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Effekt av dykking på biomarkører i en rottemodell.
Mulige konsekvenser for kort- og langtids helseeffekter for yrkesdykkere.

Denne avhandlingen er basert på tre dyrestudier som med ulike metoder tar for seg fysiologiske utfordringer som kan påvirke helsen til yrkesdykkere i et langtidsperspektiv. Den første studien evaluerer sentralnervøs skade hos rotter som har vært utsatt for simulert dykking. Dette ble gjort ved å måle serumkonsentrasjon av en biomarkør (S100B) som er sensitiv for hjerneskade. Ved hjelp av ultralyd ble rottenes hjerter undersøkt for bobler dannet under trykkreduksjon. I denne studien fant vi at rotter som hadde dykket dypt hadde en høyere konsentrasjon av S100B enn rotter som ikke hadde dykket like dypt og i tillegg at dette var korrelert til boblemengde. I det andre studiet ble effekten av et dykk på sentralnervesystemet undersøkt ytterligere ved hjelp av MR og immunhistokjemi. Her fant vi at rotter som ble utsatt for et simulert dykk viste tegn til endringer i hjernesirkulasjon en time etter dykk, men ingen tegn til strukturell skade i hjernevev 14 dager senere. I det tredje studiet ville vi studere effekten av bakteriell eksponering under dykking og mer presist hvordan *Pseudomonas aeruginosa* påvirker dannelsen av sirkulerende autoantistoffer mot HSP60 og hvordan dykking påvirker serumnivået av disse sirkulerende autoantistoffene. Resultatene fra disse forsøkene viste at rotter som ble vaksinert med bakterien *Pseudomonas aeruginosa* fikk et økende nivå av sirkulerende autoantistoffer mot HSP60, mens dette ikke ble observert hos rotter som ble kun dykket. Imidlertid viste det seg at rotter som både ble vaksinert og dykket heller ikke hadde noe økt nivå av anti-HSP60 i blodet. Dette kan forklares ved at HSP60 er uttrykt under dykking og at kryssreagerende antistoffer er bundet til HSP60. En slik kryssreaksjon kan føre til immunresponser som er uheldige i et langtids-helseperspektiv.

Tidligere rapporter som omhandler sentralnervøse effekter av dykking er basert på retrospektive data og kan derfor være vanskelige å tolke. Arbeidet som er presentert i denne avhandlingen tar for seg mulige helseutfordringer for yrkesdykkere, studert i rottemodeller. Denne fremgangsmåten gjør det mulig å utføre prospektive studier for å undersøke sykdomsfremmende effekter av en definert eksponering i ulike organsystemer.

Kandidat:	**Marianne Bjordal Havnes**
Institutt:	**Institutt for sirkulasjon og bildediagnostikk**
Veiledere:	**Andreas Møllerløkken, Ulrik Wisløff, Alf O. Brubakk og Arvid Hope**
Finansiering:	**Norsk forskningsråd og Statoil, ExxonMobil and Gassco under kompetanseprogrammet for dykking.**

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Contents

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LIST OF PAPERS

1. Havnes, Marianne Bjordal; Hjelde, Astrid; Brubakk, Alf O; Møllerløkken, Andreas.
   S100B and its relation to intravascular bubbles following decompression.
   Diving and Hyperbaric Medicine 2010; Volume 40 (4) p. 210-212

2. Havnes, Marianne Bjordal; Widerøe, Marius; Thuen, Marte; Torp, Sverre H; Brubakk, Alf O; Møllerløkken, Andreas. Simulated dives in rats lead to acute changes in cerebral blood flow on MRI, but no cerebral injuries to grey or white matter.
   European Journal of Applied Physiology [Online] (12 December 2012)

3. Havnes, Marianne Bjordal; Ahlen, Catrine; Brubakk, Alf O; Iversen, Ole-Jan. Concentration of circulating autoantibodies against HSP 60 is lowered through diving when compared to non-diving rats.
   Microbial Ecology in Health and Disease [Online], Volume 23 (31 January 2012)

ABBREVIATIONS

ACh	Acetylcholine
ADC	Apparent diffusion coefficient
AGE	Arterial gas embolism
ATA	Atmosphere absolute
BBB	Blood-brain barrier
CD68	Cluster of differentiation 68
CF	Cystic fibrosis
CNS	Central nervous system
DCEMRI	Dynamic contrast enhanced MRI
DCS	Decompression sickness
DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
EEG	Electroencephalography
ELISA	Enzyme-linked immunosorbent assay
GFAP	Glial fibrillary acidic protein
HE	Hematoxylin-eosin
HPNS	High pressure nervous syndrome
HSP	Heat shock protein
IL-6	Interleukin-6
kPa	Kilopascal
MAP-2	Microtubule-associated protein 2
MBP	Myelin basic protein
ME	Manganese enhancement
MEMRI	Manganese enhanced MRI
MRI	Magnetic resonance imaging
MSW	Meters of sea water
NSE	Neuron specific enolase
ROT	Remotely operated vehicle
ROV	Remotely operated tool
RSI	Relative signal intensity
S100B	Calcium binding protein
T_2	Transversal relaxation

TNF-α	Tumor necrosis factor
VGE	Venous gas embolism

DEFINITIONS

Biomarker: the term biomarker comprises any substance that may be taken as an indicator of a specific biological state. Biomarkers may be introduced into the body in order to visualize a process, or may consist of substances already inherent to the body, but altered in its amount or presentation by a particular physiological or pathological state.

Central nervous system (CNS): consists of the brain and the spinal cord. The CNS integrates and processes responses to signals transmitted via nervous cells.

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

Saturation: in diving, this refers to the state where the gases in the body are at equilibrium with the ambient pressure. The partial pressure of a gas, for example nitrogen, in the body will not increase further unless the partial pressure of nitrogen within the breathing medium is increased. This form of diving is usually preferred when diving deeper than 50 meters of seawater.

Supersaturation: In diving, this refers to a situation where the partial pressure of a gas in the tissue exceeds that of the ambient pressure.

Surface-based diving: The diver descends to the depth were the work is going to be performed, with duration determined by both the depth and the breathing-gas before returning to surface.

BACKGROUND

Oil exploration in the North Sea began on the UK continental shelf in the late 1950's and on the Norwegian continental shelf in the late 1960's. The oil industry is dependent on divers to maintain and inspect sub-sea petroleum production systems. In the 1990's, unmanned deep water maintenance using Remotely Operated Vehicles (ROV's) and Remotely Operated Tools (ROT's) were established. Today, divers are used in hyperbaric welding operations and in operation were use of divers is more cost efficient than ROV's and ROT's in medium depth waters (30-180 msw), for maintenance and reparation of old installations. Perception, judgement and dexterity are among the factors that make human divers the most effective choice for some tasks.

Commercial divers work both inshore and offshore and the diving activity is either surface-based or by means of saturation diving. The two methods can be further divided into groups based on the breathing gases they apply. These are depth dependent and are air, nitrox or helium-oxygen mixtures.

In saturation diving, a team of divers is compressed to the work depth in a closed chamber system ('or environment'), and stay at depth throughout the work period. From the chamber, the divers are transported to the work site by a diving bell and normally work eight hour shifts before they return to the chamber, still under pressure (1). Saturation divers working at depths deeper than 30 msw usually breath heliox, a helium-oxygen mixture, in contrast to the air or nitrox that is used at shallower depths (1). Helium is used to reduce breathing resistance, to avoid nitrogen narcosis and as it has faster tissue elimination than nitrogen.

Typical working depths in the North Sea are between 50 to 180 m with 14 days as the maximum stay at living depth. Decompression rates are depth limited; they may decrease with decreasing depth and decompression may take several days even from moderate depths. There are health challenges related to working as a saturation diver. Among the most serious are those related to the central nervous system (CNS). In several studies, saturation divers have been examined with respect to quality of life (2), memory function, problems in concentration and other

ailments (3). However, the results are conflicting and inconclusive with regard to the neurological consequences of diving. While there are almost no reports of decompression sickness (DCS) among saturation divers (1990-2010) (4), ear and skin infections due to *Pseudomonas aeruginosa* (*P. aeruginosa*) are common. Repeated exposures to *P. aeruginosa* triggers the immune system in a way that may affect circulatory health (5, 6), and it is found that saturation divers have a higher prevalence of heart disease (7).

Previous reports on the effect of diving on the CNS are based upon retrospective data and hence, can be difficult to interpret. The work presented in this thesis addresses topics relevant to possible health effects for professional divers by the use of rat models. This approach makes it possible to conduct prospective studies, investigating both the acute and long-term pathophysiological effects of a defined environmental exposure in different organ systems.

AIMS and HYPOTHESES

Under hyperbaric conditions, biological responses to elements in the confined environment, such as pathogens and pollutants, may differ from responses at normal surface pressure. It is postulated that the pressure and environmental changes associated with saturation diving will affect the physiology and have a long term pathogenic influence on the health of divers working in this environment. Therefore, the general aim of this thesis was to study the physiological challenges relevant to possible long term health effects in professional divers, with the main focus on CNS and immunological changes. Biomarkers that are potentially linked to health hazards in the hyperbaric environment were examined in rats exposed to simulated diving.

Specific aims:

I: To study the acute effects of diving on expression of the neurotropic biomarker S100B in blood, with the hypothesis that concentrations of S100B will be higher in dived animals compared to non-dived control animals.

II: To identify changes in the CNS after a dive using MRI and histology.

III: To study whether rats immunised with *P. aeruginosa* produce autoantibodies against their own HSP60 and whether diving influences the level of circulating anti-HSP60 antibodies.

INTRODUCTION

Decompression physiology has been studied for more than 100 years. The Irish philosopher and scientist, Robert Boyle, made the first observations of decompression-induced gas bubbles in 1659. In 1878, Paul Bert carried out the first systematic study demonstrating the presence of gas bubbles in blood and tissues after decompression. He described bubble formation in dogs and suggested that DCS could be avoided by a slower decompression (8). John Scott Haldane went on to base his work on Bert's discoveries and developed the first set of scientifically based decompression tables. In 1908 Haldane and co-workers published the paper 'Prevention of Compressed-Air Illness', where they postulated that staged decompression could bring the underwater workers safely back to the surface and that tissue perfusion was the limiting factor in inert gas uptake and elimination (9).

During a dive, the partial pressure of gases in the tissues increases because of the pressure difference between the environment (higher pressure) and the diver's body (lower pressure). After a time spent at depth, if the diver decompresses too fast, the change in ambient pressure may cause gas in the tissues to become supersaturated, and then come out of solution and form bubbles. This is commonly understood as the initiating sequence of DCS. The mechanisms of the pathological sequence leading to DCS are not fully understood, but mechanical damage from the expansion of bubbles, vascular endothelial damage and immunological responses are amongst the factors believed to be of importance (10). Endothelial function has been shown to be affected by diving and bubbles in animal studies and in man (11, 12).

Physiological consequences of diving

Decompression sickness (DCS)

The major risk associated with diving is related to decompression and the risk of DCS. There are two traditional diagnostic categories for DCS; type I DCS includes musculoskeletal, skin, lymphatic and fatigue effects, while type II DCS includes neurologic, cardiorespiratory ("chokes") and audiovestibular symptoms (13). This

classification is useful in a clinical setting for prognosis and treatment management. In type II cases with cerebral involvement, 75 % usually show signs and symptoms within 10 minutes after surfacing (14). Generally, the shorter the time between surfacing and developing DCS, the greater the severity and the worse the prognosis (15).

Within saturation diving in Norway today there are almost no reported cases of DCS (4). However, there will always be a risk of DCS when a worker returns to surface from depth. The importance of bubbles has been subject of discussion, but it is well documented that there is an increased risk of DCS with increasing number of bubbles (16). Although any cause-effect relationship between bubbles and development of DCS has not been established, the absence of bubbles is a good indicator of decompression safety.

Brain / CNS- neurological manifestations

The most serious form of DCS affects the CNS. In divers, neurological symptoms like numbness, paraesthesia, dizziness and coordination deficiencies are among the most often reported manifestations of DCS in recreational diving accidents (17, 18).There is no standard precedent for neurologic manifestations, however loss of consciousness and sensory and motor deficits are often involved shortly after surfacing (13).

When neurological damage occurs in divers, the suspected primary cause is vascular gas bubbles. Acute effects can be caused by extra-vascular bubbles producing pain, but vascular bubbles may grow in size and cause an infarction, inducing stroke-like symptoms (17). Bubbles can reach the brain through the arterial circulation, either through a right-to-left shunt in the heart, or they may overwhelm the pulmonary system and pass into the arteries (19). When bubbles reach the arterial circulation, they are termed arterial gas emboli (AGE). AGE can manifest as a consequence of air being forced into the pulmonary circulation during a rapid ascent from a dive, and can result in ischemia or blockage (20). Autochthonous bubble formation has also been observed in the brain (21). In the spinal cord,

autochthonous bubbles are known to traumatize neurons at the site of nucleation and to compress those adjacent (22).

A number of biomarkers (S100B, NSE and GFAP) are used in the investigation of traumatic brain injury (23). Serum levels of biomarker S100B have been shown to be increased in goats after deep dives with rapid decompression (24). S100B was also investigated in a pilot study with human subjects treated for acute DCS, however an increased concentration was not found in this case (25). Symptoms of brain injury after DCS are often mild and not disabling. However, some individuals suffer for months or years from headaches, memory changes, poor concentration and other neurological symptoms (26). They also resemble the symptoms that follow mild traumatic brain injury (26, 27). Knowledge of brain sequelae during and after a dive is still lacking, both in terms of short and long term effects. Hence, in Paper I, S100B was selected to investigate its relationship to intravascular bubbles following decompression.

In addition to the pathogenic effects of cerebral bubbles after diving, some subclinical changes are proposed. For example, a change in the blood brain barrier (BBB) permeability is found in animals performing simulated dives (28, 29). Decompression has been shown to cause increased permeability of the BBB, as illustrated by leakage of dye (Tryptan blue) into the brain tissue of decompressed rabbits, with dye concentration correlating to visible intravascular bubbles (30).

Immersion

When examining the effects of diving, the pressure gradient created by immersion itself must also be considered. Immersion causes haemodynamic changes via a redistribution of blood flow to the intra-thoracic circulation, and consequently may affect central venous pressure, stroke volume and cause increased diastolic filling and further distension of the heart (31). A rat study performed at our laboratory has shown that immersion before a dry hyperbaric dive leads to an impaired contractility and calcium handling in isolated cardiomyocytes compared to in controls rats (32).

Oxygen level

During diving, the diver may be exposed to increased partial pressures of oxygen, which may cause oxidative stress in exposed tissue, and during saturation diving elevated oxygen levels is suggested to contribute to reduced pulmonary function (33). Oxidative stress is one of the causes for endothelial senescence (34) and endothelial dysfunction (35). Endothelial cell activation may lead to increased expression of adhesion molecules and inflammatory cytokines (36). Pro-inflammatory microparticles are produced during oxidative stress and are found in increased levels in blood after diving. They have been associated with decompression and held responsible for vascular injuries both in humans (37) and in an animal model (38). Vascular health is reflected by the function of the vascular endothelium. In all blood vessels there is a monolayer of endothelial cells that make up the endothelium lying between the smooth muscle layer and the lumen of the blood vessel. The endothelium helps to supply nutrients and oxygen to underlying tissues and organs (39) and plays an important role in maintenance of the vascular homeostasis through control of vasomotor tone, blood cell trafficking, permeability, proliferation, survival, and innate and adaptive immunity; it is consequently involved in most disease states either as a cause or as a target.

Temperature

There is a long-held belief that thermal conditions affect DCS risk and that DCS risk increases with cold water exposures. The diver's temperature can affect the distribution of peripheral blood flow and hence, how much gas is taken up in solution in different tissues (40). In divers using open hot-water suits, body weight loss and dehydration during diving is showed to be due to sweating. Dehydration may reduce tissue perfusion and consequently the elimination of inert gases during decompression (41). In a review by Toner and Ball (42), no studies illustrating a definitive causal relationship between thermal conditions and DCS risk were found. However, there is still some evidence for increased DCS risk if diver is warm on the bottom, cold during decompression and cold on the surface. Conversely, cold conditions during the bottom time of the dive and warm conditions during decompression help to minimize risk of DCS and may also facilitate longer bottom

times (42, 43). These results indicate that conditions reducing on-gassing decreases risk of DCS, while conditions reducing off-gassing increases risk of DCS.

High pressure nervous syndrome (HPNS)

In deep diving (below 150 msw), the compression and pressure in itself can be a direct risk factor for high pressure nervous syndrome (HPNS) (44). Symptoms of HPNS include tremors, involuntary muscle jerks, dizziness and nausea. HPNS is associated with slow waves in the theta band and depression of alpha activity in the brain when measured by EEG (44, 45). The theta activity declines with time while the depression of overall electrical activity shows no improvement with time and worsens with increasing depth (46). However, the clinical relevance of these altered signals is not clear.

Environmental factors in saturation systems

Occupational saturation diving systems consist of a network of closed and pressurized steel chambers installed on board a vessel, from which divers are transported to their place of work in the sea by diving bells. The ambient temperature in the dive systems is typically around 28 - 30 °C with a relative humidity of around 60%, although this may reach 80 - 90 % in periods of intense dive activity. To protect the divers from low temperatures at working depth, they use heated suits that are continuously flushed with heated seawater onto the skin. The seawater is taken from operation site and is pumped through a filter, UV treated, boiled and tempered to 70 °C before sent through the umbilical where it is further cooled to 45 °C be the time it reaches the diver.

The warm and humid environment in the saturation systems favours a rich microbial flora. Gram-negative bacteria are predominant, principally the *Pseudomonas* and the coliform groups, *Klebsiella* and *Escherichia coli*. The *P. aeruginosa* bacterium have modest nutritional demands and are found commonly all over the world, occurring in both fresh and seawater, in soil and on plants and the species is noted for its metabolic versatility and its exceptional ability to adapt to and colonize various ecological niches (47). These bacteria are the cause of thousands of hospital

acquired infections every year and it is a dangerous pathogen for patients with a compromised immune system, such as those with cystic fibrosis (CF), cancer and burns (47-50). However, *P. aeruginosa* rarely infects people with an intact immune system.

There are several theories as to how these bacteria may be introduced to saturation environments. Previously it was believed that the divers brought the bacteria with them and that infection was diver-to-diver, but later studies have rejected this. Several dive vessels have been monitored to map the extension of *P. aeruginosa,* and in 2003 Ahlen et al. (51) published a study demonstrating that seawater is the source of *P. aeruginosa* infection genotype in saturation diving systems. Studies investigating how the bacteria are affected by the environment in the closed chambers have found that the high temperature, humidity and hyperoxic environment contribute to enhanced microbial growth (52).

Pathological effects of environmental factors

Health problems, such as skin and ear infections in divers working on the Norwegian Continental Shelf have been systematically registered since 1985 (53). Within the period from 1990 to 2010, only four incidents of DCS were reported to the Petroleum Safety Authority Norway, while during the same time-period, the number of outer ear infections reported was 201 (4).

These infections are usually caused by the *P.aeruginosa* bacteria (51), which has been a challenge to dive vessels since the beginning of saturation diving. Infectious outbreaks cause costly breaks in operations (54, 55). Results from a survey published in 2010 showed that there was a bacterial load in both divers and in the environment, but they also state that “the infections have no serious consequences for the health of the workers” (52).

Long term immunological effects of P. aeruginosa infections

In relation to the *P. aeruginosa* infections in saturation divers, long-term effects have not been investigated. However, long term infections have been studied in patients suffering from obstructive lung diseases like CF. Patients with CF suffer recurrently from pulmonary infections due to *P. aeruginosa* (48) and have several co-

morbidities, the most prevalent being insulin-dependent diabetes (56). It has been suggested that hyperactivity in the immune system causes destruction of the insulin producing beta-cells in the pancreas, via auto-antibodies that act against heat shock protein 60 (HSP60) (57).

Heat shock proteins are involved in the body's natural defense system and are involved in the folding and unfolding of other proteins (58). HSP60 molecules are highly phylogenetically conserved, with about 50% sequence homology between human HSP60's and those of *P. aeruginosa* (59). Thus, the presence of autoantibodies against HSP60 in patients with CF may be due to human antibodies cross-reacting in a process induced by the presence of bacterial HSP60. This binding of anti HSP-60 antibodies to HSP60 is also thought to be instrumental in the development of atherosclerosis (60). In paper III (61), we show that animals recurrently exposed to *P.aeruginosa* have an immunological response through increased concentration of anti-HSP60 in blood samples. Furthermore, immunization of mice with human sera containing high levels of anti-HSP60 induces atherosclerosis (62). Moen et al. (7) found a higher prevalence of heart diseases that could be atherosclerotic in origin, in occupational divers. Therefore, these results suggest that recurrent infections of *P.aeruginosa* in divers may indeed have consequences for their long term health.

METHODOLOGICAL CONSIDERATIONS

Animal research

The three individual studies which comprise the present thesis, all used a rat model of decompression and hence, all results must be discussed with this in mind. Using animal models is beneficial, as they facilitates controlled studies and allows tissue (particularly CNS tissue) analysis that would not be possible using human subjects. When working with human divers, various factors including diet, weight and activity level may influence the results and are difficult to control for. As most of these variables can be controlled in animal models, isolated physiological responses can be analysed. In addition, these responses are often more apparent when pushing the subjects towards limits greater than could be ethically allowed in human experiments. Therefore, animal research is eminently suitable for dive related studies where it is preferable to use large pressure differentials. In addition, by undertaking whole-animal experiments, it is more likely that a realistic physiological response, which it is possible to measure, will be provoked. Cell cultures are useful for testing exact mechanisms, but some information may also be lost by not taking cell-to cell interaction into account.

Animal model

In the present thesis, female Sprague Dawley rats were used. The choice of animal was based on years of experimental expertise at our Department and in the Applied Physiology group (63, 64). The procedures and the care of experimental animals conformed to the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, and the protocol was approved by the Norwegian Council for Animal Research. Female rats were used, as empirically they are less aggressive and easier to work with. They also have a lower growth rate (65), which is important since weight is crucial when designing a dive profile (as fatter rats are more likely to produce more bubbles) (66). In addition, rats are well suited for cerebral studies since they have a similar cerebral blood supply as in man (67).

Dive profiles

In all three of the papers, rats performed simulated air dives in a 20 L hyperbaric chamber with a continuous air supply (Fig 1). The dive profile is developed in order to provokes a considerable amount of bubbles in 50% of exposed rats, with a body weight between 280-300g (66). Consequently, this dive profile gives a high intra-variability with regard to bubble formation in the exposed groups. This is important to take into consideration when planning the amount of experimental animals that are necessary to provide meaningful results. The dive profile is used both to study the direct effects of decompression and bubble formation, but also to observe the physiological responses that become more apparent when the model is pushed to the extreme.

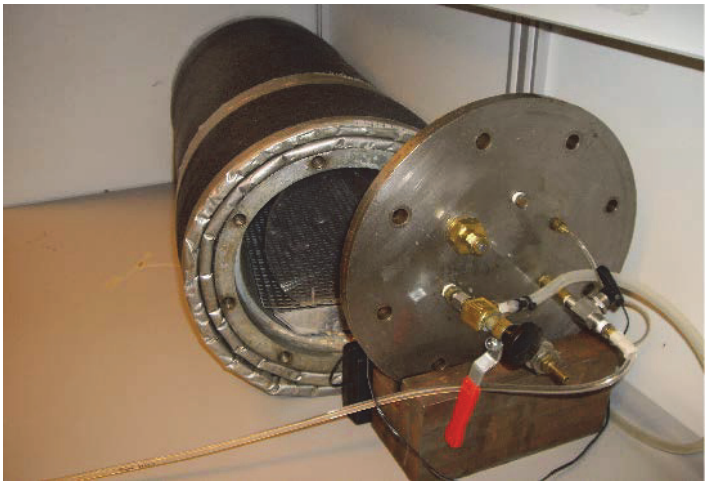

Fig 1: Hyperbaric rat chamber

Independent of dive depth, all animals were compressed at 200 kPa/min and decompressed at a rate of 50 kPa/min after 45 min. The length of the dive was chosen to simulate a saturation dive. It is predicted that the tissues of rats of around 260g body mass will start to saturate after 45 min (68).

In paper I, the rats were compressed to 60 msw (≈ 700 kPa) for 45 min. This dive profile is rather stressful, and approximately 50% of the animals that dive this profile will die from this stress. Hence, in projects where it was necessary to keep the experimental animals alive for prolonged periods after the simulated dive, the stress

caused by the dive needed to be reduced. This was achieved by reducing both the depth and the bottom time. For example in paper II, brain MRI was performed at one hour, one week and two weeks after the dive, hence the dive depth was reduced to 50m (≈ 600kPa). Three out of nine rats diving this profile died, hence it may be said that this profile is still relatively provocative, but conservative enough for most animals to survive and therefore useful for this project.

In paper III, the general stress response from a dive was of interest, rather than the more extreme response to a particularly provocative dive and so the dive depth could be reduced considerably. In order to keep the animals throughout the experimental period for nine weeks, repeated dives to 30m (≈ 400kPa) were performed.

Anaesthesia

Anaesthesia was used in all studies; during examination of rats after decompression, in order to facilitate tissue and blood sampling, to immobilise rats for investigation by transthoracic echocardiography of the heart and surrounding arteries and to avoid any discomfort to the experimental animals.

Two different types of anaesthetics were used. In paper I and III, a Haldol mix (Haldol 0.33mg, Fentanyl 0.05mg and Midazolam 0.5mg; 0.4 ml/100g of bodyweight) was used. This anaesthetic was given subcutaneously and induced anaesthesia within 10 min, so allowing the observation of several animals at once. However, one drawback is that some of the components used in the mixture may influence the physiological responses under study. Also, not all animals tolerate this anaesthetic mixture and on a few occasions, control animals died. However, since all animals received the same anaesthetics, we feel confident that the results obtained are uniform and reliable.

In paper II, Isoflurane (1%) gas was used, in combination with medical air. Isoflurane is an inhalation anaesthetic and one of its benefits is that it is easier to control the depth of anaesthesia.

Once anaesthetised, the core temperature needs to be monitored constantly. In a recent experiment where core temperature was recorded, it was found that body temperature dropped 2 - 3 degree Celsius (°C) almost immediately, despite using a heat blanket to cover the rats (unpublished data). Similar rat studies in the future should consider using a temperature controlled incubator in order to maintain a stable core temperature.

