion and diffusion. Perfusion denotes the blood flow rate in simplest terms, while diffusion refers to the gas penetration rate in tissue, or across tissue-blood boundaries. Each mechanism has a characteristic rate constant for the process. The smallest rate constant limits the gas exchange process. In the past, model distinction was made on the basis of perfusion or diffusion limited gas exchange. Supersaturation is usually regarded as the driving force leading to gas leaving solution and forming bubbles [4], and the rate of growth of these bubbles will be influenced by their initial size. According to the LaPlace equation, the gas tension inside a bubble is inversely proportional to bubble size. That is, if the gas tensions in the fluid (e.g. blood) exceed the gas tension inside the bubble, the bubble will grow. Thus, the larger the bubble, the larger the gradient for bubble growth and consequently the smaller the gradient for bubble decay. Paper I shows that having a model taking both bubble size reduction and surface tension into account might explain how a recompression phase during the decompression would decrease the number of detectable vascular gas bubbles. During a recompression, the bubble size will be reduced, and inert gas tension starts to increase with the consequence that gas will diffuse out of the bubble. Gas diffusing out of the bubble will increase gas tension in the tissue, which again reduces the uptake of gas. Furthermore, as gas tension in the tissues is low because of the effect of bubbles [100], an increase in gas tension will increase the elimination of gas. Hence, even if bubbles increase in size on subsequent ascent, they will do so at a slower rate and from a smaller size than before.

Decompression is a trade-off between dissolved gas build-up and free phase growth, and the goal of decompression theory is to prevent or control the incidence of DCS, keeping incidence and severity within acceptable limits. One has to incorporate both in order to have a decompression theory which can reflect the many processes taking place in the organism when experiencing changes in the ambient pressure.

Vascular gas bubbles, NO and endothelial function

NO is produced by endothelial cells as a response to an increase in shear stress caused by increased blood flow [101], and is the most important vasodilator released by endothelial cells [55]. Once released from the endothelium, NO diffuses through the vascular wall and into the smooth muscle cells, where it activates the cytosolic enzyme guanyl cyclase. This enzyme activation increases levels of cellular cyclic GMP, which causes relaxation of the vessel wall. In a previous study in rats, our laboratory demonstrated that NO given immediately before a 45 min air dive effectively reduced bubble formation [70]. Due to the fact that NO reduces venous tone through a reduction of the preload and hence reduces cardiac output [102] [103], part of the effect on bubble formation could have been caused by a reduction in gas uptake. In paper II we found a similar positive effect on bubble reduction by NO in a saturation dive, which makes the hypothesis of reduced bubble formation by reduced gas uptake less likely.

It is well established that an increase in venous blood flow caused by muscle contraction decrease the number of bubbles observed in the venous outflow tract after a dive [104] [105] [64]. During diving, tissues will equilibrate with the breathing gas. With an increased blood flow, this balance will be achieved more rapidly. A more rapid change in the relationship between the breathing gas and the dissolved gas pressure due to an increased blood flow in the tissues during decompression could minimize the possible gas bubble formation [105]. An alternative explanation on the effect of NO is hence that inert gas washout can be facilitated by an increase in venous blood flow. The effect of NO and exercise on vascular gas bubbles has also been observed in humans [106] [64].

The inhibitory effect of NO on bubble formation is not a new finding. Previous animal experimental work has been conducted with smaller rodents and explosion-like decompressions. Paper II showed two new, unreported findings, the positive effect on larger animals, and that NO reduced the amount of vascular gas bubbles in saturation

decompression. It is not possible to determine from paper II if an increase in blood flow leading to an improved wash-out of nitrogen or changes in endothelial properties that remove bubble nuclei are responsible for the reduction in bubble formation; both effects may be of importance. Regardless of mechanism, NO seems to be exceptionally efficient in reducing bubble formation.

