Olav Sande Eftedal

Ultrasonic detection of decompression induced vascular microbubbles

Thesis for the degree of doctor philosophiae

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Norwegian University of
Science and Technology
Faculty of Medicine
Department of Circulation and Medical Imaging

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Ultralyddeteksjon av gassbobler i blodbanen ved dykking

Gassbobler kan dannes i kroppen som følge av overmetning av gasser når man går opp til overflaten etter dykking. Det har lenge vært kjent at slike gassbobler kan føre til trykkfallsyke, men mekanismene bak er fortsatt ikke godt kartlagt. Metoder for å kunne detektere og kvantifisere gassbobler ved dekompresjon er viktige for å studere prosessene som fører til trykkfallsyke. Gassbobler i væske er svært sterke reflektorer for lyd, og bruk av standard medisinske diagnostiske ultralydapparater har vist seg å være praktisk og effektivt for deteksjon av gassbobler i blodbanen. Flere ulike ultralydteknikker og kvantifiseringsmetoder brukes, den vanligste metoden er å gradere boblelyder i ultralyd dopplersignaler etter dykking på en skala fra 0 til 5.

Hoveddelen av avhandlingen fokuserer på bruk av ultralydavbildning som et alternativ til doppler for deteksjon av gassbobler i blodet hos dykkere. I avhandlingen er det vist at kvantifisering av gassbobler i ultralydbilder kan gjøres av personer som ikke har forutgående erfaring, og at avbildning slik sett er bedre enn doppler, som krever mange måneders trening. Graderingsmetodene som brukes i avbildning og doppler er vist å være sammenlignbare, noe som muliggjør sammenligning av studier som benytter forkjellige teknikker. En studie i avhandlingen viser en statistisk sammenheng mellom mengden av detekterbare gassbobler i blodet og risikoen for trykkfallsyke. Fravær av gassbobler er en sterk indikasjon på lav eller ingen risiko, og bobledeteksjon kan derfor brukes for å evaluere dykkeprosedyrer. Resultatene er sammenfallende med hva som tidligere har vært vist med dopplerteknikk.

En studie i avhandlingen ser på forekomsten av gassbobler i blodet hos helsepersonell som assisterer pasienter ved medisinsk trykkammerbehandling. Studien viser at dagens prosedyrer er langt fra optimale og at de bør endres for å redusere risikoen for trykkfallsyke hos helsepersonell.

Den siste publikasjonen i avhandlingen beskriver en metode for estimering av risiko for trykkfallsyke ved testing av luftdykkeprosedyrer. Metoden benytter bayesiansk statistikk for å kombinere observert boblemengde ved testing av en prosedyre med tidligere etablert sammenheng mellom boblemengde og risiko for trykkfallsyke. Resultatet blir et estimat for risiko som er betydelig mer nøyaktig enn tidligere metoder. Dette betyr at man trenger færre testdykk for å avgjøre om en prosedyre er trygg eller ikke, noe som vil være viktig for utvikling og implementering av tryggere dekompresjonstabeller for luftdykking.

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LIST OF PAPERS

1. Eftedal O, Brubakk AO.
   Agreement between trained and untrained observers in grading intravascular bubble signals in ultrasonic images.
   Undersea Hyperb Med 1997; 24(4): 293-299

2. Brubakk AO, Eftedal O.
   Comparison of three different ultrasonic methods for quantification of intravascular gas bubbles.
   Undersea Hyperb Med 2001; 28(3): 131-136

3. Risberg J, Englund M, Aanderud L, Eftedal O, Flook V, Thorsen E.
   Venous gas embolism in chamber attendants after hyperbaric exposure.
   Undersea Hyperb Med 2004; 31(4): 417-429

4. Eftedal OS, Lydersen S, Brubakk AO.
   The relationship between venous gas bubbles and adverse effects of decompression after air dives.
   Undersea Hyperb Med 2007; 34(2): 99-105

5. Eftedal OS, Tjelmeland H, Brubakk AO.
   Validation of decompression procedures based on detection of venous gas bubbles: a Bayesian approach.
   Aviat Space Environ Med 2007; 78: 94-99

LIST OF TERMS AND DEFINITIONS

Autochthonous bubbles: Bubbles remaining at the location where they were created, as opposed to circulating bubbles.

Bayesian statistics: Statistics which incorporate prior knowledge and accumulated experience into probability calculations by use of Bayes' theorem.

Bounce diving: In commercial diving, bounce diving is the alternative to saturation diving (sub saturation diving). In recreational diving, a bounce dive is a descent to maximum depth and then an ascent back to the surface with the least delay.

Compressed air work: Work in hyperbaric air atmosphere. Usually tunnel work or construction work in caissons under water, where increased ambient pressure is applied to keep water out.

Dermatome: A dermatome is an area of the skin supplied by nerve fibres originating from (or converging to) a single dorsal nerve root.

Endogenous: "Arising from within", endogenous bubbles are bubbles created in the body.

Endothelium: Thin layer of specialized cells that line the interior surface of all blood vessels from the heart to the smallest capillaries. Actively involved in many aspects of vascular physiology.

Gas emboli: Gas bubbles circulating in the blood vessels.

Harmonics: A sound with a frequency that is an integer multiple of the original sound. If the frequency of the original sound is f, the harmonics have frequency $2f$ (second harmonic), 3f (third harmonic), etc.

Heliox: Mixture of helium and oxygen used as breathing gas in deep diving.

Hyperbaric: Pertaining to ambient pressure above what is found at sea level, i.e. more than 101 kilo Pascals (kPa).

Hypobaric: Pertaining to ambient pressure lower than what is found at sea level, i.e. less than 101 kPa.

Inert gas: A gas that is not reactive under normal circumstances. In diving the term is used for components of the breathing gas not participating in physiological processes, usually nitrogen and/or helium. Inert gases are the major constituent of decompression induced gas bubbles.

Intravascular: Within the blood vessels.

Negative predictive value (NPV): The probability that an individual does not have the tested condition, given that the test result is negative. Here used for the proportion of divers without detectable bubbles who have no signs or symptoms of decompression sickness.

Nitrox: Mixture of nitrogen and oxygen used as breathing gas in diving, oxygen levels are higher than in air in order to decrease bubble formation.

Paradoxical gas embolism: Air or gas emboli from the venous circulation in the systemic arterial circulation. In diving this can occur spontaneously due to a patent foramen ovale or through shunts in the pulmonary vasculature. Pulmonary shunts can be pre-existing or due to pulmonary barotrauma.

Patent foramen ovale (PFO): Defect in the wall between the right and left atrium of the heart. It is a common and usually benign defect of the heart, but can cause paradoxical gas embolism.

Pathophysiology: The physiology of disordered function.

Precordial: Pertaining to the precordium, the chest wall over the heart.

Positive predictive value (PPV): The probability that an individual does have the tested condition, given that the test result is positive. Here used for the proportion of divers with detectable bubbles who have signs or symptoms of decompression sickness.

Saturation diving: A diving technique that allows divers to remain at great depth for long periods of time (days or weeks) by living under pressure in a hyperbaric chamber. "Saturation" refers to the fact that the diver's tissues have absorbed the maximum partial

pressure of gas possible for that depth. This is significant because once the tissues become saturated, the time to ascend from depth is independent of increased bottom time. Commonly used for diving deeper than 50 meters of sea water.

Sensitivity: The ability of a test to detect a disease (or condition) when it is truly present. Here used for the proportion of cases of decompression sickness accompanied by detectable intravascular gas bubbles.

Specificity: The ability of a test to exclude the presence of a disease (or condition) when it is truly not present. Here used for the probability of having no detectable bubbles when there are no signs or symptoms of decompression sickness.

Technical diving: Non-professional diving that exceeds the scope of recreational diving, allowing deeper and longer dives. Various breathing gas mixtures are used to minimise decompression time.

Transesophageal echocardiography (TEE): Ultrasound imaging of the heart with the ultrasonic probe placed inside the esophagus. This improves image quality compared to conventional precordial imaging by shortening the distance and avoiding attenuation by lung tissue and costae (ribs).

INTRODUCTION

The first step in the pathophysiological cascade leading to decompression sickness (DCS) is the formation of gas bubbles. Although systematically studied for many years, the subsequent steps are only partially understood. The simplistic explanation of mechanical damage from expansion of bubbles is misleading; recent research has revealed that gas bubbles induce vascular endothelial damage and haematological and immunological responses that are probably central in the development of the DCS syndrome (1). Still, much work remains before the picture is complete.

The first observations of decompression induced gas bubbles were made by the Irish natural philosopher and scientist Robert Boyle in 1659. Boyle studied the reactions of various substances and animals to reduction in the ambient pressure by putting them in his newly invented air pump. Based on his observations he made the following description of the effect of pressure changes on the body (2):

"Whether […] the little Bubbles generated upon the absence of Air in the Bloud, juyces and soft parts of the Body, may by their Vast number, and their conspiring distension, variously streighten in some places, and stretch in others, the Vessels, especially the smaller ones, that convey the Bloud and Nourishment; and so by choaking up some passages, and vitiating the figure of others, disturb or hinder the due circulation of the Bloud? Not to mention the pains that such distensions may cause in some Nerves, and membranous parts, which by irritating some of them into convulsions may hasten the death of Animals, and destroy them sooner by occasion of that irritation or loss of what the Air is necessary to supply them with."

Boyle was 200 years ahead of his time. With the development of the deep-sea diving outfit and the use of increased pressure to prevent flooding in mines, tunnels and caissons, the hazards of decompression were well known in the first half of the 19th century. Attempts to explain the malady included congestion, or alternatively hypovolemia, of internal organs due to external pressure changes, frictional electricity caused by compressed air and toxaemia from tissue catabolism (3). The first systematic study demonstrating the presence of gas bubbles in blood and tissues after decompression was done by Paul Bert. In his classical work, La Pression barométrique, recherches de physiologie expérimentale (4), published in 1878, he described bubble formation and DCS in dogs, and suggested how DCS can be avoided by a slow decrease in ambient pressure to "allow time for the nitrogen of the blood to escape but also allow for the nitrogen of the tissues time to pass into the blood". Bert's

discoveries prepared the ground for the works of John Scott Haldane (5), who developed the first scientifically based decompression tables and is often referred to as “the father of decompression theory”.

With the introduction of ultrasound Doppler instruments for measurement of blood flow in the late 1950’s (6) came a tool that enabled simple, non-invasive detection of intravascular gas bubbles, but it was not until 10 years later that the first studies on Doppler detection of decompression-generated gas bubbles were published (7-9). In the 1970’s and 80’s ultrasound equipment became more sophisticated, and both Doppler and imaging techniques were applied for bubble detection in both animal and human studies.

Ultrasound instruments are by far the most widely used for detection of decompression induced gas bubbles, but other approaches have also been suggested. Mekjavic et al. (10), inspired by the classical work of Boyle, found that detection of gas bubbles in ocular tear film was a sensitive, simple and practical method for evaluation of decompression stress. Bennett et al. (11) applied the method to recreational divers and found a significant increase in bubble count after diving, there was, however, no significant correlation with inert gas load. Electrical impedance has also been used for detection and quantification of tissue bubbles (12), but has limited sensitivity. Recently, the use of electro-optical sensors has been suggested for real-time in-dive monitoring of bubbles and vital signs in peripheral vessels (13), this is, however, still at an early stage of development.

There are many questions to answer before the enigma of decompression is solved. The large individual variation in susceptibility both to bubble formation and to DCS is one. There are also large intra-individual differences in bubble formation after identical exposures. Another problem is why some bubbles cause DCS while others, so-called “silent bubbles”, do not. Can these “silent bubbles” have subclinical effects that may accumulate to long term injury? Even basic questions like how and where endogenous bubbles are formed still remain to be answered. Recently there has been increased attention to the endothelium both with respect to bubble formation and decompression injury. Several studies show reduced endothelial function after exposure to vascular bubbles (14-16), and we have suggested that this may be a central mechanism in the development of serious decompression injury, and possibly also long term injury (17). Further research on the interactions between bubbles and endothelium may lead to novel approaches in both the prevention and treatment of decompression injury and a reliable method for bubble detection is a prerequisite for such research.

There is no “gold standard” for detection of decompression induced vascular gas bubbles, but the most frequently applied method is by use of ultrasound Doppler systems. An expert interprets the Doppler signals aurally and scores bubble sounds according to a grading system. Standardized procedures for monitoring dive subjects and identifying and classifying bubbles have been suggested to enable comparison of results from different studies (18). However, the significance of intravascular bubbles as a measure for decompression stress is still debated, and there is no consensus on how bubble data should be analysed or interpreted.

The aim of the current study has been to evaluate and compare the performance of different ultrasound systems for detection of vascular gas bubbles. We have used the methods in practice to evaluate decompression stress, and we have suggested a new statistical method for validation of decompression procedures based on observed bubble grades.

DECOMPRESSION DISORDERS – NOMENCLATURE

When going through the literature, the nomenclature of decompression disorders can be quite confusing. There are a number of terms in use, and different authors use the terms differently. Decompression sickness, decompression illness, decompression injury, bends and caisson disease are all used to describe the same condition. In the fifth edition of Bennett and Elliott’s Physiology and Medicine of Diving, the editors have based the terminology upon physiologic mechanisms of injury (19): Decompression sickness are conditions arising from the evolution of a gas phase from within the body. Arterial gas embolism (AGE) is gas introduced into the arterial circulation either through a right to left shunt (an intracardial septum defect or a pulmonary shunt) or secondary to pulmonary barotrauma. Barotrauma is tissue damage caused by changes in ambient pressure affecting closed gas volumes inside or beside the body, typically lungs, sinuses, middle ear or diving mask. Decompression illness (DCI) is a term often used to encompass all forms of injury related to changes in ambient pressure.

When decompression stress is used for evaluation of the safety of procedures it is important to consider even trivial symptoms that do not require recompression treatment in a clinical setting. The presence of such symptoms probably indicate a higher level of risk, but they do not necessarily qualify for the term decompression sickness. We have therefore introduced the term “adverse effects of decompression” (AED) to include all minor signs and symptoms (Paper IV).

DECOMPRESSION SICKNESS: CLASSIFICATION, MANIFESTATIONS AND PATHOPHYSIOLOGY

Decompression sickness has been referred to as the decompression syndrome (20), reflecting that it is a clinical diagnosis comprising a wide range of symptoms precipitated by a common event: The formation of endogenous gas bubbles due to supersaturation by gases. Decompression sickness is often classified in two main categories, Type I and Type II, according to the severity and the organ systems involved (21). Type I includes cases with musculoskeletal manifestations (pain), cutaneous or lymphatic involvement and more diffuse symptoms such as malaise, anorexia and fatigue. Type II includes all cases of more serious nature, mainly neurological manifestations (both peripheral and central nervous systems) and respiratory manifestations ("chokes"). This classification is useful in a clinical setting for prognosis and treatment management. An alternative definition and classification of DCS was designed by an expert group from the US Navy and Canadian Forces in 1988 (22). These criteria were designed for more scientific purposes, mainly to enable comparison of DCS data from different studies, and were not intended for clinical use.