Bubble detection

Bubble formation is considered to be an indicator of the stress provoked by the dive and can be monitored using ultrasound (both Doppler and imaging) (Fig 2). When monitoring bubble formation in the rat, the pulmonary artery is usually chosen as the preferred position for measurement, as all of the venous blood flows through this artery. In paper I, the pulmonary artery was monitored for gas bubbles using a 10 MHz transducer connected to a FiVe ultrasound scanner (GE Vingmed Ultrasound AS, Norway) (Fig 3) and in paper II, the pulmonary artery was monitored using a 35 MHz transducer (Vevo770, Visual Sonics, Toronto, ON, Canada). Bubbles can be seen on the monitor as bright spots, and subsequently be verified with Doppler. The bubble load was graded on a 0 to 5 scale according to a previously described method (69). One of the benefits of using ultrasound is that it is a non-invasive way of detecting decompression stress and operators can be trained to grade images relatively easily. However, in experiments performed by our research group, it has been observed that bubble formation varies a great deal between rat individuals. This is also found in rats after heliox saturation dives (70). This makes assessment of the effect of any interventions challenging. We are currently studying this variation, which is also seen in other species, but the employment of relatively high subject numbers should help to maintain the robust nature of studies where bubbles are the primary measure of decompression stress.

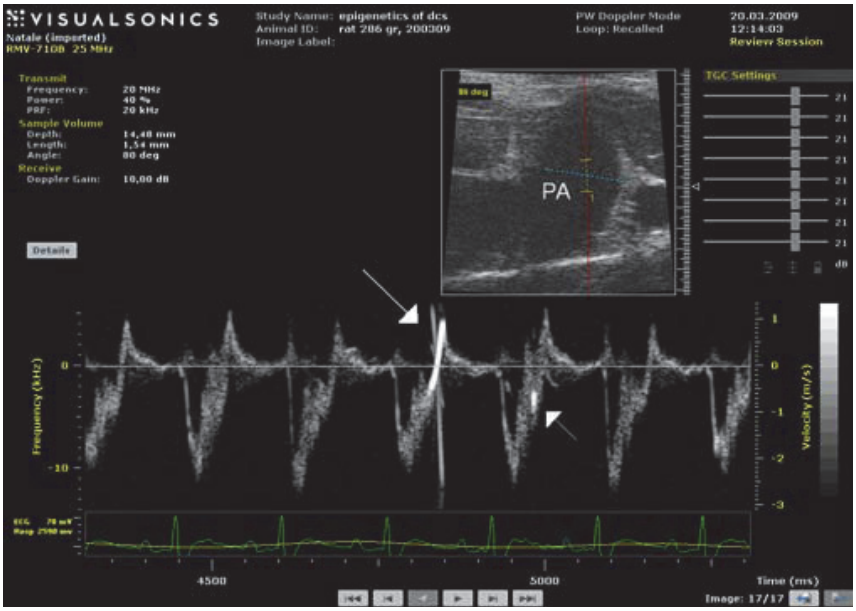

Fig 2: Ultrasound and Doppler picture of rat with bubble in pulmonary artery. The arrows show detected bubbles on Doppler (Rasdal)

Fig 3: Performing ultrasound monitoring on rats on the FiVe ultrasound scanner

Endothelial function examination by tension measurements

In paper II, we measured vascular endothelial function by a wire myograph system (Danish Myo Technology) (Fig 4) in ring segments from the abdominal aorta. The system is based on measuring force in small rings of vascular vessel segments and thus, allows you to measure responsiveness to hormones and other agonists. The measurement procedure is described in detail in a previous study (71).

Fig 4: Myograph system set up at the laboratory

Being the innermost cell-layer in blood vessels, the endothelium is of interest in relation to diving because it is in direct contact with bubbles and also because it plays an important role in maintenance of vascular homeostasis through control of vasomotor tone, blood cell trafficking, permeability, proliferation, survival, and innate and adaptive immunity (72). The endothelium is shown to be affected by diving both in animals and man (11, 12) and it is thought to be involved in most if not all disease states, either as a primary determinant of pathophysiology or as a victim of collateral damage (72).

Training and experience is imperative when using this technique in order to obtain physiologically relevant results and also, in order to be aware of several factors that can potentially influence the results. For instance, basal values and maximal values are determined prior to the experimental measurements, where the contractility and

relaxation responses of the vessel are observed. It is standard practice to report relaxation measurements as a percentage relative to the pre-test maximum, therefore an incorrect pre-test measurement will intrinsically affect the results and may make them inaccurate. Consequently, it is very important that the true basal and maximal values for the segments are found before adding new agonists.

The abdominal aorta was chosen for this study because it is easily accessible and therefore good for standardization and it has been used for analysis of endothelial function in studies performed at our laboratory (73, 74). However, due to the lack of correlation between abdominal aorta endothelial function and cerebral circulation and that the preparation for histological fixation with flushing with paraformaldehyde is not ideal for subsequent functional measurements, the results from the tension measurements were excluded from the paper. For future studies it should be considered using distributing arteries containing layers of smooth muscle with a better capability to respond to tension measurements. Endothelial measurements performed on a cerebral artery would have provided more valuable information. This should be examined in future animal studies on endothelial function in relation to diving.

Activation of the immune system by immunisation

In theory, by exposing an animal to an immunogen in a controlled way, the immune system should develop a defence against a substance that is foreign to the body. In paper III, we performed an immunisation in order to activate the immune system against the bacteria *Pseudomonas aeruginosa.*

The vaccine in paper III was developed and optimised by a technician at our laboratory. The rats were immunised with bacterial HSP60, 0.2 ml every other week, for five times in total over a nine week period. The results show that the immunization protocol is valid, as an increase in circulating antibodies was seen. However, a protocol weakness is that the animals were sacrificed shortly after the last immunization. Ideally, it would have been valuable to know for how long the activated immune response would last. To increase the knowledge on the

relationship between dive exposures and immunization, it would be better to finish the immunization protocol before diving. This can be executed in a follow up study.

Serum analyses by Enzyme linked immunosorbent assay (ELISA)

There are, to date, no specific laboratory tests to aid in the diagnosis and assessment of the severity of DCS. Presently, clinicians give subjective diagnoses based on visible symptoms and available information. Accordingly, there has recently been increasing interest in finding relevant, circulating biomarkers for DCS. Montcalm-Smith and co-workers (2007) published a paper on stress biomarkers present in rats experiencing DCS (75). They concluded that within 30 minutes there are gene expression changes in animals with signs of DCS.

Serum analyses can be performed by use of an enzyme linked immunosorbent assay (ELISA). The ELISA technique has high sensitivity and can detect the amount of a given protein, antibody, or antigen in a sample and is used as a diagnostic tool in medicine and in biomedical research. For analyses used in diagnostics, there are commercially available kits (paper I), but for other analyses it is possible to build "home-made" kits (paper III). Use of a commercially available kit ensures quality, but it may not be sensitive enough for specific scientific purposes. When extrapolating results from an ELISA, a standard curve is applied. If the measured points fall outside the range of the standard curve then they will have diminished weight in terms of accuracy and certainty.

Brain examination by magnetic resonance imaging (MRI)

In paper II, MRI was used to examine the brains of rats after simulated diving (Fig 5). The MRI scans and following analyses were performed by co-workers at the MRI-facility at NTNU using a 7T Bruker Biospec MR scanner.

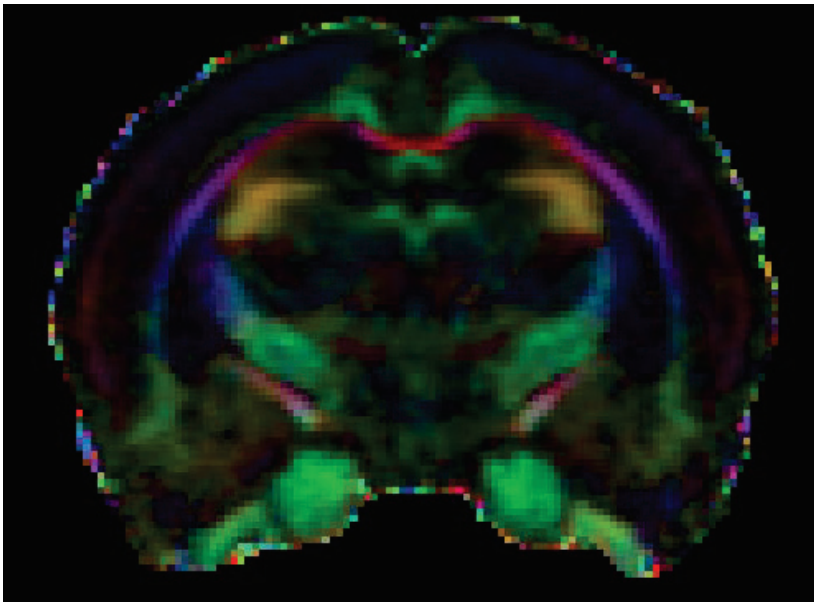

Fig 5: Image showing representative fractional anisotropy (FA) map

MRI has been used in attempts to reveal functional and structural changes in divers, but the results are conflicting. In one study, white matter spots or “lesions” were reported to be more prevalent in a group of recreational divers than in controls (76), while this is not found in other studies (77, 78)

More advanced MRI techniques, such as diffusion MRI, which maps the diffusion process of water molecules in the tissue, have also been used to track physiological changes. A Norwegian study on former divers found increased diffusion in brains of divers compared to controls and a decreased blood flow in some parts of the brain (7).

One of the challenges when using MRI is to correctly interpret any irregularities revealed and to determine whether they are real or can be explained as an artefact of the program used for analyzing the images. Thus, as with any other procedure, it is important to use well trained personnel for analyses of MRI data.

SUMMARY OF RESULTS

Paper I: S100B and its relation to intravascular bubbles following decompression

Dived rats show significantly higher levels of the CNS injury sensitive biomarker S100B in serum than control rats. Following the deepest dive to 700 kPa, there was a significantly higher bubble grade observed than following the dive to 400 kPa and S100B level was significantly higher in rats with a high bubble grade (> 2) than the rats with no bubbles or a low bubble grade (0 - 2) (Fig 6). It was concluded that the correlation between bubble grade/dive depth and an increase in the serum protein level of S100B indicated that this protein may be used as a biomarker for neurological damage caused by decompression.

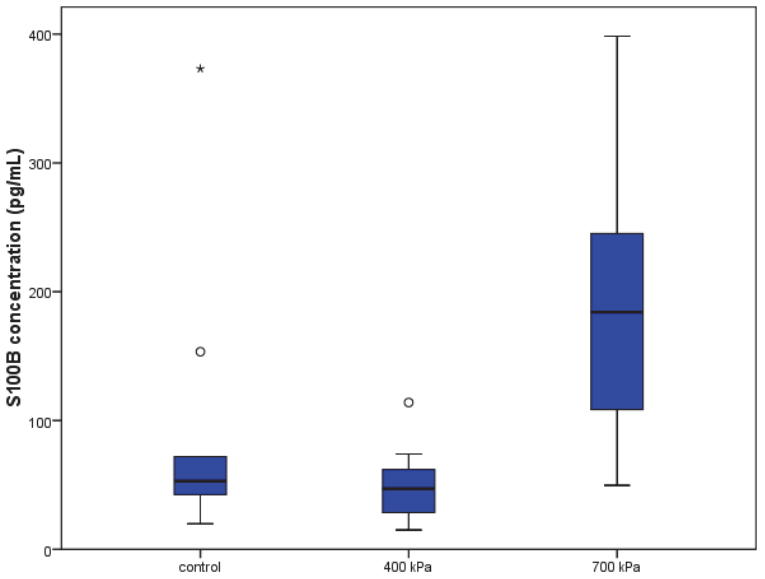

Fig 6: Box plot showing S100B concentration (pg/mL) in serum of control animals (n = 9), animals compressed to 400 kPa (n = 7) and 700 kPa (n = 11), p = 0,037.

Paper II: MRI and histology on brain from decompressed rats shows circulatory, but no structural changes

Rats exposed to simulated diving show changes in cerebral circulation one hour after decompression, having increased relative signal intensity (RSI) in the frontal cortex and thalamus (Fig 7). On examination of histology made two weeks after decompression, no differences between decompressed rats or controls at specific locations (- 3.25 mm from the bregma) corresponding to MRI findings were detected. One and two weeks after decompression, increased T_2 in the brain stem of dived rats was found. Increased T_2 signals result from a prolonged decay of magnetization of hydrogen protons after they are perturbed from alignment with the magnetic field of the MRI instrument. A rise in signal generally implies that hydrogen protons of water are less densely packed and ordered in the region of the high signal. This may be an indication of edema, but was not verified on histology (- 10.30 mm from the bregma). BBB leakage was not detected on MEMRI or histology (Fig 8).

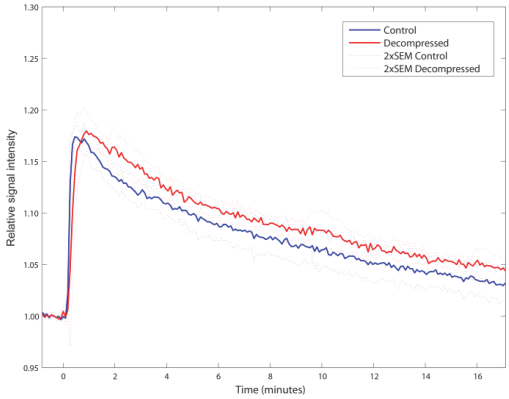

Fig 7: Plot of the mean relative signal intensity for the whole brain (cerebrum) with time after injection of contrast agent. Blue lines represent mean for control animals with 95% CI and red lines represent mean for decompressed animals with 95% CI.

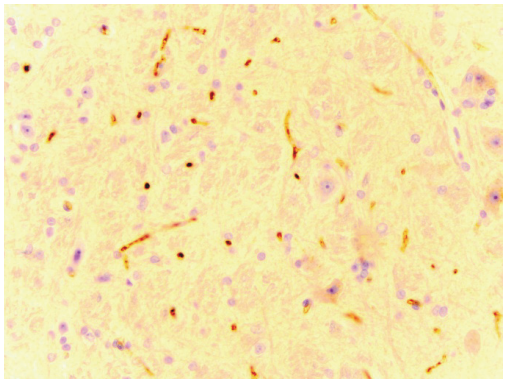

Fig 8: Pontine area stained to evaluate BBB leakage (albumin). Picture is taken with a 40x objective on a Nikon Eclipse 80i light microscope.

Paper III: Concentration of circulating autoantibodies against HSP 60 is lowered after diving in comparison to non-diving rats

This study investigated whether rats immunised with *P. aeruginosa* produced autoantibodies against their own HSP60 and whether diving influenced the level of circulating anti-HSP60 antibodies. Results showed that the immunised rats (group 1) had a significant increase in the level of autoantibodies against HSP60, while no autoantibodies were detected in the dived rats (group 2). The rats both immunised and dived (group 3) showed no significant increase in circulating autoantibodies against HSP60 (Fig 9). A possible explanation may be that HSP60 is expressed during diving and that cross-reacting antibodies are bound to HSP60.

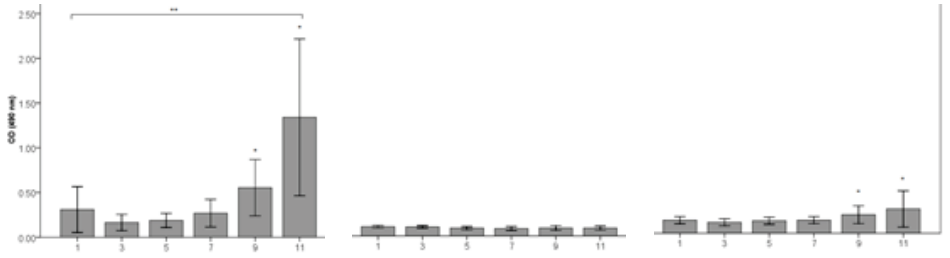

Fig 9: Bars represent level of anti-HSP60 analysed by ELISA in blood samples taken every other week, before each immunization. ** There is a significant increase in anti-HSP60 level from week one to week 11 ($p < 0.01$) in group 1. Bars represented by * is significantly different between groups 1 and 3. In group 2, there is no change in circulating anti-HSP60. Results are presented as mean OD values measured at 490nm. The vertical lines represent the standard deviation.

DISCUSSION

The present thesis investigates the effect of diving on a number of biomarkers in the rat. We aimed to identify factors affecting possible short and long term health effects in occupational divers. The main findings were that rats that have undergone simulated diving had indications of CNS injury by a higher serum level of S100B. However, dived rats did not show any structural damage in the brain on MRI and histology, but differed from non-dived control rats in terms of their cerebral circulation detected on MRI. Repeated exposure to bacterial HSP60 activated the immune system.

Central nervous system and occupational diving

The long-term effects of diving have been debated for many years. In 1993 and 2005, international consensus conferences took place in Norway to discuss this subject. At the consensus conference at Godøysund in 1993 it was concluded that: *"There is evidence that changes in bone, the central nervous system and the lung can be demonstrated in some divers who have not experienced a diving accident or other established environmental hazards. The changes are, in most cases, minor and do not influence the diver's quality of life. However, the changes are of a nature that may influence the diver's future health. The scientific evidence is limited, and future research is required to obtain adequate answers to the questions of long-term health effects of diving"* (79).

Exposure to hyperbaric environments is associated with risk of developing DCS, AGE, neurological symptoms and pulmonary dysfunction (21, 80, 81). Possible long term health effects of working as a professional diver has been discussed and studied for many years. There is still no agreement on how and to what degree the CNS is involved. Available information on the acute responses to evident CNS injury after diving is mostly based on case studies and hence, is based on small sample sizes.

In paper I, the findings indicated that there may be a level of sub-clinical CNS injury immediately after diving, indicated by an increased concentration of S100B in serum

samples from dived rats in comparison to non-dived controls. It cannot be said definitively whether the increase in S100B was due to a significantly higher amount of bubbles being present, or to the changes in pressure or oxygen concentration, as the highest bubble grades in this study were recorded after the deepest dive. However, in a recent rat study where no detectable bubbles were present after a simulated dive, the level of S100B was not increased (82). It is well documented that there is an increased risk of DCS with increasing number of bubbles (16) and neurological symptoms in divers are found to be correlated to having untreated DCS symptoms (83). Consequently, it would seem that the amount of vascular bubbles may be an important indicator of acute injury in the CNS associated with diving (84).

In a prospective pilot study investigating the relationship between acute DCS and S100B, the serum level was not elevated in human divers (25). Venous blood samples were taken prior to first recompression treatment and again after the last treatment and the average time between the dive and the first recompression treatment were 3 ± 2 days (25). Hence, the negative findings may be explained by the time lapse between dive and sample time; S100B has a relative short half-time (30- 120 minutes) (85, 86) and could therefore be excreted before samples were taken.

It has been established that the biomarker used in paper I, S100B, is released following injury to the CNS and further, the concentration of the biomarker in blood samples is related to the degree of injury after acute stroke (87). However, S100B is not only specific for brain damage and is also found in increased levels in people where no brain damage is suspected or plausible (e.g. runners) (88). Therefore, in ideal circumstances and for clinical purposes, this biomarker should be used together with other biomarkers of CNS injury.

In research related to cerebral ischemia and traumatic brain injury, considerable work has been invested in finding reliable biomarkers for diagnosis, prediction of clinical outcome and for estimating effectiveness of therapy. Cerebral ischemia provokes activation of a cascade of molecular events and consequently, several potential biomarkers are released into the peripheral blood (89). One could believe that similar cascades take place in response to neurological DCS or to cerebral

embolism due to decompression. In traumatic brain injury research, S100B is sometimes used together with neuron specific enolase (NSE) and glial fibrillary acidic protein (GFAP). While S100B is expressed in glial cells and mostly in astrocytes, NSE is primarily expressed in neurons. GFAP is not found outside the CNS, but in the astroglial cytoskeleton and is therefore more specific for CNS injury.

One of the challenges posed when using biomarkers is to choose that most suitable for the process under study. In addition, using a single biomarker to examine pathological status does not necessarily reflect anything of physiological significance, if not supported by other measurements; it will only give a snapshot of the physiological response to diving. In addition to biomarkers linked to cellular damage, inflammation sensitive biomarkers and those related to oxidative stress are of importance. Those related to ischemic stroke are, amongst others, interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α), acting as biomarkers of inflammatory reactions and ferritin and nitric oxide metabolites for oxidative processes (89). IL-6 levels in serum are found to be affected by deep open sea saturation diving (90). However, it is not known whether this elevation is due to cerebral inflammation or inflammation elsewhere in the organism.

After finding higher levels of S100B in response to diving in paper I, it was of interest to study the brains of decompressed animals further in a controlled setting, using advanced MRI techniques in vivo. In MRI, contrast agents are often used as biomarkers of cellular damage or change in circulation, and hence it is a suitable imaging technique for research involving the CNS.

In paper II, our main finding in the acute phase right after diving, was altered brain perfusion. The results from the acute phase are based on RSI measurements from DCE MRI. RSI calculations are based on measurement of the concentration of a contrast medium; hence the cause of the difference cannot be defined. It was observed that more blood is detected in two regions of the brain, the prefrontal cortex and the thalamus. It is not possible to conclude if this was caused by a leakage through the blood brain barrier. However, there are no indications of BBB leakage in the shape of the curve from the contrast agent elimination phase or in the comparison of post-contrast to pre-contrast images. The contrast agents were

injected into the tail of the rat; hence the difference in the measured signal intensity may be because of events between the tail and the brain, so the changes observed in the brain might be more a symptom than a cause.

Increased cerebral blood flow has been shown to be a result of an “overshoot” response to a decreased blood flow during hyperoxia (91). This may also be applicable to our results on increased RSI. The decrease in cerebral circulation is explained by a vasoconstriction caused by hyperoxia (92). Hyperoxia is also shown to increase cerebral cortex blood flow and possibly due to elevations of steady state $^{\cdot}NO$ concentrations (93). Moen and colleagues (7) report changes in diffusion in the cerebellum and bilateral regions in the putamen and frontal lobe. Hyperoxic ventilation is also found to cause changes in activity of brain areas involved in autonomic and hormonal control, including the hypothalamus and regions that control the hypothalamus (94). The perfusion and hormonal changes caused by inhalation of 100% O_2 could initiate a cascade of central and peripheral injuries through oxidative stress processes commonly reported with high oxygen ventilation (95).

Long term CNS effects

In paper II, it was of interest to carry out a longitudinal rat study after decompression to investigate the development of brain injury after diving. We did not find any structural changes in the brains of dived rats on MRI or on histology, but on day 14 after diving, increased T_2 in the brain stem of dived rats was found. Increased T_2 signals result from a prolonged decay of magnetization of hydrogen protons after they are perturbed from alignment with the magnetic field of the MRI instrument. A rise in signal generally implies that hydrogen protons of water are less densely packed and ordered in the region of the high signal. This may be an indication of edema formation in pontine area of brain stem on MRI. Cerebral edema caused by gas emboli are found in patients after heart surgery (96). In previous experiments cerebral edema was shown in dived rats using a simple gravimetric method (97). However, the protocol for staining and fixation used in this paper was not compatible with the procedure for measuring specific gravity; therefore we do not have

measurements on specific gravity that might have shown edema. One can speculate on whether the signs of edema formation in the pontine area are caused by gas embolization, but we cannot establish this based on our analyses. We did not confirm edema on histology performed on tissue from area matched with MRI results. H&E staining of the pontine area showed no swelling of the endothelium, no vacuolisation or any signs of anoxia. CD68, GFAP and albumin staining showed no differences between the groups. Microglia is sensitive for tissue damage and with no staining of CD68 and activated microglia, we conclude that there is no evidence of tissue damage in pons present 14 days after diving. Astrocytes, stained by GFAP, appear normal and show no sign of isomorphic gliosis or anisomorphic astrocytic gliosis. A possible explanation for the altered brain perfusion detected on MRI is a change in microvascularity due to decompression. This has been suggested previously (7).

Neurological symptoms amongst commercial divers have been evaluated in epidemiological and clinical studies. In one study, CNS lesions were seen on magnetic resonance images more prevalent in recreational divers than in controls (76). However, other studies have not been able to repeat this finding (77, 78) and it is also noteworthy that the significance of white matter lesions is not clear.

Abnormal electroencephalography (EEG) results (4-6 Hz theta activity) have been shown in the temporal or frontal regions after recompression treatment in five of 15 divers with cerebral DCS (98). A study on former divers found MRI signals indicating an increased movement of water (diffusion) in brains of divers compared to controls and a decreased blood flow (perfusion) in some parts of the brain (7). The increased diffusion was explained as a sign of the degradation process in the brain's microstructure, while changes in perfusion can be explained by changes in the blood vessel network in the brain. This study is highly relevant to the results found in our rat model, as presented in paper II.

Saturation divers report problems with concentration and memory more frequently than control subjects, and it is suggested that CNS injuries cause this deficit (3, 99). Conspicuous fatigue, visual disturbances, dizziness, nausea and changes in skin sensitivity are amongst self-reported symptoms that have connections to

decompression (83). Saturation divers who have had DCS are reported to have a poorer quality of life according to questionnaire results (2).

The effect of asymptomatic diving upon the CNS is both controversial and uncertain, and there are conflicting reports of cognitive dysfunction in divers; Todnem et al (3) reported impaired quality of life amongst saturation divers, while Ross and co-workers concluded that this was caused by factors other than diving (99). In 2010, the Norwegian National Institute of Occupational Health concluded that, based on the available literature, there is not enough evidence to draw any conclusions concerning incident-free diving causing undesirable long term effects on the CNS (100). Under-reporting of incidents is also a problem when collecting meaningful and reliable data (101). Based on divers' answers (both sports- and occupational divers) in questionnaires on the health effects of air diving, it was shown that there was a correlation between decompression problems and CNS symptoms in divers not treated for DCS. It is notable that the very mild symptoms, divers feel post decompression are often considered to be harmless and are seldom reported (83).

Environmental hazards

In the last paper (paper III), the rats' immune reaction to repeated exposures of a bacterium known to be a challenge in saturation systems, *P. aeruginosa*, was investigated. Exposure to this bacterium is known to cause skin disease in divers living in saturation systems and has led to some concerns. In the statistics for 1985-99, reported by the Norwegian petroleum directorate, infections caused by *P. aeruginosa* were highly evident. *P. aeruginosa* is a problem in dive vessels, but the long term health consequences of exposure are not the primary focus of the reported statistics. Instead, health concerns are focused on the acute effects of the bacteria. Thus, in paper III, focus centered on the possible long term effects derived from repeated exposures to *P. aeruginosa*.