Bubbles are extremely stable on hydrophobic surfaces [107]. Thus, lipid rich micro-domains on the surface of the endothelium may have a particular propensity for formation and/or stable attachment of bubble nuclei. Invaginations in the vascular wall have been suggested to represent such a stabilizing mechanism for bubbles [108]. Brubakk [109] has postulated that hydrophobic sites can exist on the surface of the endothelium in the form of caveolae. This indicates that the caveolae are attractive sites for the formation of bubble nuclei, since reduction in surface tension of hydrophobic membranes have been shown to increase the number of stable nuclei [110]. Caveolae are also the location for NO production, further supporting the attractiveness of this specific location for bubble formation. It has been speculated that NO can reduce the hydrophobicity of the endothelial wall, thus reducing the number of nuclei adhering to the surface.

Gas bubbles generated by decompression or directly infused into the venous circulation are trapped in the pulmonary capillaries [111] [112], and the pulmonary vascular endothelium is one primary site of injury with air embolization [113] [114]. Later studies have confirmed these findings [33] [14]. Activation of endothelium in the venous circulation produces EMP that can initiate endothelial dysfunction at remote sites [53]. These microparticles have a size of a few micrometers and could possibly pass through the lung filter and enter the arterial system. Therefore, changes in arterial endothelial function can occur without direct contact with the bubbles. The effect of vascular gas bubbles on the endothelium was studied in paper III were an impaired endothelial response to ACh, but not to BK, was found in the pulmonary artery. The endothelial measurements of the carotid artery did not show any significant differences between the groups in our study, although the response to ACh was low here as well. The endothelium independent response to SNP seems unaffected by the dive, the vascular bubbles and the treatment with recompression and oxygen. This confirms that the change in vasoactive response is only related to endothelial function and not to function in the vascular smooth muscle layer.

Endothelial dysfunction is an early feature of many vascular diseases, resulting in loss of normal homoeostatic pathways that act to inhibit disease processes such as inflammation, thrombosis and oxidative stress [115] [116]. The positive effect of NO with regards to reduction of detectable vascular gas bubbles supports the hypothesis that the endothelium is of importance for generation of bubbles, as one critical aspect of normal endothelial function is the production of NO by eNOS. Studies have shown that bubbles will reduce the function of the endothelium in a dose-dependent manner [33] [14], and circulating endothelial cells have been detected in blood in proportion to the severity of DCS [117]. Further, it has been shown in vitro that the surface of bubbles can act as a foreign substance and is capable of activating the alternative complement pathway [27] [43].

The finding of impaired endothelial response to ACh but not to BK indicates that the endothelial response to ACh is affected by different mechanisms. BK is also a potent vasodilator that acts by increasing the production of endothelial hyperpolarizing factor (EDHF), which again acts on the smooth muscles of the vessels by an NO-independent mechanism [118]. In normal endothelium, NO is the main vasodilator, but when the endothelium is injured, EDHF production is increased. But, some studies have shown that EDHF may have anti-inflammatory properties which reduces the adhesiveness of the endothelium similar to the effect of NO [119] which again indicates that the response to endothelial injury is quite complex [120].

The treatment used in the experiment (Paper III) did not prevent endothelial damage despite removal of the vascular bubbles. This may indicate that the response to ACh was affected by breathing 100% O_2 under pressure. It is tempting to speculate whether the same response would occur if 100% O_2 at 100 kPa in the treatment regime was used instead of 160 kPa. A previous study at our laboratory showed that recompression to neither 100 kPa breathing 100 % O_2 nor 200 kPa breathing air after a dive to 500 kPa , did not impair the endothelial function [89]. In a study by Obad et al. [77], reduction in endothelial function was prevented by giving antioxidants, Vitamin E and C, before a dive, indicating that oxygen radicals may be involved in developing the endothelial damage seen after a dive.