Several textbooks on diving medicine claim that limb pain is the most common manifestation of DCS: "Limb pain […] is by far the most common symptom of decompression sickness" (20), "The onset of aching pain in a limb is the most common manifestation of decompression sickness" (23), "Limb bends […] occurs in 85%-95% of all cases" (24). However, two recent epidemiologic studies with a total of over 4,500 DCS cases mainly from recreational diving indicate that neurological manifestations are now more common (25). In the UK Institute of Naval Medicine database the prevalence of neurological manifestations is 77% whereas limb pain is found in 49% of the cases. It has been suggested that the introduction of dive computers has led to deeper dives and longer bottom times and consequently an increased proportion of neurologic DCS (26). An alternative explanation for the apparent change in symptomatology is an increased focus on neurological damage to divers. It has been stated that the way to reduce the incidence of cerebral manifestations of DCS is to omit a full neurological examination (27), the same may apply to other neurologic manifestations.

Neurologic manifestations

The most common symptoms in neurologic DCS are sensorial disturbances like paresthesias and numbness (28). These mild cases may occur in any anatomical location, they are rarely distributed according to dermatomes and may originate from the central, peripheral or autonomous nervous systems (25). More severe neurologic DCS with overt cerebral or spinal genesis represents only a small minority of cases, but because of the potentially serious outcome with debilitating sequelae, this has traditionally been subject to the most research with respect to pathophysiology. Still, the mechanisms behind neurologic decompression sickness are debated.

In an analysis of 1070 cases of central nervous decompression sickness Francis et al. found that 77% involved the spinal cord (29). Animal studies have shown that the white matter is the primary target of decompression induced injury in the spinal cord (30;31). Theoretically, the white matter is a favourable location for bubble formation; its low perfusion means that the washout of inert gas during decompression is slow, and because of its high lipid content it is believed to have a high solubility for inert gas, although this is debated (32). Francis et al. observed autochthonous (in-situ) bubbles histologically in spinal cord white matter of dogs with signs of DCS (33). Based on scanning electron micrographs the authors postulated that the autochthonous gas bubbles they observed in white matter were extravascular (34). In a later histological study on pigs, Palmer suggested that damage to the spinal cord is caused by stationary intravascular bubbles (35). Variations in the latency of symptoms (29) and response to recompression (36) indicate that there is more than one mechanism behind decompression induced spinal cord injury, and at least 3 possible mechanisms are suggested in the literature: bubbles causing mechanical damage to nerve cell axons, bubbles causing mechanical damage to the local microvasculature and inflammatory responses induced by the bubble surface (37;38).

The generous perfusion of the brain makes it less vulnerable to local bubble formation, but more exposed to embolic bubbles. Autochthonous bubbles have been observed in the cerebrum and cerebellum in animal experiments, but only after extreme exposures with high mortality (31). Most studies focus on arterial gas emboli as the main cause in cerebral decompression sickness, and patent foramen ovale (PFO) has been shown to play a role in the occurrence of cerebral DCS (39). Studies using magnetic resonance imaging of the brain confirm gas embolism as a cause of damage (40;41). Histologically, post decompression brain lesions have been described as foci of ischemia (42), as is the case in cerebral insults from other embolic sources.

Musculoskeletal manifestations – the bends

Musculoskeletal manifestations of DCS are most commonly characterised by limb pain, usually in or in close proximity to synovial joints. Most hypotheses on the pathophysiology of musculoskeletal DCS focus on autochthonous bubbles (1). The exact location of these bubbles and the mechanisms causing pain remain debated, but low perfusion tissues such as tendons and cartilage are believed to be prone to bubble formation. The fact that the proportion of musculoskeletal DCS is particularly high in saturation diving and hypobaric exposures supports bubble formation in "slow" tissues, and studies show a significant number of cases in the absence of detectable vascular bubbles (43). Prompt relief of symptoms with early recompression also supports the participation of autochthonous bubbles in the pathogenesis (20).

Cutaneous and lymphatic manifestations

Cutaneous DCS is also often attributed to tissue bubbles. Francis and Mitchell state that cutaneous manifestations "[…] almost certainly arise as a result of autochthonous bubble formation" (25). However, in a histopatohologic study of cutaneous lesions in swine after decompression Buttolph et al. found vascular congestion, focal vasculitis and perivascular inflammatory changes compatible with reactions to intravascular bubbles (44). Wilmshurst et al. (45) have shown a correlation between right-to-left shunts and cutaneous DCS and suggest paradoxical gas embolism as a possible cause in shallow, non-provocative dives. Cutis marmorata, which is one of several cutaneous manifestations of DCS, is often considered a harbinger of more serious DCS involving the central nervous system and the lung (46;47).

Tissue swelling after decompression is attributed to lymphoedema by gas bubbles obstructing the lymphatic vessels (24). It is a rare condition, seen in less than 1% of DCS cases (25). It usually involves the trunk, but occasionally also the head and neck (27). Treatment with recompression normally gives prompt relief.

Cardiopulmonary manifestations – chokes

Cardiopulmonary DCS is rare, but represents one of the potentially lethal forms of DCS. “Chokes” generally occur after very provocative exposures and is believed to be caused by severe accumulation of gas bubbles in the pulmonary capillaries (48). Clinically it is characterised by the triad of substernal pain, cough, and dyspnea, and the first symptoms usually occur shortly after decompression. If left untreated, severe cases progress with cyanosis, respiratory acidosis, pulmonary hypertension and reduced cardiac output and eventually cardiac arrest and death (25).

It is now well documented that decompression can induce production of substantial amounts of venous gas bubbles without accompanying symptoms of decompression sickness, these are called “silent bubbles” (49). Whether these bubbles are actually benign is debated, and the lungs are of special concern with respect to possible subclinical damage, as circulating venous gas bubbles will eventually end up in the pulmonary capillaries. Nossum et al. demonstrated that small numbers of vascular gas bubbles induced endothelial dysfunction in the pulmonary artery and signs of inflammation in lung tissue of rabbits (16).

A significant reduction in pulmonary diffusion capacity has been reported in divers after clinically uneventful air dives (50) and saturation dives (51), and the authors suggest that this is, at least partly, caused by venous bubbles. The concept of silent bubbles has been subject to criticism (52) and Eckenhoff suggested that not only absence of DCS, but also limitation of vascular bubbles should be considered in evaluation of decompression procedures (53).

Other manifestations

Constitutional manifestations like headache, fatigue, flu-like symptoms and diffuse muscular pain are quite common, and are found in approximately 30% of the DCS cases in the UK Institute of Naval Medicine database (25). These manifestations are generally believed to arise from inflammatory responses to gas bubbles (1). They usually regress spontaneously.

Audiovestibular manifestations include vertigo, nausea, vomiting, tinnitus, nystagmus and impaired hearing. The symptomatology is often dramatic and debilitating, and inner ear DCS is categorised as Type II (serious). Audiovestibular manifestations are quite common, data

from Divers Alert Network (DAN) indicate that they constitute approximately 13 % of DCS cases (25). Inner ear DCS is believed to be caused either by intravascular gas bubbles in the labyrinthine vessels, or extravascular gas bubbles in the endo- or perilymph (54).

MECHANISMS OF VASCULAR BUBBLE FORMATION

Bubble formation is a ubiquitous phenomenon, still our understanding of the mechanisms behind is not complete. This is particularly true for endogenous bubble formation in decompression. De novo formation of endogenous gas bubbles requires a level of supersaturation that exceeds by far what is found in the body after a dive (55). Still, it has been shown that 50% of humans can be expected to produce endogenous gas bubbles after decompression from a steady-state pressure exposure of only 3.5 meters of seawater (msw) (56). It is therefore generally assumed that decompression bubbles grow from precursors, so-called bubble nuclei (57). It has been suggested that the gas nuclei are stabilised within hydrophobic crevices in the endothelium (58), or by a coating of surface-active molecules like surfactants (59). With stable bubble nuclei in place, their contents and size will change according to the difference between the tension of dissolved gas and the bubble gas pressure at the gas-liquid interface. The process is believed to be similar to what can be observed on the inside of a beer glass, where CO_2 from the beer diffuses into a preformed bubble attached to the glass surface, and a continuous stream of bubbles is released.

We have suggested that caveolae, lipid-rich invaginations in the vascular wall, may be favourable areas for formation and stable attachment of bubble nuclei (17). Caveolae are also important in the regulation of nitric oxide (NO) production in the endothelial cells (60). It has been shown that exogenous NO given before a dive reduces post-dive bubble formation (61) and that NO blockade increases bubble formation (62). One of many important properties of NO is to reduce the adhesiveness of cellular particles to the endothelium (63). We have postulated NO can also reduce the adhesion of bubble nuclei, and thus decrease the number of nuclei available for bubble production (17). NO may therefore be a key regulator in bubble production, and differences in NO production may explain the large inter- and intraindividual differences observed in bubble production after identical dives.

ULTRASOUND AND INTRAVASCULAR GAS BUBBLES; THEORETICAL CONSIDERATIONS

Most ultrasonic methods for medical diagnostic purposes are based on transmitting high frequency sound waves from a piezoelectric crystal (the transducer) into the body and receiving and interpreting the echoes. Tissues are heterogeneous with respect to acoustic properties, and at each interface between these heterogeneities a fraction of the ultrasound signal is reflected. For a plane wave hitting a plane interface at right angle the fraction of reflected to incident energy is given by

$$R = \frac{E_r}{E_i} = \left(\frac{Z_2 - Z_1}{Z_2 + Z_1} \right)^2 = \left(\frac{\rho_2 c_2 - \rho_1 c_1}{\rho_2 c_2 + \rho_1 c_1} \right)^2 \quad (1)$$

where Z1 and Z2 are the acoustic impedance on each side of the interface, defined as the product of density (ρ) and sound velocity (c) in the medium. Large differences in acoustic impedance yield high energy reflections from the interface. The reflections from the heterogeneities in tissues are picked up by a piezoelectric crystal and converted into electric signals. The main differences between various ultrasound modalities lie in the way these signals are processed and displayed.

Typical sound frequencies in ultrasonic diagnostic equipment range from 1 to 10 MHz and the choice of frequency depends on requirements for penetration and resolution. Increasing the frequency improves resolution but lowers penetration. Low frequencies, typically 2-4 MHz, are used for monitoring the heart and other deep structures, while higher frequencies are used for small, superficial structures like peripheral vessels or for endoscopic ultrasound where the distance to the target organ is small.

Sound velocity in air is approximately 340 m/s and the density of air at room temperature and normobaric pressure is around 1.2 kg/m^3. The corresponding values for blood and tissues are approximately 1500 m/s and 1000 kg/m^3, respectively. This means that the reflection coefficient for a gas bubble in blood or tissue is approximately 99.9%. In practice, most of the sound energy hitting the gas bubble is scattered and only a small proportion is reflected and picked up by the receiving transducer. Still, the reflected energy from a bubble in blood is much stronger than from the surrounding areas, so the bubble can be identified.

For bubbles above resonance size (0.6µm at 5 MHz (64)) there is a theoretical linear relationship between the amplitude of the reflected ultrasound and the bubble radius (65;66). It is therefore theoretically possible to determine the size of detected bubbles based on the amplitude of the echo. From measurements on calibrated bubbles in a hydromechanical cardiovascular model we have previously found that it is difficult in practice to estimate absolute bubble sizes, but possible to compare mean size in populations of bubbles, e.g. venous and arterial bubbles (67). This was demonstrated in practice by Vik et al. who observed that echoes from infused bubbles in the right ventricle had higher intensity than echoes from arterial bubbles in the same pigs, indicating that bubbles entering the arterial circulation through the lung are smaller (68).

Even though gas bubbles are strong reflectors of ultrasound, there is a limit to the size of detectable bubbles. The fact that intravascular bubbles are not detected does therefore not mean that there are no bubbles present. The detection sensitivity depends on many factors: The mode of ultrasound being used, the ultrasound frequency, geometrical properties of the transducer, positioning of the transducer and anatomical properties of the subject being monitored. Based on in vitro experiments Hills and Grulke (69) predicted a minimum detectable bubble diameter for single bubbles in the heart or large arteries of 20-25 µm. Lubbers and van den Berg estimated a minimum detection size of 30 µm (66). In comparison, Van Liew et al. from theoretical considerations predicted a minimum size of decompression bubbles of 5-10 µm (70), and Hills and Butler found bubble diameters of 19-700 µm when investigating decompression-induced vascular bubbles in living dogs (71). Christman et al. detected decompression bubbles in dogs with an ultrasound system based on second harmonic resonance and found a high prevalence of 4 µm microbubbles in the femoral veins (72).

The real-time and non-invasive nature of ultrasonic diagnostic systems and the acoustic properties of gas bubbles in blood make such systems well suited for detection of intravascular gas bubbles. However, the relationship between detectable gas bubbles and decompression stress is ambiguous, so data should be interpreted with some caution, as will be discussed later.

DOPPLER SYSTEMS IN DETECTION OF MICROBUBBLES

The Doppler ultrasonic flow meter is the simplest application of ultrasound for bubble detection. Reflected ultrasound waves are shifted in frequency proportionally to the velocity of a moving reflector. This change in frequency is called the Doppler shift, and is given by

$$\Delta f = \frac{2 f v \cos\theta}{c} \tag{2}$$

where f is the frequency of the transmitted signal, v is the velocity of the reflector, θ is the angle between the transmitted signal and the direction of the moving reflector and c is the sound velocity. The Doppler shift typically falls in the audible range 0-10kHz and is simply used as audible output. So the output Doppler signal is a sound with frequency proportional to the velocity of the reflectors and amplitude according to their acoustic properties. Reflections from stationary structures (tissue) will not have a Doppler shift and will thus not be heard in the output signal. Any gas bubbles moving with the blood flow will give very strong reflections that can be distinguished from the low amplitude flow signal from blood cells.

Doppler ultrasound systems can be either continuous wave (CW) or pulsed wave (PW). In a CW system there are two transducers; one continuously transmitting ultrasound waves and one continuously receiving reflections. A PW Doppler system comprises a single transducer which emits short bursts of ultrasound and then “listens” for echoes. As the sound velocity in the tissue is known, one can define the depth from which to receive echoes by adjusting the time delay from transmission to reception and the duration of reception. Thus, PW Doppler systems have depth resolution which can improve the signal to noise ratio. However, if the sample volume is not optimally adjusted, part of the blood flow signal will be lost. CW systems are technically simpler and cheaper than PW systems, and also easier to use. They are therefore the most commonly used for detection of intravascular gas bubbles.

Most ultrasonic scanners used for 2-dimensional imaging also have both CW and PW Doppler functions for blood flow measurements. This enables the operator to easily find an optimal position for the Doppler signal and to avoid fast moving structures like valve cusps. Ultrasound scanners are, however, expensive and complex pieces of equipment and their use has so far been limited to laboratory experiments.