As it is thought that human antibodies may cross react in a process induced by the presence of HSP60, the immune reactions were studied using anti-HSP60 as a

biomarker. The study was designed to observe three groups, each with different exposures to separate the responses: the immunologic response to the bacteria, the immunologic response with anti-HSP60 to diving and the immunologic response when combining diving with bacterial exposure. The immunologic response to the bacteria increased over time by an increasing level of circulating auto-antibodies against HSP60 in rats with repeated immunisations with *P.aeruginosa*. The pressure exposure did not itself produce circulating auto-antibodies and we did not find any increase in level of circulating antibodies during the experimental period in the dived rats. However, we were not able to detect circulating autoantibodies against HSP60 in rats both immunized and dived. This may be due to binding of the circulating auto-antibodies seen in the dived rats to HSP60 expressed during diving.

The main conclusions from paper III are that the higher autoantibody levels observed in rat serum after combining bacterial exposure and diving, indicate that cross-reacting autoantibodies are present. Hence, it seems likely that the exposure to *P. aeruginosa* in the diving environment and recurrent skin-infections (51) may give rise to production of auto-antibodies against HSP60 that in turn may give detrimental long term effects.

At present, saturation diving is not associated with a high risk of DCS and even though there is room for improvement in decompression procedures, it seems that pressure changes *per se* are not the biggest health risk for saturation divers working on the Norwegian shelf today. Saturation divers are exposed to several environmental hazards that are not directly linked to the physiology of diving. These include welding fumes, dust, radiation from underwater x-raying (in accidents), biological hazards and chemical agents (102). In essence, diving is just another risk factor intrinsic to the dangerous environment in which they work. We still know too little about the basal physiological changes that occur under static or changing pressure to predict the consequences of exposure to environmental hazards during diving.

OVERALL CONCLUSION & FUTURE PERSPECTIVES

The present thesis presents three papers that suggest specific changes in physiology during diving. We suggest that cerebral blood flow is affected by the hyperbaric conditions, that the CNS may be injured due to bubble load during dives and that exposure to the bacteria *P. aeruginosa* during diving may cause cross-reactions that are possibly harmful in a long term health perspective. These results imply that environmental control is very important to ensure safe diving for occupational saturation divers.

Working underwater will continue to draw our attention to the understanding of the biological mechanisms that maintain the physiological balance in the body of a diver, both in relation to short- and long-term health of the diver. There is a need for prospective studies of the central nervous system after saturation diving, where retrospective studies have provided inconclusive or conflicting results. Divers are in their work exposed to pollutants and potentially toxic levels of breathing gas components that both may confer adverse health effects.

With advancing technologies, future studies should aim at targeting the biochemical pathways behind the adverse effect of decompression. Continued focus should be on other biomarkers for damage to the CNS following diving, and the link from exposure to *P. aeruginosa* and to atherosclerosis suggested in the present thesis. Methods already in use need to be standardised and validated for better understanding of the physiological responses due to dive related exposures.

REFERENCES

1. Gernhardt M, Lambertsen C. Commercial diving. In: Brubakk AO NT, editor. Bennett and Elliott's Physiology and medicine of diving. Cornwall: Saunders; 2003. p. 29-45.

2. Irgens A, Gronning M, Troland K, Sundal E, Nyland H, Thorsen E. Reduced health-related quality of life in former North Sea divers is associated with decompression sickness. Occup Med (Lond). 2007 Aug;57(5):349-54.

3. Todnem K, Nyland H, Kambestad BK, Aarli JA. Influence of occupational diving upon the nervous system: an epidemiological study. Br J Ind Med. 1990 Oct;47(10):708-14.

4. Report from the DSYS database. Stavanger: The Petrolium Safety Authority Norway2010.

5. de Graeff-Meeder ER, Rijkers GT, Voorhorst-Ogink MM, Kuis W, van der Zee R, van Eden W, et al. Antibodies to human HSP60 in patients with juvenile chronic arthritis, diabetes mellitus, and cystic fibrosis. Pediatr Res. 1993 Oct;34(4):424-8.

6. Prohaszka Z, Duba J, Horvath L, Csaszar A, Karadi I, Szebeni A, et al. Comparative study on antibodies to human and bacterial 60 kDa heat shock proteins in a large cohort of patients with coronary heart disease and healthy subjects. Eur J Clin Invest. 2001 Apr;31(4):285-92.

7. Moen G, Specht K, Taxt T, Sundal E, Groning M, Thorsen E, et al. Cerebral diffusion and perfusion deficits in North Sea divers. Acta Radiol. 2010 Nov;51(9):1050-8.

8. Bert P. La Pression barometrique, recherches de physiologie experimentale. Columbus, Ohio: College Book Company; 1878.

9. Boycott AE, Damant GC, Haldane JS. The Prevention of Compressed-air Illness. J Hyg (Lond). 1908 Jun;8(3):342-443.

10. Francis TJR, Mitchell SJ. Pathophysiology of Decompression Sickness. In: Brubakk AO, Neuman TS, editors. Bennett and Elliott´s Physiology and Medicine of Diving. 5th ed. Cornwall: Saunders; 2003. p. 530-57.

11. 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.

12. 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.

13. Francis T, Mitchell S. Manifestation of decompression disorders. In: Brubakk AO NT, editor. Bennett and Elliott's Physiology and medicine of diving. Cornwall: Saunders; 2003. p. 578-99.

14. Francis TJR, Pearson RR, Robertson AG, Hodgson M, Dutka AJ, Flynn ET. Central nervous system decompression sickness: latency of 1070 human cases. Undersea Biomed Res. 1989;15(6):403-17.

15. Edmonds C, Lowry C, Pennefather J. Diving and subaquatic medicine. 3rd ed. Oxford: Butterworth-Heinemann; 1992.

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

17. Vann RD, Butler FK, Mitchell SJ, Moon RE. Decompression illness. Lancet. 2011 Jan 8;377(9760):153-64.

18. Newton H, Padilla W, Burkart J, Pearl D. Neurological manifestations of decompression illness in recreational divers - the Cozumel experience. Undersea Hyperb Med. 2007(34):349-57.

19. 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.

20. Gorman DF, Browning DM. Cerebral Vasoreactivity and Arterial Gas Embolism. Undersea Biomed Res. 1986 Sep;13(3):317-35.

21. Francis TJ, Dutka AJ, Hallenbeck JM. Patophysiology of decompression sickness. In: Bove AA, Davis JC, editors. Diving medicine. Philadelphia: Saunders; 1990. p. 170-87.

22. Francis TJR, 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;47:475-87.

23. Zurek J, Fedora M. The usefulness of S100B, NSE, GFAP, NF-H, secretagogin and Hsp70 as a predictive biomarker of outcome in children with traumatic brain injury. Acta Neurochir (Wien). 2012 Jan;154(1):93-103; discussion

24. Jurd K, Parmar K, Seddon F, Loveman G, Blogg S, Thacker J, et al. Serum S-100B as a marker of neurological events in goats following direct decompression in a simulated disabled submarine scenario. UHMS Meeting Abstracts. 2001.

25. Poff DJ, Wong R, Bulsara M. Acute decompression illness and serum s100beta levels: a prospective observational pilot study. Undersea Hyperb Med. 2007 Sep-Oct;34(5):359-67.

26. Dutka AJ. Long term effects on central nervous system. In: Brubakk AO NT, editor. Bennett and Elliott's Physiology and medicine of diving. Cornwall: Saunders; 2003. p. 680-99.

27. Nolan S. Traumatic brain injury: a review. Crit Care Nurs Q. 2005 Apr-Jun;28(2):188-94.

28. Nohara A, Yusa T. Reversibility in blood-brain barrier, microcirculation, and histology in rat brain after decompression. Undersea Hyperb Med. 1997;24(1):15-21.

29. Hjelde A, Bolstad G, Brubakk AO. The effect of air bubbles on rabbit blood brain barrier. Undersea Hyperb Med. 2002 Spring;29(1):31-8.

30. Chryssanthou C, Springer M, Lipschitz S. Blood-brain and blood-lung barrier alteration by dysbaric exposure. Undersea Biomed Res. 1977 Jun;4(2):117-29.

31. Risch WD, Koubenec HJ, Beckmann U, Lange S, Gauer OH. Effect of Graded Immersion on Heart Volume, Central Venous-Pressure, Pulmonary Blood Distribution, and Heart-Rate in Man. Pflug Arch Eur J Phy. 1978;374(2):115-8.

32. Gaustad SE, Brubakk AO, Hoydal M, Catalucci D, Condorelli G, Dujic Z, et al. Immersion before dry simulated dive reduces cardiomyocyte function and increases mortality after decompression. J Appl Physiol. 2010 Sep;109(3):752-7.

33. Thorsen E, Segadal K, Reed JW, Elliott C, Gulsvik A, Hjelle JO. Contribution of Hyperoxia to Reduced Pulmonary-Function after Deep Saturation Dives. J Appl Physiol. 1993 Aug;75(2):657-62.

34. Erusalimsky JD. Vascular endothelial senescence: from mechanisms to pathophysiology. J Appl Physiol. 2009 Jan;106(1):326-32.

35. Montezano AC, Touyz RM. Reactive oxygen species and endothelial function--role of nitric oxide synthase uncoupling and Nox family nicotinamide adenine dinucleotide phosphate oxidases. Basic Clin Pharmacol Toxicol. 2012 Jan;110(1):87-94.

36. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation. 2007 Mar 13;115(10):1285-95.

37. Yang M, Milovanova TN, Bogush M, Uzun G, Bhopale VM, Thom SR. Microparticle enlargement and altered surface proteins after air decompression are associated with inflammatory vascular injuries. J Appl Physiol. 2012 Jan;112(1):204-11.

38. Thom SR, Yang M, Bhopale VM, Huang S, Milovanova TN. Microparticles initiate decompression-induced neutrophil activation and subsequent vascular injuries. J Appl Physiol. 2011 Feb;110(2):340-51.

39. Sowa G. Caveolae, caveolins, cavins, and endothelial cell function: new insights. Front Physiol. 2012;2:120.

40. Mekjavic I, Tipton M, Eiken O. Thermal considerations in diving. In: Brubakk AO NT, editor. Bennett and Elliott's Physiology and medicine of diving. Cornwall: Saunders; 2003. p. 115-52.

41. Hope A, Hjelle J, Aanderud L, Aakvaag A. Time and temperature effects on body fluid loss during dives with the open hot-water suit. Aviat Space Environ Med. 2005 Jul;76(7):655-60.

42. Toner C, Ball R. The effect of temperature on decompression and decompression sickness: A critical review. Technical report. Silver Spring: Naval Medical Research Institute2004.

43. Gerth W, Ruterbusch V, Long E. The influence of thermal exposure on diver susceptibility to decompression sickness. Technical report. Arlington: Office of naval research2007. Report No.: NEDU-TR-06-07.

44. Bennett PB, Rostain JC. The high pressure nervous syndrome. In: Brubakk AO NT, editor. Bennett and Elliott's Physiology and medicine of diving. Cornwall: Saunders; 2003. p. 323-58.

45. Vaernes RJ, Bergan T, Warncke M. Hpns Effects among 18 Divers during Compression to 360 Msw on Heliox. Undersea Biomed Res. 1988 Jul;15(4):241-55.

46. Bennett PB, Dossett AN. EEG activity of rats compressed by inert gases to 700 feet and oxygen-helium to 4000 feet. Aerosp Med. 1973 Mar;44(3):239-44.

47. Bergan T. Human- and animal-pathogenic members of the genus Pseudomonas. In: Starr M, Stolp H, Trüfer H, Balows A, Shlegel H, editors. The Prokaryotes - a Handbook on Habitats, Isolation and Identification of Bacteria Berlin: Springer-Verlag; 1981. p. 666-700.

48. Govan JR, Nelson JW. Microbiology of lung infection in cystic fibrosis. Br Med Bull. 1992 Oct;48(4):912-30.

49. Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. Pediatr Pulm. 2002 Aug;34(2):91-100.

50. Horino T, Chiba A, Kawano S, Kato T, Sato F, Maruyama Y, et al. Clinical characteristics and risk factors for mortality in patients with bacteremia caused by Pseudomonas aeruginosa. Intern Med. 2012;51(1):59-64.

51. Ahlen C, Mandal LH, Iversen OJ. An in-field demonstration of the true relationship between skin infections and their sources in occupational diving systems in the North Sea. Ann Occup Hyg. 2003 Apr;47(3):227-33.

52. Van Rees Vellinga TP, Sterk W, Van Dijk FJ. The effectiveness of a health-surveillance program for caisson saturation divers in a tunnel-boring machine: a microbiological survey. Undersea Hyperb Med. 2010 Nov-Dec;37(6):433-46.

53. Ahlen C, Mandal LH, Iversen OJ. Identification of infectious Pseudomonas aeruginosa strains in an occupational saturation diving environment. Occup Environ Med. 1998 Jul;55(7):480-4.

54. Alcock SR. Acute otitis externa in divers working in the North Sea: a microbiological survey of seven saturation dives. J Hyg (Lond). 1977 Jun;78(3):395-409.

55. Thalman E. A prophylactic program for the prevention of otitis externa in saturation divers, research report. Washington, DC: US Navy Experimental Diving Unit, Washington Navy Yard; 1974.

56. Moran A, Hardin D, Rodman D, Allen HF, Beall RJ, Borowitz D, et al. Diagnosis, screening and management of cystic fibrosis related diabetes mellitus: a consensus conference report. Diabetes Res Clin Pract. 1999 Aug;45(1):61-73.

57. Jensen P, Johansen HK, Carmi P, Hoiby N, Cohen IR. Autoantibodies to pancreatic hsp60 precede the development of glucose intolerance in patients with cystic fibrosis. J Autoimmun. 2001 Sep;17(2):165-72.

58. Lindquist S. The heat-shock response. Annu Rev Biochem. 1986;55:1151-91.

59. Jensen P, Fomsgaard A, Hoiby N, Hindersson P. Cloning and nucleotide sequence comparison of the groE operon of Pseudomonas aeruginosa and Burkholderia cepacia. APMIS. 1995 Feb;103(2):113-23.

60. Schett G, Xu Q, Amberger A, Van der Zee R, Recheis H, Willeit J, et al. Autoantibodies against heat shock protein 60 mediate endothelial cytotoxicity. J Clin Invest. 1995 Dec;96(6):2569-77.

61. Havnes MB, Ahlen C, Iversen OJ. Concentration of circulating autoantibodies against HSP 60 is lowered through diving when compared to non-diving rats. Microbial Ecology in Health & Disease. 2012;23(0):1-5.

62. Foteinos G, Afzal AR, Mandal K, Jahangiri M, Xu Q. Anti-heat shock protein 60 autoantibodies induce atherosclerosis in apolipoprotein E-deficient mice via endothelial damage. Circulation. 2005 Aug 23;112(8):1206-13.

63. Wisloff U, Brubakk AO. Aerobic endurance training reduces bubble formation and increases survival in rats exposed to hyperbaric pressure. J Physiol. 2001 Dec 1;537(Pt 2):607-11.

64. Berge VJ, Jorgensen A, Loset A, Wisloff U, Brubakk AO. Exercise ending 30 min pre-dive has no effect on bubble formation in the rat. Aviat Space Envir Md. 2005 Apr;76(4):326-8.

65. Taconic. Sprague Dawley- Growth chart. Taconic Farms Inc; 2012 [cited 2012 07.04]; Available from: http://www.taconic.com/wmspage.cfm?parm1=740.

66. 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.

67. Weenink RP, Hollmann MW, van Hulst RA. Animal models of cerebral arterial gas embolism. J Neurosci Meth. 2012 Apr 15;205(2):233-45.

68. Lillo RS, Parker EC. Mixed-gas model for predicting decompression sickness in rats. Journal of Applied Physiology. 2000 Dec;89(6):2107-16.

69. Eftedal O, Brubakk AO. Agreement between trained and untrained observers in grading intravascular bubble signals in ultrasonic images. Undersea Hyperb Med. 1997 Winter;24(4):293-9.

70. Skogland S, Segadal K, Sundland H, Hope A. Gas bubbles in rats after heliox saturation and different decompression steps and rates. J Appl Physiol. 2002 Jun;92(6):2633-9.

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

72. Aird WC. Endothelium in health and disease. Pharmacol Rep. 2008 Jan-Feb;60(1):139-43.

73. Haram PM, Adams V, Kemi OJ, Brubakk AO, Hambrecht R, Ellingsen O, et al. Time-course of endothelial adaptation following acute and regular exercise. Eur J Cardiov Prev R. 2006 Aug;13(4):585-91.

74. Haram PM, Kemi OJ, Lee SJ, Bendheim MO, Al-Share QY, Waldum HL, et al. Aerobic interval training vs. continuous moderate exercise in the metabolic syndrome of rats artificially selected for low aerobic capacity. Cardiovasc Res. 2009 Mar 1;81(4):723-32.

75. Montcalm-Smith E, Caviness J, Chen Y, McCarron RM. Stress biomarkers in a rat model of decompression sickness. Aviat Space Environ Med. 2007 Feb;78(2):87-93.

76. Reul J, Weis J, Jung A, Willmes K, Thron A. Central nervous system lesions and cervical disc herniations in amateur divers. Lancet. 1995 Jun 3;345(8962):1403-5.

77. Tetzlaff K, Friege L, Hutzelmann A, Reuter M, Holl D, Leplow B. Magnetic resonance signal abnormalities and neuropsychological deficits in elderly compressed-air divers. Eur Neurol. 1999;42(4):194-9.

78. Rinck PA, Svihus R, de Francisco P. MR imaging of the central nervous system in divers. J Magn Reson Imaging. 1991 May-Jun;1(3):293-9.

79. Hope A, Lund T, Elliott D, Halsey M, Wiig H. Long term health effects of diving: an international consensus conference. Bergen: Norwegian Underwater technology Centre1994.

80. Mollerlokken A, Gaustad SE, Havnes MB, Gutvik CR, Hjelde A, Wisloff U, et al. Venous gas embolism as a predictive tool for improving CNS decompression safety. Eur J Appl Physiol. 2011 May 19.

81. Neuman TS. Arterial gas embolism and pulmonary barotrauma. In: Brubakk AO NT, editor. Bennett and Elliott´s Physiology and Medicine of Diving. 5th ed: Saunders; 2003. p. 557-77.

82. Kerlefsen Y. Methods for detecting brain damage after decompression: Are biomarkers a useful tool? [Master thesis]. Trondheim: NTNU; 2011.

83. Brubakk AO, Bolstad G, Jacobsen G. Helseeffekter av luftdykking. Yrkes- og sportsdykkere. Trondheim, SINTEF;1994 1994-02-16.

84. Brubakk A, Mollerlokken A. The role of intra-vascular bubbles and the vascular endothelium in decompression sickness. Diving Hyperb Med. 2009;39(3):162-9.

85. Ghanem G, Loir B, Morandini R, Sales F, Lienard D, Eggermont A, et al. On the release and half-life of S100B protein in the peripheral blood of melanoma patients. International Journal of Cancer. 2001 Nov 15;94(4):586-90.

86. Townend W, Dibble C, Abid K, Vail A, Sherwood R, Lecky F. Rapid elimination of protein S-100B from serum after minor head trauma. J Neurotrauma. 2006 Feb;23(2):149-55.

87. Herrmann M, Vos P, Wunderlich MT, de Bruijn CH, Lamers KJ. Release of glial tissue-specific proteins after acute stroke: A comparative analysis of serum concentrations of protein S-100B and glial fibrillary acidic protein. Stroke. 2000 Nov;31(11):2670-7.

88. Hasselblatt M, Mooren FC, von Ahsen N, Keyvani K, Fromme A, Schwarze-Eicker K, et al. Serum S100beta increases in marathon runners reflect extracranial release rather than glial damage. Neurology. 2004 May 11;62(9):1634-6.

89. Castellanos M, Serena J. Applicability of biomarkers in ischemic stroke. Cerebrovasc Dis. 2007;24 Suppl 1:7-15.

90. Fang YQ, Xu J, Chen Y, Xiao WB, Zhang HX, Yu FT. [Changes of serum IL-1, IL-2R and TNF-alpha levels in divers after 150 m Heliox saturation -182 m excursion in the open sea diving]. Space Med Med Eng (Beijing). 2003 Aug;16(4):307-8.

91. Bergo GW, Tyssebotn I. Effect of Exposure to Oxygen at 101 and 150 Kpa on the Cerebral-Circulation and Oxygen-Supply in Conscious Rats. Eur J Appl Physiol O. 1995 Nov;71(6):475-84.

92. Watson NA, Beards SC, Altaf N, Kassner A, Jackson A. The effect of hyperoxia on cerebral blood flow: a study in healthy volunteers using magnetic resonance phase-contrast angiography. Eur J Anaesth. 2000 Mar;17(3):152-9.

93. Thom SR, Bhopale V, Fisher D, Manevich Y, Huang PL, Buerk DG. FAST TRACK - Stimulation of nitric oxide synthase in cerebral cortex due to elevated partial pressures of oxygen: An oxidative stress response. J Neurobiol. 2002 May;51(2):85-100.

94. Macey PM, Woo MA, Harper RM. Hyperoxic brain effects are normalized by addition of CO2. PLoS Med. 2007 May;4(5):e173.

95. Iscoe S, Fisher JA. Hyperoxia-induced hypocapnia: an underappreciated risk. Chest. 2005 Jul;128(1):430-3.

96. Muth CM, Shank ES. Gas embolism. N Engl J Med. 2000 Feb 17;342(7):476-82.

97. Hjelde A, Nossum V, Steinsvik M, Bagstevold JI, Brubakk AO. Evaluation of cerebral gas retention and oedema formation in decompressed rats by using a simple gravimetric method. Scand J Clin Lab Invest. 2002;62(4):263-70.

98. Gronning M, Risberg J, Skeidsvoll H, Moen G, Aanderud L, Troland K, et al. Electroencephalography and magnetic resonance imaging in neurological decompression sickness. Undersea Hyperb Med. 2005 Nov-Dec;32(6):397-402.

99. Ross JA, Macdiarmid JI, Osman LM, Watt SJ, Godden DJ, Lawson A. Health status of professional divers and offshore oil industry workers. Occup Med (Lond). 2007 Jun;57(4):254-61.

100. Skogstad M, Bast-Pettersen R, LIe A, Wagstaff A, Bugge M, Skyberg K. Vurdering av behovet for helseoppfølging av dykkere i petroleumsvirksomheten2010.

101. Haugan T, Størseth F, Vadseth T, Drøyvold W. Utvikling av metode for kartlegging av risikoutsatte arbeidstakergrupper ift arbeidsbetinget skade og sykdom i norsk petroleumsvirksomhet. Trondheim: SINTEF Helse2007. Report No.: SINTEF A4107.

102. Ross JAS, Semple S, Duffin R, Kelly F, Feldmann J, Raab A. Characterisation of fume from hyperbaric welding operations. J Phys Conf Ser. 2009;151.

APPENDIX: Papers I-III

PAPER I

S100B and its relation to intravascular bubbles following decompression

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Key words
Biomarkers, decompression sickness, bubbles, Doppler, diving research

Abstract
(Havnes MB, Hjelde A, Brubakk AO, Møllerløkken A. S100B and its relation to intravascular bubbles following decompression. *Diving and Hyperbaric Medicine*. 2010;40(4):210-2.)
Introduction: When neurological damage occurs in divers, it is considered to be caused by gas bubbles. Entrapment of these bubbles may lead to cellular injury and cerebral oedema. S100B is a protein biomarker that is released in CNS injuries and the concentration is related to the amount of brain damage.
Methods: A total of 27 rats were randomly assigned to one of three groups. Group I served as controls (n = 9). Group II (n = 7) underwent a simulated dive to 400 kPa and Group III to 700 kPa (n = 11). In groups II and III, venous gas bubble scores were evaluated by ultrasound during the first hour after surfacing. The amount of S100B in serum after the dives was tested using a commercial ELISA kit. Bubble grades were compared to S100B protein concentrations.
Results: The average level of S100B was significantly higher in rats compressed to 700 kPa compared to the control rats, (P = 0.038) and the rats compressed to 400 kPa, (P = 0.003). There was no difference in S100B concentration between groups I and II. Following the dive to 700 kPa, there were significantly higher bubble grades observed than following the dive to 400 kPa (P = 0.001).
Conclusion: The correlation between bubble grade and an increase in serum protein level of S100B indicates that this protein may be useful as a biomarker for neurological damage caused by decompression.

Introduction

When neurological damage occurs in divers, the prime suspects are vascular gas bubbles. Most bubbles are filtered out by the pulmonary capillaries but may also break through the lung filter or enter the arterial circulation via shunts to mediate bubble-induced tissue injury.[1,2] Entrapment of these bubbles may lead to cellular injury and cerebral oedema.[3] Under normal conditions, central nervous system (CNS) tissue is separated from plasma by the blood-brain-barrier (BBB), formed by endothelial cells of the brain microvessels and their underlying basement membrane.[4] The BBB acts as a sieve to restrict passage of large molecules, including most plasma proteins, into the CNS. Increased permeability of the BBB has been demonstrated after decompression, resulting in oedema.[3,5,6] Increased permeability of the cerebral vasculature could be due to changes induced by chemical factors released or activated by microbubbles or to direct mechanical injury of blood vessels from these bubbles.[7]

S100B is a protein biomarker that is released in CNS injury, the concentration being related to the amount of brain damage.[8] Elevated S100B concentrations have been reported in patients with stroke compared to control subjects and also in elite breath-hold divers after prolonged apnea.[9,10]

Signs and symptoms of decompression sickness (DCS) differ with the pressure profile and the breathing gas, but have a common first step, namely the formation of gas bubbles. The emerging evidence of the effects of venous gas emboli on the endothelium has led to the hypothesis that these are a main cause for neurologic DCS through its adverse effects on the CNS.[11] This experiment examines whether S100B could be used as a biological marker of decompression stress in the CNS and to examine a possible correlation between bubble grade and serum S100B concentration.

Methods

All experimental procedures and the care of experimental animals conformed to the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, and the protocol was approved by the Norwegian Council for Animal Research.

A total of 27 rats (female Sprague Dawley, Scanbur, Denmark) were randomly divided into three groups. Group I was a surface control group (100 kPa) breathing air (n = 9). Groups II and III underwent simulated dives for 45 min to 400 kPa (group II, n = 7) or 700 kPa (group III, n = 11) in a 20 L hyperbaric chamber. The compression and decompression rates were similar in both groups, 200 kPa min^{-1} and 50 kPa min^{-1} respectively. During the simulated dive, the rats were awake and observed through a window in the hyperbaric chamber.