In-water recompression as treatment of DCS

The prevention of DCS through development of decompression tables has been a great success, but the disease has not been eliminated. Today, around 50% of those being treated are "undeserved hits", that is people who claim to have followed a specific dive table or computer but still ending up for treatment. The techniques required for treatment of DCS are therefore as relevant as ever [87]. In all treatment regimes for DCS the underlying idea is that if bubble volume can be reduced quickly after onset of symptoms, it is possible that their associated secondary effects can be attenuated [121]. In paper III we used a modified emergency procedure for DCS (in-water recompression (IWR)) which consisted of breathing 100% O_2 at a pressure of 160 kPa for 60 min.

The USNavy started development of low pressure oxygen tables in the early 1960´s. The initial compression depth was 200 kPa with the diver breathing 100% O_2. Depending on the patient, the treatment depth was either kept at 200 kPa if the symptoms relieved within 10 min, otherwise the chamber was pressurized to 280 kPa. Using the 200 kPa table led to a high recurrence rate, and the treatment was abandoned, and developing new treatment tables, which required an initial recompression to 280 kPa, were started. The most common treatment table being used today is the USN Treatment table 6 which recompresses to 280 kPa [83]. Traditional recompression treatments are conducted in a recompression chamber, where the possibilities of nursing the patient are present.

The need for IWR procedures has arisen as a consequence of the increasing diving activity in remote areas around the world, as IWR offers the potential of providing treatment when a chamber is not available. The nearest treatment facility can be several hours or perhaps days away, hence, the in-water procedure might be the only opportunity for adequate treatment (Gennsser, personal communication, 2006). Stipp [88] investigated the relationship between time to treatment on the outcome of neurological DCS in divers, and showed that after 6-12 h there is no further effect of the time till treatment. But the time-window before 6-12 h is significant.

The advantages of using oxygen in treatment tables are obvious and include increased nitrogen elimination gradients, avoidance of extra nitrogen loads, increasing oxygenation to tissues, decreasing treatment depths and exposure time. Recompressions also have the

advantage of immediate reduction of the bubble size [122]. In paper III we chose a low pressure level of oxygen in order to minimize the hazardous effects of oxygen under pressure. The use of oxygen does not only establish an increased partial pressure gradient for inert gas from inside to outside a bubble, but also prevents additional uptake of inert gas during the recompression phase. The highest ambient pressure at which 100% O_2 administration is practical is at 300 kPa. Above this pressure, convulsions are likely to occur due to CNS oxygen toxicity [87]. The tolerance for CNS oxygen toxicity is dependent on both exercise and immersion [123] [124], and as such, the IWR treatment depth should be as shallow as possible. Breathing 100% O_2 underwater has the potential to be a highly effective means of preventing emergence of DCS after a significant omitted decompression. But the strategy requires proper training and equipment, and is most often invoked by technical divers for emergency in-water oxygen recompression of a diver who has actually developed DCS. The major risk is oxygen toxicity manifest as a seizure. Unless the diver is wearing a full-face mask when this occurs, the very likely result is drowning [125]. The suggested initial compression depth is 190 kPa, but even at this pressure there is some risk of oxygen toxicity. Hence, reducing the treatment pressure will reduce the risk of getting oxygen seizures and thus increase the safety of the diver. Paper III shows that vascular gas bubbles can be eliminated with low pressure recompression, but the optimal time interval between a decompression accident and start of treatment remains to be investigated.

METHODOLOGICAL CONSIDERATIONS

Experimental procedure

The pig was used as experimental animal throughout this thesis, since such a model for decompression studies was already established at our research group. The pig is generally considered a good model for human physiology, but our model does have improvement potential. The anaesthetics being used is the main drawback of our model. Since we work with spontaneously breathing pigs, the choice of anaesthesia has been ketamine, with bolus injection of the muscle relaxant alpha-chloralose. Ketamine is difficult to work with, since the pig's response to the drug is very variable. Some experimental animals fall asleep at once, but others can tolerate large amounts of ketamine before any surgery can be performed. The supine position of the experimental animal is also a source of variability in our experiments. Observations of both hyperventilation and that some of the lungs show congestion, indicate that in some situations, the ventilation of the lungs may be inadequate. However, the fact that animals have been kept alive on this anaesthesia for over 16 hours with no ill effect (unpublished observations) and that our research group have published a number of papers where this specific animal model have been used [19] [90] [91] [61] [33], indicate that this might be a minor problem.