Simple CW Doppler systems are available that are dedicated for decompression applications with transducers designed for precordial monitoring of blood flow in the pulmonary artery or the right ventricle of the heart. These are the most commonly used locations for detection of intravascular gas bubbles as this is where venous blood from all parts of the body is gathered and pumped through the lungs. Peripheral veins can also be monitored; the subclavian veins are often used.

Quantification of gas bubbles in Doppler signals

The most common method for identification of bubbles in Doppler signals is by listening and estimating the number of bubble signals according to some classification scheme. The most widely used classification schemes are the Spencer code (73) and the Kisman-Masurel code (74).

The Spencer code was the first standard for classifying bubbles. It is based on precordial measurements with the monitored diver at rest, sitting or lying in the supine position. It contains five categories from 0 to IV defined by the number of cardiac cycles containing bubbles and the number of bubble signals per cardiac cycle (Table 1).

Table 1. Definition of the Spencer code.

Grade	Description
0	A complete lack of bubble signals
I	An occasional bubble signal discernible with the cardiac motion signal with the great majority of cardiac periods free of bubbles
II	Many, but less than half, of the cardiac periods contain bubble signals, singly or in groups
III	Most of the cardiac periods contain showers of single-bubble signals, but not dominating or overriding the cardiac motion signals
IV	The maximum detectable bubble signal sounding continuously throughout systole and diastole of every cardiac period, and overriding the amplitude of the normal cardiac signals

The Kisman-Masurel (KM) code is based on a systematic step-by step approach where three separate components are used for classifying the Doppler signals:

-The number of bubbles per cardiac cycle

-The percentage of cardiac cycle containing bubble signals at rest or the number of cardiac cycles with increased bubble signals after a specified movement

-The amplitude of the bubble signals as compared to the background flow signal.

Each of the three components is classified on a scale from 0 to 4 (Table 2) and this three-numbered KM code is converted to a single bubble grade 0-IV with subdivisions of + and – giving a total of 12 different values, the KM grade.

Table 2. Definition of the three components in the Kisman-Masurel code

Code	**Frequency**	**Percentage/duration**		**Amplitude**
	Bubbles per cardiac cycle	Percentage, cardiac cycles at rest	Movement, duration cardiac cycles	
0	0	0	0	No bubbles discernible
1	1-2	1-10	1-2	Barely perceptible, $A(b)^1 << A(c)^2$
2	several, 3-8	10-50	3-5	Moderate amplitude, $A(b) < A(c)$
3	Rolling drumbeat ≥ 9	50-99	6-10	Loud, $A(b) \approx A(c)$
4	Continuous sound	100	>10	Maximal, $A(b) > A(c)$

[1]A(b)- amplitude of bubble sound, [2]A(c) - amplitude of cardiac sound

For compatibility, Kisman and Masurel designed their code to match as closely as possible to the established Spencer code. If + and - are discarded in the KM grade, the two systems are essentially identical when monitoring a diver at rest, as shown in Table 3. However, the KM code includes the movement condition, which makes it more sensitive than the Spencer code, as movement has been shown to release showers of bubbles in divers who have few or no detectable bubbles at rest. Both grading systems were originally designed for precordial

measurements where the frequency of bubble signals can be related to heart cycles. The KM code is also used for peripheral vessels, usually the subclavian veins. The KM code has become the standard among many researchers (43).

Table 3. Conversion between Spencer code and KM code/KM grade

Spencer code	KM code/grade
0	0
I	111/I-, 112/I, 113/I, 211/I-, 212/I, 213/I+
II	121/I+, 122/II, 123/II, 221/II-, 222/II, 223/II+
III	232/III-, 233/III, 242/III, 243/III, 332/III, 333/III, 342/III+, 343/III+
IV	444/IV

Comparison of bubble detection results from different decompression studies not only requires standardised classification codes, but also standardised procedures for monitoring and standardised analysis and reporting of the results. A standard procedure for monitoring divers after subsaturation dives has been implemented and extensively used by Canadian researchers (18). Initially, the pulmonary artery is monitored (alternatively the right ventricular outflow tract) with the diver at rest, then after a deep knee-bend. Subsequently, both subclavian veins are investigated at rest and after clenching of the ipsilateral fist. All monitoring is performed with the diver standing and scoring is done according to the KM code. It is suggested that monitoring after sub-saturation dives is conducted within 20 minutes of reaching surface pressure and repeated at 30 to 40 minute intervals, depending on the number of subjects monitored, for at least 2 hours. For saturation dives, monitoring should be conducted several times a day during decompression and for several hours after surfacing. There is evidence that the femoral veins should be monitored rather than the subclavian veins for saturation diving; this will be discussed later.

In our experience 2 hours of monitoring is sufficient to cover peak bubble scores in most cases of sub-saturation dives. However, we have in some cases observed low-grade bubbles for several hours after surfacing (unpublished observations). In testing air tables for caisson work, Flook frequently observed time to maximum bubble grade of more than 2 hours (75), thus monitoring should proceed until the peak has clearly been covered. We have also observed transient peaks in bubble numbers that could easily be missed with 40 minute intervals between investigations. This would lead to an underestimation of maximum bubble grade and thus an overestimation of the safety of the tested procedure. We therefore suggest

that the number of subjects is limited so that monitoring can be performed at 20 minute intervals, at least for the first hour after surfacing.

Analysis of Doppler data

Analysis and presentation of Doppler data is not a straightforward task. The grading systems yield ranked, but highly non-linear, categorical data. Consequently, common parametric procedures like calculating mean values, standard deviations and time integrals are not appropriate. Non-parametric procedures like Mann-Whitney U test, Wilcoxon rank sum and Wilcoxon signed rank test can be used.

Kisman et al proposed an "index of severity" by attempting to linearise KM bubble grades into actual bubble numbers and integrating over a period of time (76). This was later renamed by Jankowski et al (77) to the Kisman Integrated Severity Score (KISS) and is defined by

$$KISS = \frac{100}{4^{\alpha}\left(t_4 - t_1\right)} \sum_{i=1}^{3} \frac{\left(t_{i+1} - t_i\right)\left(d_{i+1}^{\alpha} + d_i^{\alpha}\right)}{2} \qquad (3)$$

where t is the time of observation in minutes after reaching the surface, d is the precordial Doppler grade 0 to IV observed at time t and α is a constant that accounts for the nonlinearity of the bubble grading system, Kisman chose $\alpha = 3$. Several studies have used the KISS conversion (77-81), but the method has to our knowledge never been formally validated. KISS data are numerical, but have their origin in the non-parametric KM-code, so non-parametric tests should be preferred (81).

The single observed peak bubble grade is a commonly used parameter for presentation of Doppler data. It has some limitations in that it does not necessarily reflect the total amount of gas bubbles present after the dive. However, because of the exponential non-linearity of the grading systems, the contribution of lower bubble grades will be very small compared to the higher grades, and due to the intermittent bubble detection the duration of the peak value is usually unknown. The peak value may therefore be a reasonable approximation to the total number of bubbles produced. This is supported by the findings of Jankowski et al. (81) who compared KISS-data to linearised "snapshot" bubble grades. Also, it is not known whether the total number of gas bubbles, as represented by an integral, or the highest instantaneous production of bubbles is the better measure for decompression stress. High peaks of short duration may be more critical with respect to decompression sickness than lower levels of

bubbling over longer periods of time; Nossum et al. found that endothelial damage caused by intravascular gas bubbles was related to maximum number of bubbles rather than duration of bubble exposure (15).

Sawatzky found that the maximum bubble grade irrespective of movement/rest and location (precordial/subclavian) was the best indicator of DCS (82). He explained this by the greater ease with which bubbles can be detected in the subclavian veins compared to the precordium. Also, as previously mentioned, movement is known to mobilise stationary bubbles sticking to the inside of the vessel walls, increasing the sensitivity of the detection.

The time course of observable bubbles may also be of importance; Daniels et al. suggested an inverse relationship between time to bubble peak and the severity of the decompression profile and thus risk of decompression sickness (83). This is in accordance with our observations for sub saturation dives (unpublished observations). Conkin and co-workers also found an increased risk of DCS with early occurrence of bubbles after decompression in hypobaric exposures (84).

The human factor in bubble scoring

Regardless of which classification code is used, scoring of Doppler data is a time-consuming and labour-intensive task and requires highly trained observers. Also, even though adequately trained, both Spencer and KM codes require a significant degree of subjective interpretation on the part of the rater.

Sawatzky and Nishi proposed the use of weighted kappa statistics for assessing inter-rater agreement for bubble scores to ensure comparability between different observers (85). This gives a measure of the agreement between two observers and is completely corrected for chance agreements. The authors defined a lower acceptable level of agreement and found that it typically takes over a year to train technicians to a standard where their scoring agrees satisfactorily with the scoring of experts.

Automated bubble counting in Doppler signals

An automated system for detection and quantification of bubbles in Doppler signals would, at least in theory, overcome the flaws of manual scoring; it would give an objective, linear

measure of detected bubbles. Several attempts have been made to design systems for automatic bubble counting, most of them are based on differences in reflected energy between post decompression Doppler signals and bubble-free pre dive signals (43) in the time domain and/or in frequency spectra.

Chappell et al. showed that non-stationary signal analysis techniques are required for automated analysis of Doppler signals, and proposed a bubble detection algorithm based on Empirical Mode Decomposition (86). They also suggest the use of wavelets, which can be regarded as a bank of band-pass filters, as an alternative approach (87). A similar method was suggested by Belcher et al. who combined comb filters with enveloping and thresholding by an adaptive (self adjusting) algorithm (88). Guillerm et al. (89) and Monjaret et al. (90) used comb filters to extract information in specific frequency bands, subtracted background levels and calculated the time integral of the resulting signals. Kisman (91) used fast Fourier transform (FFT) for spectral analysis of Doppler signals to improve signal/noise ratio and perform real-time bubble detection. FFT spectral analysis was also used by Gibby et al. in an automated system for detecting venous air emboli during surgery (92;93). Other approaches include use of artificial intelligence (94), neural networks (95;96), burst detection algorithms (97) and time-frequency methods (98).

Common for most automatic detection systems is the ability to identify bubbles with some degree of accuracy in good quality Doppler signals, such as from animal experiments where the ultrasonic probe can be implanted close to a vessel. Measurements in peripheral vessels of humans also give a high signal to noise ratio and it has been shown that emboli can be detected automatically with a high level of accuracy in Doppler recordings from the subclavian veins (99) and the carotid artery (100).

Despite rapidly increasing capacity in digital signal processing, a verified, reliable automated system for detection of bubbles in the central venous circulation of humans is not available. Two fundamental problems are the sensitivity of the quality of precordial Doppler signals to small alterations in position or angle of the ultrasonic probe, and reflections from moving tissue which are similar both in amplitude and frequency to that of gas bubbles. Another problem is the difficulty in validating bubble counting systems against bubble grade information (101). The human ear is still considered the most precise instrument for identification and classification of gas bubbles in Doppler signals and manual scoring performed by an expert remains the most commonly used method.

ULTRASONIC IMAGING IN DETECTION OF MICROBUBBLES

In ultrasound imaging, a transducer emits a short pulse of ultrasound and then “listens” for echoes from reflectors, similar to the pulsed wave Doppler systems. But in contrast to the Doppler technique, the frequency of the echo is not considered. The distance from the transducer to the reflector is determined by the delay from transmission to reception of the echo and the intensity of the echo determines the brightness with which the reflector is displayed in the image.

2-dimensional (2D) ultrasonic scanning (B-mode imaging, brightness mode) is the most common mode for clinical applications. It is also the most widely used imaging technique for detection of decompression bubbles. In this mode the ultrasound beam is swept, either by mechanical movement of the transducer or by serial excitation of an array of transducers, and the 1-dimensional arrays of echoes for each transmitted pulse are put together to form a 2-dimensional image.

In M-mode imaging (motion mode) each sound pulse is sent in the same direction and only a single line-of-sight is displayed, but for each new pulse the previous line on the display is scrolled to the left. This gives a 1-dimensional image with distance from the transducer on the vertical axis and time course along the horizontal axis. This mode is commonly used in echocardiography where time resolution is critical due to rapidly moving objects like heart valves. M-mode has been used for detection of decompression-induced vascular gas bubbles (102;103) and Ikeda et al. found that the method had the same sensitivity as Doppler methods, but with less inter-observer variations (104).

As for Doppler systems, the central venous circulation, mainly the right ventricle and pulmonary artery, is the main location for detection of vascular microbubbles with imaging techniques. When imaging the heart precordially (through the thorax from the front) the right ventricle is the compartment closest to the transducer. Due to anatomical differences the optimal position for a good view of the right ventricle varies, but the fourth intercostal space just left of the sternum with the transducer pointing slightly cranially will generally give a good short axis view (Figure 1A). An alternative is a long axis 4 chamber view with the transducer placed under the left costal arch pointing cranially (Figure 1B). Both positions generally give good view of the venous and arterial circulation simultaneously.

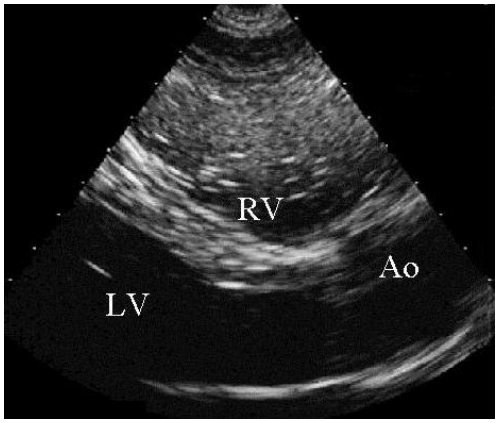

Figure 1A. Short axis view showing venous gas bubbles. One gas bubble can be seen in the left ventricle. RV- right ventricle, LV – left ventricle, Ao – aorta.

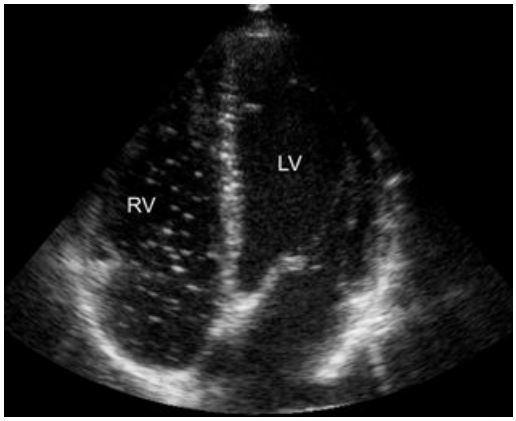

Figure 1B. Long axis view with venous gas bubbles. RV - Right ventricle, LV - left ventricle.

An optimal view of the heart can be obtained by transesophageal echocardiography (TEE) where the transducer is mounted on a gastroscope and inserted into the esophagus. The transducer is very close to the heart, enabling use of higher frequencies than with precordial imaging, so it is easy to obtain a constant view with a high level of detail (Figure 2). This technique is used clinically in examinations requiring particularly high image quality, e.g. diagnosis of patent foramen ovale (PFO), usually in combination with an ultrasound contrast agent. The use of TEE transducers is definitely uncomfortable for the patient and although complications are rare, perforation of the esophagus has been described (105). For decompression research this technique is therefore limited to animal experiments (106;107).