Immediately after surfacing, the rats were anaesthetised with a subcutaneous injection of a mixture of haloperidol 0.33 mg, fentanyl 0.05 mg and midazolam 0.5 mg; 0.4 ml per 100 g body weight. The pulmonary artery was monitored at discrete intervals (15, 30, 45 and 60 min after surfacing) for gas bubbles using a 10 MHz transducer connected to a FiVe ultrasound scanner (GE Vingmed Ultrasound AS, Norway). Bubbles are seen on the monitor screen as bright

spots in the pulmonary artery, and verified with Doppler. Bubble quantity was graded on a 0 to 5 scale according to a previously described method.[12] Results are presented as maximum bubble grade during the observation period.

S100B levels in serum drawn one hour after the dives were tested using a commercial ELISA kit (BioVendor-Laboratorní medicína, Brno-Modice, Czech Republic). Bubble grades were compared to S100B protein concentrations.

STATISTICAL ANALYSIS

Because the S100B data in the control group were not normally distributed (confirmed by the Kolmogorov-Smirnov test and Q-Q plot) and the small number of animals studied, the Mann-Whitney test was used to assess differences between the groups. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, Illinois, USA). The results are presented as medians (25th and 75th percentiles).

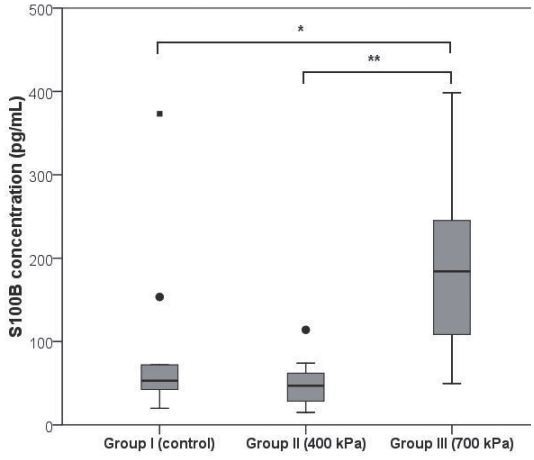
Results

There was a significant difference in S100B concentration between the rats compressed to 700 kPa (Group III) and the rats in the control group (Group 1, $P = 0.038$) (Figure 1). There was also a significantly higher S100B concentration in the rats compressed to 700 kPa (Group III) compared to those compressed to 400 kPa (Group II, $P = 0.003$) (Figure 1). There were no significant differences between Groups I and II. Following the dive to 700 kPa, there were significantly higher bubble grades observed than following the dive to 400 kPa ($P = 0.001$) (Table 1).

Discussion

We showed an increased concentration of S100B and a higher occurrence and grade of bubbles in rats compressed to 700 kPa compared to both normobaric controls and rats compressed to 400 kPa. The adverse effects of decompression have been discussed for decades, but markers for decompression stress other than the detection of vascular gas bubbles are still lacking. Although intravascular gas bubble scores are related to the risk of DCS and, higher grades with an increased incidence of DCS, there are large inter- and intra-individual differences in the response to bubbles. Thus, the search for other markers of decompression stress has continued. This inter-individual susceptibility to DCS and the fact that

Figure 1
Box plots of serum S100B concentration in undived rats and rats compressed to 400 kPa and 700 kPa, median, 25th and 75th percentiles shown; vertical lines represent the largest and smallest values except:
• outlier values > 1.5 box-lengths away;
■ extreme outlier > three box-lengths away;
(differences between groups: * P <0.05; ** P <0.005)



repetitive dives appear to result in greater tolerance to DCS due to acclimatisation, have given rise to the hypothesis that DCS might have an inflammatory basis.[13,14]

To our knowledge, there are no published data relating bubble formation and S100B concentration. However, S100B has been shown to be increased in goats after deep dives with rapid decompression.[15] These data are supported by our study in rats. On the other hand, a pilot study on S100B in human divers diagnosed and treated for acute DCS did not show an increased concentration of S100B.[16] However, a major difference between that study and ours is that the blood samples were drawn two to three days after the dives, while ours were drawn one hour after the dive. The half-life of S100B in relation to other diseases is estimated to be about 30 minutes, which might explain this difference.[17] In studies of patients with Alzheimer's disease or traumatic head injury, S100B appears to be a useful marker for brain function and, in ischaemic stroke patients, S100B concentrations correlate with infarct volume.[18–20]

Whether a high bubble grade produces brain injury in rats is not known, but it is reasonable to believe so. Injected microbubbles have been shown to affect the BBB in guinea pigs.[21] This method might give better control of the amount of bubbles than in decompressed rats, but is highly invasive and, thus, might alter other variables that could affect biomarker production.

We cannot say for sure that the concentration of S100B in serum is related to neurological DCS since we do not have

Table 1
Bubble grades after dives to 700kPa and 400kPa (number of animals in each grade; *P = 0.001*)

	Bubble grade					
	0	**1**	**2**	**3**	**4**	**5**
Group II (400 kPa; $n = 7$)	4	3	0	0	0	0
Group III (700 kPa; $n = 11$)	2	0	1	0	0	8

a neurological examination of the rats. However, recent experiments suggest that bubbles caused by diving can affect the BBB, and that there is an increased concentration of S100B in human subjects after traumatic brain injury.[22,23] Our preliminary results indicate a correlation between exposure to pressure and the expression of S100B.

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References

1 Butler BD, Hills BA. Transpulmonary passage of venous air emboli. *J Appl Physiol*. 1985;59(2):543-7.
2 Vik A, Brubakk AO, Hennessy TR, Jenssen BM, Ekker M, Slordahl SA. Venous air embolism in swine: transport of gas bubbles through the pulmonary circulation. *J Appl Physiol*. 1990;69(1):237-44.
3 Hjelde A, Nossum V, Steinsvik M, Bagstevold JI, Brubakk AO. Evaluation of cerebral gas retention and oedema formation in decompressed rats by using a simple gravimetric method. *Scand J Clin Lab Invest*. 2002;62(4):263-70.
4 Rosenblum WI. Aspects of endothelial malfunction and function in cerebral microvessels. *Lab Invest*. 1986;55(3):252-68.
5 Chryssanthou C, Springer M, Lipschitz S. Blood-brain and blood-lung barrier alteration by dysbaric exposure. *Undersea Biomed Res*. 1977;4(2):117-29.
6 Kaakkola S, Lehtosalo J, Laitinen LA. Changes in blood-brain barrier permeability to drugs in decompressed rats. *Undersea Biomed Res*. 1982;9(3):233-40.
7 Nohara A, Yusa T. Reversibility in blood-brain barrier, microcirculation, and histology in rat brain after decompression. *Undersea Hyperb Med*. 1997;24(1):15-21.
8 Herrmann M, Vos P, Wunderlich MT, de Bruijn CH, Lamers KJ. Release of glial tissue-specific proteins after acute stroke: a comparative analysis of serum concentrations of protein S-100B and glial fibrillary acidic protein. *Stroke*. 2000;31(11):2670-7.
9 Petzold A, Michel P, Stock M, Schluep M. Glial and axonal body fluid biomarkers are related to infarct volume, severity and outcome. *J Stroke Cerebrovasc Dis*. 2008;17(4):196-203.
10 Andersson JP, Liner MH, Jonsson H. Increased serum levels of the brain damage marker S100B after apnea in trained breath-hold divers: a study including respiratory and cardiovascular observations. *J Appl Physiol*. 2009;107(3):809-15.
11 Brubakk A, Møllerløkken A. The role of intra-vascular bubbles and the vascular endothelium in decompression sickness. *Diving and Hyperbaric Medicine*. 2009;39(3):162-9.
12 Eftedal O, Brubakk AO. Agreement between trained and untrained observers in grading intravascular bubble signals in ultrasonic images. *Undersea Hyperb Med*. 1997;24(4):293-9.
13 Ersson A, Walles M, Ohlsson K, Ekholm A. Chronic hyperbaric exposure activates proinflammatory mediators in humans. *J Appl Physiol*. 2002;92(6):2375-80.
14 Su CL, Wu CP, Chen SY, Kang BH, Huang KL, Lin YC. Acclimatization to neurological decompression sickness in rabbits. *Am J Physiol Regul Integr Comp Physiol*. 2004;287(5):R1214-8.
15 Jurd K, Parmar K, Seddon F, Loveman G, Blogg S, Thacker J, et al. Serum S-100b as a marker of neurological events in goats following direct decompression in a simulated disabled submarine scenario [abstract]. *UHMS Meeting Abstracts*. 2001. available at <http://rubicon-foundation.org/dspace/handle/123456789/22> (last accessed 08 November 2010)
16 Poff DJ, Wong R, Bulsara M. Acute decompression illness and serum s100beta levels: a prospective observational pilot study. *Undersea Hyperb Med*. 2007;34(5):359-67.
17 Ghanem G, Loir B, Morandini R, Sales F, Lienard D, Eggermont A, et al. On the release and half-life of S100B protein in the peripheral blood of melanoma patients. *Int J Cancer*. 2001;94(4):586-90.
18 Chaves ML, Camozzato AL, Ferreira ED, Piazenski I, Kochhann R, Dall'igna O, et al. Serum levels of S100B and NSE in Alzheimer's disease patients. *J Neuroinflammation*. 2010;7(1):6.
19 Dassan P, Keir G, Brown MM. Criteria for a clinically informative serum biomarker in acute ischaemic stroke: a review of S100B. *Cerebrovasc Dis*. 2009;27(3):295-302.
20 Wiesmann M, Steinmeier E, Magerkurth O, Linn J, Gottmann D, Missler U. Outcome prediction in traumatic brain injury: comparison of neurological status, CT findings and blood levels of S100B and GFAP. *Acta Neurol Scand*. 2010;121(3):178-85.
21 Hills BA, James PB. Microbubble damage to the blood-brain barrier: relevance to decompression sickness. *Undersea Biomed Res*. 1991;18(2):111-6.
22 Levett DZ, Millar IL. Bubble trouble: a review of diving physiology and disease. *Postgrad Med J*. 2008;84(997):571-8.
23 Blyth BJ, Farhavar A, Gee C, Hawthorn B, He H, Nayak A, et al. Validation of serum markers for blood-brain barrier disruption in traumatic brain injury. *J Neurotrauma*. 2009;26(9):1497-507.

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PAPER II

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ORIGINAL ARTICLE

Simulated dive in rats lead to acute changes in cerebral blood flow on MRI, but no cerebral injuries to grey or white matter

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Abstract In this study, the effect of a simulated dive on rat brain was investigated using several magnetic resonance imaging (MRI)-methods and immunohistochemistry. Rats were randomly assigned to a dive- or a control group. The dive group was exposed to a simulated air dive to 600 kPa for 45 min. Pulmonary artery was monitored for vascular gas bubbles by ultrasound. MRI was performed 1 h after decompression and at one and 2 weeks after the dive with a different combination of MRI sequences at each time point. Two weeks after decompression, rats were sacrificed and brains were prepared for histology. Dived rats had a different time-curve for the dynamic contrast-enhanced MRI signal than controls with higher relative signal intensity, a tendency towards longer time to peak and a larger area under the curve for the whole brain on the acute MRI scan. On MRI, 1 and 2 weeks after dive, T_2-maps showed no signal abnormalities or morphological changes. However, region of interest based measurements of T_2 showed higher T_2 in the brain stem among decompressed animals than controls after one and 2 weeks. Microscopical examination including immunohistochemistry did not reveal apparent structural or cellular injuries in any part of the rat brains. These observations indicate that severe decompression does not seem to cause any structural or cellular injury to the brain tissue of the rat, but may cause circulatory changes in the brain perfusion in the acute phase.

Keywords Diving · Cerebral circulation · MRI · Histology

Abbreviations

ADC	Apparent diffusion coefficient
AUC	Area under the curve
BBB	Blood brain barrier
CNS	Central nervous system
DCE	Dynamic contrast enhanced
DCS	Decompression sickness
DTI	Diffusion tensor imaging
EEG	Electroencephalography
FA	Fractional anisotropy
FLASH	Fast low angle shot
FOV	Field of view
MD	Mean diffusivity
MRI	Magnetic resonance imaging
MTX	Acquisition matrix
RARE	Rapid acquisition with relaxation enhancement
RD	Radial diffusivity
RC	Relative contrast
ROI	Region(s) of interest
RSI	Relative signal intensity
SD	Standard deviation
T_1	Longitudinal relaxation time
T_2	Transverse relaxation time
TE	Echo time
TR	Repetition time
TTP	Time to peak

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Introduction

Saturation diving is widely used for maintenance and inspection of off-shore subsea systems. Exposure to hyperbaric environments is associated with risk of developing decompression sickness (DCS), arterial gas embolism, neurological symptoms and pulmonary dysfunction (Francis et al. 1990; Mollerlokken et al. 2011; Neuman 2003). Amongst the self-reported symptoms following decompression are conspicuous fatigue, visual disturbances, dizziness, nausea and changes in skin sensitivity (Brubakk et al. 1994). The latter symptoms may be related to the effects of hyperbaria on the central nervous system (CNS).

The long-term health effects of diving have been a matter for discussion for many years, and several studies have been performed to examine the neurological effects of diving (Erdem et al. 2009; Irgens et al. 2007). Saturation divers have reported problems with concentration and memory more frequently than control subjects (Ross et al. 2007; Todnem et al. 1990). In recreational diving accidents, neurological symptoms such as numbness, paraesthesia, dizziness and coordination deficiencies are among the most often reported manifestations of DCS (Vann et al. 2011; Newton et al. 2007).

DCS is a clinical diagnosis associated with a number of different signs and symptoms (Vann et al. 2011). However, in serious DCS neurological symptoms dominate (Moon and Gorman 2003). When neurological damage occurs in divers, the suspected primary cause is vascular gas bubbles. Vascular gas bubbles can enter the arterial circulation by a number of methods, but most commonly due to a right-to-left shunt in the heart, or after barotrauma (Warren et al. 1988). Vascular bubbles can have mechanical, embolic and biochemical effects (Mollerlokken et al. 2011). Entrapment of these bubbles may lead to cellular injury, cerebral edema and increased permeability of the blood–brain barrier (BBB) (Hjelde et al. 2002; Kaakkola et al. 1982). Acute effects can be caused by extravascular bubbles producing pain, or vascular bubbles obstructing and causing stroke-like symptoms (Vann et al. 2011). High intensity signals in the white matter on T_2 weighted magnetic resonance images (MRI) have been seen in divers after dive injuries (Cordes et al. 2000; Hutzelmann et al. 2000), while interestingly, cerebral abnormalities observed in case studies seem to appear at different times-points and are of varying permanence (Jallul et al. 2007). Abnormal electroencephalography (EEG) results have been noted in the temporal or frontal regions after recompression treatment in divers with cerebral DCS (Gronning et al. 2005). The presence of vascular bubbles does not mean that DCS will occur, but the absence of bubbles is considered to be a good indicator of decompression safety (Sawatzky 1991).

Bubbles can also lead to delayed symptom onset in relation to the vascular system. Endothelial dysfunction has been observed after diving in experiments with animals (Nossum et al. 2002) and humans (Brubakk et al. 2005), and is believed to be caused by vascular bubbles. Inflammatory responses have also been investigated in relation to bubble formation and decompression (Bigley et al. 2008). To what extent vascular bubbles and decompression per se affect long-term health, if at all, is still controversial.

In the present study, the effect of a simulated dive on the rat brain was investigated using several MRI-methods, at 1 h, 1 and 2 weeks after decompression. The rat brains also underwent light microscopical examination including immunohistochemistry.

Methods

Fourteen Sprague-Dawley (Taconic, Denmark) rats weighing 310.75 ± 17.42 g were used in the study. All experimental procedures and the care of experimental animals conformed to the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes, and the protocol was approved by the Norwegian Council for Animal Research.

Dive protocol

Following 1 week of acclimatization, the rats were randomly assigned to one of two groups, diving ($n = 9$) or control ($n = 5$). The rats in the dive group were exposed to a simulated air dive in a 20 L hyperbaric chamber with a continuous air supply. They were compressed at a rate of 200 kPa/min to a pressure of 600 kPa, maintained at that pressure for 45 min and then decompressed to the surface (100 kPa) at a rate of 50 kPa/min. The control group was kept in their housing facilities at 100 kPa (normal ambient pressure), breathing air.

Ultrasound

Immediately after surfacing, the rats were anaesthetized (1 % isoflurane mixed with medical air), and the pulmonary artery was monitored for vascular gas bubbles for 30 min by transthoracic echocardiography using a 35 MHz probe (Vevo770, Visual Sonics, Toronto, ON, Canada). Bubbles were identified on the monitor as bright spots in the pulmonary artery and verified with Doppler. The amount of bubbles in the pulmonary artery was graded on a 0–5 scale according to a previously described method (Eftedal and Brubakk 1997), where bubble grade 0 = no bubbles, 1 = occasional bubbles, 2 = at least one bubble/4th heart cycle, 3 = at least one bubble/heart cycle,

4 = continuous bubbling and 5 = massive bubbling, also described as "white-out" as individual bubbles cannot be seen. The animals were observed for signs of neurological decompression sickness, such as walking difficulties or paresis, before and after the MRI.

Magnetic resonance imaging

MRI was performed 1 h after decompression (acute MRI) and at 1 and 2 weeks after the dive, with a different combination of MRI sequences at each time point. All MRI was performed using a 7 Tesla magnet (Biospec 70/20 AS, Bruker Biospin MRI, Ettlingen, Germany) with water-cooled (BGA-12, 400 mT/m) gradients. A volume resonator was used for RF transmission, and an actively decoupled rat head surface coil was used for RF reception (Bruker Biospin MRI). During scanning, the anaesthetized (Isoflurane 4 % induction and 2 % maintenance in 30 % O_2, 70 % N_2) rats lay prone in a dedicated water heated rat bed. The head of every animal was fixed in the same position with inbuilt earplugs, tooth bar and nose-mask, to assure the same placement within the magnet from scan to scan.

Acute MRI was performed after the ultrasound, within 1 h after the dive. Before the MRI acquisition, the rats were anaesthetized and a 25 Gauge neoflon was inserted in the tail vein. After a gradient echo, fast low angle shot (FLASH) pilot scan (acquisition time 1 min), a series of T_2-weighted images were obtained to visualise anatomical changes and oedema using a turbo spin echo (rapid acquisition with relaxation enhancement, RARE) sequence with RARE-factor = 4, effective echo time (TE) = 25/50/75 ms, repetition time (TR) = 4,000 ms, 3 averages, acquisition time 7 min 12 s. Diffusion weighted images were obtained using an echo planar imaging sequence with 3 directions and 6 b-values (100/200/400/600/800/1,000 ms), TE = 53.47 ms, TR = 3,000 ms, 6 averages, acquisition time 8 min 24 s. For all of these scans, 17 coronal slices were acquired.

To visualise acute changes in brain perfusion and possible disruption of the BBB, dynamic contrast enhancement (DCE) studies were performed: at first, a T_1-map was acquired using a RARE sequence with RARE-factor = 4, TE = 7.1 ms, TR = 341/562/845/1,243/1,913/5,000 ms, 1 average and acquisition time 7 min 55 s. This was followed by a pre-contrast T_1-weighted image (RARE): TE = 7.0 ms, TR = 350 ms, 8 averages and acquisition time 1 min 41 s. Acquisition matrix (MTX) was 256 × 144 zero-filled to 256 × 192 giving an isotropic in-plane resolution of 156 × 156 μm^2. Thereafter, a time-series of T_1-weighted images was acquired (RARE-factor = 4, TE = 7.0, TR = 300 ms, MTX 128 × 72, zero-filled to 128 × 96, 1 average). With each image taking 5.4 s to acquire, 200 images were acquired over 18 min. After 60 s of acquisition, a dose of 0.3 mmol/kg 0.25 M gadolinium-based contrast agent (Omniscan, GE Healthcare, United Kingdom) (total volume ~0.36 ml) was injected intravenously through the neoflon over a period of 5 s. Finally, a post-contrast T_1-weighted image was acquired with the same parameters as the pre-contrast T_1-weighted scan. For all acquisitions, the field of view (FOV) was 40 × 30 mm and 7 slices á 1 mm was acquired.

The next day, animals were injected with a single dose of 40 mg $MnCl_2$ (# 7773-01-5, Sigma-Aldrich Inc., St. Louis, USA) per kg bodyweight (~318 μmol Mn^{2+}/kg) at a concentration of 100 mM intra-peritoneally to serve as MRI contrast for detecting subsequent inflammation and gliosis 1 week after (Wideroe 2009).

On the follow-up, MRI made seven and 14 days after the dive and T_2-weighted images were acquired with the same parameters as described for the acute MRI to study anatomical changes and possible edema associated with tissue pathology. In addition, to evaluate manganese-uptake, a 3D data set was obtained on day seven using a T_1-weighted gradient echo FLASH sequence with flip-angle = 30°, TR = 12 ms, TE = 3.25 ms. FOV = 30 × 35 × 20 mm and MTX was 192 × 168 × 96 zero-filled to 192 × 224 × 128 and the interpolated resolution was 156 μm isotropic. Images were averaged 16 times and acquisition time was 52 min with 16 averages. The transmit field of the volume-coil was considered homogeneous within the FOV, while the spatially inhomogeneous sensitivity of the surface coil used in the 3D T_1-weighted FLASH acquisition was corrected for using two additional scans in coupled and single coil operation: 3D T_1-weighted FLASH sequences with the same FOV and contrast parameters as described above but with matrix size 32 × 32 × 32. Acquisition time was two min for each scan. Correction of the high resolution 3D data set was performed using in-house developed software (MATLAB ver. R2010a), and is described in detail elsewhere (Wideroe 2009).

On both 7 and 14 days after the decompression, diffusion tensor imaging (DTI) was performed to evaluate specific white matter injury and to look for changes in white matter. The DTI was acquired with an Echo planar imaging sequence using 30 directions and b = 1,000 ms, 5 images with b = 0 ms: FOV = 40 × 40 mm, MTX = 172 × 172 giving a resolution of 233 × 233 μm^2. On day 7, TE = 37.5, TR = 3,000 ms, 17 slices á 1 mm were acquired with two averages giving an acquisition time of 14 min. On day 14 TE = 37.5, TR = 5,000 ms, 33 slices at 0.5 mm were acquired with six averages giving an acquisition time of 1 h 10 min.

MR image analysis

In-house developed software (MATLAB ver. R2010a, Math Works Inc, Natick MA, USA) was used to calculate

apparent diffusion coefficient (ADC) maps by fitting a mono-exponential model to the signal intensity of the images with different b-values, while T_2-maps were calculated by fitting a mono-exponential model to the signal intensity of the images with different TE-values. The same software was also used to calculate DCE parameters using the average signal intensities within the region of interest specified below. The following DCE parameters were calculated based on the T_1-weighted image series acquired during and after gadolinium-based contrast injection: relative signal intensity (RSI) 1.5 min after contrast injection, $RSI_{1.5min}$, area under the curve (AUC) during the five first min after contrast injection, AUC_{5min} and time to peak signal (TTP).

All MR images were visually evaluated with respect to morphological changes and with abnormal signal areas. In addition, Medical Image Processing, Analysis and Visualization software (ver. 5.3.4, Centre for Information Technology (CIT), National Institutes of Health (NIH)) (McAuliffe et al. 2001) were used for regions of interest (ROI) analyses of the image data. ROIs in the frontal, parietal and occipital cortex, hippocampus, putamen, thalamus and brain stem at the level of pons were drawn in the T_2-maps (Fig. 1) and copied to the ADC-maps and T_1-weighted images to ensure the same placement of ROIs in all image sets. Average voxel values in each of these regions were calculated and compared between groups. The same ROIs were also used to calculate DCE parameters, as described above. For the T_1-weighted images used for manganese-enhanced MRI 1 week after the dive, ROI were also drawn in muscle areas lateral to the brain on both sides. Using the average signal intensity from muscle, the mean relative contrast (RC) was calculated in all the other ROI using the formula:

$$\overline{RC}_{ROI} = \frac{\overline{SI}_{ROI}}{\overline{SI}_{muscle}}$$

Where RC_{ROI} is the relative contrast and SI_{ROI} is the mean signal intensity of the region of interest and SI_{muscle} is the mean signal intensity from the muscle ROI.

DTI analyses were performed with the tools of the FMRIB software library (FSL ver. 4.1.4, Oxford Centre for Functional MRI of the Brain, UK; www.fmrib.ox.ac.uk/fsl). Images were pre-processed to reduce image artefacts due to motion and eddy current distortions by affine transformation and co-registration of the diffusion encoded images to the b_0 images. Single data sets with severe ghosting artefacts were excluded from further analyses (day 21: $n = 6$, day 42: $n = 5$). Brains segmented out using the Brain Extraction Tool before FDT ver2.0 (both part of FSL) was used to fit a voxel wise diffusion tensor model to the diffusion image data (Behrens et al. 2003). Maps for the fractional anisotropy (FA), mean (MD), radial (RD) and axial diffusivity were created for all animals for days 7 and 14 after decompression. ROI were drawn in the internal capsule, external capsule, hippocampal fimbria, body and splenium of corpus callosum on the FA-maps. Mean FA, MD, RD and axial diffusivity were calculated in each ROI in each animal.

Histology

Two weeks after decompression, the rats were sacrificed with an overdose of pentobarbital (300 mg/kg) and perfused with 4 % paraformaldehyde in phosphate-buffered saline. Brains were post-fixed in the same fixative and embedded in paraffin, then cut in 8 μm thick coronal slices corresponding to −3.25 and −10.30 mm from the bregma (Paxinos and Watson 2008) and stained with hematoxylin–eosin (H&E) (Cell Path Ltd, UK, Chemiteknikk, Norway and Sigma Aldrich, Germany). The sections were also stained with Luxol fast blue (Chemiteknikk, Norway) for myelin. For immunohistochemistry, the paraffin sections were incubated with antibodies against anti-MAP-2 for neuronal integrity (Sigma, USA), anti-glial fibrillary protein (anti-GFAP) (Millipore, Norway) as a marker for reactive astrocytes, anti-cleaved caspase 3 (Cell Signaling Technology Inc., USA) for apoptotic calls, anti-myelin basic protein (anti-MBP) (Covance, USA) for myelin, anti-CD68:FITC (AbD Serotec, Germany) for activated microglia/macrophages and rabbit anti-rat albumin (Nordic, the Netherlands) for BBB leakage. After primary antibody incubation, sections were incubated with rat-anti-FITC-biotin (Roche, Basel, Switzerland), horse-anti-mouse-biotin (Vector Laboratories, Burlingame, CA), goat- anti-rabbit (Vector Laboratories, USA) or Dako Envision+System-HRP (Dako, Denmark). Visualization was performed using a Vectastain ABC kit (Vector Laboratories Inc., USA) and Diaminobenzidine (DAB) kit (Vector Laboratories Inc., USA).