Detection of gas bubbles by ultrasound

The use of ultrasound to detect intravascular gas bubbles is based on the combination of the non-invasive and real-time nature of ultrasonic systems combined with the acoustic properties of gas bubbles in blood. The most common detection method is the use of ultrasonic Doppler equipment which transforms reflections from moving gas bubbles into audible sound. The audible signal is then estimated by means of a non-linear grading system, and the Spencer and the Kisman-Masurel codes are the most commonly used [93].

In resent years, ultrasonic imaging systems have become more available and have been shown to be well suited for detection of intravascular gas bubbles [126]. As the ultrasonic Doppler method requires extensive training both with regards to the monitoring itself and to the interpretation of the Doppler signals [93], the use of ultrasound imaging techniques requires

far less training, even by persons with little previous experience [126]. It has been shown that the bubble grades from the different detection methods can be directly compared at rest [127].

The venous blood is the easiest place to detect bubbles. The pulmonary artery or the right ventricle of the heart are the most commonly used locations for detection of intravascular gas bubbles both with Doppler (precordical detection) and with imaging systems (both precordical and transesophageal echocardiographic measurements). All the venous blood is transported through this area before it is pumped through the lungs. Experiments suggest that gas nuclei are not present in the blood stream and that bubbles observed with ultrasonic techniques can originate from tissues and/or microcapillaries and migrate into the circulation [128]. Gas nuclei have been found in the outermost layer of the skin that did cavitate when they where irradiated by ultrasound [129]. The only other tissues in which bubbles are routinely observed are the joints, including the spinal cord. These are the structures most frequently affected by DCS. Tissues in which bubbles do not form at physiologic supersaturations would be expected to be affected only by vascular bubbles that originate at other sites, i.e., lungs, brain [130].

Ultrasonic bubble detection has its limitations as a predictive tool for bubble-induced illness. Present technology is only practical for bubble detection in flowing blood; bubbles are usually only detected on the venous side of the circulation, from which most are removed by the pulmonary capillaries. Nevertheless the appearance of many venous bubbles can overwhelm the filtration abilities of the pulmonary capillary network and have been shown to correlate with clinical DCS in humans [130] [131]. A method utilizing high resolution imaging was developed by Daniels *et al* [132] which enabled detection of both stationary and moving bubbles. Unfortunately, the system has not been developed further, and today there are no available ultrasonic detection methods for stationary bubbles. Since there seems to be no clear relationship between vascular gas bubbles and DCS, the detection of bubbles by ultrasound can not be used as diagnostic criteria for DCS. However, there is evidence today that intravascular bubbles cause subclinical damage that may have long-term effects; thus quantification of bubbles in the venous system can offer a graded measure of decompression safety [93] [98] [131].

The use of a Transesophageal Echocardiographic (TEE) probe was the main detection method used during the whole study, and this method has been used extensively in our research

group. The probe gives a good view of both the right pulmonary artery and the aorta and is more or less perfect for the studies we have performed. Most of the time it was easy to position the probe, but in some pigs echoes from the lungs disturbed the image and made it more difficult to interpret. Although ultrasonic images seem to have a lower threshold for detection of gas bubbles than the Doppler method [93], only a two-dimensional slice of the pulmonary artery or the aorta is available for detection and quantification of gas bubbles. In addition, it is not verified exactly how small the gas bubbles can be, and still be detected. The threshold is both dependent on the frequency of the transducer and the depth from the probe at which bubbles are to be detected [133]. The sensitivity of our detection method is high, but the specificity is low. For our research on decompression and vascular bubbles, this is one of the main areas where future ultrasonic probes with higher frequencies can bring about more insights and knowledge.