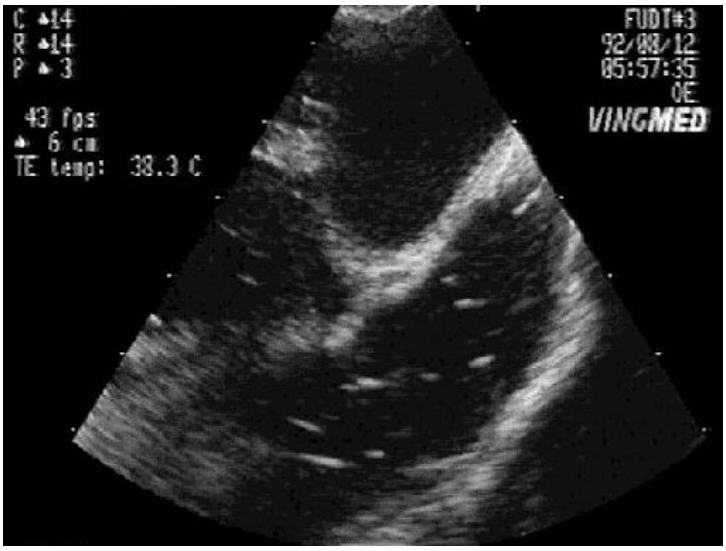

Figure 2. Transesophageal echocardiography from decompression experiment with pig.

Quantification of vascular gas bubbles in ultrasound images

Automatic detection of gas bubbles in ultrasound images is hampered by variations in image quality and the problem of maintaining a constant intravascular window. As for Doppler systems, it can be difficult to discriminate reflections from bubbles in the central circulation from that of surrounding tissues. Quantification of gas bubbles is therefore most easily done semi-quantitatively by use of a grading scheme.

We have suggested a 6-level grading code for quantification of gas bubbles (Table 4) and shown that this code can be used accurately by untrained observers (Paper I), unlike interpretation of Doppler signals. The main challenge in the use of 2D scanning is to obtain an image quality that is sufficient to identify bubble signals. In our experience individual anatomical variations are of importance and image quality seems to be inversely correlated to age and subcutaneous fat (unpublished observations).

Table 4. Grading code for ultrasonic images

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

As with Doppler codes the image grading code yields ranked, ordinal data. The same problems and restrictions with respect to statistical analyses and interpretation of the data therefore apply to the image grading code as for Doppler codes.

Automated bubble counting

We have developed and implemented a computer program that can automatically detect and count gas vascular gas bubbles in 2D images in real time (108;109). The system has been used mainly with TEE imaging in animal decompression experiments, a method that generally gives images with a high signal to noise ratio. The computer program searches a pre-defined intravascular area for high intensity bubble echoes. Pattern recognition algorithms are used for identification of bubble signals, and the system has been verified by simultaneous manual bubble counts. Bubble detection is performed continuously during and after decompression and the number of bubbles is related to the detection area as bubbles/cm^2. With this method it is easy to calculate time integrals to get an estimate of total amount of free gas. Data may be analysed using parametric statistics, either as they are or after log transformation. We have not verified whether such data are generally Normally distributed, and this is an issue that should be looked into before more specific recommendations about statistical analyses can be given.

The ability to count bubbles has enabled us to determine the relationship between image bubble grades and actual number of bubbles present. Table 5 shows a comparison between bubble grades from images, from Doppler signals and from automated counting (110). The results are based upon an approximation from several hundred animal experiments and show that both grading systems are highly non-linear with an exponential relationship to the number of bubbles. The established correspondence can be used for transforming bubble scores into bubble numbers, making direct comparison of results from different procedures easier.

Table 5. Relationship between Doppler bubble grades (KM), image bubble grade (EB) and counted number of bubbles.

KM grade	EB grade	Number of bubbles per cm^2
0	0	0
I-	1	0.01
I	1	0.05
I+	1	0.1
II-	2	0.15
II	2	0.2
II+	2	0.3
III-	3	0.5
III	3	1
III+	4	2
IV-	4	5
IV	5	10

Detection of tissue bubbles

The first use of ultrasound imaging in decompression was done to study bubble formation in the hind legs of guinea pigs (111). The method was further developed by Daniels and colleagues (112;113) and with high resolution ultrasound imaging the technique enabled detection of moving and stationary bubbles as small as 10µm diameter (114). Bubble detection is based on changes in reflected ultrasound intensity with occurrence of bubbles and the system has an electronic integrator for automatic estimation of gas volume (115). The method has been used for both non-saturation and saturation dives (83) and an instrument for human studies has also been made based on the same method (116). A major limitation of the method is the occurrence of artefacts when the subject moves, for example echoes from deformation of structures, which is essentially the same problem that is encountered in all automated ultrasound-based bubble detection systems. The system does not appear to have been developed further.

Combined Doppler/imaging ultrasound instruments

Most ultrasonic scanners now have a built-in Doppler unit for blood flow measurements. Aided by 2D imaging it is possible to position the sample volume of the Doppler to optimise the signal to noise ratio. For PW Doppler the whole sample volume can be placed inside the pulmonary artery and reflections from valves and other moving tissues can be avoided. Also for CW Doppler the image guiding will be helpful in getting a good flow signal. The sample volume can easily be moved to include the arterial flow signal and thus pick up signals from arterial bubbles. The Doppler signals can be graded using a standard code, but it is also possible that the signals obtained are of a quality sufficient to perform automated counting by one of the previously described methods. It has been shown that image assisted Doppler systems are more sensitive than 2D imaging systems for human studies (117), and image guidance for positioning of the sample volume will also increase the specificity compared to “blind” Doppler systems.

Harmonics in bubble detection

In addition to reflecting and scattering ultrasound at the incident frequency (f_0), microbubbles also respond non-linearly and generate higher harmonics (2 f_0, 3 f_0, ...), subharmonics ($f_0/2$, $f_0/3$, ...) and ultraharmonics (3 $f_0/2$, 5 $f_0/2$, ...) (118;119). Harmonics become detectable when the incident frequency approaches the resonance frequency of the bubble, making the bubble oscillate. This resonance frequency is inversely proportional to the bubble diameter, and for a bubble in blood it is approximately 9.5 MHz at 1 µm and 0.3 MHz at 20 µm (120). The non-linear response from tissue and surrounding blood is weaker than from gas bubbles, so detection of harmonics can greatly enhance the ability to pick out bubble signals. Furthermore, because the resonance frequency depends on the size of the bubble, this technique could be used for estimation of bubble size. Second harmonic reflections are extensively used in contrast enhanced ultrasound imaging and many ultrasound scanners now have the option of displaying 2^{nd} harmonics by use of band pass filters.

The flip side of the coin is that the resonance frequencies for relevant bubble sizes is below what is normally used for diagnostic ultrasound. Christman et al. (72) developed a second harmonic resonant bubble detector and were able to detect bubbles of diameter 4 µm in the femoral veins of dogs after decompression using an emitted frequency of 1.6 MHz. As

previously stated, most decompression bubbles are considerably larger than this. Eatock at al. concluded that application of non-linear response for detection of bubbles is limited to bubbles of diameter 20 µm or less (121) and can therefore only detect a fraction of the bubbles present.

Palanchon et al. (122;123) designed and implemented a multifrequency transducer with two independent elements capable of transmitting ultrasound from 100 kHz to 600 kHz. In an in-vitro test of the system they found that 2nd harmonics and subharmonics could be used to accurately classify and size air emboli with diameters ranging from 10 µm to 105 µm. An alternative approach using 2nd harmonics was suggested by Magari et al (124). They combined an imaging frequency of 2.5 MHz with a low-frequency "pump signal" swept from 22 kHz to 220 kHz to make bubbles oscillate at resonance. With this combination of frequencies they were able to detect and estimate the size of vascular gas bubbles in the range from 30 µm to 200 µm in the vena cava of a dog after decompression. Yet another approach was suggested by Didenkulov et al. (125) who looked at the non-linear Doppler effect, i.e. harmonics in the Doppler signal. By using 2 transducers with slightly different frequencies (2.5 MHz fixed and 2.18-2.05 MHz variable frequency) they could excite bubbles with resonance frequencies corresponding to the frequency difference, 70 to 200 KHz, corresponding to bubble diameter 90 to 30 µm. The resulting non-linear Doppler shift was found to be very large compared to that from the linear scattering, both theoretically and experimentally. All these 3 systems elegantly solves the problem of low resonance frequencies for decompression bubbles, but to our knowledge none of them have so far been used in decompression research.

VASCULAR BUBBLES AND DECOMPRESSION SICKNESS

There is no unambiguous relationship between the presence of detectable vascular gas bubbles and the occurrence of DCS. Intravascular gas bubbles have been observed in large quantities in divers with no symptoms and, conversely, there are studies reporting cases of decompression sickness not accompanied by detectable gas bubbles. However, most studies indicate a higher incidence of DCS with increasing number of bubbles.

Studying the relationship between intravascular bubbles and DCS is not straightforward. The difficulties of obtaining reliable ultrasonic data and in the subsequent interpretation have already been discussed. In addition, diagnosing decompression sickness is a complex task. The diagnosis is usually based on symptoms rather than signs and in practice it is difficult to group

outcome categorically in “yes” and “no” with respect to DCS, there will always be subtle cases where the appropriate label is “maybe”.

The diagnostic criteria for decompression sickness will to a certain extent depend on the aim of the diagnosis. In a clinical setting the criteria are used to decide whether recompression treatment should be instituted. In an experimental setting for verification of decompression procedures the criteria should be broader. In a paper on US Navy practice on decompression table validation, Thalmann states (126): “Minor symptoms such as fatigue or transient niggles must be considered as they probably indicate a higher level of decompression stress than completely asymptomatic tables”. The same approach should be used for establishing the correspondence between intravascular gas bubbles and decompression stress. In 1988 a group of diving medical experts from the US Navy and the Canadian Forces established a set of diagnostic criteria for DCS designed to enable comparison of datasets from different studies (22). These criteria are comprehensive and include cases not requiring recompression treatment.

The correspondence between intravascular gas bubbles and DCS has been investigated in a number of studies. Although most studies have used Doppler ultrasound and Spencer or KM codes for bubble grading, a comparison of the different studies is difficult. There are differences in physical properties of the Doppler equipment, different monitoring procedures are used with respect to location and timing and different diagnostic criteria are used for DCS. The experience of the personnel doing the monitoring and bubble grading is critical, but this is rarely described in the studies. The studies indicate that the bubble/DCS relationship depends on the type of exposure, e.g. bounce dive versus saturation dives, but also for similar exposures there is considerable variation between the studies.

In an extensive review of 19,000 cases of limb pain DCS, Sowden et al. (127) found a predominance of upper limb involvement in bounce divers and aviators and lower limb involvement in saturation divers and compressed air workers. Based on Sawatzky’s conclusion that the parts of the body with signs and symptoms of DCS generally have large numbers of Doppler-detected bubbles (82) it therefore seems appropriate that procedures for bubble detection in peripheral veins take into account the type of exposure.

Subsaturation dives

The most extensive study on bubble/DCS correspondence in bounce dives was presented by Sawatzky in his master thesis (82), where he systematically analyzed maximum Doppler scores and DCS incidence in 1,726 nitrox (nitrogen and oxygen) dives and 1,508 Heliox (helium and oxygen) dives. The data were obtained from chamber decompression trials at Defence and Civil Institute of Environmental Medicine (DCIEM) in Toronto, Canada. The uniqueness of these data lie both in their quality and quantity: It is the most comprehensive collection of data published, the data are collected according to the recommended standards for Doppler monitoring (18) and the Doppler grading is performed by verified competent personnel. DCS diagnoses were made according to the previously mentioned criteria (22). The most important of Sawatzky's data are reproduced in table 6.

Table 6. DCIEM data on Doppler detected bubbles and DCS incidence in bounce dives. "Overall maximum grade" is the highest obtained score regardless of position (precordial or subclavian veins) or rest/movement.

Condition	KM Grade	Air dives			Heliox dives		
		Exposures	DCS	% DCS	Exposures	DCS	%DCS
Chest, rest	0	1264	7	0.6	945	6	0.6
	I	131	0	0.0	105	2	1.9
	II	137	8	5.8	184	1	0.5
	III	191	25	13.1	272	22	8.1
	IV	3	1	33.3	2	1	50.0
Chest, movement	0	1164	3	0.3	879	7	0.8
	I	109	2	1.8	70	0	0.0
	II	111	3	2.7	114	1	0.9
	III	305	26	8.5	313	11	3.5
	IV	37	5	13.5	132	13	9.8
Overall maximum grade	0	819	0	0.0	623	1	0.2
	I	287	3	1.0	214	1	0.5
	II	183	2	1.1	187	0	0.0
	III	365	27	7.4	347	15	4.3
	IV	72	9	12.5	137	15	10.9

Sawatzky concluded that the risk of developing DCS increases with increasing Doppler grades and the best indicator of that risk is the single highest Doppler grade regardless of location. He explained this with the greater ease with which bubbles can be detected in the subclavian veins where the signal to noise ratio is higher compared to precordial measurements, indirectly stating that precordial Doppler detection of bubbles is inaccurate, even when performed by experts. This is supported by the findings of Eckenhoff et al., who found an increased sensitivity with subclavian monitoring as compared to precordial (56).

Other studies support Sawatzky's conclusions. One of the first studies on bubbles and DCS was done by Spencer and Johanson (73) who reported from 174 bounce dives including both chamber and open-water dives. Scoring was done with the Spencer code (precordial at rest) and the results showed an increased risk of DCS with increasing bubble grades, from 1% for grade 0 to 80% for grade IV. Vann et al. studied the bubble/DCS correspondence in 286 nitrox bounce dives using Spencer's bubble grading scale (128). They found that precordial grades 0 to II was associated with 3% or less probability of DCS, grade III 9% to 18% probability and grade IV 20% to 50% probability. Neuman et al. also found a statistically significant relationship between Doppler score and DCS in two series of bounce dives (129).

We have studied gas bubbles detected by echocardiography and what we have called "adverse effects of decompression" (AED) in 203 air bounce dives (paper 4). AED is defined as all signs and symptoms which may arise from the decompression, including, but not limited to, decompression sickness. A combined logistic regression analysis showed no difference between our data and Sawatzky's data.

There are studies where the authors find no correspondence between detected bubbles and DCS. In a series of 150 deep (100-200 msw) chamber bounce dives Powell et al. found that gas bubbles detected by Doppler at the surface following decompression had little prognostic value for joint pain ("the bends") (130). The authors did not report any cases of DCS with other symptomatology. Bubble detection was done precordially at rest and scoring performed according to the Spencer scale. Bayne et al. conducted a double-blind, prospective trial of Doppler bubble detection in 83 chamber exposures to 285 feet of sea water with standard US Navy decompression (131). 8 divers suffered from DCS, 3 of these had no detectable bubbles. Again, Doppler detection was done precordially at rest according to the Spencer scale. A statistical analysis of the data indicated a 25 to 50% probability that the clinical DCS diagnosis and detection of bubbles were independent events.