The sections were examined for neuropathology using a Nikon Eclipse 80i light microscope and were analysed by a blinded investigator. To assess any gliosis or vascular proliferation both hemispheres were examined, and the number of GFAP-reactive astrocytes and albumin-labelled vessels were calculated using a 40× objective with an ocular grid.

Statistics

PASW Statistics 18 (release 18.0.2, SPSS Inc., Chicago, IL, USA) was used for all statistical analysis and the level of significance was set to 0.05. Two-sided *t* tests were used to analyze differences in ADC, T_2, DCE parameters, relative contrast in the T_1-weighted images, and DTI parameters between groups of decompressed and control animals.

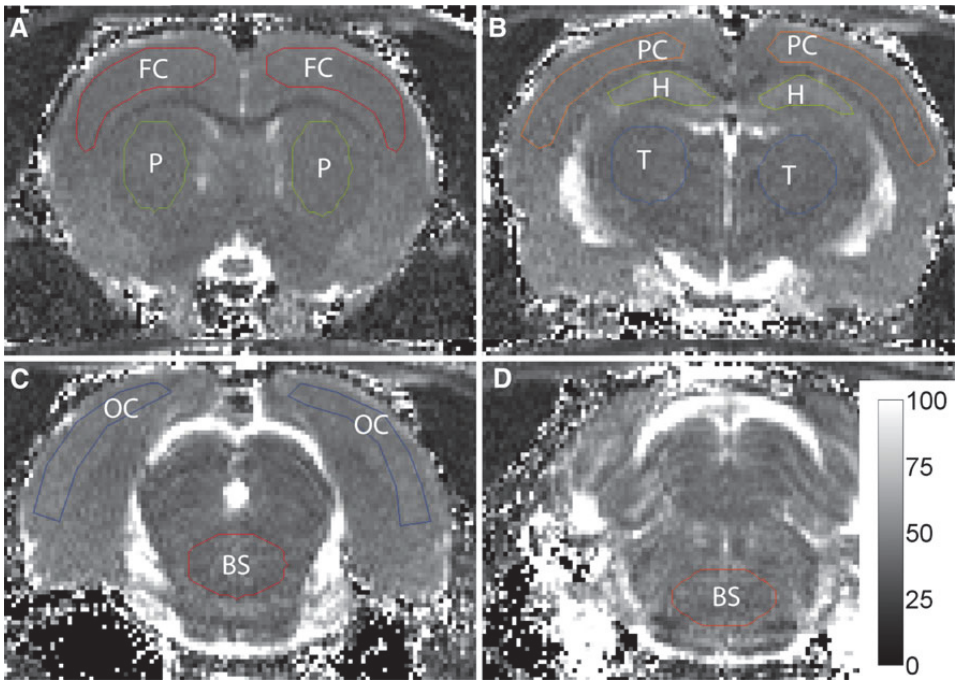

Fig. 1 T_2-maps of image slices throughout the brain showing regions of interest used in the analyses. *FC* frontal cortex, *P* Putamen, *PC* Parietal cortex, *H* Hippocampus, *T* Thalamus, *OC* occipital cortex, *BS* brain stem. *Colour bar* indicates T_2-values (ms)

Histology was analysed by a semi quantitative method by a blinded and trained neuropathologist (SHT).

Results

Bubble formation and clinical outcome

Of the nine rats in the diving group, three died and six had bubble loads graded between 2 and 4 (median 2) following decompression. The rats that died had considerable bubble loads (visible in tissue after sacrifice), with two dying immediately after the dive and the third showing neurological symptoms of DCS in the form of temporary paralysis of the hind legs; it died after the first MRI scan. The remaining six animals had no clinical symptoms.

Acute MRI findings

Decompressed rats had a different time-curve for the dynamic contrast-enhanced MR signal than controls, with higher RSI ($P = 0.017$), a tendency towards longer time to peak ($P = 0.11$) and a larger area under the curve for the whole brain ($P = 0.099$) (Fig. 2). Region of interest based analyses of the dynamic contrast-enhanced MRI (DCE MRI) data that showed differences between decompressed and control animals in frontal cortex and thalamus. Decompressed animals had higher mean RSI ($P = 0.023$, Table 1) and a tendency towards higher TTP and AUC in

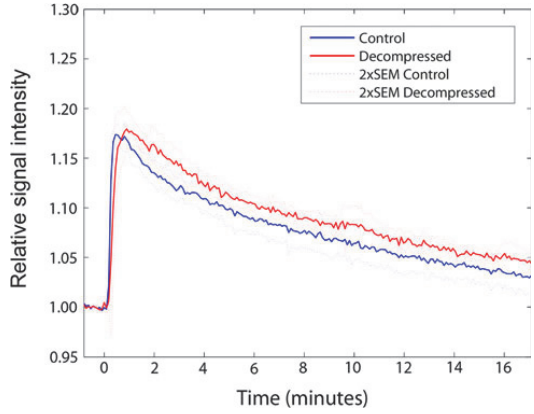

Fig. 2 *Plot* of the mean relative signal intensity for the whole brain (cerebrum) with time after injection of contrast agent. *Blue line* represent mean for control animals with 95 % CI (*blue dotted line*) and *red line* represent mean for decompressed animals with 95 % CI (*red dotted line*)

the frontal cortex than control animals ($P = 0.076$ and $P = 0.068$, respectively). In the thalamus, AUC was higher among decompressed animals ($P = 0.033$, Table 1) with a tendency towards higher RSI and TTP ($P = 0.068$ and $P = 0.104$, respectively). For all other areas, there were no significant differences between the two groups.

Interestingly, the variation in all three parameters (RSI, TTP and AUC) was higher among decompressed animals than controls. There were no specific areas with increased signal in the post-contrast image compared to the pre-contrast image. The ADC-maps and T_2-maps did not show any focal changes indicating pathology in neither the decompressed nor the control animals. Measurements of ADC and T_2 in several brain areas showed no differences between the groups (Tables 2 and 3).

MRI 1 and 2 weeks after decompression

The T_2-maps showed no signal abnormalities or morphological changes 1 or 2 weeks after the decompression. Region of interest based measurements of T_2 showed higher T_2 in the brain stem among decompressed animals than controls after 1 and 2 weeks, with the same tendency seen in thalamus (Table 3). There was also a similar reduction in T_2 in both groups from time 0 to week 1, with a slight increase to week 2 (Table 3) which was related to the administration of manganese on day 1 after decompression. Visual inspection of T_1-weighted images after 1 week showed similar manganese-enhancement in both groups, and region based analysis of the images did not show any differences between groups in relative contrast 1 week after administration of $MnCl_2$ (Table 4).

Table 2 Apparent diffusion coefficient (ADC) in different brain areas acutely after decompression

	Control		Decomp.	
	Mean	SD	Mean	SD
Frontal cortex	776.3	54.5	795.4	67.1
Parietal cortex	778.8	80.5	817.9	65.4
Occipital cortex	826.3	71.5	824.6	97.2
Hippocampus	830.0	56.4	879.3	74.4
Putamen	761.6	38.9	765.4	40.3
Thalamus	783.3	47.9	814.2	65.4
Brain stem	856.3	80.6	849.0	117.8

Mean ADC (10^{-6} mm^2/s) with standard deviation (SD) in groups of control and decompressed rats

No specific white matter abnormalities were seen on DTI and parameters such as fractional anisotropy (FA) (Fig. 3), mean, axial and radial diffusivity were not different between groups in the measured white matter structures (Table 5).

Histology

In routine haematoxylin and eosin (H&E) sections and after histochemical and immunohistochemical analyses, no histopathological changes were observed with regard to neuropil, neurons, glial cells, vessels or leptomeninges. In particular, no signs of degeneration of neurons (no red neurons), demyelination, gliosis, inflammation, microglial activation or endothelial injury were detected. Furthermore, no parenchymal immunostaining for albumin was noted consistent with no vascular leakage (Fig. 4).

Table 1 Calculated parameters from the dynamic contrast-enhanced imaging

	$RSI_{1.5min}$				TTP (min)				AUC_{5min}			
	Control		Decomp.		Control		Decomp.		Control		Decomp.	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Frontal cortex	1.05	0.02	1.09*	0.02	0.20	0.05	0.88^+	0.64	0.17	0.08	0.31^+	0.11
Parietal cortex	1.10	0.03	1.09	0.02	0.36	0.07	0.67	0.37	0.40	0.19	0.34	0.07
Occipital cortex	1.09	0.03	1.11	0.01	0.56	0.19	0.81	0.59	0.38	0.12	0.41	0.07
Hippocampus	1.09	0.03	1.11	0.02	0.65	0.36	1.06	0.46	0.37	0.14	0.47	0.06
Putamen	1.08	0.01	1.09	0.02	0.54	0.26	1.17^+	0.59	0.35	0.07	0.38	0.03
Thalamus	1.08	0.01	1.10^+	0.02	0.43	0.28	1.62	1.27	0.35	0.03	0.44*	0.06
Brain stem	1.07	0.03	1.10	0.04	0.97	0.63	2.27	1.54	0.33	0.05	0.35	0.11

Mean relative signal intensity 1.5 min after injection ($RSI_{1.5min}$), time to peak after injection (TTP) in min and area under the curve 5 min from injection (AUC_{5min}) with standard deviation (SD) in different brain areas in groups of control and decompressed rats acutely after decompression

P values from two-sided *t* test with unequal variances

Significance is indicated by * $P < 0.05$, ** $P < 0.01$

$P < 0.1$ is indicated by $^+$

Table 3 T_2 in brain areas at different times after decompression

	Acute				1 week				2 weeks			
	Control		Decomp.		Control		Decomp.		Control		Decomp.	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Frontal cortex	49.5	1.1	50.1	1.5	47.1	0.6	47.5	0.9	48.1	0.6	48.3	0.9
Parietal cortex	50.8	0.6	50.9	1.5	48.4	0.5	49.1*	0.5	49.8	0.6	50.0	0.8
Occipital cortex	52.9	0.9	52.3	1.8	50.4	1.2	51.0	0.5	52.0	0.6	52.2	0.5
Hippocampus	55.1	0.3	55.1	1.4	51.3	0.9	51.6	1.4	53.2	0.8	52.8	1.8
Putamen	49.2	1.4	50.5	1.4	45.1	1.3	45.4	1.5	46.6	0.6	47.2	1.0
Thalamus	48.0	1.0	48.4	1.3	43.4	0.6	44.1	0.7	44.9	0.6	45.8*	0.8
Brain stem	51.7	0.9	51.7	1.9	46.6	1.0	48.1*	1.1	48.5	0.6	49.9**	0.4

Mean T2 (ms) with standard deviation (SD) in groups of control and decompressed rats. Acutely, 1 and 2 weeks after decompression

P values from two-sided *t* test with unequal variances

Significance is indicated by * $P < 0.05$, ** $P < 0.01$

Table 4 Manganese-enhanced MRI

	Control		Decomp.	
	Mean	SD	Mean	SD
Frontal cortex	1.82	0.37	2.05	0.16
Parietal cortex	1.91	0.29	2.04	0.13
Occipital cortex	1.75	0.12	1.73	0.11
Hippocampus	2.10	0.28	2.04	0.16
Putamen	1.97	0.22	1.95	0.15
Thalamus	1.93	0.18	1.82	0.18
Brain stem	1.90	0.16	1.82	0.13

Mean relative contrast with standard deviation (SD) on T_1-weighted MRI in different brain areas in groups of control and decompressed rats after 1 week. Increased relative contrast indicated manganese-enhancement

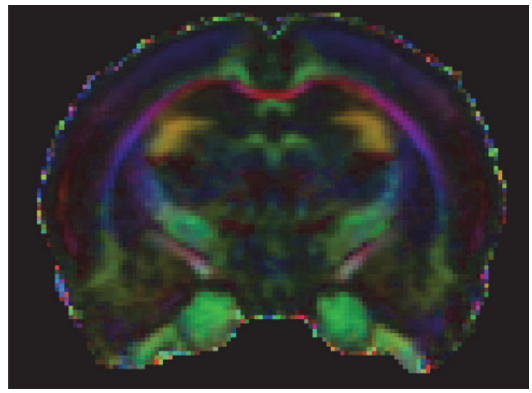

Fig. 3 Image shows representative fractional anisotropy (*FA*) map

Discussion

The present study is, to our knowledge, the first controlled, longitudinal study where MRI has been used to evaluate effects of decompression. The results indicate that decompression causes altered brain perfusion in the acute phase, with increased T_2 in the brain stem on MRI in the 2 weeks after decompression.

To study the ongoing process of the physiological responses to a dive, three time points were chosen for measurement, at 1 h, 1 and 2 weeks after decompression in experimental animals. The dive profile that we used caused bubble formation in all rats, with neurological symptoms (paresis of the hind limbs) noted in one rat within 24 h and immediate death caused in two rats. The death of three rats indicates the severity of the dive profile. The rats that died had considerable amounts of gas present in their vascular system and tissue. Therefore, death was most probably due to a large number of vascular gas bubbles causing cardio-vascular collapse and shock leading to death (Muth and Shank 2000).

The first MRI measurements were designed to look for acute effects in the brain. DCE MRI was performed to assess brain perfusion and permeability of the BBB. The gadolinium-based contrast agent, Omniscan, used in this study remains in the vasculature under normal homeostasis, but is known to leak across the BBB when its integrity is compromised (Wardlaw et al. 2008). The signal change and shape of the signal curve reflects the amount of contrast agent in the brain circulation and any redistribution of the contrast agent from the circulation to the brain tissue. In the present study, the DCE measurements showed that decompressed rats had increased RSI and AUC compared to controls. This indicates an increased blood flow to the brain tissue, and may be explained by an increased oxygen demand secondary to a tissue hypoxia–ischemia caused by the decompression stress. Perfusion changes are previously

Table 5 Diffusion Tensor Imaging results

	Week 1				Week 2			
	Control		Decomp.		Control		Decomp.	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Corpus callosum body	0.76	0.03	0.73	0.08	0.73	0.04	0.75	0.03
Corpus callosum splenium	0.79	0.03	0.73	0.08	0.69	0.04	0.67	0.08
External capsule	0.48	0.01	0.47	0.03	0.46	0.01	0.47	0.02
Hippocampal fimbria	0.71	0.03	0.65	0.06	0.75	0.01	0.73	0.04
Internal capsule	0.67	0.05	0.63	0.06	0.73	0.06	0.75	0.02
All structures	0.58	0.02	0.55	0.03	0.58	0.02	0.58	0.01

Mean fractional anisotropy (FA) and standard deviation (SD) in different white matter structures in groups of control and decompressed rats after 1 week

P values from two-sided *t* test with unequal variances

documented in occupational divers in watershed areas of the brain on MRI, and are explained by possible changes in the function of the cerebral microvasculature (Moen et al. 2010). Since DCE was only performed at one time point in our study, the duration of such circulatory changes are uncertain.

As the shape of the signal curves from the DCE in the elimination phase was similar between decompressed and control animals and there were no areas with increased signal intensity in the post-contrast images compared to the pre-contrast images, it was concluded that there was no significant leakage over the BBB in response to the decompression at the time of imaging in the present study. Decompression has previously been shown to cause increased permeability of the BBB, as illustrated by leakage of dye (Trypan blue) into brain tissue of decompressed rabbits with dye concentration correlating to visible intravascular bubbles (Chryssanthou et al. 1977). We did, however, not find any leakage of albumin in our immunostained brain tissue sections, which would have indicated a BBB leakage. However, using histochemical methods such as Evans blue, increased BBB permeability after decompression has been shown to be temporary and reversible (Nohara and Yusa 1997). In the present study, the acute MRI acquisition started 1 h after the decompression and the DCE was performed last of all imaging, starting approximately 2 h after the decompression. Hence, any increased permeability of the BBB may have been reversed at the time of imaging. Future studies should, therefore, aim to perform DCE imaging immediately after the decompression to establish whether this dive protocol causes temporary changes to the BBB permeability. It is important to establish whether there is a change in BBB permeability in response to diving, since this may have consequences for drug administration to divers and compressed air workers. If the BBB is more permeable at a certain time point, then drugs and environmental toxins may penetrate the brain in amounts that could produce toxic or undesirable effects (Chryssanthou et al. 1977). Thus, changes in the integrity of the BBB do not necessarily have any adverse effects per se, but exposure to potentially damaging drugs or environments while it is compromised may do.

Except for the changes in DCE MRI, no focal or general changes indicating cerebral injury were found on anatomical (T_1 and T_2) or diffusion weighted imaging 1 h after the decompression. The early time point of imaging may explain lack of signal changes on T_1 and T_2, but diffusion

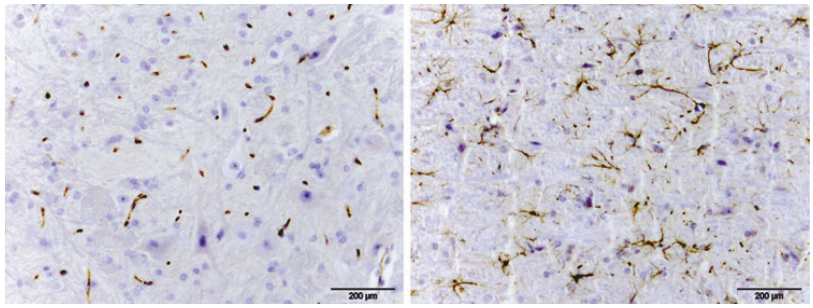

Fig. 4 Albumin and GFAP stain from brain stem

weighted imaging has previously been shown to be a very sensitive method for detecting ischemic lesions (van Everdingen et al. 1998). However, the lack of signs of injury on acute MRI is not surprising, since all but one of the animals showed no neurological signs at that time. In previous studies, focal CNS injuries on conventional MRI were found in the presence of neurological symptoms and signs (Yoshiyama et al. 2007; Jallul et al. 2007; Gronning et al. 2005; Reuter et al. 1997). Moreover, even in the presence of clinical neurological signs suggesting brain involvement, abnormalities on cerebral MRI are uncommon, occurring only in 25 % of the patients in one study (Reuter et al. 1997) and none in another (Gronning et al. 2005).

Hence, lack of detectable injury on acute MRI does not exclude the presence of cerebral injury or that injury can evolve. In fact, on follow-up 1 and 2 weeks after the decompression, changes in T_2 were found in brain stem and thalamus among decompressed animals. These delayed findings are in accordance with previously published clinical reports, where MRI abnormalities, especially increased T_2 indicating focal CNS injuries, have been found several weeks after the decompression (Reuter et al. 1997; Hierholzer et al. 2000; Jallul et al. 2007). These studies showed MRI abnormalities mostly in the spinal cord, and this is despite the fact that MRIs made during the first 24 h after onset of symptoms (Jallul et al. 2007) were normal. In the present study, we did not image the spine, but the T_2 changes were located in the basal parts of the brain. These brain areas are supplied by the basal artery and may have poorer collateral circulation than the neo-cortex, and thus represent more vulnerable areas of the brain in case of large arterial air embolism. The primary cause of increased T_2 is increased tissue water content that can be taken as an indication of tissue injury with secondary edema. Reduced capillary density may also lead to increased T2 (Norris 2006). However, histological examinations did not show any signs of tissue injury or vascular changes in the areas with increased T_2 or in any other brain areas. The origin of the increased T_2 is, therefore, uncertain.

The lack of other findings on MRI after the acute phase could mean that the technique is not sensitive enough to detect subtle tissue changes. However, the MRI results were supported by histological and immunohistochemical examinations that did not show any structural changes in any part of the brain.

One of the hypotheses of this study was that decompression leads to cerebral white matter injuries. However, such injuries may be too subtle to detect on histological examination and anatomical MR imaging, but could be detected using more functional imaging techniques such as DTI where the quantity and directionality of the water diffusion of the tissue can be measured. Injuries to axons and reduced myelination both give specific changes in the quantity and directionality of water diffusion, but no such effects could be detected in our study. Hence, there were no indications that the decompression caused any harmful effects to central cerebral white matter.

There have been several other attempts to study long-term effects in animal models; the CNS has been studied in goats subjected to several (mean 12.5), relatively severe dives over a number of years. In the brains of three out of 36 animals, lesions were seen on MRI (T_2). However, this was seen in goats with no history of DCS. No evidence of any histopathological damage in the brains of dived animals was found through staining with H&E and glial fibrillary acidic protein (GFAP) (Blogg et al. 2004; Woodger et al. 2001). One suggestion for the lack of significant brain lesions detected in these dived goats was that goats have a slightly different carotid blood supply than humans, with a rete that might act as a filter to some bubbles that pass into the arterial circulation (Daniel et al. 1953).

Conclusions

In conclusion, the present study indicates that severe decompression does not seem to cause any structural or cellular injury to the brain tissue of the rat, but may cause circulatory changes in the brain perfusion.

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Conflict of interest The authors report no conflict of interest. The authors alone are responsible for the content and writing the paper.

References

Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, Matthews PM, Brady JM, Smith SM (2003) Characterization and propagation of uncertainty in diffusion-weighted MR imaging. Magn Reson Med 50(5):1077–1088

Bigley NJ, Perymon H, Bowman GC, Hull BE, Stills HF, Henderson RA (2008) Inflammatory cytokines and cell adhesion molecules in a rat model of decompression sickness. J Interf Cytokine Res 28(2):55–63

Blogg SL, Loveman GA, Seddon FM, Woodger N, Koch A, Reuter M, Gennser M, White MG (2004) Magnetic resonance imaging and

neuropathology findings in the goat nervous system following hyperbaric exposures. Eur Neurol 52(1):18–28
Brubakk AO, Bolstad G, Jacobsen G (1994) Helseeffekter av luftdykking. Yrkes- og sportsdykkere (Health effects of air diving. Occupational- and sports divers) (trans: SINTEF), Trondheim
Brubakk AO, Duplancic D, Valic Z, Palada I, Obad A, Bakovic D, Wisloff U, Dujic Z (2005) A single air dive reduces arterial endothelial function in man. J Physiol 566(Pt 3):901–906
Chryssanthou C, Springer M, Lipschitz S (1977) Blood-brain and blood-lung barrier alteration by dysbaric exposure. Undersea Biomed Res 4(2):117–129
Cordes P, Keil R, Bartsch T, Tetzlaff K, Reuter M, Hutzelmann A, Friege L, Meyer T, Bettinghausen E, Deuschl G (2000) Neurologic outcome of controlled compressed-air diving. Neurology 55(11):1743–1745
Daniel PM, Dawes JDK, Prichard MML (1953) Studies of the carotid rete and its associated arteries. Philos T Roy Soc B 237(645): 173–208
Eftedal O, Brubakk AO (1997) Agreement between trained and untrained observers in grading intravascular bubble signals in ultrasonic images. Undersea Hyperb Med 24(4):293–299
Erdem I, Yildiz S, Uzun G, Sonmez G, Senol MG, Mutluoglu M, Mutlu H, Oner B (2009) Cerebral white-matter lesions in asymptomatic military divers. Aviat Space Environ Med 80(1):2–4
Francis TJ, Dutka AJ, Hallenbeck JM (1990) Patophysiology of decompression sickness. In: Bove AA, Davis JC (eds) Diving medicine, vol 2nd. Saunders, Philadelphia, pp 170–187
Gronning M, Risberg J, Skeidsvoll H, Moen G, Aanderud L, Troland K, Sundal E, Thorsen E (2005) Electroencephalography and magnetic resonance imaging in neurological decompression sickness. Undersea Hyperb Med 32(6):397–402
Hierholzer J, Tempka A, Stroszczynski C, Amodio F, Hosten N, Haas J, Felix R (2000) MRI in decompression illness. Neuroradiology 42(5):368–370
Hjelde A, Nossum V, Steinsvik M, Bagstevold JI, Brubakk AO (2002) Evaluation of cerebral gas retention and oedema formation in decompressed rats by using a simple gravimetric method. Scand J Clin Lab Invest 62(4):263–270
Hutzelmann A, Tetzlaff K, Reuter M, Muller-Hulsbeck S, Heller M (2000) Does diving damage the brain? MR control study of divers' central nervous system. Acta Radiol 41(1):18–21
Irgens A, Gronning M, Troland K, Sundal E, Nyland H, Thorsen E (2007) Reduced health-related quality of life in former North Sea divers is associated with decompression sickness. Occup Med (Lond) 57(5):349–354
Jallul S, Osman A, El-Masry W (2007) Cerebro-spinal decompression sickness: report of two cases. Spinal Cord 45(1):116–120
Kaakkola S, Lehtosalo J, Laitinen LA (1982) Changes in blood-brain barrier permeability to drugs in decompressed rats. Undersea Biomed Res 9(3):233–240
McAuliffe MJ, Lalonde FM, McGarry D, Gandler W, Csaky K, Trus BL (2001) Medical image processing, analysis and visualization in clinical research. Comp Med Sy: 381–386
Moen G, Specht K, Taxt T, Sundal E, Groning M, Thorsen E, Troland K, Irgens A, Gruner R (2010) Cerebral diffusion and perfusion deficits in North Sea divers. Acta Radiol 51(9):1050–1058
Mollerlokken A, Gaustad SE, Havnes MB, Gutvik CR, Hjelde A, Wisloff U, Brubakk AO (2011) Venous gas embolism as a predictive tool for improving CNS decompression safety. Eur J Appl Physiol 12:401–409
Moon RE, Gorman DF (2003) Treatment of the decompression disorders. In: Brubakk AO, Neuman TS (eds) Bennett and Elliott's physiology and medicine of diving. 5th edn. Saunders, pp 600–651
Muth CM, Shank ES (2000) Gas embolism. N Engl J Med 342(7):476–482
Neuman TS (2003) Arterial gas embolism and pulmonary barotrauma. In: Brubakk AO NT (ed) Bennett and Elliott's physiology and medicine of diving. 5th edn. Saunders, pp 557–577
Newton H, Padilla W, Burkart J, Pearl D (2007) Neurological manifestations of decompression illness in recreational divers—the Cozumel experience. Undersea Hyperb Med 34:349–357
Nohara A, Yusa T (1997) Reversibility in blood-brain barrier, microcirculation, and histology in rat brain after decompression. Undersea Hyperb Med 24(1):15–21
Norris DG (2006) Principles of magnetic resonance assessment of brain function. J Magn Reson Imaging 23(6):794–807
Nossum V, Hjelde A, Brubakk AO (2002) Small amounts of venous gas embolism cause delayed impairment of endothelial function and increase polymorphonuclear neutrophil infiltration. Eur J Appl Physiol 86(3):209–214
Paxinos G, Watson C (2008) The rat brain in stereotaxic coordinates. Academic press, London
Reuter M, Tetzlaff K, Hutzelmann A, Fritsch G, Steffens JC, Bettinghausen E, Heller M (1997) MR imaging of the central nervous system in diving-related decompression illness. Acta Radiol 38(6):940–944
Ross JA, Macdiarmid JI, Osman LM, Watt SJ, Godden DJ, Lawson A (2007) Health status of professional divers and offshore oil industry workers. Occup Med (Lond) 57(4):254–261
Sawatzky K (1991) The relationship between intravscular Doppler-detected gas bubbles and decompression sickness after bounce diving in humans. York University, Toronto
Todnem K, Nyland H, Kambestad BK, Aarli JA (1990) Influence of occupational diving upon the nervous system: an epidemiological study. Br J Ind Med 47(10):708–714
van Everdingen KJ, van der Grond J, Kappelle LJ, Ramos LMP, Mali WPTM (1998) Diffusion-weighted magnetic resonance imaging in acute stroke. Stroke: J Cereb Circ 29(9):1783–1790
Vann RD, Butler FK, Mitchell SJ, Moon RE (2011) Decompression illness. Lancet 377(9760):153–164
Wardlaw JM, Farrall A, Armitage PA, Carpenter T, Chappell F, Doubal F, Chowdhury D, Cvoro V, Dennis MS (2008) Changes in background blood-brain barrier integrity between lacunar and cortical ischemic stroke subtypes. Stroke: J Cereb Circ 39(4):1327–1332
Warren LP Jr, Djang WT, Moon RE, Camporesi EM, Sallee DS, Anthony DC, Massey EW, Burger PC, Heinz ER (1988) Neuroimaging of scuba diving injuries to the CNS. AJR Am J Roentgenol 151(5):1003–1008
Widerøe M, Olsen Ø, Pedersen TB, Goa PE, Kavelaars A, Heijnen C, Skranes J, Brubakk AM, Brekken C (2009) Manganese-enhanced magnetic resonance imaging of hypoxic-ischemic brain injury in the neonatal rat. Neuroimage 45:880–890
Woodger N, Palmer AC, Blakemore WF (2001) A double blind study of the neuropathology in goats exposed to hyperbaric conditions. Offshore technology report. Department of clinical veterinary medicine, University of Cambridge, Cambridge
Yoshiyama M, Asamoto S, Kobayashi N, Sugiyama H, Doi H, Sakagawa H, Ida M (2007) Spinal cord decompression sickness associated with scuba diving: correlation of immediate and delayed magnetic resonance imaging findings with severity of neurologic impairment—a report on 3 cases. Surg Neurol 67(3):283–287

PAPER III

Original Article

COACTION PUBLISHING

Concentration of circulating autoantibodies against HSP 60 is lowered through diving when compared to non-diving rats

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Objective: Skin and ear infections, primarily caused by *Pseudomonas aeruginosa* (*P. aeruginosa*), are recurrent problems for saturation divers, whereas infections caused by *P. aeruginosa* are seldom observed in healthy people outside saturation chambers. Cystic fibrosis (CF) patients suffer from pulmonary infections by *P. aeruginosa*, and it has been demonstrated that CF patients have high levels of autoantibodies against Heat shock protein 60 (HSP60) compared to controls, probably due to cross-reacting antibodies induced by *P. aeruginosa.* The present study investigated whether rats immunised with *P. aeruginosa* produced autoantibodies against their own HSP60 and whether diving influenced the level of circulating anti-HSP60 antibodies.