CONCLUSION AND FUTURE PERSPECTIVES

The present work has demonstrated that the amount of vascular gas bubbles detected during and after decompression can be affected by changing the decompression profile in a way that can not be explained by traditional decompression models, and we suggest that a gas phase model is needed to describe the decompression. Further, we reduced the amount of vascular gas bubbles by injecting a short acting NO donor before start of decompression from saturation, showing for the first time that nitrates have a protective effect in larger animals. And finally we showed that the time gap between a decompression incident and a chosen treatment for 60 min was too long to avoid impaired endothelial function despite removal of gas bubbles in the circulation, indicating that treatment should be initiated as fast as possible.

The incidence of DCS has been reduced over the last 40 years, but the relative number of incidents of DCS involving the CNS has increased. While supersaturation has been a major focus in nearly all research within this field, the future research will focus more on biochemical pathways to uncover the secrets of the bubbles, both in their generation and their pathophysiological effect.

The use of biochemical agents to modify decompression and to reduce the risk of bubble formation is important, despites the very fact that the preventive use of drugs in commercial

diving is forbidden by international labour laws. But in situations where one is forced to decompress more quickly than an established decompression table would allow, such a preventive drug could be useful. An example of such a scenario is with a disabled submarine. Two specific points have been made to the ameliorative effect of nitrates on bubble formation which needs to be investigated. One is the fact that nitrates inhibit platelet aggregation and leukocyte adhesion, which has been suggested as sites for bubble formation [134]. The other point is that it remains to be investigated whether the effect of nitrates is just a haemodynamic effect or not.

Bubbles need something to grow from; de novo formation is considered unrealistic in any human decompression situation. In blood vessels, nuclei are probably attached to the blood vessels endothelium where they grow into bubbles that are dislodged into the blood stream. Thus, any process that influences the surface properties of the endothelium may affect bubble formation in the vascular system. In the endothelial cells, there are specific structures which need future attention, and that are the caveolae. Caveolae normally function to facilitate the uptake of fluid by the cell. In the process of pinocytosis, the caveolae close and pinch off to form pinosomes, little fluid-filled bubbles within the cell. Endothelial NO synthase (eNOS) has been localized to caveolae, and Linder et al. [135] have shown that molecules in the NO-signaling pathway such as soluble guanylyl cyclase, cAMP-dependent protein kinase and cGMP-dependent protein kinase are also co-localized in caveolae. Because exogenous NO reduces bubble formation, it is possible that bubble nuclei are also co-localized in the caveolae with eNOS and NO-related molecules. Using eNOS knock-out mice should be investigated for such relationships in the future.

With the development in ultrasonic imaging computers, it will be possible to look for, in vivo, attractive sites for both generation of and growth of bubbles as well as determining the size of the bubbles. With the aid of contrast agents and new detection methods with ultrasound, stationary gas bubbles will probably become detectable again.

Further studies on emergency treatment-situations (recompression treatments) should also be conducted. Based on our findings in paper III, it is obvious that by waiting 60 min before initiating treatment, the endothelium is damaged despites the following removal of vascular bubbles by recompression and oxygen. Today the recommended treatment is 190 kPa breathing oxygen, and it would be too early to make any recommendations to change that

procedure based on our study presented here. Future studies with IWR should investigate the immediate effect of a recompression, both to 190 kPa and to 160 kPa, keeping the effects of oxygen toxicity in their mind.

There is evidence that the occurrence of at least some forms of DCS is not entirely consistent with purely physical processes. As an arguable result, inability to predict or control DCS severity is perhaps the most glaring deficiency of modern DCS prevention algorithms [9]. This is largely due to the relatively mild nature of the DCS cases that are in the data available for model calibration. Because purposeful experimentation to severe outcomes is impossible with humans, expansion of model capability to cover more severe cases will require an improved understanding of how changes in bubble location, size and profusion translate into changes in DCS severity. Then we will have an ability to quantitatively scale results from animal experiments to humans.

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51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

1990

52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

1991

65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.

68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

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82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

1994

92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.

109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANSER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.

139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.

168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM

198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL

224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS

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