As DCS is caused by bubbles primarily containing inert gases (132), the composition of the breathing gas should intuitively have no influence on the relationship between bubbles and DCS. Still, in 2 series of bounce dives with different partial pressure of oxygen in the breathing gas during decompression Powell and Johansen found a tendency towards more symptoms of DCS with lower bubble grades in the low oxygen group (133). They postulated that higher arterial oxygen tensions increased the tolerance to venous gas bubbles. However, their observations were limited to 32 exposures and the differences were not statistically significant. Sawatzky found no difference between the air and heliox dives in the relationship of Doppler grades with DCS risk when the single highest Doppler grade was used. In an in-vitro study of bubble-induced platelet aggregation Thorsen et al. found no difference between bubbles containing different inert gases with and without oxygen (134).

Compressed air work

Almost all exposures to maximum pressure in compressed air work are longer than almost all exposures to maximum pressure in air diving (135). Flook predicted that after 7.5 hours at bottom pressure breathing air, brain and muscle is fully loaded with nitrogen while fat contains 94% of the full load (136). Compressed air work, with shifts frequently as long as 6 to 8 hours (137), is therefore in practice close to shallow air saturation diving with respect to decompression physiology.

The reported incidence of decompression related problems in compressed air work is considerably lower than the true incidence. Workers hesitate to report their symptoms because frequent treatment may risk them their job in the tunnel. Using an anonymous reporting system Kindwall found a DCS incidence of up to 26% for some shifts without any workers reporting for treatment (137). Experience over many years have shown that all air decompression schedules for compressed air work are inadequate in preventing DCS and dysbaric osteonecronis (138). Oxygen tables have been shown to be much safer with respect to decompression injury, but there has been resistance in the industry to adopt oxygen decompression due to the potential fire hazard (137).

In a field study of 37 compressed air workers doing a total of 95 exposures we found 29 cases of precordial bubble grade 3 and 24 cases of grade 2 bubbles using ultrasound imaging (136). 18 exposures were not accompanied by detectable bubbles precordially or in peripheral veins (subclavian and popliteal veins). Working pressure was 0.95 bar (gage) and decompression was performed on air no stop (5 minutes) or according to the Blackpool tables. There were no

reports of DCS, which is peculiar considering the amount of vascular bubbles observed. It should be noted that there was no anonymous symptom reporting system.

Gotoh and Nashimoto detected bubbles after 152 exposures in 91 caisson workers. Doppler measurements were performed precordially within 60 minutes of decompression at rest and after movement of upper extremities (139), and scoring was done according to the Spencer scale. They found gas bubbles in all cases of DCS requiring recompression treatment (13 bends and 3 chokes) and in 24 cases of mild DCS not requiring treatment. Nine cases of mild DCS were not accompanied by detectable bubbles, this gave a DCS incidence as high as 14% for bubble grade 0. There were 48 symptom-free exposures accompanied by detectable bubbles.

In a study of direct ascent from 34 shallow air saturation exposures Eckenhoff et al. (140) concluded that only the duration of detectable bubbles, and not the bubble grade, correlated with symptoms of DCS. Bubbles were detected precordially at rest and after deep knee-bends and scored according to the KM-code. Detectable bubbles lasted for up to 12 hours after decompression.

In conclusion, there are few studies on DCS and bubbles in compressed air work. There is reason to believe that DCS is considerably more common than what is reported, and field studies show that frequently used tables produce a lot of vascular gas bubbles. Dysbaric osteonecrosis is also of special concern in compressed air work and is probably caused by inadequate decompression tables. With Sowden's findings of symptoms predominantly from the lower limbs in compressed air work (127), bubble detection studies should include the popliteal or femoral veins.

Saturation dives

There are few systematic studies on bubbles and DCS in saturation diving, most studies are case reports from experimental saturation dives with few subjects. A saturation dive is a time and resource demanding undertaking and it is rarely possible to include more than 8-10 divers in each dive. Most cases of DCS appear while the diver is still under pressure (141), so bubble detection should be performed in the chamber during decompression.

In a study of 125 exposures in 29 heliox saturation dives, Gardette found 23 cases of muscle or joint pain (142). Five of these cases were not accompanied by detectable gas bubbles, yielding an incidence of 10% for bubble grade 0. Doppler bubble detection was performed precordially

at rest and after movement and bubbles were graded according to the Spencer scale. The study showed an increasing risk of muscle and joint pain with increasing bubble grade, with a 34% incidence for grade III bubbles after movement. There were no cases of grade IV bubbles and no cases of serious decompression sickness.

Eckenhoff and Vann (143) reported from 77 nitrox saturation man-dives with seven cases of DCS, all pain-only localized to the knees. Doppler detection of bubbles was performed precordially at rest and after movement (3 deep knee-bends). Detectable bubbles were found in 26 of the subjects, but there was no clear connection between the observation of bubbles and symptoms.

In a case report from a 300 msw saturation dive with six divers Ikeda et al. found venous gas bubbles in a diver with transient knee pain at the end of the decompression (103). The other five divers were asymptomatic and had no detectable gas bubbles. Bubble detection was done precordially with M-mode imaging after surfacing.

We have previously monitored decompression from a 450 msw saturation dive using 2D ultrasonic imaging (144). Four divers participated, two divers had pain only DCS (knee pain) accompanied by bubble grades 3 and 4 towards the end of the decompression. The other two divers had no symptoms, one had maximum bubble grade 2, the other had no detectable bubbles.

In upward excursions from 300 to 250 msw during an experimental saturation dive Brubakk et al. (145) found arterial bubbles in the carotid artery of all six divers participating. There were no clinical cases of neurological decompression sickness, but post dive examinations gave indications of a minor cerebral lesion in the diver with the largest amount of carotid bubbles. Hjelle et al. (146) also observed bubbles in the carotid artery of one diver after deep knee-bends at the end of a saturation decompression from 360 msw, this was not accompanied by DCS. Brubakk (52) suggested that prolonged exposure to increased environmental pressure, increased pulmonary artery pressure and hyperoxia can affect the function of the lung as a bubble filter and cause bubbles to go through to the arterial side in decompression from deep dives. It may therefore be important to limit the number of decompression induced gas bubbles in saturation diving regardless of the DCS incidence.

Most studies seem to indicate that there is a correspondence between detectable vascular bubbles and the incidence of DCS in saturation diving, but the number of cases not accompanied by detectable bubbles seems to be higher than for subsaturation diving. Gardette

(142) postulated that the high incidence of pain not accompanied by detectable bubbles could be caused by extravascular bubbles which are not detectable by Doppler, or the bubbles could be too small to be detected. As previously mentioned, there is some evidence that musculoskeletal DCS is caused by autochthonous gas bubbles, supporting Gardette's theory.

Pain only decompression sickness is by far the most common manifestation in saturation diving. In an analysis of US Navy saturation diving data Berghage found that all cases of DCS were pain-only and 96% of the joint pain was confined to the diver's knees. This is in contrast to sub saturation diving where 2 comprehensive studies show that neurologic manifestations are more common (25). With the high proportion of symptoms from the lower extremities, Doppler studies on saturation decompressions should include the femoral veins. Experimental support for this view is given by the studies of Hjelle et al. (146) and Eatock and Nishi (147).

One problem in establishing the bubble/DCS correspondence for saturation diving is the low DCS incidence with the current procedures. In Norwegian offshore saturation diving there have been 4 cases of DCS reported since 1990. In this period the average activity has been approximately 70,000 man-hours in saturation per year (148). DCS therefore appears to be a minor problem in saturation diving, at least in the Norwegian sector. However, as in compressed air work, there is reason to believe that the actual incidence is higher than the reported incidence.

Hypobaric exposures

Hypobaric exposures are in principle similar to decompression from saturation in that the subjects start the decompression from saturation. Rapid decompressions to hypobaric conditions occur in extravehicular activity (EVA) in space where the pressure inside the space suit can be as low as 30 kPa (30% of normobaric) or in aviation by accidental loss of cabin pressure. "Prebreathing" of pure oxygen or oxygen-rich nitrox mixtures is often used to decrease the DCS risk and the subjects usually breathe pure oxygen also during the hypobaric exposure.

An extensive collection of data regarding hypobaric exposures, decompression sickness and venous gas bubbles can be found in the Hypobaric Decompression Sickness Databank (HDSD) (149). In 1992 this databank contained 378 records representing 130,012 hypobaric chamber experiments performed since 1942. A number of studies on hypobaric exposures have been published based on information from HDSD. One study by Conkin et al (150) investigated the

correlation between DCS and bubbles in 1322 exposures, mainly EVA simulations. There were 480 exposures with detectable bubbles and 168 cases of DCS. Bubbles were detected precordially with a Doppler system and graded according to the Spencer code. The authors found that the absence of detectable bubbles was highly correlated with the absence of symptoms, with a negative predictive value (NPV) of 0.98. For grades III and IV they found DCS incidences of 19% and 48%, respectively, and a corresponding positive predictive value (PPV) of 0.39. The authors concluded that vascular gas bubbles is a necessary, but not sufficient, condition for DCS and that information about gas bubbles is useful to assess the risk of DCS in hypobaric decompressions. In a complementary study of data from the same source, the authors found that the PPV is increased if bubbles are detected early in the exposure, if number of bubbles increases rapidly or stays high for a prolonged period during the exposure (84).

Kumar et al investigated 516 cases of bubbles and DCS in EVA simulations at the NASA-Johnson Space Center (151) and concluded that absence of precordially Doppler detectable bubbles was useful in excluding DCS (sensitivity 96%) and that bubble detection was useful in making therapeutic decisions with non-specific symptoms.

It is an interesting fact that although DCS is common in simulated EVA there are no documented cases of DCS during EVA in space (152). Neither simulated weightlessness (153) nor restriction of movement (154) to mimic conditions in space does not influence the DCS incidence in simulated EVA, and the reason for the discrepancy remains unknown.

In another review study of 2044 hypobaric exposures with 819 cases of DCS from the Air Force Research Laboratory DCS Research Database Pilmanis et al. found a considerably higher DCS risk with lower bubble grades (155) (grade 0-19%, I-26%, II-50%, III-52%, IV-62%). The studies contained in the database are all designed to provoke DCS in a substantial portion of subjects, and with an overall incidence of over 40% they have certainly succeeded! Bubble detection in the studies was performed precordially with a combined ultrasonic Doppler/imaging system and grading was performed according to a modified Spencer scale. With these figures the usefulness of Doppler detected bubbles in excluding DCS is more questionable. In a study of various clinical manifestations of DCS in the same database, Balldin et al. found that only 27 out of 49 cases (55%) of central nervous system (CNS) manifestations were accompanied by detectable bubbles (156). They concluded that echo imaging has limited application for use as a predictor of altitude CNS DCS.

The existence of large databases with bubble/DCS occurrence is exceptional for hypobaric exposures. It is peculiar and disquieting that the databases seem to give so unequal answers to the correspondence between gas bubbles and DCS. The reason for the discrepancy is not clear, but the difference in overall incidence of DCS shows that the decompression stress is more severe in the Air Force Research Laboratory DCS Research Database than in the Hypobaric Decompression Sickness Databank (40.1% vs. 12.7%). The question is then why this increased decompression stress is not reflected in a correspondingly higher number of detectable bubbles. A number of smaller studies support the HDSD data in showing a high negative predictive value of no detectable bubbles (157-161), but the high number of exposures in the Air Force Database implies that the findings should not be omitted.

Manifestations of hypobaric DCS is another field of controversy. There seems to be agreement in the literature that musculoskeletal manifestations are most common, but the predominant location of symptoms is disputed. As previously mentioned, Sowden in his review of the diving accident database at the Institute of Naval Medicine (127) found involvement mainly of the upper limbs. Ryles and Pilmanis (162) found 83% musculoskeletal manifestations in the Air Force Research Laboratory DCS Research Database, of which knee pain made up a large majority. Conkin et al. made similar findings in the NASA Hypobaric Decompression Sickness Databank with 85% of DCS manifestations originating from the lower body. Also, previous reviews (20) as well as theoretical similarities with decompression from saturation dives support these observations. If peripheral veins are included in bubble detection during hypobaric exposures, the femoral or popliteal veins should therefore be preferred.

BUBBLE DETECTION AND DECOMPRESSION STRESS; PRACTICAL USE OF BUBBLE DETECTION

The data presented for sub saturation dives in the previous chapter strongly indicate a correspondence between detectable venous gas bubbles and the risk of decompression sickness. With a total of 3,234 exposures Sawatzky’s data presented in Table 6 are qualitatively and quantitatively the most extensive data set available. There is only one case of DCS not accompanied by detectable bubbles. The negative predictive value is 0.999 and the sensitivity of detectable bubbles as a test for DCS is 0.99. On the other hand there are 1720 exposures where bubbles were detected without any symptoms of DCS, and the positive predictive value is only 0.04, so detectable bubbles only yields a 4% chance of having DCS. Even when using bubble grades III and IV as test criterion, the positive predictive value is as low as 0.07. The

data therefore strongly suggest that the absence of detectable bubbles is a good indicator of decompression safety, but the occurrence of bubbles, even high grades, is a poor predictor of decompression sickness.

In a clinical setting bubble detection could theoretically be used as a tool for excluding the DCS diagnosis. In practice, however, this would call for surveillance by highly trained personnel at 20-30 minute intervals for at least 2 hours after surfacing, which is clearly not an option. A more feasible area of application for bubble detection is in assessing the safety of decompression procedures. In a UHMS workshop in 1989 it was concluded that new procedures should be validated primarily by extensive, dedicated laboratory testing before being put into the field for operational evaluation (163). Traditionally the criterion of success for such testing has been the observed incidence of DCS compared to a certain pre-defined maximum level. The main problem with evaluating decompression procedures this way is the large number of dives required to determine DCS risk with any degree of certainty: From the binomial distribution we find that more than 300 exposures with no incidents are needed to confirm a DCS incidence below 1% with a 95% confidence interval. For recreational diving the incidence should be considerably lower than this, so the expenses and time required for validation can actually prevent new procedures from being implemented. Also, this method for validation of procedures will inevitably lead to decompression injury among the test subjects. Furthermore, the DCS diagnosis is based on symptoms and is therefore subjective. Divers may choose not to report symptoms, or may report symptoms due to apprehension or from other causes not related to the decompression (43). Occurrence of vascular bubbles is more objective and cannot be hidden by the diver.

At Defence Research and Development Canada (DRDC, formerly DCIEM) bubble detection has been used for table validation for many years (164). An empirically selected limit of KM grade II or greater in 50% of the subjects has been used to discriminate between stressful and acceptable procedures. We have previously suggested that by designing decompression procedures so that less than 50% of the subjects have bubbles scores of III and IV, the DCS risk should be less than 5%. Such simple criteria will reduce the number of dives required for validation compared with observation of DCS alone, but they do not make full use of the information obtained by bubble detection.