Methods: A total of 24 rats were randomly assigned to one of three groups ('immunised', 'dived' and 'immunised and dived').The rats in group 1 and 3 were immunised with the bacteria *P. aeruginosa*, every other week. Groups 2 and 3 were exposed to simulated air dives to 400 kPa (4 ata) with 45 min bottom time, every week for 7 weeks. Immediately after surfacing, the rats were anaesthetised and blood was collected from the saphenous vein. The amount of anti-HSP60 rat antibodies in the serum was analysed by enzyme linked immunosorbent assay.

Results: The immunised rats (group 1) showed a significant increase in the level of autoantibodies against HSP60, whereas no autoantibodies were detected in the dived rats (group 2). The rats both immunised and dived (group 3) show no significant increase in circulating autoantibodies against HSP60. A possible explanation may be that HSP60 is expressed during diving and that cross-reacting antibodies are bound.

Keywords: *saturation diving*; *infection*; *long-term effects*; *anti-HSP60*; *immunisation*

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Saturation diving is widely used in the North Sea for maintenance and inspection of off-shore sub-sea petroleum production systems. Exposure to hyperbaric environments is associated with a risk of developing decompression sickness (DCS), arterial gas embolism, neurological symptoms and pulmonary dysfunctions (1–3). Divers are usually compressed in their working and living environment for 12–24 days and are exposed to an ambient pressure of 0.6–2.1 MPa (50–200 msw). The hyperbaric working and living environment is warm and humid and so maintains a rich microbial flora (4).

Health problems, such as skin and ear infections, in divers working on the Norwegian Continental Shelf have been systematically registered since 1985 (4). Within the period from 1990 to 2010, four incidents of DCS and 201 incidents of outer ear infection were reported to the Petroleum Safety Authority Norway (5).

Skin and ear infections in saturation diving are usually caused by *Pseudomonas aeruginosa* (*P. aeruginosa*) (6). Such infections have been common since the beginning of saturation diving, and infectious outbreaks have caused costly breaks in operations (7, 8). The *P. aeruginosa*

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bacterium is commonly found all over the world, occurring in both fresh- and seawater, soil and on plants, and the species is noted for its metabolic versatility and its exceptional ability to adapt to and colonise various ecological niches.

Infections caused by *P. aeruginosa* are seldom observed in healthy people outside a saturation chamber, but the bacterium is well known as an opportunistic pathogen. Patients with cystic fibrosis (CF) suffer recurrently from pulmonary infections due to *P. aeruginosa* (9). Insulin-dependent diabetes is the most prevalent co-morbidity condition in CF (10), and it has been suggested that destruction of the insulin-producing beta-cells in the pancreas is caused by autoantibodies that act against heat shock protein 60 (HSP60) (11). HSP60 molecules are highly phylogenetically conserved with about 50% sequence homology between human HSP60s and those of *P. aeruginosa* (12). Thus, the presence of autoantibodies against HSP60 in patients with CF may be due to human antibodies cross-reacting in a process induced by the presence of bacterial HSP60.

Heat shock proteins are involved in folding and unfolding of other proteins (13) and are expressed in response to various stressors such as hyperoxia, hypoxia, heat, cold, exercise, some heavy metals and drugs, and many of these factors are involved in diving (14). HSP60, a member of this family, is highly expressed *in vitro* in endothelial cells. It is normally an intracellular protein, but in response to various stresses it is expressed on the surface (15). Binding of anti-HSP60 antibodies to HSP60 has been suggested to be present in the development of atherosclerosis (16). Furthermore, immunisation of mice with human sera containing high levels of anti-HSP60 induces atherosclerosis (17). They even found a marked induction of atherosclerotic lesions after a single injection of purified anti-HSP antibodies (17).

Hence, a relevant question is whether *P. aeruginosa* infections amongst saturation divers may induce production of autoantibodies that might cross-react and bind to human HSP60.

In the present study, we investigated whether rats immunised with *P. aeruginosa* produced autoantibodies against rat HSP60 and whether the autoantibody level was affected by diving.

Material and methods

A total of 24 young female Sprague–Dawley albino rats (Scanbur, Denmark), weighing 0.262 ± 0.013 kg, were used in the experiment. All animals used in the experiment were bought at the same time, from the same supplier and had equal amount of time for acclimatisation. All experimental procedures and the care of experimental animals conformed to the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, and the protocol was approved by the Norwegian Council for Animal Research.

Following 1 week of acclimatisation, the rats were randomly assigned to one of three groups, 'Immunised', 'Dived' and 'Immunised and dived' ($n = 8$ for each group). There was no significant difference in weight between the groups.

One strain of *P. aeruginosa* (genotype E) isolated from an infected saturation diver was used in this study (4). The isolated bacterium was inactivated by 65°C for 30 min. Cultures were solved in sterile and filtered phosphate buffered saline (PBS) buffer (pH 7.2) and diluted to fit optical density (OD) of 600 nm To ensure that the vaccine is sterile, growth was examined by coating 100 µl of the vaccine on Blood Agar and incubating at 37°C for 2 days. The vaccine was preserved in aliquots at −80°C until vaccinations.

The rats in groups 1 and 3 were immunised with *P. aeruginosa* crude antigen, 0.2 ml every other week, from week 1 to week 9, in total five times. Two weeks after the first immunisation, groups 2 and 3 were exposed to simulated air dives. The rats only subjected to pressure exposure had injections of saline solution (0.9% NaCl, B. Braun, Melsungen, Germany), at the same time as the other ones had immunisations. The compressions were performed in a 20-L hyperbaric chamber with continuous air supply. Both dive groups were compressed (200 kPa/min) to 400 kPa (4 ata) with 45 min bottom time. The decompression rate was 50 kPa/min. The dive protocol in both groups was repeated every seventh day for 7 weeks, in total seven times.

Immediately after surfacing, the rats were anaesthetised with a subcutaneous injection of a mixture of Haldol 0.33 mg, Fentanyl 0.05 mg and Midazolan 0.5 mg at a dose of 2.5 ml/kg of body weight. Blood was collected from the saphenous vein. After blood sampling, the rats were moved to their housing facilities where they were allowed to recover.

Two weeks after the last test protocol was performed, the rats received a 1.2-ml subcutaneous injection of the same anaesthetic mixture as described previously and were sacrificed by heart puncture.

Serological analyses: Enzyme linked immunosorbent assay (ELISA) for detecting antibodies against rat HSP60.

Sera were analysed by indirect ELISA. Recombinant rat HSP60 (Stressgen, Victoria, Canada) was diluted at a ratio of 1:1,000 in coating buffer, which contained 1.59 g of Na_2CO_3, 2.93 g of $NaHCO_3$ and 1 L of distilled water (pH 9.6), and 100 µl/well were incubated in microplates (Sterilin) overnight at room temperature. Plates were then washed three times with PBS containing 0.05% Tween 20 (PBS-T). Plates were pre-incubated at room temperature with 300 ml/well of blocking buffer, containing 1% skimmed milk powder (Molico,

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Nestlè) in PBS, for 30 min. After washing three times with PBS-T, wells were incubated in duplicate with rat serum in a dilution of 1:10 ml/well, in blocking buffer, for 2 h. Plates were washed three times with PBS-T and incubated with polyclonal rabbit anti-rat IgG/ HRP (DakoCytomation, Denmark), diluted at a ratio of 1:1,000 in blocking buffer, for 1 h at room temperature. After washing four times with PBS-T, 100 ml of freshly made Sigmafast OPD (containing 0.4 mg/ml o-phenylenediamine, 0.4 mg/ml urea hydrogen peroxide and 0.05 M phosphate-citrate in 20 ml distilled water, pH 5.0) (Sigma, USA) was added to each well. After 30 min, the reaction was stopped with 50 ml of 2 M H_2SO_4 and plates were read at 490 nm. OD values were derived from duplicate determinations.

Statistics

The results are presented as mean ± S.D. Mann–Whitney and the Wilcoxon signed-rank test were used to analyse the ELISA results. The level of statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS 14.0 (SPSS Inc., Chicago, Illinois, USA).

Results

The results from the ELISA measurements of anti-HSP60 antibodies in serum are shown in Figs 1, 2 and 3. In the immunised group (group 1), there was a significant increase in anti-HSP60 level from week 1 to week 11 ($p \leq 0.01$) (Fig. 1). No significant increase in the concentration of free anti-HSP60 antibodies was detected in the diving group (group 2, Fig. 2) or in the immunised and dived group (group 3, Fig. 3). There are significantly higher levels of anti-HSP60 at week 9 ($p = 0.011$) and 11 ($p = 0.006$) in group 1, compared to group 3.

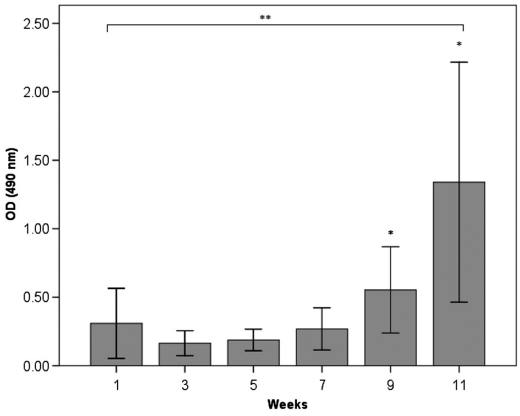

Fig. 1. Longitudinal study of anti-HSP60 level in serum in the immunised group (group 1). Bars represent level of anti-HSP60 analysed by ELISA in blood samples taken every other week, before each immunisation. Notes: **There is a significant increase in anti-HSP60 level from week 1 to week 11 ($p < 0.01$). Bars represented by * are significantly different from same week in group 3 (Fig. 3). Results are presented as mean optical density (OD) values measured at 490 nm. The vertical lines represent the standard deviation.

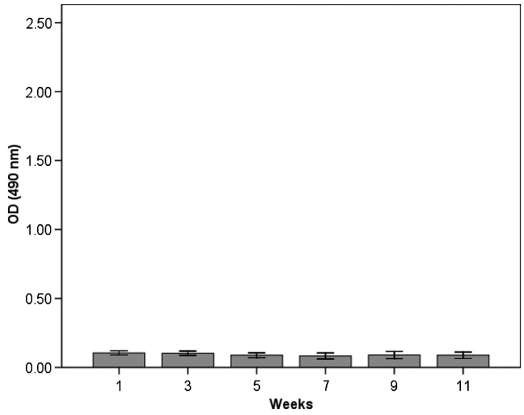

Fig. 2. Longitudinal study of anti-HSP60 level in serum in the dived group (group 2). Notes: Bars represent level of anti-HSP60 analysed by ELISA in blood samples taken every other week/dive, immediately after surfacing/decompression. There is no change in circulating anti-HSP60. Results are presented as mean OD values measured at 490 nm. The vertical lines represent the standard deviation.

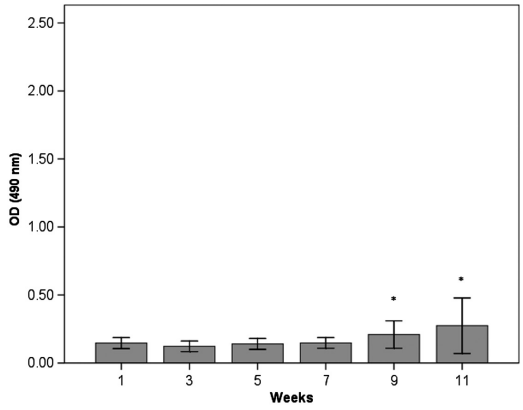

Fig. 3. Longitudinal study of anti-HSP60 level in serum in the immunised and dived group (group 3). Notes: Bars represent level of anti-HSP60 analysed by ELISA in blood samples taken every other week/dive immediately after surfacing/decompression. In contrast to the immunised rats (group 1), there is no significant change in level of circulating anti-HSP60.Bars represented by * are significantly different from same week in group 1 (Fig. 1). Results are presented as mean OD values measured at 490 nm. The vertical lines represent the standard deviation.

Discussion

This study demonstrates that the level of circulating autoantibodies against HSP60 significantly increases over time in rats with repeated immunisations with *P. aeruginosa* (group 1). The dive rats (group 2) did not show any increase in the level of circulating antibodies during the experimental period, but more surprisingly, we were not able to detect circulating autoantibodies against HSP60 in immunised rats when the blood sample was taken immediately after diving (group 3).

The increased level of autoantibodies against HSP60 in the immunised rats in the current study is in accordance with the situation seen in patients infected by the bacteria *P. aeruginosa* (18). High levels of HSP60 autoantibodies are associated with an increased risk of coronary heart disease (19, 20) and have been associated with the development of type-1 diabetes in CF patients (11).

The animals only subjected to pressure did not show any increased level of circulating autoantibodies against HSP60. Hence, the pressure exposures did not themselves produce circulating autoantibodies.

When rats immunised with *P. aeruginosa* were exposed to dives, they were not observed to have the same rise in the level of circulating antibodies against HSP60 compared to the immunised, non-diving rats. One possible explanation for this may be that diving suppresses the immune response. An alternative explanation may be that HSP60 molecules are expressed on endothelial cells in such a way that the cross-reacting epitopes are exposed to the surface and, thus, enable binding between circulating anti-HSP antibodies and exposed HSP60 epitopes.

There is considerable research on cross-reacting autoantibodies in relation to development of atherosclerosis and in relation to several pathological reactions in CF patients. Bindings between anti-HSP60 antibodies to HSP60 have been demonstrated (16), and such bindings may in turn give rise to inflammatory reactions (11, 18–24).

We are not aware of any studies evaluating level of autoantibodies against HSP60 in saturation divers. Observations in the present study of higher autoantibody level after combining bacterial exposure and diving point in the direction of having cross-reacting autoantibodies. Hence, it seems likely that the exposure to *P. aeruginosa* in the diving environment and recurrent skin infections (6) may give rise to production of autoantibodies against HSP60.

Conflict of interest and funding

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References

1. Mollerlokken A, Gaustad SE, Havnes MB, Gutvik CR, Hjelde A, Wisloff U, et al. Venous gas embolism as a predictive tool for improving CNS decompression safety. Eur J Appl Physiol 2012; 112(2); 401–9.
2. Francis TJR, Mitchell SJ. Pathophysiology of decompression sickness. In: Brubakk AO, Neuman TS, eds. Bennett and Elliott's physiology and medicine of diving. 5th ed. Saunders, Philadelphia; 2003, pp. 530–57.
3. Neuman TS. Arterial gas embolism and pulmonary barotrauma. In: Brubakk AO, Neuman TS, eds. Bennett and Elliott's physiology and medicine of diving. 5th ed. Saunders, Philadelphia; 2003, pp. 557–77.
4. Ahlen C, Mandal LH, Iversen OJ. Identification of infectious Pseudomonas aeruginosa strains in an occupational saturation diving environment. Occup Environ Med 1998; 55(7): 480–4.
5. Report from the DSYS database. Stavanger: the petroleum safety authority. Norway, 2010.
6. Ahlen C, Mandal LH, Iversen OJ. An in-field demonstration of the true relationship between skin infections and their sources in occupational diving systems in the North Sea. Ann Occup Hyg 2003; 47(3): 227–33.
7. Thalman E. A prophylactic program for the prevention of otitis externa in saturation divers, research report. Washington, DC: US Navy Experimental Diving Unit, Washington Navy Yard; 1974.
8. Alcock SR. Acute otitis externa in divers working in the North Sea: a microbiological survey of seven saturation dives. J Hyg (Lond) 1977; 78(3): 395–409.
9. Govan JR, Nelson JW. Microbiology of lung infection in cystic fibrosis. Br Med Bull 1992; 48(4): 912–30.
10. Moran A, Hardin D, Rodman D, Allen HF, Beall RJ, Borowitz D, et al. Diagnosis, screening and management of cystic fibrosis related diabetes mellitus: a consensus conference report. Diabetes Res Clin Pract 1999; 45(1): 61–73.
11. Jensen P, Johansen HK, Carmi P, Hoiby N, Cohen IR. Autoantibodies to pancreatic hsp60 precede the development of glucose intolerance in patients with cystic fibrosis. J Autoimmun 2001; 17(2): 165–72.
12. Jensen P, Fomsgaard A, Hoiby N, Hindersson P. Cloning and nucleotide sequence comparison of the groE operon of *Pseudomonas aeruginosa* and Burkholderia cepacia. APMIS 1995; 103(2): 113–23.
13. Lindquist S. The heat-shock response. Annu Rev Biochem 1986; 55: 1151–91.
14. Brubakk AO, Eftedal OS, Wisløff U. Endothelium and diving. In: Aird W, ed., Endothelial Biomedicine. Cambridge University Press, Cambridge; 2007. pp. 497–505.
15. Xu Q, Schett G, Seitz CS, Hu Y, Gupta RS, Wick G. Surface staining and cytotoxic activity of heat-shock protein 60 antibody in stressed aortic endothelial cells. Circ Res 1994; 75(6): 1078–85.
16. Schett G, Xu Q, Amberger A, Van der Zee R, Recheis H, Willeit J, et al. Autoantibodies against heat shock protein 60 mediate endothelial cytotoxicity. J Clin Invest 1995; 96(6): 2569–77.
17. Foteinos G, Afzal AR, Mandal K, Jahangiri M, Xu Q. Anti-heat shock protein 60 autoantibodies induce atherosclerosis in apolipoprotein E-deficient mice via endothelial damage. Circulation 2005; 112(8): 1206–13.
18. de Graeff-Meeder ER, Rijkers GT, Voorhorst-Ogink MM, Kuis W, van der Zee R, van Eden W, et al. Antibodies to human

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HSP60 in patients with juvenile chronic arthritis, diabetes mellitus, and cystic fibrosis Pediatr Res 1993; 34(4): 424–8.
19. Prohaszka Z, Duba J, Horvath L, Csaszar A, Karadi I, Szebeni A, et al. Comparative study on antibodies to human and bacterial 60 kDa heat shock proteins in a large cohort of patients with coronary heart disease and healthy subjects. Eur J Clin Invest 2001; 31(4): 285–92.
20. Prohaszka Z, Duba J, Lakos G, Kiss E, Varga L, Janoskuti L, et al. Antibodies against human heat-shock protein (hsp) 60 and mycobacterial hsp65 differ in their antigen specificity and complement-activating ability. Int Immunol 1999; 11(9): 1363–70.
21. Alard JE, Dueymes M, Youinou P, Jamin C. Modulation of endothelial cell damages by anti-Hsp60 autoantibodies in systemic autoimmune diseases. Autoimmun Rev 2007; 6(7): 438–43.
22. Jamin C, Dugue C, Alard JE, Jousse S, Saraux A, Guillevin L, et al. Induction of endothelial cell apoptosis by the binding of anti-endothelial cell antibodies to Hsp60 in vasculitis-associated systemic autoimmune diseases. Arthritis Rheum 2005; 52(12): 4028–38.
23. Lamb JR, Bal V, Mendez-Samperio P, Mehlert A, So A, Rothbard J, et al. Stress proteins may provide a link between the immune response to infection and autoimmunity. Int Immunol 1989; 1(2): 191–6.
24. Wick G, Schett G, Amberger A, Kleindienst R, Xu Q. Is atherosclerosis an immunologically mediated disease? Immunol Today 1995; 16(1): 27–33.

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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

2002

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

2003

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

2004

235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA

244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

2005

248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

2006

269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT

272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
290. Jakob Nakling: RESULTS AND CONSEQUENCES OF ROUTINE ULTRASOUND SCREENING IN PREGNANCY – A GEOGRAPHIC BASED POPULATION STUDY
291. Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY
292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN

297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

2007

298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY
300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
301. Arne Skjold: MAGNETIC RESONANCE KINETICS OF MANGANESE DIPYRIDOXYL DIPHOSPHATE (MnDPDP) IN HUMAN MYOCARDIUM. STUDIES IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION
302. Siri Malm: LEFT VENTRICULAR SYSTOLIC FUNCTION AND MYOCARDIAL PERFUSION ASSESSED BY CONTRAST ECHOCARDIOGRAPHY
303. Valentina Maria do Rosario Cabral Iversen: MENTAL HEALTH AND PSYCHOLOGICAL ADAPTATION OF CLINICAL AND NON-CLINICAL MIGRANT GROUPS
304. Lasse Løvstakken: SIGNAL PROCESSING IN DIAGNOSTIC ULTRASOUND: ALGORITHMS FOR REAL-TIME ESTIMATION AND VISUALIZATION OF BLOOD FLOW VELOCITY
305. Elisabeth Olstad: GLUTAMATE AND GABA: MAJOR PLAYERS IN NEURONAL METABOLISM
306. Lilian Leistad: THE ROLE OF CYTOKINES AND PHOSPHOLIPASE A_2S IN ARTICULAR CARTILAGE CHONDROCYTES IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS
307. Arne Vaaler: EFFECTS OF PSYCHIATRIC INTENSIVE CARE UNIT IN AN ACUTE PSYCIATHRIC WARD
308. Mathias Toft: GENETIC STUDIES OF LRRK2 AND PINK1 IN PARKINSON'S DISEASE
309. Ingrid Løvold Mostad: IMPACT OF DIETARY FAT QUANTITY AND QUALITY IN TYPE 2 DIABETES WITH EMPHASIS ON MARINE N-3 FATTY ACIDS
310. Torill Eidhammer Sjøbakk: MR DETERMINED BRAIN METABOLIC PATTERN IN PATIENTS WITH BRAIN METASTASES AND ADOLESCENTS WITH LOW BIRTH WEIGHT
311. Vidar Beisvåg: PHYSIOLOGICAL GENOMICS OF HEART FAILURE: FROM TECHNOLOGY TO PHYSIOLOGY
312. Olav Magnus Søndenå Fredheim: HEALTH RELATED QUALITY OF LIFE ASSESSMENT AND ASPECTS OF THE CLINICAL PHARMACOLOGY OF METHADONE IN PATIENTS WITH CHRONIC NON-MALIGNANT PAIN
313. Anne Brantberg: FETAL AND PERINATAL IMPLICATIONS OF ANOMALIES IN THE GASTROINTESTINAL TRACT AND THE ABDOMINAL WALL
314. Erik Solligård: GUT LUMINAL MICRODIALYSIS
315. Elin Tollefsen: RESPIRATORY SYMPTOMS IN A COMPREHENSIVE POPULATION BASED STUDY AMONG ADOLESCENTS 13-19 YEARS. YOUNG-HUNT 1995-97 AND 2000-01; THE NORD-TRØNDELAG HEALTH STUDIES (HUNT)
316. Anne-Tove Brenne: GROWTH REGULATION OF MYELOMA CELLS
317. Heidi Knobel: FATIGUE IN CANCER TREATMENT – ASSESSMENT, COURSE AND ETIOLOGY
318. Torbjørn Dahl: CAROTID ARTERY STENOSIS. DIAGNOSTIC AND THERAPEUTIC ASPECTS
319. Inge-Andre Rasmussen jr.: FUNCTIONAL AND DIFFUSION TENSOR MAGNETIC RESONANCE IMAGING IN NEUROSURGICAL PATIENTS
320. Grete Helen Bratberg: PUBERTAL TIMING – ANTECEDENT TO RISK OR RESILIENCE ? EPIDEMIOLOGICAL STUDIES ON GROWTH, MATURATION AND HEALTH RISK BEHAVIOURS; THE YOUNG HUNT STUDY, NORD-TRØNDELAG, NORWAY
321. Sveinung Sørhaug: THE PULMONARY NEUROENDOCRINE SYSTEM. PHYSIOLOGICAL, PATHOLOGICAL AND TUMOURIGENIC ASPECTS
322. Olav Sande Eftedal: ULTRASONIC DETECTION OF DECOMPRESSION INDUCED VASCULAR MICROBUBBLES
323. Rune Bang Leistad: PAIN, AUTONOMIC ACTIVATION AND MUSCULAR ACTIVITY RELATED TO EXPERIMENTALLY-INDUCED COGNITIVE STRESS IN HEADACHE PATIENTS