In a study of venous gas bubbles in chamber attendants for hyperbaric oxygen therapy we found a considerable number of bubbles both in a standard protocol and in 2 revised protocols with increased levels of oxygen in the breathing gas (Paper III). A practical approach was taken with a requirement of no grade III bubbles for a procedure to be acceptable for operational use.

This limitation was exceeded in all 3 tested protocols, and the study resulted in The Haukeland University Hospital discontinuing all elective HBO treatment in multiplace chambers to eliminate the risk of inflicting DCS to chamber attendants.

It was obvious from the chamber attendant study that some means of estimating DCS risk from observed bubble grades would be desirable. We have designed a method based on Bayesian statistics (paper V) where each bubble grade is assigned a DCS risk based on established data. In our method we used Sawatzky's nitrox data from Table 6. This set of risks is combined with observed bubble grades in a number of test dives for the new procedure. In this way we can estimate the DCS risk and, more importantly, calculate a 95% credible interval for the estimate. A credible interval is a posterior probability interval, used for purposes similar to those of confidence intervals in frequentist statistics. We found that this method can reduce the number of dives needed for table validation by approximately 95% compared to the binomial DCS observation method. It is also important that a procedure can be rejected as unsafe before a single case of DCS is encountered, so the hazard to the test subjects is reduced.

As previously mentioned, we have developed a sensitive system for automatic bubble detection and quantification in animal studies. Although the results in animal experiments are not directly comparable to human exposures, comparison of bubble numbers in new and established procedures tested under the same conditions should give an indication of safety before validation in human trials. This was used Brubakk and Arntzen (165) in comparing new surface decompression procedures to established USN procedures. Another important area for animal research is in improving the knowledge of the pathophysiology of decompression related injury. An example is studies on the interactions between gas bubbles and endothelium (17).

As we have seen, the bubble/DCS correspondence for exposures other than sub saturation dives is more ambiguous. For saturation dives there is a considerable number of DCS cases not accompanied by detectable bubbles. These are mainly musculoskeletal manifestations. Neurologic DCS has been associated with large number of vascular bubbles also for saturation decompression (43). This has led to recommendations for slowing down decompression speed or administrating increased oxygen breathing gas mixtures if high bubble grades are encountered (74).

For hypobaric exposures the existing data are not easily interpreted. 2 major studies with 1322 and 2044 subjects respectively, give distinctly different outcome with respect to the sensitivity of bubble detection to decompression sickness. Conkin et al. found a 1.5% DCS incidence with grade 0 bubbles (150), whereas Pilmanis et al. found 19% (155). Kumar et al. concluded that

Doppler measurements were useful in making therapeutic decisions on DCS when confronted with non-specific symptoms at altitude (151). Due to the ambiguity of other published data this should be done with caution.

Doppler studies have been used for evaluation of procedures for compressed air work both in field studies (136) and in experimental studies (75;166). There are, however, few data on the relationship between detectable bubbles and DCS incidence, so there is no easy way to interpret the bubble data. The data set published by Gotoh and Nashimoto (139) indicates that bends are related to detectable bubbles, and serious DCS (chokes) was only observed with grade III and IV bubbles. The number of exposures is too small to draw any firm conclusions, and more studies should be performed to work out recommendations for maximum allowable bubble numbers or enable the use of our Bayesian method for procedure validation.

CONCLUSIONS AND FUTURE PERSPECTIVES

Reviewing the existing literature we have concluded that the number of detectable vascular gas bubbles is associated with the risk of developing decompression sickness after bounce dives. This is supported by our own findings (Paper IV). Absence of detectable bubbles is a strong indicator of decompression safety and this relationship should be used in verification of decompression procedures.

We have investigated decompression procedures for attendants in hyperbaric oxygen treatment (Paper III). These procedures have generally been considered safe, but both clinical experience and the occurrence of high grade venous bubbles show that this should be reconsidered. The same probably applies to other decompression procedures, particularly at the deeper end of the bounce diving tables, where decompression sickness is not uncommon. Technical diving, with deeper dives and use of different breathing gases is a growing area where new procedures are often implemented on a trial-and-error basis without previous validation. The need for a standard method for identification of safe decompression procedures is therefore evident.

We have suggested a method for evaluation of the safety of decompression procedures based on bubble detection and have shown that this will greatly decrease the number of dives needed to verify or reject a procedure (Paper V) compared to existing methods. This means that improved procedures can be implemented quicker and will therefore ultimately lead to safer diving.

We have found that bubble detection with 2-dimensional ultrasound imaging is easier than Doppler detection (Paper I). Contrary to Doppler detection, reliable bubble detection with ultrasound imaging does not require months of extensive training. This makes the method more available for use. Moreover, the different grading systems for quantification of bubbles in Doppler signals and images can be directly compared (Paper II).

The ideal bubble detection system should automatically detect and count bubbles continuously during and after decompression. We have implemented such a system for use in decompression studies of anesthetised animals and believe this will be an important tool in further research on the basic mechanisms behind decompression injury. For human studies, however, an ideal detection system will require further development in ultrasound technology.

As with other types of electronic equipment, ultrasound systems are getting increasingly sophisticated, while prices and sizes are dropping. Portable hand held devices are now capable of producing images and Doppler signals with a quality comparable to state-of-the-art equipment available five years ago. Combined with built-in capabilities of sending signals via high-speed wireless networks for remote expert interpretation, this facilitates field studies in remote locations. Demands for new clinical areas of application has lead to enhanced image quality through development of better transducers and new methods for signal processing. Of particular interest is the increased use of ultrasound contrast agents, as they have acoustic properties comparable to microbubbles. Advances in ultrasound contrast imaging can therefore probably be translated to detection of decompression-induced microbubbles. At the moment only 2^{nd} harmonics are used routinely, but research on higher order harmonics and subharmonics indicates that this may improve bubble to tissue ratio further. If so, an ideal bubble detection system could be feasible in the near future.

SUMMARY OF PAPERS

Paper I: Agreement between trained and untrained observers in grading intravascular bubble signals in ultrasonic images

We evaluated the performance of 27 untrained observers in using a dedicated scoring system for grading intravascular bubbles in ultrasound images. It has previously been reported that it takes typically a year to learn to grade bubbles in Doppler signals, and the aim of this study was to see if image grading could be done accurately without previous training. The untrained observers graded bubbles in 40 segments of video recordings from decompression experiments; 20 segments from animal experiments with transesophageal echocardiography and 20 segments from precordial imaging of divers. The results were compared to gradings performed by trained observers. We found that the correspondence between untrained and trained observers was good and concluded that bubble grading in 2-dimensional echocardiography does not require extensive training, contrary to what has been shown for Doppler signal interpretation.

Paper II: Comparison of three different ultrasonic methods for quantification of intravascular gas bubbles

Different decompression studies use different grading systems for quantification of vascular bubbles. To be able to compare such studies, the agreement between different systems must be established. In this study we compared the image grading scale to the Spencer scale for Doppler signals both from “blind” and image-assisted Doppler systems. We found that agreement was good and that grades from the different systems can be directly compared with the subject at rest. After movement the agreement was less good, but this comparison was based on few observations. We concluded that it is possible to directly compare Doppler and image grades.

Paper III: Venous gas embolism in chamber attendants after hyperbaric exposure

This study was initiated after a case of serious neurological decompression sickness in a chamber attendant assisting routine hyperbaric oxygen therapy (HBOT). In the study ultrasound Doppler and imaging was used to assess decompression stress after routine HBOT exposures and revised protocols with increased levels of oxygen in the breathing gas and/or slower decompression. We found that the routine protocol exposed attendants to a significant decompression stress in terms of intravascular bubbles, and that the suggested revised protocols also produced too many gas bubbles to be acceptable for operational use.

Paper IV: The relationship between venous gas bubbles and adverse effects of decompression after air dives

We compared gas bubbles detected by ultrasound imaging and signs and symptoms of decompression stress after 204 air dives. We found that detection of venous gas bubbles is a highly sensitive, although not specific, predictor of decompression stress. Our results are in agreement with previously published correspondence between Doppler detected bubbles and decompression sickness incidence. We conclude that bubble detection should be used to validate decompression procedures.

Paper V: Validation of decompression procedures based on detection of venous gas bubbles: a Bayesian approach

The requirement for numerous test dives makes validation of new decompression procedures extremely resource demanding. We propose a new method for validation of decompression procedures based on detection of vascular gas bubbles and previous knowledge about the correspondence between gas bubbles and decompression sickness incidence. The method makes use of Bayesian statistics to estimate the risk of decompression sickness for the tested procedure. The new method will greatly reduce the number of dives required to approve or reject a procedure and can facilitate introduction of new and safer decompression tables.

REFERENCE LIST

(1) Francis TJR, Mitchell SJ. Pathophysiology of decompression sickness. In: Brubakk AO, Neuman TS, editors. Bennett and Elliott's Physiology and Medicine of Diving. 5th edition, London: Saunders; 2003: 530-56.

(2) Boyle R. New Pneumatical Experiments about Respiration. Philosophical Transactions 1670;5:2011-58.

(3) Goad RF. Diagnosis and Treatment of Decompression Sickness. General Survey. In: Shilling CW, Carlston CB, Mathias RA, editors. The Physician's guide to diving medicine. New York: Plenum Press; 1984:283-312.

(4) Bert P. Barometric pressure. Researches in experimental physiology (1878). Translated by Hitchcock MA, Hitchcock FA. Colombus, Ohio: College Book Company; 1943. [Reprinted by the Undersea Medical Society 1978].

(5) Boycott AE, Damant GCC, Haldane JB. The prevention of compressed air illness. Journal of Hygiene 1908;8:342-443.

(6) Satomura S. Ultrasonic Doppler method for the inspection of cardiac functions. J Acoust Soc Am 1957;29:1181-5.

(7) Spencer MP, Campbell SD, Sealey JL, Henry FC, Lindbergh J. Experiments on decompression bubbles in the circulation using ultrasonic and electromagnetic flowmeters. J Occup Med 1969 May;11(5):238-44.

(8) Spencer MP, Campbell SD. Development of bubbles in venous and arterial blood during hyperbaric decompression. Bull Mason Clin 1968;(22):26-32.

(9) Gillis MF, Karagianes MT, Peterson PL. Bends: detection of circulating gas emboli with external sensor. Science 1968 Aug 9;161(841):579-80.

(10) Mekjavic IB, Campbell DG, Jaki P, Dovsak PA. Ocular bubble formation as a method of assessing decompression stress. Undersea Hyperb Med 1998;25(4):201-10.

(11) Bennett MH, Doolette DJ, Heffernan N. Ocular tear film bubble counts after recreational compressed air diving. Undersea Hyperb Med 2001;28(1):1-7.

(12) Jossinet J, Fourcade C, Gardette B. An application of bioelectrical impedance for the detection of tissular bubbles in the diver: preliminary results. Med Biol Eng Comput 1981 Jul;19(4):419-25.

(13) Egozi N, Grossman Y. A new concept for electro optical sensor for monitoring circulatory gas bubble formation and vital signs during diving. In: Thorsen E, Hope A, editors. Proceedings of the 32nd Annual Scientific Meeting of the European Underwater and Baromedical Society. Bergen, Norway: EUBS; 2006: 99.

(14) Brubakk AO, Duplancic D, Valic Z, Palada I, Obad A, Bakovic D, et al. A single air dive reduces arterial endothelial function in man. J Physiol 2005 Aug 1;566(Pt 3):901-6.

(15) Nossum V, Koteng S, Brubakk AO. Endothelial damage by bubbles in the pulmonary artery of the pig. Undersea Hyperb Med 1999;26(1):1-8.

(16) Nossum V, Hjelde A, Brubakk AO. Small amounts of venous gas embolism cause delayed impairment of endothelial function and increase polymorphonuclear neutrophil infiltration. Eur J Appl Physiol 2002 Jan;86(3):209-14.

(17) Brubakk AO, Eftedal O, Wisløff U. Endothelium and diving. In: Aird W, editor. Handbook of the endothelium. Cambridge University Press; In press 2007.

(18) Eatock BC, Nishi RY. Procedures for Doppler ultrasonic monitoring of divers for intravascular bubbles. Downsview, Ontario: Defence and Civil Institute of Environmental Medicine; 1986. Report No.: 86-C-25.

(19) Brubakk AO, Neuman TS. Preface. In: Brubakk AO, Neuman TS, editors. Bennett and Elliott's Physiology and Medicine of Diving. 5th ed. London: Saunders; 2003: XI-XII.

(20) Hills BA. Decompression sickness. New York: John Wiley & Sons, Ltd.; 1977:29-47.

(21) Kidd DJ, Elliott DH. Decompression disorders in divers. In: Bennett PB, Elliott DH, editors. The Physiology and Medicine of Diving and Compressed Air Work, Bennett & Elliott 2nd edition. London: Bailliére Tindall; 1975: 471-95.

(22) Temple DJ, Ball R, Weathersby PK, Parker EC, Survanashi SS. The dive profiles and manifestations of decompression sickness cases after air and nitrogen-oxygen dives. Technical report no. 99-03, 2nd vol. Bethesda, Maryland: Naval Medical research Center; 1999.

(23) Francis TJR, Dutka AJ, Hallenbeck JM. Pathophysiology of decompression sickness. In: Bove AA, Davis JC, editors. Diving Medicine. 2nd edition ed. Philadelphia: W.B.Saunders Company; 1990. p. 170-87.

(24) Goad RF. Diagnosis and treatment of decompression sickness. In: Shilling CW, Carlston CB, Mathias RA, editors. The physician's guide to diving medicine. New York: Plenum Press; 1984: 283-312.

(25) Francis TJR, Mitchell SJ. Manifestations of decompression disorders. In: Brubakk AO, Neuman TS, editors. Bennett and Elliott's Physiology and Medicine of Diving. 5th edition, London: Saunders; 2003: 578-99.

(26) Andric D, Petri NM, Stipancevic H, Petri LV, Kovacevic H. Change of occurrence of type 1 and type 2 decompression sickness of divers treated at the Croatian Naval Medical Institute in the period from 1967 to 2000. Int Marit Health 2003;54(1-4):127-34.

(27) Edmonds C, Lowry C, Pennefather J. Decompression sickness: clinical manifestations. Diving and Subaquatic Medicine. 3rd edition. Oxford: Butterworth-Heinemann Ltd; 1992: 159-78.

(28) Dick AP, Massey EW. Neurologic presentation of decompression sickness and air embolism in sport divers. Neurology 1985 May;35(5):667-71.

(29) Francis TJ, Pearson RR, Robertson AG, Hodgson M, Dutka AJ, Flynn ET. Central nervous system decompression sickness: latency of 1070 human cases. Undersea Biomed Res 1988 Nov;15(6):403-17.

(30) Broome JR, Dick EJ, Jr. Neurological decompression illness in swine. Aviat Space Environ Med 1996 Mar;67(3):207-13.

(31) Dick EJ, Jr., Broome JR, Hayward IJ. Acute neurologic decompression illness in pigs: lesions of the spinal cord and brain. Lab Anim Sci 1997 Feb;47(1):50-7.

(32) Lango T, Morland T, Brubakk AO. Diffusion coefficients and solubility coefficients for gases in biological fluids and tissues: a review. Undersea Hyperb Med 1996 Dec;23(4):247-72.

(33) Francis TJ, Pezeshkpour GH, Dutka AJ, Hallenbeck JM, Flynn ET. Is there a role for the autochthonous bubble in the pathogenesis of spinal cord decompression sickness? J Neuropathol Exp Neurol 1988 Jul;47(4):475-87.

(34) Francis TJ, Pezeshkpour GH, Dutka AJ. Arterial gas embolism as a pathophysiologic mechanism for spinal cord decompression sickness. Undersea Biomed Res 1989 Nov;16(6):439-51.

(35) Palmer AC. Nature and incidence of bubbles in the spinal cord of decompressed goats. Undersea Hyperb Med 1997 Sep;24(3):193-200.

(36) Moon RE, Gorman DF. Treatment of the decompression disorders. In: Brubakk AO, Neuman TS, editors. Bennett and Elliott's Physiology and Medicine of Diving. 5th edition, London: Saunders; 2003: 600-50.

(37) Francis TJ, Griffin JL, Homer LD, Pezeshkpour GH, Dutka AJ, Flynn ET. Bubble-induced dysfunction in acute spinal cord decompression sickness. J Appl Physiol 1990 Apr;68(4):1368-75.

(38) Broome JR, Dick EJ, Dutka AJ. Multifocal CNS haemorrhage as a cause of recompression treatment failure in a pig model of neurological decompression illness (DCI). Undersea Hyperb Med 1994;21(suppl); 69.

(39) Germonpre P, Dendale P, Unger P, Balestra C. Patent foramen ovale and decompression sickness in sports divers. J Appl Physiol 1998 May;84(5):1622-6.

(40) Reuter M, Tetzlaff K, Hutzelmann A, Fritsch G, Steffens JC, Bettinghausen E, et al. MR imaging of the central nervous system in diving-related decompression illness. Acta Radiol 1997 Nov;38(6):940-4.

(41) Warren LP, Jr., Djang WT, Moon RE, Camporesi EM, Sallee DS, Anthony DC, et al. Neuroimaging of scuba diving injuries to the CNS. AJR Am J Roentgenol 1988 Nov;151(5):1003-8.

(42) Dutka AJ. Long term effects on the central nervous system. In: Brubakk AO, Neuman TS, editors. Bennett and Elliott's Physiology and Medicine of Diving. 5th edition, London: Saunders; 2003: 680-99.

(43) Nishi RY, Brubakk AO, Eftedal OS. Bubble detection. In: Brubakk AO, Neuman TS, editors. Bennett and Elliott's physiology and medicine of diving. 5th edition. London: Saunders; 2003: 501-29.

(44) Buttolph TB, Dick EJ, Jr., Toner CB, Broome JR, Williams R, Kang YH, et al. Cutaneous lesions in swine after decompression: histopathology and ultrastructure. Undersea Hyperb Med 1998;25(2):115-21.

(45) Wilmshurst PT, Pearson MJ, Walsh KP, Morrison WL, Bryson P. Relationship between right-to-left shunts and cutaneous decompression illness. Clin Sci (Lond) 2001 May;100(5):539-42.

(46) Conkin J. How should cutis marmorata be treated? Aviat Space Environ Med 1999 Sep;70(9):939-40.

(47) Zwart BP. Treatment of cutis marmorata (cutis). Aviat Space Environ Med 2000 Apr;71(4):457.

(48) Balldin UI, Pilmanis AA, Webb JT. Pulmonary decompression sickness at altitude: early symptoms and circulating gas emboli. Aviat Space Environ Med 2002 Oct;73(10):996-9.

(49) Behnke AR. Decompression sickness following exposures to high pressures. In: Fulton JF, editor. Decompression Sickness, Caisson Sickness, Diver's and flier's Bends and Related Syndromes. London: W.B. Saunders Company; 1951: 53-114.

(50) Dujic Z, Eterovic D, Denoble P, Krstacic G, Tocilj J, Gosovic S. Effect of a single air dive on pulmonary diffusing capacity in professional divers. J Appl Physiol 1993 Jan;74(1):55-61.

(51) Thorsen E, Segadal K, Kambestad BK. Mechanisms of reduced pulmonary function after a saturation dive. Eur Respir J 1994 Jan;7(1):4-10.

(52) Brubakk A.O. Silent vascular gas bubbles: Facts or ficton? Undersea Biomed Res 1989;16(suppl):69.

(53) Eckenhoff RG. The role of monitoring venous gas emboli after decompression. Undersea Biomed Res 1985 Dec;12(4):485-6.

(54) Molvær OI. Otorhinolaryngological aspects of diving. In: Brubakk AO, Neuman TS, editors. Bennett and Elliott's Physiology and Medicine of Diving. 5th edition, London: Saunders; 2003: 227-64.

(55) Hemmingsen EA. Nucleation of bubbles in vitro and in vivo. In: Brubakk AO, Hemmingsen BB, Sundnes G, editors. Supersaturation and bubble formation in fluids and organisms. Trondheim: Tapir Publishers; 1988: 43-59.

(56) Eckenhoff RG, Olstad CS, Carrod G. Human dose-response relationship for decompression and endogenous bubble formation. J Appl Physiol 1990 Sep;69(3):914-8.

(57) Blatteau JE, Souraud JB, Gempp E, Boussuges A. Gas nuclei, their origin, and their role in bubble formation. Aviat Space Environ Med 2006 Oct;77(10):1068-76.

(58) Harvey EN. Physical Factors in Bubble Formation. In: Fulton JF, editor. Decompression Sickness, Caisson Sickness, Diver's and flier's Bends and Related Syndromes. London: W.B. Saunders Company; 1951: 90-114.

(59) Yount DE. Growth of bubbles from nuclei. In: Brubakk AO, Hemmingsen BB, Sundnes G, editors. Supersaturation and bubble formation in fluids and organisms. Trondheim: Tapir Publishers; 1988: 131-77.

(60) Shaul PW. Regulation of endothelial nitric oxide synthase: location, location, location. Annu Rev Physiol 2002;64:749-74.

(61) Wisloff U, Richardson RS, Brubakk AO. Exercise and nitric oxide prevent bubble formation: a novel approach to the prevention of decompression sickness? J Physiol 2004 Mar 16;555(Pt 3):825-9.

(62) Wisloff U, Richardson RS, Brubakk AO. NOS inhibition increases bubble formation and reduces survival in sedentary but not exercised rats. J Physiol 2003 Jan 15;546(Pt 2):577-82.

(63) Vural KM, Oz MC. Endothelial adhesivity, pulmonary hemodynamics and nitric oxide synthesis in ischemia-reperfusion. Eur J Cardiothorac Surg 2000 Sep;18(3):348-52.

(64) Brubakk AO. Ultrasonic methods for detection of gas bubbles. In: Brubakk AO, Hemmingsen BB, Sundnes G, editors. Supersaturation and Bubble Formation in Fluids and Organisms. Trondheim: Tapir Publishers; 1989: 353-86.

(65) Nishi RY. The scattering and absorption of sound waves by a gas bubble in a viscous liquid. Acustica 1975;33(2):173-9.

(66) Lubbers J, van den Berg JW. An ultrasonic detector for microgasemboli in a bloodflow line. Ultrasound Med Biol 1977;2(4):301-10.

(67) Eftedal O, Brubakk AO. Gas bubble size and reflected ultrasound in an in-vitro system. Proceedings of the XIXth Annual Meeting of European Undersea Biomedical Society. Trondheim, Norway: SINTEF Unimed; 1993:263-7.

(68) Vik A, Brubakk AO, Hennessy TR, Jenssen BM, Ekker M, Slørdahl SA. Venous air embolism in swine: transport of gas bubbles through the pulmonary circulation. J Appl Physiol 1990 69(1):237-44.

(69) Hills BA, Grulke DC. Evaluation of ultrasonic bubble detectors in vitro using calibrated microbubbles at selected velocities. Ultrasonics 1975 Jul;13(4):181-4.

(70) Van Liew HD, Conkin J, Burkard ME. How big are decompression-sickness bubbles? Proceedings of the XIXth Annual Meeting of European Undersea Biomedical Society. Trondheim, Norway: SINTEF Unimed; 1993:258-62.

(71) Hills BA, Butler BD. Size distribution of intravascular air emboli produced by decompression. Undersea Biomed Res 1981 Sep;8(3):163-70.

(72) Christman CL, Catron PW, Flynn ET, Weathersby PK. In vivo microbubble detection in decompression sickness using a second harmonic resonant bubble detector. Undersea Biomed Res 1986 Mar;13(1):1-18.

(73) Spencer MP, Johanson DC. Investigation of new principles for human decompression schedules using the Doppler ultrasonic blood detector. Tech report to ONR on Contract N00014-73-C-0094. Seattle, Washington: Institute for Environmental Medicine and Physiology; 1974.

(74) Kisman K, Masurel G. Method for evaluating circulating bubbles detected by means of the Doppler ultrasonic method using the 'K.M. code'. (English translation of 283 CERTSM 1983). Toulon: Centre d'Etudes et de Recherches Techniques Sous-Marines; 1983.

(75) Flook V. Trials of a Blackpool table decompression with oxygen as the breathing gas. Health and Safety Executive; 2001. Report No.: 369/2001.

(76) Kisman K, Masurel G, LaGrue Deal. Evaluation de la qualité d'une décompression basée sur la détection ultrasonore des bulles. Méd Aéro Spat Méd Sub Hyp 1978;XVII(67):293-7.

(77) Jankowski LW, Nishi RY, Eaton DJ, Griffin AP. Exercise during decompression reduces the amount of venous gas emboli. Undersea Hyperb Med 1997 Jun;24(2):59-65.

(78) Nishi RY, Kisman KE, Eatock BC, Buckingham IP, Masurel G. Assessment of decompression profiles and divers by Doppler ultrasonic monitoring. In: Bachrach AJ, Matzen MM, editors. Underwater Physiology VII: Proceedings of the Seventh Symposium on Underwater Physiology. Bethesda, Maryland: Undersea Medical Society; 1981:717-27.

(79) Curry TB. Nitrogen elimination and venous gas embolism as related to the pathophysiology of decompression sickness: effects of age, blood lipids, and negative pressure breathing. PhD Thesis. Buffalo, New York: State University of New York at Buffalo; 1999.

(80) Carturan D, Boussuges A, Vanuxem P, Bar-Hen A, Burnet H, Gardette B. Ascent rate, age, maximal oxygen uptake, adiposity, and circulating venous bubbles after diving. J Appl Physiol 2002 Oct;93(4):1349-56.

(81) Jankowski LW, Tikusis P, Nishi RY. Exercise effects during diving and decompression on postdive venous gas emboli. Aviat Space Environ Med 2004 Jun;75(6):489-95.

(82) Sawatzky KD. The relationship between intravascular Doppler-detected gas bubbles and decompression sickness after bounce diving in humans. MSc Thesis. Toronto, Ontario: York University; 1991.

(83) Daniels S. Ultrasonic monitoring of decompression procedures. Philos Trans R Soc Lond B Biol Sci 1984 Jan 7;304(1118):153-75.

(84) Conkin J, Foster PP, Powell MR, Waligora JM. Relationship of the time course of venous gas bubbles to altitude decompression illness. Undersea Hyperb Med 1996 Sep;23(3):141-9.

(85) Sawatzky KD, Nishi RY. Assessment of inter-rater agreement on the grading of intravascular bubble signals. Undersea Biomed Res 1991 Sep;18(5-6):373-96.

(86) Chappell MA, Payne SJ. A method for the automated detection of venous gas bubbles in humans using empirical mode decomposition. Ann Biomed Eng 2005 Oct;33(10):1411-21.

(87) Chappell MA, Rowley AB, Payne SJ. Automatic Doppler Bubble Detection: The Utility of Wavelets. In: Thorsen E, Hope A, editors. Proceedings of the 32nd Annual Scientific Meeting of the European Underwater and Baromedical Society. Bergen, Norway: EUBS; 2006: 43-7.

(88) Belcher EO. Quantification of bubbles formed in animals and man during decompression. IEEE Trans Biomed Eng 1980 Jun;27(6):330-8.

(89) Guillerm R, Masurel G, Monjaret M, David H, Schmidlin B. La détection ultrasonore par effet Doppler des bulles intravasculaires chez le miniporc aprés exposition hyperbare: Rôle filtrant du poumon. Bull Med sub hyp 1973;(10):50-4.

(90) Moulinier H, Masurel G. Detection of bubbles in blood vessels and the evaluation of their flow. Med Biol Eng Comput 1978 Sep;16(5):585-8.

(91) Kisman K. Spectral analysis of Doppler ultrasonic decompression data. Ultrasonics 1977 May;15(3):105-10.

(92) Gibby GL, Ghani GA. Computer-assisted Doppler monitoring to enhance detection of air emboli. J Clin Monit 1988 Jan;4(1):64-73.

(93) Gibby GL. Real-time automated computerized detection of venous air emboli in dogs. J Clin Monit 1993 Nov;9(5):354-63.

(94) Eatock BC, Sweeney D. Digital processing of Doppler ultrasonic signals for intravascular bubbles. Downsview, Ontario: Defence and Civil Institute of Environmental Medicine; 1987. Report No.: 87-RR-19.

(95) Strong K, Westenskow DR, Fine PG, Orr JA. A preliminary laboratory investigation of air embolus detection and grading using an artificial neural network. Int J Clin Monit Comput 1997;14(2):103-7.

(96) Sutherland J. Automated cardiac monitoring using holographic/quantum neural technology. PCAI 1999; 13(5):20-2.

(97) Marsolier J-L, Glover JR, Kumar KV, Powell MR. Computer automated detection of gas bubbles in precordial blood flow using Doppler ultrasound. Undersea Hyperb Med 1995;22(suppl):31.

(98) Buruk MY, Guler EC, Egi SM, Eftedal O, Sankur B. Analysis of precordial Doppler ultrasound recordings using time-frequency methods to detect decompression bubbles. Undersea Hyperb Med 1995;22(suppl):30-1.

(99) Tufan K, Ademoglu A, Kurtaran E, Yildiz G, Aydin S, Egi SM. Automatic detection of bubbles in the subclavian vein using Doppler ultrasound signals. Aviat Space Environ Med 2006 Sep;77(9):957-62.

(100) Cullinane M, Reid G, Dittrich R, Kaposzta Z, Ackerstaff R, Babikian V, et al. Evaluation of new online automated embolic signal detection algorithm, including comparison with panel of international experts. Stroke 2000 Jun;31(6):1335-41.

(101) Payne SJ, Chappell MA. Automated determination of bubble grades from Doppler ultrasound recordings. Aviat Space Environ Med 2005 Aug;76(8):771-7.

(102) Ikeda T, Okamoto Y, Hashimoto A. Bubble formation and decompression sickness on direct ascent from shallow air saturation diving. Aviat Space Environ Med 1993 Feb;64(2):121-5.