324. Svein Brekke: TECHNIQUES FOR ENHANCEMENT OF TEMPORAL RESOLUTION IN THREE-DIMENSIONAL ECHOCARDIOGRAPHY
325. Kristian Bernhard Nilsen: AUTONOMIC ACTIVATION AND MUSCLE ACTIVITY IN RELATION TO MUSCULOSKELETAL PAIN
326. Anne Irene Hagen: HEREDITARY BREAST CANCER IN NORWAY. DETECTION AND PROGNOSIS OF BREAST CANCER IN FAMILIES WITH *BRCA1*GENE MUTATION
327. Ingebjørg S. Juel : INTESTINAL INJURY AND RECOVERY AFTER ISCHEMIA. AN EXPERIMENTAL STUDY ON RESTITUTION OF THE SURFACE EPITHELIUM, INTESTINAL PERMEABILITY, AND RELEASE OF BIOMARKERS FROM THE MUCOSA
328. Runa Heimstad: POST-TERM PREGNANCY
329. Jan Egil Afset: ROLE OF ENTEROPATHOGENIC *ESCHERICHIA COLI* IN CHILDHOOD DIARRHOEA IN NORWAY
330. Bent Håvard Hellum: *IN VITRO* INTERACTIONS BETWEEN MEDICINAL DRUGS AND HERBS ON CYTOCHROME P-450 METABOLISM AND P-GLYCOPROTEIN TRANSPORT
331. Morten André Høydal: CARDIAC DYSFUNCTION AND MAXIMAL OXYGEN UPTAKE MYOCARDIAL ADAPTATION TO ENDURANCE TRAINING

2008

332. Andreas Møllerløkken: REDUCTION OF VASCULAR BUBBLES: METHODS TO PREVENT THE ADVERSE EFFECTS OF DECOMPRESSION
333. Anne Hege Aamodt: COMORBIDITY OF HEADACHE AND MIGRAINE IN THE NORD-TRØNDELAG HEALTH STUDY 1995-97
334. Brage Høyem Amundsen: MYOCARDIAL FUNCTION QUANTIFIED BY SPECKLE TRACKING AND TISSUE DOPPLER ECHOCARDIOGRAPHY – VALIDATION AND APPLICATION IN EXERCISE TESTING AND TRAINING
335. Inger Anne Næss: INCIDENCE, MORTALITY AND RISK FACTORS OF FIRST VENOUS THROMBOSIS IN A GENERAL POPULATION. RESULTS FROM THE SECOND NORD-TRØNDELAG HEALTH STUDY (HUNT2)
336. Vegard Bugten: EFFECTS OF POSTOPERATIVE MEASURES AFTER FUNCTIONAL ENDOSCOPIC SINUS SURGERY
337. Morten Bruvold: MANGANESE AND WATER IN CARDIAC MAGNETIC RESONANCE IMAGING
338. Miroslav Fris: THE EFFECT OF SINGLE AND REPEATED ULTRAVIOLET RADIATION ON THE ANTERIOR SEGMENT OF THE RABBIT EYE
339. Svein Arne Aase: METHODS FOR IMPROVING QUALITY AND EFFICIENCY IN QUANTITATIVE ECHOCARDIOGRAPHY – ASPECTS OF USING HIGH FRAME RATE
340. Roger Almvik: ASSESSING THE RISK OF VIOLENCE: DEVELOPMENT AND VALIDATION OF THE BRØSET VIOLENCE CHECKLIST
341. Ottar Sundheim: STRUCTURE-FUNCTION ANALYSIS OF HUMAN ENZYMES INITIATING NUCLEOBASE REPAIR IN DNA AND RNA
342. Anne Mari Undheim: SHORT AND LONG-TERM OUTCOME OF EMOTIONAL AND BEHAVIOURAL PROBLEMS IN YOUNG ADOLESCENTS WITH AND WITHOUT READING DIFFICULTIES
343. Helge Garåsen: THE TRONDHEIM MODEL. IMPROVING THE PROFESSIONAL COMMUNICATION BETWEEN THE VARIOUS LEVELS OF HEALTH CARE SERVICES AND IMPLEMENTATION OF INTERMEDIATE CARE AT A COMMUNITY HOSPITAL COULD PROVIDE BETTER CARE FOR OLDER PATIENTS. SHORT AND LONG TERM EFFECTS
344. Olav A. Foss: "THE ROTATION RATIOS METHOD". A METHOD TO DESCRIBE ALTERED SPATIAL ORIENTATION IN SEQUENTIAL RADIOGRAPHS FROM ONE PELVIS
345. Bjørn Olav Åsvold: THYROID FUNCTION AND CARDIOVASCULAR HEALTH
346. Torun Margareta Melø: NEURONAL GLIAL INTERACTIONS IN EPILEPSY
347. Irina Poliakova Eide: FETAL GROWTH RESTRICTION AND PRE-ECLAMPSIA: SOME CHARACTERISTICS OF FETO-MATERNAL INTERACTIONS IN DECIDUA BASALIS
348. Torunn Askim: RECOVERY AFTER STROKE. ASSESSMENT AND TREATMENT; WITH FOCUS ON MOTOR FUNCTION
349. Ann Elisabeth Åsberg: NEUTROPHIL ACTIVATION IN A ROLLER PUMP MODEL OF CARDIOPULMONARY BYPASS. INFLUENCE ON BIOMATERIAL, PLATELETS AND COMPLEMENT

350. Lars Hagen: REGULATION OF DNA BASE EXCISION REPAIR BY PROTEIN INTERACTIONS AND POST TRANSLATIONAL MODIFICATIONS
351. Sigrun Beate Kjøtrød: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN ASSISTED REPRODUCTION
352. Steven Keita Nishiyama: PERSPECTIVES ON LIMB-VASCULAR HETEROGENEITY: IMPLICATIONS FOR HUMAN AGING, SEX, AND EXERCISE
353. Sven Peter Näsholm: ULTRASOUND BEAMS FOR ENHANCED IMAGE QUALITY
354. Jon Ståle Ritland: PRIMARY OPEN-ANGLE GLAUCOMA & EXFOLIATIVE GLAUCOMA. SURVIVAL, COMORBIDITY AND GENETICS
355. Sigrid Botne Sando: ALZHEIMER'S DISEASE IN CENTRAL NORWAY. GENETIC AND EDUCATIONAL ASPECTS
356. Parvinder Kaur: CELLULAR AND MOLECULAR MECHANISMS BEHIND METHYLMERCURY-INDUCED NEUROTOXICITY
357. Ismail Cüneyt Güzey: DOPAMINE AND SEROTONIN RECEPTOR AND TRANSPORTER GENE POLYMORPHISMS AND EXTRAPYRAMIDAL SYMPTOMS. STUDIES IN PARKINSON'S DISEASE AND IN PATIENTS TREATED WITH ANTIPSYCHOTIC OR ANTIDEPRESSANT DRUGS
358. Brit Dybdahl: EXTRA-CELLULAR INDUCIBLE HEAT-SHOCK PROTEIN 70 (Hsp70) – A ROLE IN THE INFLAMMATORY RESPONSE ?
359. Kristoffer Haugarvoll: IDENTIFYING GENETIC CAUSES OF PARKINSON'S DISEASE IN NORWAY
360. Nadra Nilsen: TOLL-LIKE RECEPTOR 2 –EXPRESSION, REGULATION AND SIGNALING
361. Johan Håkon Bjørngaard: PATIENT SATISFACTION WITH OUTPATIENT MENTAL HEALTH SERVICES – THE INFLUENCE OF ORGANIZATIONAL FACTORS.
362. Kjetil Høydal : EFFECTS OF HIGH INTENSITY AEROBIC TRAINING IN HEALTHY SUBJECTS AND CORONARY ARTERY DISEASE PATIENTS; THE IMPORTANCE OF INTENSITY,, DURATION AND FREQUENCY OF TRAINING.
363. Trine Karlsen: TRAINING IS MEDICINE: ENDURANCE AND STRENGTH TRAINING IN CORONARY ARTERY DISEASE AND HEALTH.
364. Marte Thuen: MANGANASE-ENHANCED AND DIFFUSION TENSOR MR IMAGING OF THE NORMAL, INJURED AND REGENERATING RAT VISUAL PATHWAY
365. Cathrine Broberg Vågbø: DIRECT REPAIR OF ALKYLATION DAMAGE IN DNA AND RNA BY 2-OXOGLUTARATE- AND IRON-DEPENDENT DIOXYGENASES
366. Arnt Erik Tjønna: AEROBIC EXERCISE AND CARDIOVASCULAR RISK FACTORS IN OVERWEIGHT AND OBESE ADOLESCENTS AND ADULTS
367. Marianne W. Furnes: FEEDING BEHAVIOR AND BODY WEIGHT DEVELOPMENT: LESSONS FROM RATS
368. Lene N. Johannessen: FUNGAL PRODUCTS AND INFLAMMATORY RESPONSES IN HUMAN MONOCYTES AND EPITHELIAL CELLS
369. Anja Bye: GENE EXPRESSION PROFILING OF *INHERITED* AND *ACQUIRED* MAXIMAL OXYGEN UPTAKE – RELATIONS TO THE METABOLIC SYNDROME.
370. Oluf Dimitri Røe: MALIGNANT MESOTHELIOMA: VIRUS, BIOMARKERS AND GENES. A TRANSLATIONAL APPROACH
371. Ane Cecilie Dale: DIABETES MELLITUS AND FATAL ISCHEMIC HEART DISEASE. ANALYSES FROM THE HUNT1 AND 2 STUDIES
372. Jacob Christian Hølen: PAIN ASSESSMENT IN PALLIATIVE CARE: VALIDATION OF METHODS FOR SELF-REPORT AND BEHAVIOURAL ASSESSMENT
373. Erming Tian: THE GENETIC IMPACTS IN THE ONCOGENESIS OF MULTIPLE MYELOMA
374. Ole Bosnes: KLINISK UTPRØVING AV NORSKE VERSJONER AV NOEN SENTRALE TESTER PÅ KOGNITIV FUNKSJON
375. Ola M. Rygh: 3D ULTRASOUND BASED NEURONAVIGATION IN NEUROSURGERY. A CLINICAL EVALUATION
376. Astrid Kamilla Stunes: ADIPOKINES, PEROXISOME PROFILERATOR ACTIVATED RECEPTOR (PPAR) AGONISTS AND SEROTONIN. COMMON REGULATORS OF BONE AND FAT METABOLISM
377. Silje Engdal: HERBAL REMEDIES USED BY NORWEGIAN CANCER PATIENTS AND THEIR ROLE IN HERB-DRUG INTERACTIONS
378. Kristin Offerdal: IMPROVED ULTRASOUND IMAGING OF THE FETUS AND ITS CONSEQUENCES FOR SEVERE AND LESS SEVERE ANOMALIES

379. Øivind Rognmo: HIGH-INTENSITY AEROBIC EXERCISE AND CARDIOVASCULAR HEALTH
380. Jo-Åsmund Lund: RADIOTHERAPY IN ANAL CARCINOMA AND PROSTATE CANCER

2009

381. Tore Grüner Bjåstad: HIGH FRAME RATE ULTRASOUND IMAGING USING PARALLEL BEAMFORMING
382. Erik Søndenaa: INTELLECTUAL DISABILITIES IN THE CRIMINAL JUSTICE SYSTEM
383. Berit Rostad: SOCIAL INEQUALITIES IN WOMEN'S HEALTH, HUNT 1984-86 AND 1995-97, THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
384. Jonas Crosby: ULTRASOUND-BASED QUANTIFICATION OF MYOCARDIAL DEFORMATION AND ROTATION
385. Erling Tronvik: MIGRAINE, BLOOD PRESSURE AND THE RENIN-ANGIOTENSIN SYSTEM
386. Tom Christensen: BRINGING THE GP TO THE FOREFRONT OF EPR DEVELOPMENT
387. Håkon Bergseng: ASPECTS OF GROUP B STREPTOCOCCUS (GBS) DISEASE IN THE NEWBORN. EPIDEMIOLOGY, CHARACTERISATION OF INVASIVE STRAINS AND EVALUATION OF INTRAPARTUM SCREENING
388. Ronny Myhre: GENETIC STUDIES OF CANDIDATE TENE3S IN PARKINSON'S DISEASE
389. Torbjørn Moe Eggebø: ULTRASOUND AND LABOUR
390. Eivind Wang: TRAINING IS MEDICINE FOR PATIENTS WITH PERIPHERAL ARTERIAL DISEASE
391. Thea Kristin Våtsveen: GENETIC ABERRATIONS IN MYELOMA CELLS
392. Thomas Jozefiak: QUALITY OF LIFE AND MENTAL HEALTH IN CHILDREN AND ADOLESCENTS: CHILD AND PARENT PERSPECTIVES
393. Jens Erik Slagsvold: N-3 POLYUNSATURATED FATTY ACIDS IN HEALTH AND DISEASE – CLINICAL AND MOLECULAR ASPECTS
394. Kristine Misund: A STUDY OF THE TRANSCRIPTIONAL REPRESSOR ICER. REGULATORY NETWORKS IN GASTRIN-INDUCED GENE EXPRESSION
395. Franco M. Impellizzeri: HIGH-INTENSITY TRAINING IN FOOTBALL PLAYERS. EFFECTS ON PHYSICAL AND TECHNICAL PERFORMANCE
396. Kari Hanne Gjeilo: HEALTH-RELATED QUALITY OF LIFE AND CHRONIC PAIN IN PATIENTS UNDERGOING CARDIAC SURGERY
397. Øyvind Hauso: NEUROENDOCRINE ASPECTS OF PHYSIOLOGY AND DISEASE
398. Ingvild Bjellmo Johnsen: INTRACELLULAR SIGNALING MECHANISMS IN THE INNATE IMMUNE RESPONSE TO VIRAL INFECTIONS
399. Linda Tømmerdal Roten: GENETIC PREDISPOSITION FOR DEVELOPMENT OF PREEMCLAMPSIA – CANDIDATE GENE STUDIES IN THE HUNT (NORD-TRØNDELAG HEALTH STUDY) POPULATION
400. Trude Teoline Nausthaug Rakvåg: PHARMACOGENETICS OF MORPHINE IN CANCER PAIN
401. Hanne Lehn: MEMORY FUNCTIONS OF THE HUMAN MEDIAL TEMPORAL LOBE STUDIED WITH fMRI
402. Randi Utne Holt: ADHESION AND MIGRATION OF MYELOMA CELLS – IN VITRO STUDIES –
403. Trygve Solstad: NEURAL REPRESENTATIONS OF EUCLIDEAN SPACE
404. Unn-Merete Fagerli: MULTIPLE MYELOMA CELLS AND CYTOKINES FROM THE BONE MARROW ENVIRONMENT; ASPECTS OF GROWTH REGULATION AND MIGRATION
405. Sigrid Bjørnelv: EATING– AND WEIGHT PROBLEMS IN ADOLESCENTS, THE YOUNG HUNT-STUDY
406. Mari Hoff: CORTICAL HAND BONE LOSS IN RHEUMATOID ARTHRITIS. EVALUATING DIGITAL X-RAY RADIOGRAMMETRY AS OUTCOME MEASURE OF DISEASE ACTIVITY, RESPONSE VARIABLE TO TREATMENT AND PREDICTOR OF BONE DAMAGE
407. Siri Bjørgen: AEROBIC HIGH INTENSITY INTERVAL TRAINING IS AN EFFECTIVE TREATMENT FOR PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE
408. Susanne Lindqvist: VISION AND BRAIN IN ADOLESCENTS WITH LOW BIRTH WEIGHT
409. Torbjørn Hergum: 3D ULTRASOUND FOR QUANTITATIVE ECHOCARDIOGRAPHY

410. Jørgen Urnes: PATIENT EDUCATION IN GASTRO-OESOPHAGEAL REFLUX DISEASE. VALIDATION OF A DIGESTIVE SYMPTOMS AND IMPACT QUESTIONNAIRE AND A RANDOMISED CONTROLLED TRIAL OF PATIENT EDUCATION
411. Elvar Eyjolfsson: 13C NMRS OF ANIMAL MODELS OF SCHIZOPHRENIA
412. Marius Steiro Fimland: CHRONIC AND ACUTE NEURAL ADAPTATIONS TO STRENGTH TRAINING
413. Øyvind Støren: RUNNING AND CYCLING ECONOMY IN ATHLETES; DETERMINING FACTORS, TRAINING INTERVENTIONS AND TESTING
414. Håkon Hov: HEPATOCYTE GROWTH FACTOR AND ITS RECEPTOR C-MET. AUTOCRINE GROWTH AND SIGNALING IN MULTIPLE MYELOMA CELLS
415. Maria Radtke: ROLE OF AUTOIMMUNITY AND OVERSTIMULATION FOR BETA-CELL DEFICIENCY. EPIDEMIOLOGICAL AND THERAPEUTIC PERSPECTIVES
416. Liv Bente Romundstad: ASSISTED FERTILIZATION IN NORWAY: SAFETY OF THE REPRODUCTIVE TECHNOLOGY
417. Erik Magnus Berntsen: PREOPERATIV PLANNING AND FUNCTIONAL NEURONAVIGATION – WITH FUNCTIONAL MRI AND DIFFUSION TENSOR TRACTOGRAPHY IN PATIENTS WITH BRAIN LESIONS
418. Tonje Strømmen Steigedal: MOLECULAR MECHANISMS OF THE PROLIFERATIVE RESPONSE TO THE HORMONE GASTRIN
419. Vidar Rao: EXTRACORPOREAL PHOTOCHEMOTHERAPY IN PATIENTS WITH CUTANEOUS T CELL LYMPHOMA OR GRAFT-vs-HOST DISEASE
420. Torkild Visnes: DNA EXCISION REPAIR OF URACIL AND 5-FLUOROURACIL IN HUMAN CANCER CELL LINES

2010

421. John Munkhaugen: BLOOD PRESSURE, BODY WEIGHT, AND KIDNEY FUNCTION IN THE NEAR-NORMAL RANGE: NORMALITY, RISK FACTOR OR MORBIDITY ?
422. Ingrid Castberg: PHARMACOKINETICS, DRUG INTERACTIONS AND ADHERENCE TO TREATMENT WITH ANTIPSYCHOTICS: STUDIES IN A NATURALISTIC SETTING
423. Jian Xu: BLOOD-OXYGEN-LEVEL-DEPENDENT-FUNCTIONAL MAGNETIC RESONANCE IMAGING AND DIFFUSION TENSOR IMAGING IN TRAUMATIC BRAIN INJURY RESEARCH
424. Sigmund Simonsen: ACCEPTABLE RISK AND THE REQUIREMENT OF PROPORTIONALITY IN EUROPEAN BIOMEDICAL RESEARCH LAW. WHAT DOES THE REQUIREMENT THAT BIOMEDICAL RESEARCH SHALL NOT INVOLVE RISKS AND BURDENS DISPROPORTIONATE TO ITS POTENTIAL BENEFITS MEAN?
425. Astrid Woodhouse: MOTOR CONTROL IN WHIPLASH AND CHRONIC NON-TRAUMATIC NECK PAIN
426. Line Rørstad Jensen: EVALUATION OF TREATMENT EFFECTS IN CANCER BY MR IMAGING AND SPECTROSCOPY
427. Trine Moholdt: AEROBIC EXERCISE IN CORONARY HEART DISEASE
428. Øystein Olsen: ANALYSIS OF MANGANESE ENHANCED MRI OF THE NORMAL AND INJURED RAT CENTRAL NERVOUS SYSTEM
429. Bjørn H. Grønberg: PEMETREXED IN THE TREATMENT OF ADVANCED LUNG CANCER
430. Vigdis Schnell Husby: REHABILITATION OF PATIENTS UNDERGOING TOTAL HIP ARTHROPLASTY WITH FOCUS ON MUSCLE STRENGTH, WALKING AND AEROBIC ENDURANCE PERFORMANCE
431. Torbjørn Øien: CHALLENGES IN PRIMARY PREVENTION OF ALLERGY. THE PREVENTION OF ALLERGY AMONG CHILDREN IN TRONDHEIM (PACT) STUDY.
432. Kari Anne Indredavik Evensen: BORN TOO SOON OR TOO SMALL: MOTOR PROBLEMS IN ADOLESCENCE
433. Lars Adde: PREDICTION OF CEREBRAL PALSY IN YOUNG INFANTS. COMPUTER BASED ASSESSMENT OF GENERAL MOVEMENTS
434. Magnus Fasting: PRE- AND POSTNATAL RISK FACTORS FOR CHILDHOOD ADIPOSITY
435. Vivi Talstad Monsen: MECHANISMS OF ALKYLATION DAMAGE REPAIR BY HUMAN AlkB HOMOLOGUES
436. Toril Skandsen: MODERATE AND SEVERE TRAUMATIC BRAIN INJURY. MAGNETIC RESONANCE IMAGING FINDINGS, COGNITION AND RISK FACTORS FOR DISABILITY

437. Ingeborg Smidesang: ALLERGY RELATED DISORDERS AMONG 2-YEAR OLDS AND ADOLESCENTS IN MID-NORWAY – PREVALENCE, SEVERITY AND IMPACT. THE PACT STUDY 2005, THE YOUNG HUNT STUDY 1995-97
438. Vidar Halsteinli: MEASURING EFFICIENCY IN MENTAL HEALTH SERVICE DELIVERY: A STUDY OF OUTPATIENT UNITS IN NORWAY
439. Karen Lehrmann Ægidius: THE PREVALENCE OF HEADACHE AND MIGRAINE IN RELATION TO SEX HORMONE STATUS IN WOMEN. THE HUNT 2 STUDY
440. Madelene Ericsson: EXERCISE TRAINING IN GENETIC MODELS OF HEART FAILURE
441. Marianne Klokk: THE ASSOCIATION BETWEEN SELF-REPORTED ECZEMA AND COMMON MENTAL DISORDERS IN THE GENERAL POPULATION. THE HORDALAND HEALTH STUDY (HUSK)
442. Tomas Ottemo Stølen: IMPAIRED CALCIUM HANDLING IN ANIMAL AND HUMAN CARDIOMYOCYTES REDUCE CONTRACTILITY AND INCREASE ARRHYTHMIA POTENTIAL – EFFECTS OF AEROBIC EXERCISE TRAINING
443. Bjarne Hansen: ENHANCING TREATMENT OUTCOME IN COGNITIVE BEHAVIOURAL THERAPY FOR OBSESSIVE COMPULSIVE DISORDER: THE IMPORTANCE OF COGNITIVE FACTORS
444. Mona Løvlien: WHEN EVERY MINUTE COUNTS. FROM SYMPTOMS TO ADMISSION FOR ACUTE MYOCARDIAL INFARCTION WITH SPECIAL EMPHASIS ON GENDER DIFFERECES
445. Karin Margaretha Gilljam: DNA REPAIR PROTEIN COMPLEXES, FUNCTIONALITY AND SIGNIFICANCE FOR REPAIR EFFICIENCY AND CELL SURVIVAL
446. Anne Byriel Walls: NEURONAL GLIAL INTERACTIONS IN CEREBRAL ENERGY – AND AMINO ACID HOMEOSTASIS – IMPLICATIONS OF GLUTAMATE AND GABA
447. Cathrine Fallang Knetter: MECHANISMS OF TOLL-LIKE RECEPTOR 9 ACTIVATION
448. Marit Følsvik Svindseth: A STUDY OF HUMILIATION, NARCISSISM AND TREATMENT OUTCOME IN PATIENTS ADMITTED TO PSYCHIATRIC EMERGENCY UNITS
449. Karin Elvenes Bakkelund: GASTRIC NEUROENDOCRINE CELLS – ROLE IN GASTRIC NEOPLASIA IN MAN AND RODENTS
450. Kirsten Brun Kjelstrup: DORSOVENTRAL DIFFERENCES IN THE SPATIAL REPRESENTATION AREAS OF THE RAT BRAIN
451. Roar Johansen: MR EVALUATION OF BREAST CANCER PATIENTS WITH POOR PROGNOSIS
452. Rigmor Myran: POST TRAUMATIC NECK PAIN. EPIDEMIOLOGICAL, NEURORADIOLOGICAL AND CLINICAL ASPECTS
453. Krisztina Kunszt Johansen: GENEALOGICAL, CLINICAL AND BIOCHEMICAL STUDIES IN *LRRK2* – ASSOCIATED PARKINSON'S DISEASE
454. Pål Gjerden: THE USE OF ANTICHOLINERGIC ANTIPARKINSON AGENTS IN NORWAY. EPIDEMIOLOGY, TOXICOLOGY AND CLINICAL IMPLICATIONS
455. Else Marie Huuse: ASSESSMENT OF TUMOR MICROENVIRONMENT AND TREATMENT EFFECTS IN HUMAN BREAST CANCER XENOGRAFTS USING MR IMAGING AND SPECTROSCOPY
456. Khalid S. Ibrahim: INTRAOPERATIVE ULTRASOUND ASSESSMENT IN CORONARY ARTERY BYPASS SURGERY – WITH SPECIAL REFERENCE TO CORONARY ANASTOMOSES AND THE ASCENDING AORTA
457. Bjørn Øglænd: ANTHROPOMETRY, BLOOD PRESSURE AND REPRODUCTIVE DEVELOPMENT IN ADOLESCENCE OF OFFSPRING OF MOTHERS WHO HAD PREECLAMPSIA IN PREGNANCY
458. John Olav Roaldset: RISK ASSESSMENT OF VIOLENT, SUICIDAL AND SELF-INJURIOUS BEHAVIOUR IN ACUTE PSYCHIATRY – A BIO-PSYCHO-SOCIAL APPROACH
459. Håvard Dalen: ECHOCARDIOGRAPHIC INDICES OF CARDIAC FUNCTION – NORMAL VALUES AND ASSOCIATIONS WITH CARDIAC RISK FACTORS IN A POPULATION FREE FROM CARDIOVASCULAR DISEASE, HYPERTENSION AND DIABETES: THE HUNT 3 STUDY
460. Beate André: CHANGE CAN BE CHALLENGING. INTRODUCTION TO CHANGES AND IMPLEMENTATION OF COMPUTERIZED TECHNOLOGY IN HEALTH CARE
461. Latha Nrugham: ASSOCIATES AND PREDICTORS OF ATTEMPTED SUICIDE AMONG DEPRESSED ADOLESCENTS – A 6-YEAR PROSPECTIVE STUDY