(103) Ikeda T, Suzuki S, Shimizu K, Okamoto Y, Llewellyn ME. M-mode ultrasonic detection of microbubbles following saturation diving: a case report and proposal for a new grading system. Aviat Space Environ Med 1989 Feb;60(2):166-9.

(104) Ikeda T, Okamoto Y, Mizukami H, Hashimoto A. Comparison between ultrasonic M-mode and Doppler bubble detection. In: Sterk W, Geeraedts L, editors. EUBS 1990 Proceedings. Amsterdam, The Netherlands: The Foundation for Hyperbaric Medicine; 1990: 35-40.

(105) Min JK, Spencer KT, Furlong KT, DeCara JM, Sugeng L, Ward RP, et al. Clinical features of complications from transesophageal echocardiography: a single-center case series of 10,000 consecutive examinations. J Am Soc Echocardiogr 2005 Sep;18(9):925-9.

(106) Reinertsen RE, Flook V, Koteng S, Brubakk AO. Effect of oxygen tension and rate of pressure reduction during decompression on central gas bubbles. J Appl Physiol 1998 Jan;84(1):351-6.

(107) Vik A, Jenssen BM, Eftedal O, Brubakk AO. Relationship between venous bubbles and hemodynamic responses after decompression in pigs. Undersea Hyperb Med 1993 Sep;20(3):233-48.

(108) Eftedal O, Brubakk AO. Detecting intravascular gas bubbles in ultrasonic images. Med Biol Eng Comput 1993 Nov;31(6):627-33.

(109) Eftedal O, Mohammadi R, Rouhani M, Torp H, Brubakk AO. Computer real time detection of intravascular bubbles. In: Cimsit M, editor. Proceedings EUBS 1994, XXth Annual Meeting of the European Underwater and Baromedical Society on Diving and Hyperbaric Medicine. Istanbul, Turkey: HITAM; 1994:490-4.

(110) Eftedal O, Brubakk AO, Nishi RY. Ultrasonic evaluation of decompression: The relationship between bubble grades and bubble numbers. Undersea Hyperb Med 1998;25(suppl):35-6.

(111) Rubissow GJ, Mackay RS. Ultrasonic imaging of in vivo bubbles in decompression sickness. Ultrasonics 1971 Oct;9(4):225-34.

(112) Daniels S, Davies JM, Paton WD, Smith EB. The detection of gas bubbles in guinea-pigs after decompression from air saturation dives using ultrasonic imaging. J Physiol 1980 Nov;308:369-83.

(113) Daniels S, Paton WD, Smith EB. Ultrasonic imaging system for the study of decompression-induced gas bubbles. Undersea Biomed Res 1979 Jun;6(2):197-207.

(114) Daniels S, Bowser-Riley F, Vlachonikolis IG. The relationship between gas bubbles and symptoms of decompression sickness. In: Brubakk AO, Hemmingsen BB, Sundnes G, editors. Supersaturation and Bubble Formation in Fluids and Organisms. Trondheim: Tapir Publishers; 1989: 387-402.

(115) Daniels S, Davies JM, Eastaugh KC, Paton WDM, Smith EB. Monitoring bubble formation with an integrating pulse-echo ultrasonic method. In: Bachrach AJ, Matzen MM, editors. Underwater Physiology VII: Proceedings of the Seventh Symposium on Underwater Physiology. Bethesda, Maryland: Undersea Medical Society; 1981:729-40.

(116) Davies JM. Studies of bubble formation after decompression. PhD Thesis. Oxford, UK: Department of Pharmacology, University of Oxford; 1983.

(117) Boussuges A, Molenat F, Carturan D, Gerbeaux P, Sainty JM. Venous gas embolism: detection with pulsed Doppler guided by two-dimensional echocardiography. Acta Anaesthesiol Scand 1999 Mar;43(3):328-32.

(118) Basude R, Wheatley MA. Generation of ultraharmonics in surfactant based ultrasound contrast agents: use and advantages. Ultrasonics 2001 Oct;39(6):437-44.

(119) Shankar PM, Krishna PD, Newhouse VL. Subharmonic backscattering from ultrasound contrast agents. J Acoust Soc Am 1999 Oct;106(4 Pt 1):2104-10.

(120) de Jong N, Hoff L, Skotland T, Bom N. Absorption and scatter of encapsulated gas filled microspheres: theoretical considerations and some measurements. Ultrasonics 1992 Mar;30(2):95-103.

(121) Eatock BC, Nishi RY, Johnston GW. Numerical-Studies of the Spectrum of Low-Intensity Ultrasound Scattered by Bubbles. Journal of the Acoustical Society of America 1985;77(5):1692-701.

(122) Palanchon P, Bouakaz A, Klein J, de JN. Emboli detection using a new transducer design. Ultrasound Med Biol 2004 Jan;30(1):123-6.

(123) Palanchon P, Bouakaz A, Klein J, de JN. Multifrequency transducer for microemboli classification and sizing. IEEE Trans Biomed Eng 2005 Dec;52(12):2087-92.

(124) Magari PJ, Kline-Schoder RJ, Stoedefalke BH, Butler BD. A non-invasive, in-vivo, bubble sizing instrument. Proceedings of the 1997 IEEE Ultrasonics Symposium, 97CH13118 Institute of Electrical & Electronic Engineers; 1997:1205-10.

(125) Didenkulov IN, Yoon SW, Sutin AM, Kim EJ. Nonlinear Doppler effect and its use for bubble flow velocity measurement. Journal of the Acoustical Society of America 1999 Nov;106(5):2431-5.

(126) Thalmann ED. USN experience on decompression table validation. In: Schreiner HR, Hamilton RW, editors. Validation of decompression tables. The 37th Undersea and Hyperbaric Medical Society Workshop. Bethesda, MD: UHMS, Inc.; 1989: 33-42.

(127) Sowden LM, Kindwall EP, Francis TJ. The distribution of limb pain in decompression sickness. Aviat Space Environ Med 1996 Jan;67(1):74-80.

(128) Vann RD, Dick AP, Barry PD. Doppler bubble measurements and decompression sickness. Undersea Biomed Res 1982;9(suppl):24.

(129) Neuman TS, Hall DA, Linaweaver PGJ. Gas phase separation during decompression in man: ultrasound monitoring. Undersea Biomed Res 1976 Jun;3(2):121-30.

(130) Powell MR, Thoma W, Fust HD, Cabarrou P. Gas phase formation and Doppler monitoring during decompression with elevated oxygen. Undersea Biomed Res 1983 Sep;10(3):217-24.

(131) Bayne CG, Hunt WS, Johanson DC, Flynn ET, Weathersby PK. Doppler bubble detection and decompression sickness: a prospective clinical trial. Undersea Biomed Res 1985 Sep;12(3):327-32.

(132) Weathersby PK, Hart BL, Flynn ET, Walker WF. Role of oxygen in the production of human decompression sickness. J Appl Physiol 1987 Dec;63(6):2380-7.

(133) Powell MR, Johanson DC. Ultrasound monitoring and decompression sickness. In: Shilling CW, Beckett MW, editors. Underwater Physiology VI, Proceedings of the sixth symposium on underwater physiology. Bethesda, MD: FASEB; 1978: 503-10.

(134) Thorsen T, Klausen H, Lie RT, Holmsen H. Bubble-induced aggregation of platelets: effects of gas species, proteins, and decompression. Undersea Hyperb Med 1993 Jun;20(2):101-19.

(135) Flook V. Decompression problems in compressed air work - an assessment of risk and of options for risk reduction. Trondheim, Norway: SINTEF; 1998. Report No.: STF78 F98111.

(136) Flook V, Eftedal O. Field and theoretical studies of decompression bubbles in compressed air work at 0.95 bar. Trondheim, Norway: SINTEF; 1997. Report No.: STF79 F97112.

(137) Kindwall EP. Compressed air work. In: Brubakk AO, Neuman TS, editors. Bennett and Elliott's Physiology and Medicine of Diving. 5th edition, London: Saunders; 2003: 17-28.

(138) Kindwall EP. Compressed air tunnelling and caisson work decompression procedures: development, problems, and solutions. Undersea Hyperb Med 1997;24(4):337-45.

(139) Gotoh Y, Nashimoto I. Decompression bubbles in caisson workers (author's transl). Nippon Eiseigaku Zasshi 1977 Oct;32(4):529-33.

(140) Eckenhoff RG, Osborne SF, Parker JW, Bondi KR. Direct ascent from shallow air saturation exposures. Undersea Biomed Res 1986 Sep;13(3):305-16.

(141) Berghage TE. Decompression sickness during saturation dives. Undersea Biomed Res 1976 Dec;3(4):387-98.

(142) Gardette B. Correlation between decompression sickness and circulating bubbles in 232 divers. Undersea Biomed Res 1979 Mar;6(1):99-107.

(143) Eckenhoff RG, Vann RD. Air and nitrox saturation decompression: a report of 4 schedules and 77 subjects. Undersea Biomed Res 1985 Mar;12(1):41-52.

(144) Brubakk AO, Holmes C, Eftedal O. Decompression from saturation, Aurora dive April/may 1993. Trondheim, Norway: SINTEF; 1993. Report No.: STF23 F93041.

(145) Brubakk AO, Peterson R, Grip A, Holand B, Onarheim J, Segadal K, Kunkle TD, Tonjum S. Gas bubbles in the circulation of divers after ascending excursions from 300 to 250 msw. J Appl Physiol 1986 Jan;60(1):45-51.

(146) Hjelle JO, Eatock BC, Nordahl SH, Dick APK. Doppler monitoring during 3 dives to 360 msw. In: Program and Abstracts, XIIIth Annual Meeting. Palermo, Italy: EUBS; 1987:357-64.

(147) Eatock BC, Nishi RY. Doppler ultrasonic detection of intravascular bubbles during decompression from the 1985 Can/UK saturation dives to 100 and 360 msw. Downsview, Ontario: DCIEM; 1986. Report No.: 86-R-10.

(148) Report from diver database DSYS 2005. Petroleum Safety Authority Norway, Stavanger; 2006.

(149) Conkin J, Bedahl SR, Van Liew HD. A computerized databank of decompression sickness incidence in altitude chambers. Aviat Space Environ Med 1992 Sep;63(9):819-24.

(150) Conkin J, Powell MR, Foster PP, Waligora JM. Information about venous gas emboli improves prediction of hypobaric decompression sickness. Aviat Space Environ Med 1998 Jan;69(1):8-16.

(151) Kumar VK, Billica RD, Waligora JM. Utility of Doppler-detectable microbubbles in the diagnosis and treatment of decompression sickness. Aviat Space Environ Med 1997 Feb;68(2):151-8.

(152) Woodard D. Decompression sickness during simulated EVA. Aviat Space Environ Med 2005 Dec;76(12):1188.

(153) Balldin UI, Pilmanis AA, Webb JT. The effect of simulated weightlessness on hypobaric decompression sickness. Aviat Space Environ Med 2002 Aug;73(8):773-8.

(154) Webb JT, Beckstrand DP, Pilmanis AA, Balldin UI. Decompression sickness during simulated extravehicular activity: ambulation vs. non-ambulation. Aviat Space Environ Med 2005 Aug;76(8):778-81.

(155) Pilmanis AA, Kannan N, Krause KM, Webb JT. Relating venous gas emboli (VGE) scores to altitude decompression sickness (DCS) symptoms. Aviat Space Environ Med 1999 70(4):364.

(156) Balldin UI, Pilmanis AA, Webb JT. Central nervous system decompression sickness and venous gas emboli in hypobaric conditions. Aviat Space Environ Med 2004 Nov;75(11):969-72.

(157) Dixon GA, Krutz RW, Jr., Fischer JR. Decompression sickness and bubble formation in females exposed to a simulated 7.8 psia suit environment. Aviat Space Environ Med 1988 Dec;59(12):1146-9.

(158) Dixon GA, Adams JD, Harvey WT. Decompression sickness and intravenous bubble formation using a 7.8 psia simulated pressure-suit environment. Aviat Space Environ Med 1986 Mar;57(3):223-8.

(159) Balldin UI, Borgstrom P. Intracardial bubbles during decompression to altitude in relation to decompression sickness in man. Aviat Space Environ Med 1976 Feb;47(2):113-6.

(160) Olsson RM, Fitzpatrick EL, Adams JD, Burton RR. Intravascular bubble formation and the prediction of bends. Preprints of 1983 Annual Scientific Meeting. Washington DC: Aerospace Medical Association; 1983: 122-3.

(161) Eatock BC, Gray GW, Ford GS. Evaluation, with Doppler ultrasonic bubble detection, of pre-breathing oxygen for reducing the incidence of decompression sickness. Preprints of 1983 Annual Scientific Meeting. Washington DC: Aerospace Medical Association; 1983: 126-7.

(162) Ryles MT, Pilmanis AA. The initial signs and symptoms of altitude decompression sickness. Aviat Space Environ Med 1996 Oct;67(10):983-9.

(163) Hamilton RW, Schreiner HR. Editorial summary: validation of decompression tables. In: Schreiner HR, Hamilton RW, editors. Validation of decompression tables. The 37th Undersea and Hyperbaric Medical Society Workshop. Bethesda, Maryland: UHMS, Inc.; 1989:163-7

(164) Nishi RY, Eatock BC. The role of bubble detection in table validation. In: Schreiner HR, Hamilton RW, editors. Validation of decompression tables. The 37th Undersea and Hyperbaric Medical Society Workshop. Bethesda, Maryland: UHMS, Inc.; 1989:133-8.

(165) Brubakk AO, Arntzen AJ. The effect of in-water decompression profile on bubble formation following surface decompression with oxygen. Undersea Hyperb Med 2001;28(suppl):84.

(166) Flook V, Eastman D, Lafleur D, Lamont D. Benefits of using oxygen on compressed air decompressions in UK. Undersea Hyperb Med 2001;28(suppl):50.

Dissertations at the Faculty of Medicine, NTNU

1977

1. Knut Joachim Berg: EFFECT OF ACETYLSALICYLIC ACID ON RENAL FUNCTION
2. Karl Erik Viken and Arne Ødegaard: STUDIES ON HUMAN MONOCYTES CULTURED *IN VITRO*

1978

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34. Terje Skjærpe: NONINVASIVE QUANTITATION OF GLOBAL PARAMETERS ON LEFT VENTRICULAR FUNCTION: THE SYSTOLIC PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT.
35. Eyvind Rødahl: STUDIES OF IMMUNE COMPLEXES AND RETROVIRUS-LIKE ANTIGENS IN PATIENTS WITH ANKYLOSING SPONDYLITIS.
36. Ketil Thorstensen: STUDIES ON THE MECHANISMS OF CELLULAR UPTAKE OF IRON FROM TRANSFERRIN.
37. Anna Midelfart: STUDIES OF THE MECHANISMS OF ION AND FLUID TRANSPORT IN THE BOVINE CORNEA.
38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

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43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

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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.

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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.

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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.

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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.

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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
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