462. Håvard Bersås Nordgaard: TRANSIT-TIME FLOWMETRY AND WALL SHEAR STRESS ANALYSIS OF CORONARY ARTERY BYPASS GRAFTS – A CLINICAL AND EXPERIMENTAL STUDY

Cotutelle with University of Ghent: Abigail Emily Swillens: A MULTIPHYSICS MODEL FOR IMPROVING THE ULTRASONIC ASSESSMENT OF LARGE ARTERIES

2011

463. Marte Helene Bjørk: DO BRAIN RHYTHMS CHANGE BEFORE THE MIGRAINE ATTACK? A LONGITUDINAL CONTROLLED EEG STUDY
464. Carl-Jørgen Arum: A STUDY OF UROTHELIAL CARCINOMA: GENE EXPRESSION PROFILING, TUMORIGENESIS AND THERAPIES IN ORTHOTOPIC ANIMAL MODELS
465. Ingunn Harstad: TUBERCULOSIS INFECTION AND DISEASE AMONG ASYLUM SEEKERS IN NORWAY. SCREENING AND FOLLOW-UP IN PUBLIC HEALTH CARE
466. Leif Åge Strand: EPIDEMIOLOGICAL STUDIES AMONG ROYAL NORWEGIAN NAVY SERVICEMEN. COHORT ESTABLISHMENT, CANCER INCIDENCE AND CAUSE-SPECIFIC MORTALITY
467. Katrine Høyer Holgersen: SURVIVORS IN THEIR THIRD DECADE AFTER THE NORTH SEA OIL RIG DISASTER OF 1980. LONG-TERM PERSPECTIVES ON MENTAL HEALTH
468. MarianneWallenius: PREGNANCY RELATED ASPECTS OF CHRONIC INFLAMMATORY ARTHRITIDES: DISEASE ONSET POSTPARTUM, PREGNANCY OUTCOMES AND FERTILITY. DATA FROM A NORWEGIAN PATIENT REGISTRY LINKED TO THE MEDICAL BIRTH REGISTRY OF NORWAY
469. Ole Vegard Solberg: 3D ULTRASOUND AND NAVIGATION – APPLICATIONS IN LAPAROSCOPIC SURGERY
470. Inga Ekeberg Schjerve: EXERCISE-INDUCED IMPROVEMENT OF MAXIMAL OXYGEN UPTAKE AND ENDOTHELIAL FUNCTION IN OBESE AND OVERWEIGHT INDIVIDUALS ARE DEPENDENT ON EXERCISE-INTENSITY
471. Eva Veslemøy Tyldum: CARDIOVASCULAR FUNCTION IN PREECLAMPSIA – WITH REFERENCE TO ENDOTHELIAL FUNCTION, LEFT VENTRICULAR FUNCTION AND PRE-PREGNANCY PHYSICAL ACTIVITY
472. Benjamin Garzón Jiménez de Cisneros: CLINICAL APPLICATIONS OF MULTIMODAL MAGNETIC RESONANCE IMAGING
473. Halvard Knut Nilsen: ASSESSING CODEINE TREATMENT TO PATIENTS WITH CHRONIC NON-MALIGNANT PAIN: NEUROPSYCHOLOGICAL FUNCTIONING, DRIVING ABILITY AND WEANING
474. Eiliv Brenner: GLUTAMATE RELATED METABOLISM IN ANIMAL MODELS OF SCHIZOPHRENIA
475. Egil Jonsbu: CHEST PAIN AND PALPITATIONS IN A CARDIAC SETTING; PSYCHOLOGICAL FACTORS, OUTCOME AND TREATMENT
476. Mona Høysæter Fenstad: GENETIC SUSCEPTIBILITY TO PREECLAMPSIA : STUDIES ON THE NORD-TRØNDELAG HEALTH STUDY (HUNT) COHORT, AN AUSTRALIAN/NEW ZEALAND FAMILY COHORT AND DECIDUA BASALIS TISSUE
477. Svein Erik Gaustad: CARDIOVASCULAR CHANGES IN DIVING: FROM HUMAN RESPONSE TO CELL FUNCTION
478. Karin Torvik: PAIN AND QUALITY OF LIFE IN PATIENTS LIVING IN NURSING HOMES
479. Arne Solberg: OUTCOME ASSESSMENTS IN NON-METASTATIC PROSTATE CANCER
480. Henrik Sahlin Pettersen: CYTOTOXICITY AND REPAIR OF URACIL AND 5-FLUOROURACIL IN DNA
481. Pui-Lam Wong: PHYSICAL AND PHYSIOLOGICAL CAPACITY OF SOCCER PLAYERS: EFFECTS OF STRENGTH AND CONDITIONING
482. Ole Solheim: ULTRASOUND GUIDED SURGERY IN PATIENTS WITH INTRACRANIAL TUMOURS
483. Sten Roar Snare: QUANTITATIVE CARDIAC ANALYSIS ALGORITHMS FOR POCKET-SIZED ULTRASOUND DEVICES
484. Marit Skyrud Bratlie: LARGE-SCALE ANALYSIS OF ORTHOLOGS AND PARALOGS IN VIRUSES AND PROKARYOTES
485. Anne Elisabeth F. Isern: BREAST RECONSTRUCTION AFTER MASTECTOMY – RISK OF RECURRENCE AFTER DELAYED LARGE FLAP RECONSTRUCTION – AESTHETIC OUTCOME, PATIENT SATISFACTION, QUALITY OF LIFE AND SURGICAL RESULTS;

HISTOPATHOLOGICAL FINDINGS AND FOLLOW-UP AFTER PROPHYLACTIC MASTECTOMY IN HEREDITARY BREAST CANCER

486. Guro L. Andersen: CEREBRAL PALSY IN NORWAY – SUBTYPES, SEVERITY AND RISK FACTORS
487. Frode Kolstad: CERVICAL DISC DISEASE – BIOMECHANICAL ASPECTS
488. Bente Nordtug: CARING BURDEN OF COHABITANTS LIVING WITH PARTNERS SUFFERING FROM CHRONIC OBSTRUCTIVE PULMONARY DISEASE OR DEMENTIA
489. Mariann Gjervik Heldahl: EVALUATION OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER BASED ON MR METHODOLOGY
490. Lise Tevik Løvseth: THE SUBJECTIVE BURDEN OF CONFIDENTIALITY
491. Marie Hjelmseth Aune: INFLAMMATORY RESPONSES AGAINST GRAM NEGATIVE BACTERIA INDUCED BY TLR4 AND NLRP12
492. Tina Strømdal Wik: EXPERIMENTAL EVALUATION OF NEW CONCEPTS IN HIP ARTHROPLASTY
493. Solveig Sigurdardottir: CLINICAL ASPECTS OF CEREBRAL PALSY IN ICELAND. A POPULATION-BASED STUDY OF PRESCHOOL CHILDREN
494. Arne Reimers: CLINICAL PHARMACOKINETICS OF LAMOTRIGINE
495. Monica Wegling: KULTURMENNESKETS BYRDE OG SYKDOMMENS VELSIGNELSE. KAN MEDISINSK UTREDNING OG INTERVENSJON HA EN SELVSTENDIG FUNKSJON UAVHENGIG AV DET KURATIVE?
496. Silje Alvestad: ASTROCYTE-NEURON INTERACTIONS IN EXPERIMENTAL MESIAL TEMPORAL LOBE EPILEPSY – A STUDY OF UNDERLYING MECHANISMS AND POSSIBLE BIOMARKERS OF EPILEPTOGENESIS
497. Javaid Nauman: RESTING HEART RATE: A MATTER OF LIFE OR DEATH – PROSPECTIVE STUDIES OF RESTING HEART RATE AND CARDIOVASCULAR RISK (THE HUNT STUDY, NORWAY)
498. Thuy Nguyen: THE ROLE OF C-SRC TYROSINE KINASE IN ANTIVIRAL IMMUNE RESPONSES
499. Trine Naalsund Andreassen: PHARMACOKINETIC, PHARMACODYNAMIC AND PHARMACOGENETIC ASPECTS OF OXYCODONE TREATMENT IN CANCER PAIN
500. Eivor Alette Laugsand: SYMPTOMS IN PATIENTS RECEIVING OPIOIDS FOR CANCER PAIN – CLINICAL AND PHARMACOGENETIC ASPECTS
501. Dorthe Stensvold: PHYSICAL ACTIVITY, CARDIOVASCULAR HEALTH AND LONGEVITY IN PATIENTS WITH METABOLIC SYNDROME
502. Stian Thoresen Aspenes: PEAK OXYGEN UPTAKE AMONG HEALTHY ADULTS – CROSS-SECTIONAL DESCRIPTIONS AND PROSPECTIVE ANALYSES OF PEAK OXYGEN UPTAKE, PHYSICAL ACTIVITY AND CARDIOVASCULAR RISK FACTORS IN HEALTHY ADULTS (20-90 YEARS)
503. Reidar Alexander Vigen: PATHOBIOLOGY OF GASTRIC CARCINOIDS AND ADENOCARCINOMAS IN RODENT MODELS AND PATIENTS. STUDIES OF GASTROCYSTOPLASTY, GENDER-RELATED FACTORS, AND AUTOPHAGY
504. Halvard Høilund-Kaupang: MODELS AND METHODS FOR INVESTIGATION OF REVERBERATIONS IN NONLINEAR ULTRASOUND IMAGING
505. Audhild Løhre: WELLBEING AMONG SCHOOL CHILDREN IN GRADES 1-10: PROMOTING AND ADVERSE FACTORS
506. Torgrim Tandstad: VOX POPULI. POPULATION-BASED OUTCOME STUDIES IN TESTICULAR CANCER
507. Anna Brenne Grønskag: THE EPIDEMIOLOGY OF HIP FRACTURES AMONG ELDERLY WOMEN IN NORD-TRØNDELAG. HUNT 1995-97, THE NORD-TRØNDELAG HEALTH STUDY
508. Kari Ravndal Risnes: BIRTH SIZE AND ADULT MORTALITY: A SYSTEMATIC REVIEW AND A LONG-TERM FOLLOW-UP OF NEARLY 40 000 INDIVIDUALS BORN AT ST. OLAV UNIVERSITY HOSPITAL IN TRONDHEIM 1920-1960
509. Hans Jakob Bøe: LONG-TERM POSTTRAUMATIC STRESS AFTER DISASTER – A CONTROLLED STUDY OF SURVIVORS' HEALTH 27 YEARS AFTER THE CAPSIZED NORTH SEA OIL RIG
510. Cathrin Barbara Canto, Cotutelle with University of Amsterdam: LAYER SPECIFIC INTEGRATIVE PROPERTIES OF ENTORHINAL PRINCIPAL NEURONS
511. Ioanna Sandvig: THE ROLE OF OLFACTORY ENSHEATHING CELLS, MRI, AND BIOMATERIALS IN TRANSPLANT-MEDIATED CNS REPAIR

512. Karin Fahl Wader: HEPATOCYTE GROWTH FACTOR, C-MET AND SYNDECAN-1 IN MULTIPLE MYELOMA
513. Gerd Tranø: FAMILIAL COLORECTAL CANCER
514. Bjarte Bergstrøm: INNATE ANTIVIRAL IMMUNITY – MECHANISMS OF THE RIG-I-MEDIATED RESPONSE
515. Marie Søfteland Sandvei: INCIDENCE, MORTALITY, AND RISK FACTORS FOR ANEURYSMAL SUBARACHNOID HEMORRHAGE. PROSPECTIVE ANALYZES OF THE HUNT AND TROMSØ STUDIES
516. Mary-Elizabeth Bradley Eilertsen: CHILDREN AND ADOLESCENTS SURVIVING CANCER: PSYCHOSOCIAL HEALTH, QUALITY OF LIFE AND SOCIAL SUPPORT
517. Takaya Saito: COMPUTATIONAL ANALYSIS OF REGULATORY MECHANISM AND INTERACTIONS OF MICRORNAS

Godkjent for disputas, publisert post mortem: Eivind Jullumstrø: COLORECTAL CANCER AT LEVANGER HOSPITAL 1980-2004

518. Christian Gutvik: A PHYSIOLOGICAL APPROACH TO A NEW DECOMPRESSION ALGORITHM USING NONLINEAR MODEL PREDICTIVE CONTROL
519. Ola Storrø: MODIFICATION OF ADJUVANT RISK FACTOR BEHAVIOURS FOR ALLERGIC DISEASE AND ASSOCIATION BETWEEN EARLY GUT MICROBIOTA AND ATOPIC SENSITIZATION AND ECZEMA. EARLY LIFE EVENTS DEFINING THE FUTURE HEALTH OF OUR CHILDREN
520. Guro Fanneløb Giskeødegård: IDENTIFICATION AND CHARACTERIZATION OF PROGNOSTIC FACTORS IN BREAST CANCER USING MR METABOLOMICS
521. Gro Christine Christensen Løhaugen: BORN PRETERM WITH VERY LOW BIRTH WEIGHT – NEVER ENDING COGNITIVE CONSEQUENCES?
522. Sigrid Nakrem: MEASURING QUALITY OF CARE IN NURSING HOMES – WHAT MATTERS?
523. Brita Pukstad: CHARACTERIZATION OF INNATE INFLAMMATORY RESPONSES IN ACUTE AND CHRONIC WOUNDS

2012

524. Hans H. Wasmuth: ILEAL POUCHES
525. Inger Økland: BIASES IN SECOND-TRIMESTER ULTRASOUND DATING RELATED TO PREDICTION MODELS AND FETAL MEASUREMENTS
526. Bjørn Mørkedal: BLOOD PRESSURE, OBESITY, SERUM IRON AND LIPIDS AS RISK FACTORS OF ISCHAEMIC HEART DISEASE
527. Siver Andreas Moestue: MOLECULAR AND FUNCTIONAL CHARACTERIZATION OF BREAST CANCER THROUGH A COMBINATION OF MR IMAGING, TRANSCRIPTOMICS AND METABOLOMICS
528. Guro Aune: CLINICAL, PATHOLOGICAL, AND MOLECULAR CLASSIFICATION OF OVARIAN CARCINOMA
529. Ingrid Alsos Lian: MECHANISMS INVOLVED IN THE PATHOGENESIS OF PRE-ECLAMPSIA AND FETAL GROWTH RESTRICTION. TRANSCRIPTIONAL ANALYSES OF PLACENTAL AND DECIDUAL TISSUE
530. Karin Solvang-Garten: X-RAY REPAIR CROSS-COMPLEMENTING PROTEIN 1 – THE ROLE AS A SCAFFOLD PROTEIN IN BASE EXCISION REPAIR AND SINGLE STRAND BREAK REPAIR
531. Toril Holien: BONE MORPHOGENETIC PROTEINS AND MYC IN MULTIPLE MYELOMA
532. Rooyen Mavenyengwa: *STREPTOCOCCUS AGALACTIAE* IN PREGNANT WOMEN IN ZIMBABWE: EPIDEMIOLOGY AND SEROTYPE MARKER CHARACTERISTICS
533. Tormod Rimehaug: EMOTIONAL DISTRESS AND PARENTING AMONG COMMUNITY AND CLINIC PARENTS
534. Maria Dung Cao: MR METABOLIC CHARACTERIZATION OF LOCALLY ADVANCED BREAST CANCER – TREATMENT EFFECTS AND PROGNOSIS
535. Mirta Mittelstedt Leal de Sousa: PROTEOMICS ANALYSIS OF PROTEINS INVOLVED IN DNA BASE REPAIR AND CANCER THERAPY
536. Halfdan Petursson: THE VALIDITY AND RELEVANCE OF INTERNATIONAL CARDIOVASCULAR DISEASE PREVENTION GUIDELINES FOR GENERAL PRACTICE
537. Marit By Rise: LIFTING THE VEIL FROM USER PARTICIPATION IN CLINICAL WORK – WHAT IS IT AND DOES IT WORK?

538. Lene Thoresen: NUTRITION CARE IN CANCER PATIENTS. NUTRITION ASSESSMENT: DIAGNOSTIC CRITERIA AND THE ASSOCIATION TO SURVIVAL AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH ADVANCED COLORECTAL CARCINOMA
539. Berit Doseth: PROCESSING OF GENOMIC URACIL IN MAN AND MOUSE
540. Gro Falkenér Bertheussen: PHYSICAL ACTIVITY AND HEALTH IN A GENERAL POPULATION AND IN CANCER SURVIVORS – METHODOLOGICAL, OBSERVATIONAL AND CLINICAL ASPECTS
541. Anne Kari Knudsen: CANCER PAIN CLASSIFICATION
542. Sjur Urdson Gjerald: A FAST ULTRASOUND SIMULATOR
543. Harald Edvard Mølmen Hansen: CARDIOVASCULAR EFFECTS OF HIGH INTENSITY AEROBIC INTERVAL TRAINING IN HYPERTENSITIVE PATIENTS, HEALTHY AGED AND YOUNG PERSONS
544. Sasha Gulati: SURGICAL RESECTION OF HIGH-GRADE GLIOMAS
545. John Chr. Fløvig: FREQUENCY AND EFFECT OF SUBSTANCES AND PSYCHOACTIVE MEDICATIONS THE WEEK BEFORE ADMISSION TO AN ACUTE PSYCHIATRIC DEPARTMENT
546. Kristin Moksnes Husby: OPTIMIZING OPIOID TREATMENT FOR CANCER PAIN – CLINICAL AND PHARMACOLOGICAL ASPECTS
547. Audun Hanssen-Bauer: X-RAY REPAIR CROSS-COMPLEMENTING PROTEIN 1 ASSOCIATED MULTIPROTEIN COMPLEXES IN BASE EXCISION REPAIR
548. Marit Saunes: ECZEMA IN CHILDREN AND ADOLESCENTS – EPIDEMIOLOGY, COURSE AND IMPACT. THE PREVENTION OF ALLERGY AMONG CHILDREN IN TRONDHEIM (PACT) STUDY, YOUNG-HUNT 1995-97
549. Guri Kaurstad: CARDIOMYOCYTE FUNCTION AND CALCIUM HANDLING IN ANIMAL MODELS OF INBORN AND ACQUIRED MAXIMAL OXYGEN UPTAKE
550. Kristian Svendsen: METHODOLOGICAL CHALLENGES IN PHARMACOEPIDEMIOLOGICAL STUDIES OF OPIOID CONSUMPTION
551. Signe Nilssen Stafne: EXERCISE DURING PREGNANCY
552. Marius Widerøe: MAGNETIC RESONANCE IMAGING OF HYPOXIC-ISCHEMIC BRAIN INJURY DEVELOPMENT IN THE NEWBORN RAT – MANGANESE AND DIFFUSION CONTRASTS
553. Andreas Radtke: MOLECULAR METHODS FOR TYPING *STREPTOCOCCUS AGALACTIAE* WITH SPECIAL EMPHASIS ON THE DEVELOPMENT AND VALIDATION OF A MULTI-LOCUS VARIABLE NUMBER OF TANDEM REPEATS ASSAY (MLVA)
554. Thor Wilhelm Bjelland: PHARMACOLOGICAL ASPECTS OF THERAPEUTIC HYPOTHERMIA
555. Caroline Hild Hakvåg Pettersen: THE EFFECT OF OMEGA-3 POLYUNSATURATED FATTY ACIDS ON HUMAN CANCER CELLS – MOLECULAR MECHANISMS INVOLVED
556. Inga Thorsen Vengen: INFLAMMATION AND ATHEROSCLEROSIS – RISK ASSOCIATIONS IN THE HUNT SURVEYS
557. Elisabeth Balstad Magnussen: PREECLAMPSIA, PRETERM BIRTH AND MATERNAL CARDIOVASCULAR RISK FACTORS
558. Monica Unsgaard-Tøndel: MOTOR CONTROL EXERCISES FOR PATIENTS WITH LOW BACK PAIN
559. Lars Erik Sande Laugsand: INSOMNIA AND RISK FOR CARDIOVASCULAR DISEASE
560. Kjersti Grønning: PATIENT EDUCATION AND CHRONIC INFLAMMATORY POLYARTHRITIS – COPING AND EFFECT
561. Hanne Gro Wenzel: PRE AND POST-INJURY HEALTH IN PERSONS WITH WHIPLASH: THE HUNT STUDY. EXPLORATION OF THE FUNCTIONAL SOMATIC MODEL FOR CHRONIC WHIPLASH
562. Øystein Grimstad: TOLL-LIKE RECEPTOR-MEDIATED INFLAMMATORY RESPONSES IN KERATINOCYTES
563. Håkon Olav Leira: DEVELOPMENT OF AN IMAGE GUIDANCE RESEARCH SYSTEM FOR BRONCHOSCOPY
564. Michael A. Lang: DIVING IN EXTREME ENVIRONMENTS: THE SCIENTIFIC DIVING EXPERIENCE

565. Helena Bertilsson: PROSTATE CANCER-TRANSLATIONAL RESEARCH. OPTIMIZING TISSUE SAMPLING SUITABLE FOR HISTOPATHOLOGIC, TRANSCRIPTOMIC AND METABOLIC PROFILING
566. Kirsten M. Selnæs: MR IMAGING AND SPECTROSCOPY IN PROSTATE AND COLON CANCER DIAGNOSTICS
567. Gunvor Steine Fosnes: CONSTIPATION AND DIARRHOEA. EFFECTIVENESS AND ADVERSE EFFECTS OF DRUGS
568. Areej Elkamil: SPASTIC CEREBRAL PALSY: RISK FACTORS, BOTULINUM TOXIN USE AND PREVENTION OF HIP DISLOCATION
569. Ruth Derdikman Eiron: SYMPTOMS OF ANXIETY AND DEPRESSION AND PSYCHOSOCIAL FUNCTION IN MALES AND FEMALES FROM ADOLESCENCE TO ADULTHOOD: LONGITUDINAL FINDINGS FROM THE NORD-TRØNDELAG HEALTH STUDY
570. Constantin Sergiu Jianu: PROTON PUMP INHIBITORS AND GASTRIC NEOPLASIA IN MAN
571. Øystein Finset Sørdal: THE ROLE OF GASTRIN AND THE ECL CELL IN GASTRIC CARCINOGENESIS
572. Lisbeth Østgaard Rygg: GROUP EDUCATION FOR PATIENTS WITH TYPE 2 DIABETES – NEEDS, EXPERIENCES AND EFFECTS
573. Viola Lobert: IDENTIFICATION OF NOVEL REGULATORS OF EPITHELIAL POLARITY AND CELL MIGRATION
574. Maria Tunset Grinde: CHARACTERIZATION OF BREAST CANCER USING MR METABOLOMICS AND GENE EXPRESSION ANALYSIS
575. Grete Kjelvik: HUMAN ODOR IDENTIFICATION STUDIES IN HEALTHY INDIVIDUALS, MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE
576. Tor Eivind Bernstein: RECTAL CANCER SURGERY. PROGNOSTIC FACTORS RELATED TO TREATMENT
577. Kari Sand: INFORMED CONSENT DOCUMENTS FOR CANCER RESEARCH: TEXTUAL AND CONTEXTUAL FACTORS OF RELEVANCE FOR UNDERSTANDING
578. Laurent Francois Thomas: EFFECTS OF SINGLE-NUCLEOTIDE POLYMORPHISMS ON microRNA-BASED GENE REGULATION AND THEIR ASSOCIATION WITH DISEASE
579. Øystein Sandanger: THE INNATE IMMUNE SYSTEM: A PARADOXICAL MEDIATOR OF HOST DEFENSE, TISSUE REPAIR AND COLLATERAL DAMAGE
580. Line Knutsen Lund: MENTAL HEALTH IN LOW BIRTH WEIGHT INDIVIDUALS APPROACHING ADULTHOOD
581. Nils Kristian Skjærvold: AUTOMATED BLOOD GLUCOSE CONTROL – DEVELOPMENT AND TESTING OF AN ARTIFICIAL ENDOCRINE PANCREAS USING AV NOVEL INTRAVASCULAR GLUCOSE MONITOR AND A NEW APPROACH TO INSULIN PHARMACOLOGY
582. Håvard Kallestad: SLEEP DISTURBANCE: CLINICAL SIGNIFICANCE IN MENTAL HEALTH CARE AND COGNITIVE FACTORS
583. Anders Wallenius: URACIL-DNA GLYCOSYLASE, ACTIVATION-INDUCED DEAMINASE AND REGULATION OF ADAPTIVE IMMUNE RESPONSES
584. Gry Børmark Hoftun: CHRONIC NON-SPECIFIC PAIN IN ADOLESCENCE PREVALENCE, DISABILITY, AND ASSOCIATED FACTORS – YOUNG-HUNT AND HUNT 3, 2006-2008
585. Elisabeth Hansen: THE SIGNIFICANCE OF RESISTANCE TRAINING AND PSYCHOBIOLOGY IN PRIMARY PREVENTION OF TYPE 2 DIABETES AMONG PEOPLE WITH IMPAIRED GLUCOSE TOLERANCE
586. Ragnhild Omli: URINARY INCONTINENCE AND URINARY TRACT INFECTIONS IN THE ELDERLY: RISK FACTORS AND CONSEQUENCES
587. Christina Sæten Fjeldbo: GASTRIN-MEDIATED REGULATION OF GENE EXPRESSION; A SYSTEMS BIOLOGY APPROACH
588. Yunita Widyastuti: RISK FACTORS FOR COMMON COMPLICATIONS FOLLOWING ADULT HEART SURGERY
589. Anders Thorstensen: 2D AND 3D ECHOCARDIOGRAPHY DURING INOTROPIC ALTERATIONS AND AFTER RECENT MYOCARDIAL INFARCTION
590. Torstein Schrøder-Aasen: EFFECTS OF PURPLE CONEFLOWER (ECHINACEA PURPUREA) ON CYP3A4 METABOLISM AND P-GLYCOPROTEIN MEDIATED TRANSPORT *IN VITRO*

591. Saeed Mehdizadeh: ADAPTIVE BEAMFORMERS FOR ULTRASOUND IMAGING OF ACOUSTICALLY HARD TISSUES
592. Reidar Brekken: ULTRASOUND-BASED ESTIMATION OF STRAIN IN ABDOMINAL AORTIC ANEURYSM

2013

593. Marianne Bjordal Havnes: THE EFFECT OF DIVING ON BIOMARKERS IN THE RAT. POSSIBLE CONSEQUENCES FOR SHORT AND LONG-TERM HEALTH EFFECTS IN OCCUPATIONAL DIVERS